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ELECTROPHYSIOLOGICAL STUDIES OF THE VISUAL PATHWAYS IN ALZHEIMER'S DISEASE AND PARKINSON'S DISEASE

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Doctor of Philosophy

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THE UNIVERSITY OF ASTON IN BIRMINGHAM.

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SUMMARY.

It is known that parallel pathways exist within the visual system. These have been described as magnocellular and parvocellular as a result of the layered organisation of the lateral geniculate nucleus and extend from the retina to the cortex. Dopamine (DA) and acetylcholine (ACH) are neurotransmitters that are present in the visual pathway. DA is present in the retina and is associated with the interplexiform cells and horizontal cells. ACH is also present in the retina and is associated with displaced amacrine cells; it is also present in the superior colliculus. DA is found to be significantly depleted in the brain of Parkinson's disease (PD) patients and ACH in Alzheimer's disease (AD) patients For this reason these diseases were used to assess the function of DA and ACH in the electrophysiology of the visual pathway.

Experiments were conducted on young normals to design stimuli that would preferentially activate the magnocellular or parvocellular pathway. These stimuli were then used to evoke visual evoked potentials (VEP) in patients with PD and AD, in order to assess the function of DA and ACH in the visual pathway. Electroretinograms (ERGs) were also measured in PD patients to assess the role of DA in the retina. In addition, peripheral ACH function was assessed by measuring VEPs, ERGs and contrast sensitivity (CS) in young normals following the topical instillation of hyoscine hydrobromide (an anticholinergic drug).

The results indicate that the magnocellular pathway can be divided into two: a cholinergic tectal-association area pathway carrying luminance information, and a non-cholinergic geniculo-cortical pathway carrying spatial information. It was also found that depletion of DA had very little effect on the VEPs or ERGs confirming a general regulatory function for this neurotransmitter.

Keywords: Magnocellular - Parvocellular - Dopamine - Acetylcholine -Evoked potentials.

"There is no failure except in no longer trying; there is no defeat except from within, no really insurmountable barrier save our own inherent weakness of purpose" Kin Hubbard.

This thesis is dedicated to my parents
Roger and Barbara Daniels.

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CHAPTER 1.

1. ALZHEIMER'S DISEASE.

1.1. Definition.

Alzheimer's disease is a degenerative neurologic disorder characterized by the insidious onset of a progressive dementia in middle and late life (Katz and Rimmer, 1989)

Dementia is an acquired syndrome of intellectual impairment produced by brain dysfunction (Cummings and Benson, 1983). It results in a decline of memory and other cognitive functions, in comparison with the patient's previous level of function, as determined by a history of decline in performance and by abnormalities noted from clinical examination and neuropsychological tests (Davison, 1986). There are over 60 disorders that cause dementia, Alzheimer's Disease accounts for 60% (Katzman, 1986). Until recently the term Alzheimer's Disease was reserved for those patients whose dementia occurred between the age of 45 and 65 years (presenile); this has now been revised to include an identical condition occurring in those over 65 years of age now known as senile dementia of the Alzheimer type (SDAT).

Post-mortem studies on the brains of Alzheimer's disease patients have shown that certain characteristic changes take place, these include cerebral atrophy, ventricular dilation, neuronal degeneration and loss, degenerating neuronal processes, senile plaques, neurofibrillary tangles and granulovacuolar degeneration. In addition there are characteristic neurochemical changes, the most severe of which being a marked reduction in the neurotransmitter acetylcholine.

1.2. Signs and Symptoms.

Typical Alzheimer's disease usually begins with the insidious onset of memory impairment. Early in the disease, recent memory and the ability to learn and retain new information is defective. Often the patient is aware of their cognitive deficits at this stage (Bennet and Evans, 1992). They may constantly repeat questions and statements or may forget phone messages and appointments, they may get lost while driving or walking particularly in unfamiliar surroundings, they may have difficulty performing quite simple tasks such as making a cup of tea and may use

written notes as memory aids. At this stage they may remember even small details of their remote past.

As the disease progresses, deficits in remote memory become more prominent, and other cognitive deficits appear. They begin to look untidy and wear the same clothes for days and become less able to undertake domestic chores. Forgetting the names of family members is common typically the grandchildren first, followed by the children and then the spouse. Persons become less emotionally responsive (Reisberg 1983, ii).

As the dementia continues, the patients become unable to function alone and are unable to perform simple tasks such as cutting their own food. They lose the urge or talent to wash and bathe themselves and are unable to do so without assistance. Patients become incontinent and become unstable in their movements eventually losing their psychomotor abilities. All memories and cognitive capacities gradually disappear to the extent of forgetting their own name and hence their own identity. Calculating and concentrating ability and ultimately the ability to speak is lost; patients can only stare blankly and grunt.

Cummings and Benson (1983) have divided the clinical course of the disease into three stages:

Stage l (duration of disease 1-3 years):

The presence of memory disturbances are usually indicative of onset of Alzheimer's disease. The patient frequently has amnesia, has an impaired ability to learn new material, and information is rapidly lost from the short term memory. The patient may show poor reasoning and judgement in certain tasks and problems. Carelessness in work habits and household chores become evident and the patient may become lost in familiar surroundings. They may also become apathetic and/or suspicious.

Stage ll (duration of disease 2-10 years):

Memory is more severely effected. Language problems appear with aphasia and difficulty with word naming. The patient will repeat words and phrases and have difficulty comprehending the spoken language. They also have difficulty with calculation skills. Ideational apraxia (completing a simple task in the wrong order, e.g. making a cup of tea), and ideomotor apraxia (the inability to complete a task on command that can usually be completed spontaneously) occurs. Agnosia,

particularly visual agnosia occurs e.g. the patient is unable to name body parts. The apathy changes to restlessness with frequent pacing.

Stage lll (duration of disease 8-12 years):
All intellectual capabilities are severely impaired. Language problems become more marked, vocalization is reduced to the production of repetitive sounds and eventually mutism may occur. Motor disabilities are evident with a gradual development of extrapyramidal rigidity, spasticity and quadraplegia in flexion. Seizures are uncommon but may occur in the later stages of the illness. Terminally, urinary and fecal incontinence occurs and primitive reflexes including grasp and suck responses become evident. Eventually the patient dies of aspiration pneumonia, urinary tract infection or infection of decubitus ulcers.

1.2.1. Evaluation.

An impression of a patient's mental status is generally discerned from the history, description of the patient's activities by family members, and results of general physical, neurologic, and selected laboratory examinations. A formal mental assessment is also necessary to establish the presence and extent of dementia. Cummings and Benson (1983) provide a list of functions that should be assessed when making an evaluation of an Alzheimer's patient:

STATE OF AWARENESS:
i. Depressed or fluctuating levels of arousal.
ii. Distractability

GENERAL APPEARANCE AND BEHAVIOUR:
i. Eating and sleeping patterns.
ii. Self care of patient (eg cleanliness).
ii. Behaviour of patient towards others.

MOOD AND AFFECT:
i. Mood = the inner feelings of the patient.
iii. Affect = outward expression of emotion.

LANGUAGE FUNCTION:
i. Motor aspects of verbal output (dystharia, slowness, dysprosody, dysrhythmia, unusual inflections in verbal production)
ii.Comprehension of spoken language.
iii. Repetition of spoken language (ability to repeat words on command).

iv. Word-finding ability.
v. Reading
vi. Writing.

VISUOSPATIAL FUNCTIONS. i.e. ability of copy drawings both in 2 and 3 dimensions.

RELATED CORTICAL FUNCTIONS.

i. Praxis (ability to carry out purposeful movements on oral or verbal command).
ii. Topographic disorientation (ability to find their way in familiar parts of their own neighbourhood or home, and map localisation).
iii. Right-left disorientation.
iv. Finger agnosia.
v. Identification of body parts.
vi. Unawareness or neglect (note if the patient tends to ignore or neglect one portion of the body - particularly one side).
vii. Dressing difficulties.
viii. Motor sequences (ability to carry out sequential hand movements).

TESTS OF MEMORY.

i. Immediate recall.
ii. Ability to learn new material.
iii. Ability to retrieve old learned information.
iv. Confabulation (the presentation by a patient of bizarre or incorrect information to general questioning).
v. Forgetfulness (a problem in initiating retrieval, not learning new material).

COGNITIVE FUNCTION.

i. Calculating ability.
ii. Interpretation of proverbs (ability to abstract).
iii. Similarities and differences.

THOUGHT CONTENT.

i. Morbid thoughts and preoccupation.
ii. Abnormal beliefs and interpretations.

iii. Abnormal perception of the environment, body and self.

A number of standardized tests have been developed to aid diagnosis of Alzheimer's disease which are also used in patient evaluation. These are discussed in the next section.

1.2.3. Diagnosis.

1.2.3.1. Diagnostic Criteria.

An assured diagnosis of Alzheimer's disease has proved to be difficult due to the fact that there are over 60 possible causes of dementia. The problems in diagnosing the disease are mainly due its heterogeneous nature. It is insidious in onset, therefore initial suspicion of presence of AD depends on the sensitivity of the family and friends of the patient.

The only sure way to diagnose AD is by cerebral biopsy or on autopsy, but these are both invasive techniques, the latter not being of much benefit to the patient! Early diagnosis is based on recognition of characteristic clinical features. The third edition of the 'Diagnostic and Statistical Manual of Mental Diseases (DMS-lll)' (1980) of the American Psychiatric Association presented an operational definition for dementia (Jorm and Henderson, 1985; Benson, 1987):

DIAGNOSTIC CRITERIA FOR DEMENTIA ACCORDING TO DSM-III.

A. A loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning.

B. Memory impairment.

C. At least one of the following:

(1). Impairment of abstract thinking, as manifested by concrete interpretation of proverbs, inability to find similarities and differences between related words, difficulty in defining words and concepts, and other similar tasks;

(2). Impaired judgment;

(3). Other disturbances of higher cortical function, such as aphasia (disorder of language due to brain dysfunction), apraxia (inability to carry out motor activities despite intact comprehension and motor function), agnosia (failure to recognize or identify objects despite intact

sensory function), "constructional difficulty" (e.g., inability to copy three-dimensional figures, assemble blocks, or arrange sticks in specific designs);

D. State of consciousness not clouded (i.e., does not meet the criteria for Delirium or Intoxication, although these may be superimposed).

E. Either (1) or (2):

(1). Evidence from the history, physical examination or laboratory tests of a specific organic factor that is judged to be etiologically related to the disturbance;

(2). In the absence of such evidence, an organic factor necessary for the development of the syndrome can be presumed if conditions other than Organic Mental Disorders have been reasonably excluded and if the behavoural change represents cognitive impairment in a variety of areas.

As an appendum to this definition, a disorder that became known as primary degenerative dementia (PDD) was introduced. PPD is considered a euphemism for Alzheimer's disease by many workers.

DIAGNOSTIC CRITERIA FOR PRIMARY DEGENERATIVE DEMENTIA ACCORDING TO DSM-III.

A. Dementia (see above table).

B. Insidious onset with uniformly progressive deteriorating course.

C. Exclusion of all other specific causes of dementia by the history, physical examination and laboratory tests.

This definition has since been improved by Jorm and Henderson (1985). The National Institute of neurologic and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) together presented criteria for the clinical diagnosis of dementia of the Alzheimer's type (McKhann *et al*, 1984; Huppert and Tym, 1986):

"Dementia is the decline in memory and other cognitive functions in comparison with the patient's previous level of functions as determined by a history of decline in performance and by abnormalities noted from clinical examination and neuropsychological tests. A diagnosis of dementia cannot be made when concousness is impaired by delirium, drowsiness, stupor or coma or when other clinical abnormalities prevent adequate evaluation of mental status. Dementia is a diagnosis based on behaviour and cannot be determined by computerized

tomography, electroencephalography or other laboratory instruments although specific causes of dementia may be identified by these means".

The additional clinical criteria proposed for Alzheimer's disease are that the disorder has an insidious onset, is usually progressive and the dementia occurs in the absence of other systemic or brain diseases that would account for the progressive cognitive deficit and personality change.

They also introduced the nomenclature of 'probable' AD, 'possible' AD and 'definite' AD. 'Definite' AD requires histopathological confirmation. 'Probable' AD is used if there is a typical insidious onset with progression and the exclusion of other possible causes. 'Possible" AD is used if the presentation or course is somewhat aberrant, or in the presence of other significant disease where AD is considered the most likely course of the progressive dementia.

Additional diagnostic criteria have been put forward by the national Institute on Aging (NIA) in 1980 (Katzman *et al*, 1988) and by the Medical Research Council (MRC) in 1987. A comparison of these diagnostic criteria is given in table 1.1 adapted from Katzman and colleagues (1988).

1.2.3.2. Establishing a diagnosis.

The diagnosis of dementia and a judgment regarding the type of dementia must be based largely on clinical findings supported by appropriate radiological and laboratory investigations. The following steps have been recommended to be taken to establish a diagnosis of dementia (Huppert and Tym, 1986; Lehmann, 1989).

(i). History.

A carefully taken history is essential in establishing a diagnosis of dementia. Information regarding heredity, earliest awareness and observation of symptoms, the patient's premorbid intellectual attainments, personality and social functions should be obtained from the patient and/or from a close relative or caretaker. Data on current symptoms, disabilities and changes in habits of daily life should be obtained. Often specific questions should be asked such as can the patient still dress alone?

Table 1.1. Comparison of diagnostic criteria for dementia.

† = Jorm and Henderson modification of DSM-III.
* = eg language, construction, praxis, or personality change.
R = required.
+ = desirable/not required.

Criteria	DSM-III	ADRDA /NINCDS	NIA/ AMA	J&H †	MRC
Loss of intellectual abilities.	R	R	R	R	R
Confirmation on mental status tests.		R		R	R
Impaired social or occupational function.	R			R	
Memory impairment	R	R	R	R	R
Impairment of additional area of cognition (*).	R	+	R	+	R
State of concious-ness not clouded -alert, awake.	R	R	R	R	R
Evidence of organic factor or absence of conditions other than organic mental syndrome.	R			R	

(ii). Cognitive function.

A systematic examination of the patient's mental state should be undertaken. A number of standardised diagnostic interviews and rating scales have been developed for this purpose. Examples of standardized diagnostic interviews include the Geriatric Mental State (BMS) of Copeland *et al* (1976), the Comprehensive Assessment and Referral Evaluation (CARE) of Gurtland *et al* (1977), the Diagnostic Interview (DIS) based on DSM-III criteria (Robins *et al*, 1981), and the Cambridge Mental Disorders of the Elderly Examination (CAMDEX) of Roth *et al* (1986).

Within many of these interviews are included cognitive rating scales and specific psychometric scales. Examples of cognitive rating scales include the Global Deterioration Scale (Reisberg, 1983) (see Appendix 6), which describes seven clinical phases of cognitive decline in Alzheimer's disease, and the Clinical Dementia Rating (CDR) of Hughes *et al* (1982) which rates dementia along a five-point scale (none, questionable, mild, moderate, severe) on the basis of the person's performance in six areas of daily living: memory, orientation, judgment/problem solving, community affairs, home/hobbies, and personal care. There are many others - many of which are listed in a review by Huppert and Tym (1986) - and include information regarding appearance, demeanour, mood, speech, thought content, perceptual disturbances in addition to results from other psychometric tests.

Examples of specific psychometric tests include the Wechsler Adult Intelligence Scale (WAIS) which includes assessments of vocabulary, similarities, digit span, digit symbol, block design, object assembly, performance IQ and verbal IQ (Fuld, 1983); the information-concentration-orientation test of Blessed *et al* (Katzman *et al* 1988) and the more popular Mini Mental State Examination (MMSE) which only takes 5-10 minutes to administer.

(iii). Physical examination.

These tests include blood pressure and CNS examination. Sight and Hearing examinations and assessment of gait.

(iv). Laboratory investigation.

These include full blood count, urea and electrolyte profile, tests of thyroid and liver function, determination of the vitamin B12 level, a serolergic test for syphilis. These are done to rule out a metabolic or endocrine deficiency as the cause of a treatable dementia. Examination of cerebrospinal fluid should be considered for exclusion purposes, but not as routine. Routine blood, serum and urine tests are all normal in Alzheimer's disease, although research investigations have found certain abnormalities.

(v) Further investigations.

These can include chest and skull X rays, CT scans, MRI scans, PET scans, SPECT scans, and EEG and VEP assessments.

Computed Tomography (CT).

Computer Tomography is a computer-constructed imaging technique of a thin slice through the body (in this case the head) derived from X-ray absorption data collected during a circular scanning motion. The current clinical use of CT in the assessment of patients suspected of having Alzheimer's disease is to exclude focal etiologies such as tumors, abscesses, hydrocephalus or stroke, and to describe the extent of the diffuse brain changes (De Leon and George, 1983; Khachaturian, 1980). Typical patterns of atrophy are sometimes diagnostic of Huntington's disease and Pick's disease (Katzman *et al*, 1988). Binswanger disease also has a characteristic CT scan revealing lateral and third ventricle dilation and periventricular white matter abnormalities. These lesions appear as lucencies and are patchy in distribution (Friedland and Luxenberg, 1988). CT evidence of multiple infarction is more common in patients with Multi-infarct dementia (MID) than in AD.

During normal aging, CT scan analysis reveals that both ventricular size and sulcal prominence increases over the lifespan (Jacoby and Levy, 1980; De Leon and George, 1988). It has been suggested that in Alzheimer's disease there are ventricular and sulcal changes and an increase in brain atrophy superimposed on the age-related changes, these disease-related changes being also associated with the magnitude of the cognitive deficit. (Friedland and Luxenberg, 1988). It has been reported that among linear ventricular measures, the width of the third ventricle was the best correlate of cognitive deterioration. The pathologic significance of this third

ventricle is not known - it has been suggested that this change may reflect the destruction of the nucleus basilis of Meynert (De Leon and George, 1983). However, visualization of enlarged sulci and/or ventricles is not a reliable predictor of dementia and dementia patients without atrophy and atrophy in patients without dementia have been described (Cummings and Benson, 1983).

Additional parameters used to differentiate Alzheimer's disease from controls have included indices of tissue X-ray density and gray matter-white matter discriminability. Loss of gray/white discrimination and decreased mean density has been shown (Friedland and Luxenberg, 1988). However this can be influenced by the position of the CT slice relative to the base of the skull due to the influence of the bone. De Leon *et al* (1989) used CT scans to demonstrate periventricular white matter lesions in 16% of 89 normals and 30% of 151 Alzheimer's disease patients - these lesions were associated with increasing age and with gait disturbances in the Alzheimer's disease group. Khachaturian (1980) however, states that CT scans are of little value in the early diagnosis of Alzheimer's disease and cannot indicate the degree or type of dementia - this is due to the resolution of the image not being of sufficient quality to identify small infarcts or reduced gray/white matter discrimination.

Computer tomography however, does have a use in investigating the extent and progression of these changes if CT scans are performed on a regular basis over one year or more (Friedland and Luxenberg, 1988).

Cerebral Blood Flow (CBF).

Studies of cerebral blood flow demonstrate dynamic metabolic alterations occurring in the brain of the demented patient. Oxidative metabolism of the brain regulates the CBF. The cerebral metabolic rate (CMR) reduction found in AD leads to secondary CBF reduction: thus the flow adapts to reduced metabolic demands (Ingvar, 1983). Methods of measuring global or regional CBF or CMR are based upon tracer techniques. A method of measuring global CBF is based upon the inhalation of nitrous oxide for 10 minutes. Two curves are obtained by arterial and venous cerebral sampling during equilibration of the brain tissue. The area between the curves is used to calculate the blood flow. Regional CBF can be measured by ^{133}Xenon (^{133}Xe) clearance techniques. ^{133}Xe is a gamma-emitting radioactive gas that is used to label the brain by intracarotic or intravenous injection or inhalation. A

battery of detectors placed at the side of the head are used to record the arrival and subsequent clearance of the isotope from a number of brain regions.

Since studies started in the 1960s it has been shown that in AD the total mean regional CBF showed a reduction proportional to the degree of dementia. Decreases in blood flow have been demonstrated to be most pronounced in the posterior temporal and parieto-occipital regions. In addition, diminished posterior hemispheric flow correlates with fluent aphasic, and reduced frontal lobe flow correlates with reduced spontaneous speech, echolia and meutism (Cummings and Benson, 1983; Ingvar, 1983; Friedland and Luxenberg, 1988).

Meyer (1983) used ^{133}Xe inhalation method to show that the fast flow of gray matter (F1) was reduced in early AD although there was some overlap with normal subjects. It was also demonstrated that reduction in F1 values varied directly with the severity of the dementia, duration of the dementia and the degree of brain atrophy using CT scanning. Cerebral vasodilator responsiveness during 5% carbon dioxide inhalation was also demonstrated to be preserved. Meyer (1983) states that measurement of regional CBF by inhalation of ^{133}Xe is a harmless and useful test for establishing differential diagnosis of AD, Multi infarct dementia (MID) and depression.

Positron Emission Tomography (PET).

PET is a quantitative imaging technique employed to localize and measure physiologic and biochemical processes in the brain and other organs (Eidelberg, 1992). PET differs from CT in that it represents regional brain function and not structure (Ferris and De Leon, 1983). A subject is given a small quantity of a compound that emitts positron radioactivity. During radioactive decay, these isotopes emit positrons that rapidly annihilate with electrons, producing two photons diverging at 180°; the photons can be detected by electronic coincidence counting (Benson, 1982). The spatial and temporal distribution of the radiotracer is quantitatively studied in the course of the PET imaging study. PET techniques are used to measure local brain energetics, for example, regional metabolic rate for glucose, regional cerebral blood flow, regional metabolic rate for oxygen, for quantification of specific transport and storage processes and assessment of receptor binding kinetics.

^{18}F-fluorodeoxyglucose (FDG) is a tracer compound used to determine rates of glucose utilization. During the scan, the patient remains stationary while the gantry rotates about the head and performs a series of linear and angular scans. Before the scan, a bolus of tracer is administered intravenously. Thirty to 45 minuets after the injection (approximate time required for the metabolic action to reach a steady state), serial 10mm transverse scans are obtained parallel to the canthomedial (eye-ear) reference.

Benson (1982) found that in AD cerebral glucose metabolism was reduced in frontal and parietal association cortices while the calcarine cortex and peri-rolandic motor and sensory areas were close to normal in metabolic activity. This study also indicated reduced glucose metabolism in normal subjects with advancing age.

Ferris and De Leon (1983) found that cerebral glucose metabolism was reduced at the basal ganglia level (frontal, caudate, thalamus and temporal) and the centrum semiovale level (frontal, parietal and white matter) in AD patients compared to normals. The results also indicated a consistant, moderate degree of relationship between degree of impairment and reduction in regional brain metabolism.

A review by Friedland and Luxenberg (1988) suggests that in general AD presents with a temporal-parietal cortex metabolic impairment and also left-right asymmetries. These asymmetries are persistent as the disease progresses and are related to the behavioural deficit, age of onset, and clinical course. They also present a study that found no age-related changes in regional cerebral glucose metabolism in healthy individuals. Similar findings were presented for oxygen utilization. Heiss *et al* (1989) also state that AD shows a metabolic disturbance that is most prominent in the parieto-occipito-temporal association cortex and later in the frontal lobe, while primary cortical areas, basal ganglia, thalamus, and cerebellum are not affected.

PET is also used to differentially diagnose other dementias. Multi infarct dementia (MID) produces diffuse lesions throughout the brain that appear as multiple lesions in the cortex, deep nuclei, subcortical white matter and cerebellum using PRT-FDG, more lesions are detected with PRT than CT scanning (Friedland and Luxenberg, 1988). In Huntington's disease marked depression in caudate and putamen regional cerebral glucose metabolism is found; and PRT-FDG scans reveal diminished global glucose utilization rates without focal accentuation in cortex of Wilson's disease patients.

Single Photon Emission Tomography (SPECT).

This technique does not require a local cyclotron as a positron source and may provide a more economical and readily usable substitute for PET, especially in CBF studies. SPECT studies of regional CBF have been performed using ^{133}Xe and the tracers N-isopropyl-p-iodoamphetamine (IMP), N,N-N'-trimethyl-N'-(2)hydroxy-3-methyl-5-iosdobenzyl-1,3 (HIPDM), both labelled with iodene-123, and d,1-hexamethly-propyleneamine oxide labelled with technetium 99m (HM-PAO).

SPECT studies in AD using IMP show decreased regional CBF in temporal and parietal cortex (Friedland and Luxenberg (1988). Gemmell *et al* (1989) using HM-PAO also showed bilateral perfusion defects in the temporo-parieto-occipital region of AD patients. Only 29% of patients showed this defect alone, 46% had frontal perfusion defects as well as the bilateral temporo-parieto-occipital deficits.

Frlich *et al* (1989) also used HM-PAO as a tracer for the SPECT analysis of two groups of AD patients - moderately and severely demented respectively. The study indicated stage-dependent regional differences in CBF in AD patients. Temporo-parietal flow deficits were again demonstrated - extending to frontal regions as the disease progresses.

Magnetic Resonance Imaging (MRI).

This technique permits high resolution imaging of brain morphology without subjecting the patients to the dangers of ionizing radiation (Khachaturian, 1980). It is based on the magnetic properties of hydrogen nuclei and their response to externally applied magnetic fields, and the exaltation of those protons within such a field by a radiofrequency pulse. It is capable of producing accurate measurements of brain and CSF volume and can discriminate gray and white matter. It can also detect small, localized physical - chemical changes associated with abnormal morphological changes such as small infarcts, brain tissue damage, and cell protein changes.It is of great value in evaluating the presence of brain tumors, blood clots, multiple infarctions, and other lesions that can cause dementia (Friedland and Luxenberg, 1988). The multiple cerebral infarct of MID, and the white matter lesions of Binswanger's disease are also visible on MRI.

For a number of years MRI has demonstrated white matter lesions associated with dementia and for unique multiple sclerosis plaques (Budinger, 1987). Filley *et al* (1989) showed that MRI was quite effective in demonstrating cerebral atrophy in Alzheimer's disease. Compared with the normal group, the AD patients showed significant loss of brain parenchyma, reflected in both ventricular enlargement and cortical atrophy. White matter lesions were apparent in both groups, but were more notable in the patients with AD. De-Leon *et al* (1989) found that white matter lesions were associated with increased asymmetry of white matter cerebral glucose metabolism. Indeed among AD patients, the presence of white matter lesions was associated with a significant preservation of temporal lobe glucose metabolism. Their data identified an area in the AD brain where regional glucose metabolism showed increase.

To date, MRI does not provide an effective means of diagnosis of AD but may be of particular importance in the future.

Electroencephalography (EEG).

The electroencephalogram (EEG) is a non-invasive recording technique that provides a direct sample of brain activity. It provides a useful means of assessing cerebral physiologic changes associated with aging and dementia in man as it is unaffected by the influence of motivational factors or practice effects (Obrist, 1980; Fenton, 1986).

Several changes have been described in the EEG of normal aged subjects (Obrist, 1980; Busse, 1983; Fenton, 1986; Visser, 1991):
(a). Alpha rhythm frequency slowing - from around 10Hz in the young adult, to 9.5-9.95Hz at 60 years, 9.0-9.5Hz at 70 years, and 8.5-9.0 after 80 years.
(b). Increase in the quantity of the beta rhythm. This rhythm at 15-30Hz is usually less than 25μV and bifrontal, rolandic or diffuse in distribution - the percentage of normal aged subjects with a slight excess of beta activity doubles from 12% in young adults to 24% at 70 years, followed by a gross reduction in the over 80years.
(c). Increase in slow activity. This consists of theta (4-7Hz) and delta (1-3Hz) activity of generalized distribution, which slows in 12% of young adults but in 24% of subjects over 70years.
(d). Decrease of alpha rhythm blocking (normally the alpha rhythm is blocked on opening the eyes, this reaction diminishes with increasing age).

(e). Focal slow (delta) activity - these are normally located in the anterior temporal region particularly over the left side and are found in 20% of the 40-59 age group increasing to 30-40% in the over 60s.
(f). Sleep pattern. Overall sleep becomes more fragmented - this is associated with a marked reduction in stage 4 (high-amplitude slow waves) and a moderated decrease in the amount of time occupied by rapid eye movement waves (REM) sleep. There is also a decline in the number of 12-14 cycles per second spindle bursts.

Patients with dementia often present with a slowing of the alpha rhythm over both hemispheres, a moderate to marked amount of diffuse theta and delta activity and a bilaterally symmetrical decline in low voltage beta activity (Fenton, 1986). In the more severe dementias, alpha rhythm can be totally absent and there is often diminished alpha activity reaction (Visser, 1991). Focal abnormalities are more commonly found in patients with vascular dementias (up to 50%) although they can be found in a minority of patients with primary dementia. Fenton (1986) also states that the occipital response to photic stimuli at fast flicker rates tended to disappear in demented patients. Paroxysmal EEG events have also been noted in demented patients - these are transient high voltage waves that arise suddenly from the background EEG and are rare in normal healthy subjects.

The above EEG abnormalities are all found in varying degrees in Alzheimer's disease, although they are not always found in the early stages of the disease. In 1984 Duffy *et al* used brain electrical activity mapping to demonstrate increased EEG slowing and reduced fast activity (synchronization) in patients with presenile and senile dementia of the Alzheimer type. In addition they found that in presenile dementia this slowing was maximal over the right posterior temporal and to a lesser extent, left midtemporal to anterior temporal areas whereas those with senile dementia revealed maximal slowing over the midfrontal and anterior frontal lobes bilaterally. Thus they state that in the older age range, the regions that best discriminate the demented patient from controls are the frontal lobes, in the younger age range temporal lobe features are powerful discriminators.

Coben *et al* (1990) found that patients with AD had a high % power of delta and theta activity but lower alpha and beta activity than controls. The most consistent and significant differences between the two groups were that the AD group had a higher % theta and a lower mean frequency. They also considered detectability of individuals with AD and found the highest sensitivity was obtained when considering the % power of theta activity. The sensitivity was low (20%) but was

associated with high specificity (100%). However, they conclude that "any role of EEG frequency analysis in detecting senile dementia of the Alzheimer type at its mild state would be very limited".

Soininen *et al* (1991) measured serial EEGs in AD patients over a 3 year period. They found that in the early stages of the disease 50% of patients had normal EEGs with no deterioration during first year follow up. By the third year, only 8% of patients had normal EEGs - the remainder demonstrating progressive slowing during follow up. A large amount of slow activity in early AD predicted a poor outcome by year 3. They found that in their small sample, absolute theta amplitude was the most important discriminating parameter of outcome.

In an attempt to simplify EEG interpretation, Baggio *et al* (1991) presented a method of using a graphic technique, which performed high resolution spectral imaging capable of visualizing simultaneously the power spectra, coherence and phase differences between pairs of electrodes. They based their preliminary study on the alpha band, and found that a fragmentation of power over different frequencies and leads, together with a shift of the power peak from occipital to parietal or anterior regions were the main features that differentiated senile dementia of the Alzheimer type from normal controls.

It thus seems likely that most AD patients will have an abnormal EEG - but so will patients who have other forms of dementia. Pick disease, however, often presents with a normal or only slightly abnormal EEG. Even when diffuse theta and delta frequencies are present, the alpha activity is better preserved than in AD (Fenton, 1986, Visser, 1991).

Huntigton's disease usually presents with an irregular low-voltage (<10μV) fast pattern. However, such changes tend to become apparent when the disease is clinically well established. Creutzfeldt Jakob Disease (CJD) has a characteristic EEG. It shows only mild, generalized, background slowing which can be more marked over one hemisphere or appear focal. In addition there is a pattern of distinctive periodic triphasic sharp waves occurring at 0.5-1.0 second intervals. They may have a unilateral onset but eventually become bilateral and synchronous. This pattern is not found in all cases of CJD, and may rarely appear in advanced AD patients.

Cerebral Biopsy.

The definitive diagnosis of AD, Pick disease and CJD depends on confirmation by microscopic examination of the presence of characteristic changes in neurons of the cerebral cortex. In AD, these include senile plaques and neurofibrillary tangles. In Pick disease these include Pick bodies (abnormal inclusions in neurons), and in CJD, the spongy appearance of the cortex resulting from a particular pattern of nerve cell drop out and gliosis. This can only be done by cerebral biopsy which involves the removal of a small piece of cerebral cortex by either open surgery or needle biopsy under stereotactic or CT guidance. The tissue then undergoes histological, microscopic, biochemical and virological examination and investigation. Any form of surgical procedure carries risk, in this case the risks include postoperative haemorrhage, spread of infection (particularly CJD), post operative epilepsy, cardiac arrest and in some cases death has occurred.

Biological Markers.

This is an area currently attracting much attention as the identification of a specific biological marker of AD that can be used clinically would be an important advance in the diagnosis of the disease. One method is to determine and measure the presence of paired helical filament antigen in the cerebrospinal fluid as this would indirectly reveal the among of neurofibrillary tangles in the brain. Investigations are also being carried out on the use of blood tests to assess the presence of beta-peptide precursor protein which is characteristic of the specific amyloid found in senile plaques (Katzman, 1988; Lehmann, 1989).

CSF fluid can also be used to test for the presence of acetylcholinesterase - known to be reduced in the AD brain, or somatostatin or norepinephrine. However, details with regard to their concentration in the CSF remains sceptical (Katzman, 1988).

Table 1.2 provides a list of laboratory tests used to identify other conditions that might cause or exacerbate dementia.

Table 1.2.
Diagnostic Evaluation for Dementia (from Bennet and Evans, 1992).

(* Useful in routine evaluation)

- Blood, serum, or plasma
  - Chemistry profile*
    - Metabolic disturbances
    - Endocrinopathies
  - Complete blood count*
    - Infections
    - Anemia
  - Vitamin B_{12} and folate*
    - Vitamin B_{12} deficiency
  - Thyroid function tests*
    - Hyper or Hypothyroidism
  - Syphilis serology*
    - Tertiary syphilis
  - Sedimentation rate and autoimmune profile
    - Inflamatory disease
  - Drug screen and levels
    - Sedative hypnotics
    - Cardiac
    - Antidepressants
  - Heavy metal screen
    - Lead
    - Mercury
    - Arsenic
    - Copper
  - Ceruloplasmin
    - Wilson's disease
  - Long-chain fatty acids
    - Adrenoleukodystrophy
- Electrocardiogram*
  - Arrhythmia
  - Myocardial infarction
  - Left ventricular hypertrophy
- Chest radiograph
  - Pneumonia
  - Cardiomegaly
  - Tumor
- Urine analysis
  - 24-hour excretion of heavy metals

- Arylsulfatase A
  - Metachromatic leukodystrophy
- Brain scan (CT or MRI)*
  - Vascluar disease (MRI more sensitive but less specific)
  - Mass lesions
    - Primary brain tumor
      - Subfrontal meningioma
      - Butterfly glioma
    - Metastatic brain tumor
      - Lung
      - Breast
  - Subdural hematomas (chronic subdural hematoma may be difficult to appreciate on CT, especially when bilateral)
    - Cerebral abscesses
  - Symptomatic hydrocephalus
  - Demyelinating disease (MRI superior)
- Electroencephalography
  - Creutzfeldt-Jakob disease
  - Temporal lobe status
  - Adult-onset petit mal status
  - Depression
- Lumbar puncture
  - Meningitis
  - Syphilis
  - Demyelinating disease
  - Inflamatory disease
- Angiography
  - Inflamatory disease (eg, primary central nervous system vasculitis, systemic lupus erythematosis etc)
- Cerebral biopsy
  - Vasculitis
  - Research settings for diagnosis

1.3. Anatomy.

Relating dementia to brain anatomy is difficult task as so little is known about the dementing process - indeed relatively little is known about brain function. The brain is a ball of soft tissue that weights no more than 1.5 kilograms, and yet it is

responsible for all our sensory, motor, voluntary, and involuntary function, our psychy and our personality. Its complexity is astounding and is beyond the scope of this chapter.

From the signs and symptoms of dementia it seems logical to assume that changes within the brain resulting in dementia cannot be restricted to one localization - but must involve many brain regions. Figure 1.1 summarises the parts of the brain thought to be involved in Alzheimer's disease (and Parkinson's disease - see chapter 2).

The symptoms of memory loss are perhaps the most difficult to explain. Researchers have studied people suffering from amnesia caused by brain damage in an attempt to piece together the way the brain handles memories. For example, patients with damage to the temporal lobes may find it difficult to recognise animals, but are perfectly capable of recognising other inanimate objects. It has been implicated that the brain places knowledge in different 'stores' according to how it was obtained, verbally or visually. Damage to the hippocampus results in the patients being unable to remember events that took place after the brain damage, but can still recall events that took place before the injury occurred (Young and Concar, 1992). It is thought that the hippocampus is required for memory storage for only a limited period, the more permanent memory storage is thought to be the cortex. How the cortex stores memories is still unknown, a possibility is that they are coded as patterns of electrical activity within specific networks of neurons connected by synapses. To act as a 'memory' a cluster of neurons must be able to 'recall a specific pattern of electrical activity on demand. Any pathological process interfering with this complex association between neurons will effect the ability to recall memories and to store new ones.

1.4. Pathology of Alzheimer's disease.

Post-mortem studies on the brains of Alzheimer's disease patients have shown that certain characteristic changes take place, these include cerebral atrophy, ventricular dilation, neuronal degeneration and loss, degenerating neuronal processes, senile plaques, neurofibrillary tangles and granulovacuolar degeneration.

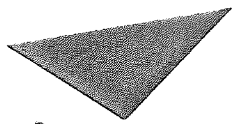

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Figure 1.1. Diagram to show regions of the brain associated with Alzheimer's disease and Parkinon's disease (from Brown, 1992).

1.4.1. Cytoskeletal Pathology.

1.4.1.1. Neurofibrillary Tangles (NFT).

Neurofibrillary tangles are abnormal neurons in which the cytoplasm is filled with bundles of submicroscopic filamentous structures. They are found within the cerebral cortex, specifically the association areas of the frontal, temporal and parietal lobes, also the hippocampus, amygdala, entorhinal area, and locus ceruleus (Mann, 1985; Ferry, 1988). The association cortex is involved in carrying out tasks such as memory and decision-making rather than sensation or the control of movement. They are not found in the cerebellum, spinal cord or peripheral nervous system. The concentration of these lesions is strongly correlated with the degree of dementia (Terry and Davies, 1980; Price, 1986).

Neurofibrillary tangles can be viewed occasionally using routine hematoxyline and eosin stain, but silver impregnated stains such as Bodian or Bielschowsky are preferred. Thioflavine-S stain is commonly used as it is less expensive and although the NFTs have to be viewed in ultra violet light - this stain provides high resolution and distinctness (fig 1.2.) Congo red stain viewed with polarized illumination has also been used (Terry and Katzman, 1983). They are composed of 10 nanometer filaments arranged as paired helical filaments with a periodicity of 80 nanometers, thought to be modified neurofilaments (Wisniewski and Terry, 1976; Terry and Davies, 1980; Terry and Katzman, 1983; Cummings and Benson, 1983; Mann, 1985; Wurtman, 1985; Price, 1986). In general paired helical filaments (PHF) occur within neurons as densely packed groups displacing other cytoplasmic organelles. They are often seen in the axon and dendrites and are also present within the neurites of senile plaques (Mann, 1985). There is a great deal of uncertainty about the structure of these filaments, but they are thought to contain a high molecular weight protein that is insoluble and highly resistant to digestion by enzymes. Using monoclonal antibodies Wischick and his colleagues at the Medical Research Council's Laboratory of Molecular biology in Cambridge have identified one of the components as the protein Tau (cited in Ferry, 1988). Others have shown a similarity between some amino acid sequences of paired helical filaments and human amyloid protein (Davison, 1986). In addition, a non-protinaceous component containing aluminium, silicon, sodium and calcium has been detected in NFT.

While the frequency of NFTs in AD greatly exceeds that usually encountered in mentally able persons of similar age, their presence is not restricted to AD. They are present in small, but increasing numbers in old age, in Parkinson-dementia complex of Guam, in traumatic encephalopathy of boxers, Parkinson's disease, middle aged persons with Down's syndrome amongst others (Cummings and Benson, 1983; Mann, 1985; De Estable-Puig *et al*, 1986).

1.4.1.2. Senile Plaques (SP).

Senile plaques (SP) follow an identical distribution to NFT. The classic histological description is that they are spherical foci with an overall diameter of 120-200 micrometers (De Estable-Puig *et al*, 1986) and a core diameter of 13 micrometers (Davison, 1986). Typical plaques have a three tiered structure. The outer layer consists of degenerating neurite processes containing intracellular paired filaments as well as a large number of lamellar dense bodies and many mitochondria of varying stages of alteration; the middle zone consists of swollen axons and dendrites, and a central core made up of amyloid and aluminosilicates (fig 1.3), (Terry and Davies, 1980; Cummings and Benson, 1983, Davison 1986; De Estable-Puig *et al*).

SPs have been divided into three categories based on their presumed stage of degeneration (Wisniewski and Terry, 1976; Mann, 1985):

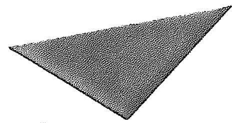
(1). A primitive plaque consisting of a small number of distended neurites with either no or only a small amount of central amyloid. A few astrocytic processes and the occasional microglial cell may also be present.

(2). A 'mature' or classical plaque with a dense central core of amyloid surrounded by numerous swollen neurites, astrocytic processes and microglia.

(3). A 'burnt -out' plaque in which the neuronal elements have been lost and which consist almost entirely of a central core with abundant astrocytic and microglial cells.

The senile plaques are well displayed using silver impregnated stains, Congo red or Thioflavine-S. There seems to be a correlation between the number of senile plaques and severity of dementia (Terry and Katzman, 1983; Price, 1986).

Figure 1.2. and Figure 1.3.



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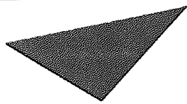
1.2. A thioflavine S stained neuron with a well formed neurofibrillary tangle. The PHF glow bright yellow in ultraviolet illumination (from Terry and Katzman, 1983).



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1.3. Diagram showing an electron micrograph of a senile plaque. A = amyloid star. *Arrows* point at thr degenerating neurites (from Wisniewski and Terry, 1976).

As previously mentioned NFT and SPs are found in the brains of non-demented aged subjects. Mann *et al* (1987) found that they were more likely to occur at greatest density within the amygdala and hippocampus rather than within the neocortex, nucleus basilis or olfactory bulbs and tracts. They speculated that the 'amygdala and hippocampus are sites of early or critical involvement in Alzheimer's disease'.

Pearson *et al* (1985) investigated the distribution of NFT and SPs in the neocortex of patients with AD. They found that the cortical association areas of the temporal, parietal and frontal lobes were all severely involved, whereas the the motor, somatic, sensory and primary visual areas were virtually unaffected. NFTs were found in clusters primarily in the supra- and infra- granular layers, particularly layers III and V. The SPs were unclustered, and occurred in all layers, particularly layers II and III.

The distribution of SPs in AD patients has also been investigated by Armstrong and colleagues (1988) who found that they were nearly always found clumped in the tissue examined, with the regularly spaced clump being a consistent feature. The regular spacing of these clumps were thought to follow the columnar organisation of the cortex. They also found regular clumping of SPs in the hippocampus and suggest that this was due to the SPs forming at the projection sites of subcortical afferents. They also investigated the differential distribution of cored and uncored plaques and suggest that cored plaques may be related to capillaries (and may result from leakage of proteins from capillaries) and the uncored plaques may be related to the development of abnormal neurites or NFTs.

The same group (1990) investigated the clustering properties of NFTs as well as SPs, and found that both occurred in regularly spaced clusters in the neocortex and hippocampus. They tentatively suggest that SPs and NFT follow a pattern of development beginning with SPs in the upper zones of the cortex, followed by development of NFT in the same zone but in a functionally related site to the SP site, followed by NFT and SP development in the lower zones of the cortex but on the same columns as the upper zones.

Lewis *et al* (1987) investigated the distribution of NFT and SP in the visual and auditory cortices in AD patients. They found that NFTs were rarely found in the primary visual cortex, but their number increased progressively in association areas 18 to 20 in a manner that parallels their position in the proposed hierarchial

organization of the visual system. This has since been confirmed by Armstrong *et al* (1990). Similarly Lewis *et al* found very few NFTs in the primary auditory cortex, but a 10-fold increase in the auditory association cortex (area 22). In addition they confirmed the results of Pearson *et al* (1985) that NFTs were more commonly found in layers III and V - and that their distribution is very similar to the distribution of pyramidal cells associated with cortico-cortical projections. In contrast, SPs had less distinctive distribution patterns and their numbers did not appear to differ substantially between primary and association regions.

1.4.1.3. Granulovacuolar degeneration (GVD).

Granulovacuolar degeneration is another histological feature of Alzheimer's disease. These are clusters of intracytoplasmic vacuoles of up to 5 microns in diameter, containing a granule 0.5-1.5 microns in size (Cummings and Benson, 1983; Mann, 1985; De Estable-Puig *et al*, 1986). They occur within the pyramidal cells of the hippocampus, and their presence correlates with loss of these cells - suggesting that the development of GVD is associated with cell death (Terry and Davies, 1980; Price, 1986). Preliminary immunocytochemical studies have demonstrated that the granules show tubulin-like immunoreactivity (Price, 1986).

1.4.1.4. Hirano Bodies.

These are eosinophillic rod-shaped lesions that are essentially limited to the hippocampus - lying either in or near the cytoplasm of the pyramidal cells. It has a structure of close-packed filaments or sheets arranged in alternating rows at right angles to each other (Terry and Katzman, 1983). They have a long axis of up to 30μm and a short one of up to 15μm (Mann, 1985). although they are found in normal individuals, they are found in increased numbers in AD, Parkinson's disease and Pick's disease.

1.4.2. Neurodegeneration of Alzheimer's disease.

Atrophy of the brain is a common finding in Alzheimer's disease; it is easily detected on macroscopic examination. It is characterized by decreased brain weight (often weighing less than 1000gm), narrow convolutions and widened sulci (Cummings and Benson, 1983; De Estable-Puig *et al*, 1986; Davison, 1986, Ferry, 1988). When the brain is sectioned, ventricular dilation is evident. The atrophy occurs mainly in the frontal and temporal lobes of the cerebral cortex, with possible shrinkage of the hippocampus and amygdaloid (Mann,. 1986). Sparing of the

occipital cortex and primary motor and somatosensory cortices may be apparent. The basal ganglia and thalamus, other than the massa intermedia, are not grossly shrunken. The midbrain and brainstem also appear normal on gross examination (Terry and Katzman, 1983).

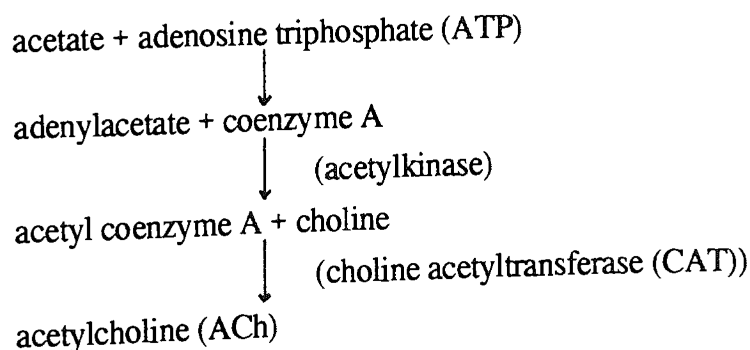
Neuronal loss occurs in subcortical, cortical and brain stem regions. There is an apparent loss of large cells (diameter above 30 micrometers) from the basal nucleus of Meynert, which is the principal source of cholinergic fibres to the amygdala and neocortex (Price, 1986). Some patients show decreased numbers of nerve cells in the locus coeruleus, these cells are catecholaminergic and show structural pathology in their distal axons and terminals e.g. in the neocortex and hippocampus (Roth, 1986). Neurons of the serotoninergic raphe nuclei have also been shown to degenerate in AD (Price, 1986; Mann, 1986).

Loss of large neurons has also been found in the frontal and temporal cortices and in the hippocampus, with reductions of up to 33% (Terry and Katzman, 1983; Mann, 1986; Davison, 1986). Substantial decreases in the number of large neurons (presumably pyramidal cells) have been noted in the superior, middle, inferior frontal gyrus, cingulate gyrus and superior and middle temporal gyrus (Mann, 1986). Cell loss has also been reported in other areas associated with cerebral cortex such as the amygdala and the periventricular nucleus of the hypothalamus (Mann, 1986; Price, 1986; Kazman, 1986).

1.4.3. Neurochemistry of Alzheimer's Disease.

1.4.3.1. Cholinergic system.

Acetylcholine is a neurohormonal neurotransmitter synthesised from choline and acetyl coenzyme A following a complex sequence of enzymatic reactions:



CAT is synthesised in the cell bodies of neurons, travels slowly down the axon and is found to be predominantly located in nerve terminals. The distribution of CAT in the brain is similar to that of both acetylcholine and the high affinity uptake of

choline. Hydrolysis of ACh at the cholinergic synapse is principally governed by acetylcholinesterase (AChE). The activities of AChE is distributed unevenly in conjunction with cholinergic markers such as CAT. Highest levels are found in areas such as the caudate nucleus and putamen, and the lowest levels are found in the cerebral cortex (apart from the white matter). In the cortex, AChE is apparently confined mainly in presynaptic axonal processes of the cholinergic system and their terminal ramifications (Perry and Perry, 1983; Simms and Bowen, 1983).

In Alzheimer's disease many nerve cells of the nucleus basilis of Meynert develop NFTs. Eventually these cholinergic neurons degenerate leaving behind extracellular NFT (Price, 1986). This cell death results in reduced cholinergic innervation to the amygdala, hippocampus and neocortex (Simms and Bowen, 1983; Roth, 1986; Price, 1986). Up to 30-90% reductions in cholinergic activity have been reported in these regions (Simms and Bowen, 1983; Terry and Katzman, 1983; Cummings and Benson, 1983; Katzman, 1986).

There have been a number of studies demonstrating reduced CAT and AChE concentration in the AD brain, and these have been extensively reviewed (Terry and Davies, 1980; Simms and Benson, 1983; Perry and Perry, 1983; Terry and Katzman, 1983; Cummings and Benson, 1983; Price, 1986; Davison, 1986; Mann, 1986; Katzman, 1986 are examples). Reduced CAT activity is most marked in the hippocampus and neocortex, particularly in areas demonstrating histopathological changes such as SPs and NFTs.

The loss of AChE is not as extensive as CAT activity and is not apparent at earlier stages of the disease (Perry and Parry, 1983). But the loss occurs in the same regions as the CAT activity loss. It has also been shown that in both normal elderly and in AD patients, SPs and NFTs are associated with AChE histochemical activity and it has been speculated that AChE is involved in their production

Cholinergic loss is mainly a presynaptic phenomenon as most post-synaptic muscarinic receptors remain unaltered (Terry and Davis, 1980; Davison, 1986; Katzman, 1986). However, muscarinic receptors can be classified into M1 and M2 and there is a possibility that there may be some M2 receptor loss in AD.

ACh loss is thought to play a major role in the reduced mental ability of AD patients. This hypothesis stems from studies revealing a correlation between neocortical CAT activity in post mortem samples and mental test scores determined

six months prior to death of AD patients (Simms and Bowen, 1983; Terry and Katzman, 1983; Roth, 1986). In addition, reduced mental capacity has been shown to be reduced in young individuals receiving anticholinergic drugs (chapter 3).

Although cholinergic deficit plays an important part in the pathophysiology of AD, it cannot account for the massive neuronal fallout or other histological changes found in AD (Roth, 1986). This is because cholinergic nerve endings constitute less than 10% of the total nerve terminals and probably even less in the neocortex.

1.4.3.2. Noradrenergic system.

There have been varying results from studies investigating noradrenaline concentration in the AD brain. Some have found it to be present in normal concentrations. Some have found it to be low in putamen and frontal cortex, but normal in hippocampus, cingulate gyrus, caudate nucleus, hypothalamus, thalamus, mesencephalon and pons. Although some hippocampal losses have been noted (Terry and Katzman, 1983).

Since cellular losses have been described in the basal ganglia of some AD brains - it doesn't seem surprising that this results in reduced noradrenaline as it is these pigmented neurons that are the source of cortical noradrenaline.

1.4.3.3. Serotoninergic system.

Some groups have found serotonin (5-hydroxytryptamine or 5-HT) to be of normal concentration in the AD brain (Terry and Katzman, 1983). Others have found 5-HT and 5-HT receptors to be reduced. These receptors may be localised on the tangle-forming glutaminergic neurons of the cortex (Bowen and Davidson, 1985). More severely affected samples of temporal cortex and limbic areas have revealed reduced 5-HT levels and may be the result of cell dysfunction in the raphe nucleus.

1.4.3.4. Peptidergic system.

Somatostatin is a peptide neurotransmitter present in medium-sized and large neurons in the cerebral cortex and the hippocampus. Significant reductions in concentration have been found in several of the neocortex, midtemporal regions and hypothalamus in the AD brain, the loss being almost equal to that of CAT (Terry and Katzman, 1983; Katzman, 1986). Somatostatin has been identified in some

NFTs in the cerebral cortex, and abnormal clusters of somatostatin terminals have been found in SPs (Katzman, 1986). In addition, considerable losses of somatostatin receptors have been noted.

Substance-P, Cholecystokinin, vasoactive intestinal peptide, neuropeptide Y and neurotensin have all found to be reduced in the AD brain (Cummings and Benson, 1983; Katzman, 1986).

1.4.3.5. Dopaminergic system.

Uncertainty remains regarding dopamine concentrations in the AD brain. It is generally accepted that the basal ganglia show reduced levels of dopamine and homovanillic acid (a dopaminergic metabolite) (Carlsson, 1980).

1.4.3.6. Gamma-aminobutyric acid (GABA) system.

GABA concentrations are not found to be altered in AD patients when post mortem factors are considered.

1.4.3.7. Amino-Acids.

Glutamate is the neurotransmitter thought to be involved in the large neurons that are lost or effected by NFTs in the AD cerebral cortex. Reductions in concentration have been found in the cortex and basal ganglia (Davison, 1986). In addition, supersensitivity of glutamate receptors of the caudate receptors of the caudate nucleus have been noted (Ferry, 1988). Supersensitivity occurs when receptors are deprived of their usual supply of transmitter.

1.5. Epidemiology and Etiology of Alzheimer's disease.

1.5.1. Epidemiology.

Due to the difficulties involved in the accurate diagnosis of Alzheimer's disease - detailed prevalence and incidence studies are also difficult to conduct. Prevalence refers to the total number of persons with a disorder within a given population at a fixed point in time. There has been a great deal of variation among these studies reflecting differences in methodology, in ages of the individuals sampled, and in the definition of dementia. Figures have ranged from 1.1% to 6.2% of persons of 65 years having severe dementia and 2.6 to 15.4% having mild to moderate dementia;

39% of these having having dementia of the Alzheimer type (Cummings and Benson, 1983,); this figure increases to 50% for those of 85 years of age (Rogan and Sullivan, 1991).

A study of prevalence rates in a Stockholm parish in December 1987 by Fratiglioni *et al* (1991) found that 7.9% of the population between 75 and 79 years had dementia, 14.5% of those between 80 and 84 years, 26.3% of those between 85 and 89 years and 15.8% of those over 90 years had dementia; and 54% of these cases were dementia of the Alzheimer type. They found no difference between male and female as regards the prevalence of dementia and types of dementia.

A review by Fischer and Berner (1991) states that at least 2% of people aged between 70 to 79 years and at least 5% of those aged over 80 years suffer from advanced dementia. There are probably many more suffering with mild to moderate dementia. In addition they cite a meta analytical study by Jorm and colleagues (1987) that found a constant doubling of prevalence rates every 5.1 years. Due to the progressive increase in life expectancy - these figures are likely to rise. At autopsy about 60% of dementia cases in the elderly are diagnosed as senile dementia of the Alzheimer type.

Iqbal (1991) presents studies of prevalence rates of AD in the United States of America. It is stated that 11% of the population who are 65 years of agé and older have mild to moderate dementia and 44% have severe dementia. 55% of these cases of senile dementia are of the Alzheimer type. Another approximately 20% of these dementia patients have a combination of AD and cerebrovascular dementia. This review also points out that AD is the fourth leading cause of death in adults in the United States after heart disease, cancer, and stroke.

A review of prevalence studies conducted in the United Kingdom is presented by Ineichen (1987), and states that the overall rate of dementia in the population over 60 years ranged from 24.6% to 2.5%, but the type of dementia is not specified.

Henderson (1986) and Fischer and Berner (1991) also suggest that the prevalence of AD is greatest in Western countries, is reduced in Japan where Multi ifarct dementia is thought to be the most common form of dementia, and rare in the Third World countries such as Nigeria.

Incidence is the number of new cases of a disorder first developed or diagnosed during a specified time interval, the data is usually obtained through special surveys- the figures must be age adjusted or age specific in any comparison.

Henderson (1986), and Ineichen, (1987) present reviews of incidence studies of AD. They cite studies by Akesson ((1969) who found a 3 year incidence of 0.38% for AD in a population of 4198 persons over 60 years of age; Bergmann *et al* (1973) who found an annual incidence rate of 0.8% over 2-4 years in Newcastle upon Tyne; Hagnell *et al* (1981, 1983) who found incidence rates of 0.7% and 0.5% for males and females respectively in the 70 -79 year olds and 1.9% and 2.5% respectively in the over 80 year olds over 25 years; and Mortimer *et al* (1981) who calculated an annual incidence rate of 1% in persons over 65 years old.

1.5.1.1. Risk Factors.

Many epidemiological studies have been conducted in an attempt to discover whether the prevalence of the disease could be associated with possible risk factors. Amaducci *et al* (1986) found that in a study conducted in Italy, advanced age of the mother at birth and family history of dementia were associated with increased incidence of AD. No association was found with thyroid disease, herpes zoster infection, head trauma, occupation, or family history of mental retardation (including Down's syndrome).

Joya-Pardo *et al*, (1991) in a study conducted in Columbia showed a significant association of AD with family history of dementia. They also found associations with family history of Down's syndrome and smoking but they did not reach significance. Associations with head trauma, ingestion of aluminium-containing antacids, history of Thyroid disease, parental age at the subject's birth, birth order, fertility and woman's parity were not significant, neither were malaria or tuberculosis.

Kokmen and Beard (1991) found a positive association of AD with age in Rochester, Minnesota. They also found positive association with episodes of depression but did not reach significance.They found no association with history of head injury, exposure to radiation (particularly the head) or Hashimoto's thyroiditis.

In China, Li *et al* (1992) found a positive association between AD and family history of dementia, some environmental exposures at work such as farm work, rural living, exposure to painting and solvents (but were not found to be significant), and left-handedness. No association was found with birth order, head injury, blood transfusions, the use of antacids with Al, analgesics, tranquilizers, alcohol, or tobacco. A negative association between arthritis and AD was found.

Other studies have found AD to be more prevalent in females compared to males (reviewed by Ineichen, 1987; Fischer and Berner, 1991) - but this may due to the increased life expectancy of women.

Two types of AD are thought to exist, early and late onset AD. Both, however have the same histopathological features.

1.5.2. Etiology.

The cause of Alzheimer's disease is still unknown and it is likely that a combination of factors are involved:

1.5.2.1. Age:

From the epidemiological studies detailed above, it can be seen that the prevalence and incidence of AD increases with age. Post mortem studies have shown that an aged brain often shows all of the histological changes of Alzheimer's disease even if the patient was not demented. AD differs from aged controls by the greater frequencies, wider distributions, and greater severities of the pathologies (Price, 1986). Matsuyama (1983) present a study analysing the incidence of NFTs, SPs and GVD in 617 brains obtained from a Tokyo population. The results are shown graphically in figure 1.4, and it can be seen that there in an obvious increase in incidence of NFTs and SPs as age increases. GVD is rare in persons under 60 years old, but increase in frequency above 60 years and are present in approximately 75% of cases over 80 years old.

1.5.2. 2. Familial, Genetic and Chromosomal factors:

There appears to be at least two forms of Alzheimer's disease, the familial form (dominant or early onset) which represents 1/3 of all cases and the sporadic form (late onset) (Drachman and Lippa, 1991). The familial form seems to follow an autosomal dominant transmission, is associated with more profound deficits in cognitive ability (Brandt *et al*, 1989) and its onset is early although variable (Matsuyama, 1983; Wurtman, 1985). A case of identical twins illustrated a separation in age of onset of 13 years - indicating that an environmental or metabolic factor may be contributing (Katzman, 1986). Even in late onset AD, a review by Matsuyama (1983) indicates that there is some genetic component involved, as a higher prevalence of AD was found in persons having a family history of the disease, this was also confirmed by Farrer *et al*, 1990) - however, the mode of inheritence is not known.

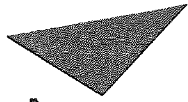
Chromosomal abnormalities have been investigated in an attempt to establish the mode of transmission of the disease. Early studies concentrated on increased aneuploidy (abnormal chromosome numbers) in AD patients. These have been reviewed by Matsuyama (1983) and Fischman (1983), and it can be seen that there is a variety of results, some finding chromosome loss in AD patients (particularly females) and others finding increased chromosome numbers. A more likely mode of inheritence is a genetic abnormality on a particular chromosome. Attempts have been made to isolate such a chromosome and variations in reports have resulted. Suggestions include chromosome 6 and 14 (Cummings and Benson, 1983), chromosome 21 (Ferry 1988) or indeed it could demonstrate heterogenous transmission. The most promising seems to be a defect on chromosome 21. This defective gene on chromosome 21 has only been found in those AD patients demonstrating the early onset form of the disease (Ferry, 1988).

Patients with Down's syndrome who survive beyond their 40th decade develop SP, NFT and reduced acetyltransferase in the neocortex and hippocampus in the same distribution as that in typical Alzheimer's disease (Wisniewski and Wisniewski, 1980). Thus the presence of trisomy of chromosome 21 in the cells of patients with Down's syndrome appears to be sufficient (although not necessarily) the cause of Alzheimer's disease (Katzman, 1980) . More evidence is the fact that the gene that makes the protein amyloid is situated on chromosome 21. This protein happens to be a component in the core of the senile plaques in Alzheimer's disease. The sporadic form of the disease has its onset later in life and does not appear to show the same chromosomal abnormalities.

1.5.2.3. Infective agents:

Senile plaques have been observed in human 'slow virus" encephalopathies (Kune and Creutzfeldt Jacob disease) and in animal encephalopathies (natural scrapie of sheep and goats) - suggesting a viral hypothesis (Wurtman, 1985; De Estable-Puig *et al*, 1986; Drachman and Lippa, 1991). The olfactory bulb has been suggested as a possible site of entry of an infectious agent and spreads through the brain via the existing network of fibres linking the pyramidal cells in the cortex. The olfactory bulb is a small structure underneath the frontal lobe that is the first relay station for nerve fibres coming from small receptors in the nose. The bulb degenerates in all elderly people but in Alzheimer patients the surviving area develops tangles (Pearson *et al*, 1985). It has also been shown that Alzheimer patients have a sense of smell that is worse than that of age matched normals (Ferry 1985). The infectious

Figure 1.4



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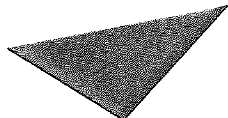
Incidence of Alzheimer-type neurofibrillary change with age (from Matsuyama, 1983).



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Incidence of Alzheimer-type senile plaque change with age (from Matsuyama, 1983).

agent could be a normal product of our genes triggered into activity under the influence of other genes or of factors in the environment.

It now appears that the agents causing scrapie and CJD may not be viruses at all, but a prion (an unusual infective agent containing neither DNA nor RNA). In scrapie they appear as aggregates forming rod-like structures and when stained with congo red, resemble the amyloid seen in the brains of sheep with scrapie and in some people with CJD. It is possible that the amyloid found in AD may be a collection of prions (Wurtman, 1985; Drachman and Lippa, 1991).

Evidence contradicting this hypothesis is the fact that attempts to induce Alzheimer's disease in animals by injecting preparations from the brain of a diseased individual have failed. However Manveldis at Yale succeeded in causing brain damage in hamsters by injecting them with blood cells taken from relatives of Alzheimer disease patients (cited in Ferry 1988).

1.5.2.4. Toxic agents:

Aluminium (Al) has been suggested as a causative agent in Alzheimer's disease. This is a common metal in the Earth's crust and its salts inevitably find their way into food and water. For industrial purposes Aluminium is recovered from bauxite, it is used in packaging materials and utensils, in aviation and automobile industries and Al compounds (especially sulphates) are used in water purification procedures. Certain drugs e.g. certain antacids used to treat stomach ulcers, contain Al compounds (van der Voet *et al*, 1991). Levels of Aluminium vary in the environment and one would expect the incidence of Alzheimer's disease to follow an identical distribution. Research in this area is still in progress.

Neurofibrillary changes have been induced in animals (e.g. cats and rabbits) if Aluminium chloride is injected (Crapper, 1976). In addition, studies have shown that cats and rabbits injected with Al salts suffer from reduced learning abilities and reduced performance in memory tasks. This is followed by progressive deterioration in motor control, with difficulty executing body righting, increased muscle tone, ataxia of gait, tremors, myoclonic jerks and seizures (Crapper, 1986; Crapper Mc Lachlam *et al* , 1991).

A form of encephalopathy resulting in dementia is known to exist in patients on long term haemodialysis with dialysate high in Al (Hughes, 1989; Van der Voet, 1991). It is characterised by speech disturbances, twitching, myoclonic jerks, motor apraxia, seizures, visual and auditory hallucinations, paranoid behaviour and

dementia. The brain of such patients contains an accumulation of Al in the grey cortex but there are no SPs, and NFT are infrequent.

Crapper *et al* (1975) have detected elevated concentrations of Aluminium in the human brain with Alzheimer's disease, although this remains controversial (Pearl and Brody, 1980). However, alumino silicates are a consistent and specific feature of the central core of senile plaques, and high concentrations of Al have been found in the bundles of paired helical filaments that make up the NFTs (Pearl and Brody, 1980; Crapper Mc Lachlan *et al*, 1991; Van der Voet, 1991). Al has also shown to induce the abnormal phosphorylation of Tau (principal subunit of NFTs) and Alumino silicates can seed the formation of amyloid peptides (major protein found in SPs) in vivo.

There have been several epidemiological studies investigating links between Al in the environment and the incidence of AD.Martyn and Candy (1991) conducted a survey in 88 county districts within England and Wales to assess the relationship between Al concentration in drinking water and the incidence of AD. They found that a positive association between diagnosed rates of AD and the average residual Al concentrations present in drinking water supplies was present. The relationship was more pronounced when only those under the age of 65 years were considered. They also examined the relationship between bone Al concentration (as an indicator of long term exposure to Al) and the presence of histopathological features of AD. They found no relation between the presence of SPs or NFTs and concentration of Al in bone.

A similar study was conducted by Michael *et al* (1991) on a community around Bordeaux. They found a significant relationship between the Al concentration in drinking water and the risk if AD which persists after adjustment for age, educational level and place of residence. A review of studies presented by Crapper Mc Lachlan (1991) found similar results. However, this relationship should be confirmed with autopsy findings.

1.5.2.5. Immune function:

Behan and Feldman (1970) found serum protein abnormalities in 66% of patients with Alzheimer's disease (cited in Cummings and Benson, 1983). These abnormalities included reductions in albumin, alph-1-antitrypsin, alph-2-macroglobulin and laptoglobulin fractions. There are also elevated levels of brain antibody (Cummings and Benson, 1983; Nandy, 1980). Amyloid is a product of

cells involved in the immune system, and altered immune function could explain its presence in senile plaques and occasional occurrence in cerebral vessels.

1.5.2.6. Abnormal Protein.

The most extensively considered possible neurotoxic factor in AD is beta-Amyloid due to its presence in SPs and as deposits in and around blood vessels. However, it is not known whether this abnormal protein is deposited as a result of a genetic defect, or as a by-product of when some pathological process attacks the cell membrane. The protein that behaves abnormally to create NFTs is thought to be Tau (Kerry, 1988; Drachman and Lippa, 1991).

1.5.2.7. Microtubular function:

Microtubular dysfunction contributes to the nourofibrillary pathology of Alzheimer's disease and the abnormal mitosis of Down's syndrome. A genetic predisposition to this type of dysfunction may contribute to the presence of Alzheimer's disease.

1.5.2.8. Trauma:

It has been suggested that individuals with Alzheimer's disease have an increased incidence of a history of head trauma (Price, 1986). It is well established that boxers show a clinical syndrome of dementia associated with the presence of NFT and are said to be "punch drunk".

1.6. Treatment of Alzheimer's disease.

There is no specific treatment for AD to date and management remains symptomatic. Treatment strategies are directed towards improving cognitive function based on replacement of neurotransmitter deficiencies or on improving overall cerebral metabolic rate.

1.6.1. Treatment based on the cholinergic system.

The deficit in the cholinergic system in AD and the involvement of cholinergic systems in learning and memory has led to the hypothesis that drugs which increase cholinergic transmission should be therapeutically useful in the treatment of memory disorders, (Corkin 1981). Although ACh is not the only neurotransmitter altered in AD, it is however the one found to be consistently decreased. Four strategies, are available to improve function in the cholinergic system (Roberts, 1982; Drachman, 1983; Rosenberg *et al*, 1983; Growdon and Wurtman, 1983; Ban, 1989; Mayeux, 1990):

i. ACh precursors: Choline and lecithin increase plasma choline levels in humans. Unfortunately, patients have failed to demonstrate a consistent benefit.

ii. Acetylcholinesterase inhibitors: Physostigmine is a centrally active acetylcholinesterase inhibitor which prevents the enzymatic hydrolysis of synaptically released ACh, thereby increasing the ACh concentrations at the cholinergic synapse. The cognitive functions improved but it is modest and variable (Corkin 1981). Physostigmine unfortunately has the disadvantage of a very short half-life.

iii. ACh receptor agonists: Arecoline a muscarinic agonist, has been used experimentally in young subjects and demonstrated a significant increase in memory function.

iv. General metabolic enhancers: Piracetam (Nootropil), a GABA derivative, in combination with choline, produces a sharp improvement in retention in animals. Results from human studies are not yet available.

1.6.1.1. ACh precursors.

As the memory deficits found in AD are thought to be the result of reduced ACh - attempts have been made for a number of years to improve memory by replacing lost ACh. Choline and Lecithin are the two most investigated substances. The

majority of reports indicate that short term use of Choline or Lecithin alone does not improve any aspect of AD (Corkin, 1981; Growdon and Wurtman, 1983; Crook, 1985).

The failure of cholinergic precursors may be due to insufficient acetyl coenzyme A, which is required for ACh production. In view of this, Acetyl-L-carnitine has also been used in an attempt to treat AD. This is a weak cholinergic agonist because it is structurally similar to ACh. The acetyl group may aid the formation of acetyl coenzyme A. It has been shown that acetyl-L-carnitine reverses amnesia, oedema, and eletrolyte imbalance following ischemia in animals, and may increase verbal fluency in demented patients without funtional improvement in activities of daily living (Mayeux, 1990).

A pilot study was conducted on a small number of AD patients using a combination of Lecithin and Thyrotropin-Releasing-Hormone (TRH) by Lampe *et al* (1991). TRH is a small neuropeptide which is widely distributed throughout the mammalian CNS and has a potent facilitatory affect on CNS cholinergic transmission. Results of this study suggest the possibility that the cognitive performance of their AD patients may have been relatively improved during the period of TRH and Lecithin co-administration - further investigation is necessary.

1.6.1.2. Acetylcholinesterase inhibitors.

Cholinesterase inhibitors act by preserving synaptically released acetylcholine. However, intestinal absorption is highly variable and unpredictable. Physostigmine has been used on a number of occasions with varying results. Slight improvement in recent memory, immediate recall, retrieval from long-term storage have been reported. Others have found no improvement (Growdon and Wurtman, 1983; Hollander *et al,* 1986; Thal *et al* , 1989; Mayeux, 1990). Side effects include nausia and vomiting.

A more recent cholinesterase inhibitor called Tetrahydroaminoacridine (THA) has been used in trials for the treatment of AD. Alhainen *et al* (1991) found that orientation, attention and other cognitive functions other than memory responded to treatment. In addition they found that it reversed the increase in theta power, decreased alpha power and increased delta power of the EEG found in AD. Slight improvements in scores on neuropsychological tests was also found by Ahlin *et al* (1991) following administration of THA. However, one major disadvantage of this drug is that it results in elevated liver transaminase levels (Gamzu, 1990).

Metrifonate (MTF) is an organophosphorous cholinesterase inhibitor with a duration of brain cholinesterase four times longer than Physostigmine. However it is not a directly acting inhibitor, but requires nonenzymatic metabolism to form the active compound, dichlorvos (2,2-dichlorovinyl dimethyl phosphate). Statistically significant improvements in the AD assessment scale scores has been observed in patients following MTF administration (Giacobini and Becker, 1991). Excessive build up of the drug in the brain is prevented by the considerable blood - brain barrier for the compound and rapid metabolism.

Combinations of cholinesterase inhibitors with other drugs have been used in an attempt to improve the results. Peter and Lavin (1983) found that Physostigmine combined with Lecithin agumented long-term verbal memory processes in some patients with AD. Thal *et al* (1983) also found that this drug combination improved memory function in a group of AD patients.

Combinations of THA and Lecithin have also been investigated (Sitaram *et al,* 1983; Chatellier and Lacomblez, 1990). The former group found a small improvement in serial learning tasks in only a subgroup of AD patients and the latter group could find no beneficial effects from this combination of drugs.

1.6.1.3. ACh receptor agonists.

Cholinergic agonists act by stimulating muscarinic and nicotinic postsynaptic receptors in the peripheral and central nervous system (Mayeux, 1990). Since muscarinic post-synaptic binding sites are not effected in AD, this form of treatment is potentially useful in cases where cholinergic neurons are no longer functioning. Cholinergic agonists include nicotine, muscarine, arecoline, pilocarpine, oxotremorine, RS-86, AF102B, BM-5 (Hollander, *et al*, 1986). Nicotine is known to increase concentration and performance, increase free recall and long term recall, and also decreases intrusion error in normal subjects. However, it also increases anxiety, depression and fear (Lapchak *et al*, 1989). A study on a group of AD patients (Sunderland, 1988) found that administration of nicotine had no beneficial effect on cognitive function and that the side effects of anxiety and depression were marked.

Arecholine (a muscarinic agonist) has been shown to enhance learning in normal young humans, in rodents and in aged primates, and it has also resulted in an improvement in a small group of AD patients (Hollander, *et al,* 1989). However, its extremely short half life makes it extremely impractical to use clinically.

Bethanechol, a potent nicotinic cholinergic agonist, has little effect on memory or other cognitive function (Mayeux, 1990).

Pilocarpine has not been found to be useful and Oxotremorine is plagued by distressing cholinergic side effects (depression, chills and tremor). Results using RS86 have been mixed and side effects are severe (Hollander *et al*, 1986).

Lack of clinical success of these cholinergic agonists may be due to their lack of selectivity for the brain regions, and their adverse side effects. AF102B is a full muscarinic agonist that is M1 receptor selective and has been shown to reverse hyoscine hydrobromide induced cognitive impairments in rats (Fischer *et al*, 1990). This drug may, in the future, be useful in the treatment of AD.

1.6.1.4.. General metabolic enhancers.

Nootropics are a class of stimulant psychoactive drugs that have physiologic and behavioural effects in experimental animals but lack the usual toxic side effects (Schneck, 1983; Mayeux, 1990). Several actions of nootropic drugs on brain cholinergic mechanisms have been demonstrated. Piracetam, oxiracetam, aniracetam, pyroglutamic acid, tenilsetam, ebiratide, vinpocetine, naloxone, beta-carbolines and phosphatidyiserine are able to antagonize amnesia induced by hyoscine hydrobromide (Pepeau and Spignoli, 1990). They have been used for a number of conditions associated with cognitive impairment such as senile dementia, memory disturbances, coma, acute and chronic alcoholism, developmental learning disorders, post traumatic encephalopathy, post-operative concousness of patients undergoing neurosurgery and cerebral arteriosclerosis (Schneck, 1983; Mayeux, 1990). The primary action is believed to be stimulation of the GABA system.

Most studies have been conducted using piracetam - although as yet there is very little information regarding its action in the AD brain. A pilot study on 7 AD patients treated with a combination of piracetam and choline chloride showed improved mean performance in memory storage tasks and recall trials (Schneck, 1983). This drug also increases regional cerebral metabolism measured by PET (Mayeux, 1990).

1.6.2. Treatment based on non-cholinergic systems.

Other agents that have been used include cerebral vasodilators, CNS stimulants, anabolic agents, anticoagulants, vitamins, chelating agents, hyperbaric oxygen and precursor amino-acids but none show any beneficial effect. Minor tranquilizers should be avoided as they increase confusion and have a detrimental effect on

cognition; major tranquilizers such as phenothiazines are a better choice. Depression may be treated with anti-depressants as long as they are chosen to induce the least anticholinergic side effects, tricyclic antidepressants should therefore be avoided, MAO inhibitors are a better choice (Meier-Ruge, 1983; Hollister, 1985; Mayeux, 1985).

Vasodilators have been used in an attempt to increase blood flow to the brain. Examples include papaverine, cyclandelate, nifedipine and benzyclan. However - it is now accepted that such agents have little value in the treatment of AD (Roberts, 1982; Meier-Ruge, 1983; Yesavage, 1983; Hollister, 1985).

Neuropeptides such as chlorpromazine, thioridazine, and haloperidol are used in the treatment of specific symptoms such as suspicousness, hallucinations, sleeplessness, agitation, emotional ability or agressiveness. However, care must be taken as these drugs can have adverse effects on activities of daily living and cognitive function (Meier-Ruge, 1983; Mayeux, 1990).

Neuropeptides are a class of compounds that function as either neurotransmitter or neuromodulators. Adrenocorticotrophic hormone (ACTH) and vasopressin (VP) specifically are thought to be of particular relevance to the process of attention, memory and other cognitive function (Ferris, 1983; Crook, 1985). Ferris (1983) found that ACTH resulted in a small improvement in recall, mood improvement, reduced depression and increased energy in a small group of AD patients; and that vasopressin resulted in a small improvement in certain memory measures.

The use of nerve growth factor (NGF) in the treatment of AD is growing in interest. NGF has been shown to prevent both the loss of septal-hippocampal cholinergic neurons induced by transection of the fimbna-fornix pathway and the reduction in cortical choline acetyltransferase activity caused by injection of the excitatory neurotoxin ibotenic acid into the nucleus basilis (Potter and Morrison, 1991). Potter and Morrison demonstrated that a variety of NGFs could reverse the effects of the cholinergic neurotoxin AF64A in the lateral ventricles of rat brain. Treatment with selected combinations of growth factors may ultimately prove effective at restoring function in a variety of neurodegenerative diseases such as AD.

Experiments involving the transplantation of suitably chosen fetal brain tissue into the adult animal brain with a view to promoting regeneration of lesioned regions is also of particular importance (Roberts, 1982). Bjorklund and Gage (1988) have used fetal grafts of basal forebrain cholinergic neurons to substitute for a lost or age-impaired cholinergic afferent input to the hippocampal formation or neocortex in

rats. They also transplanted into the frontoparietal neocortex of rats with ibotenic acid lesions of the nucleus basilis. Hippocampal lesions resulted in memory impairments that could be reversed following transplantation. Lesion of the nucleus basilis of Meynert also resulted in long lasting learning and memory deficits that were improved following cholinergic rich basal forebrain tissue transplants. Transplant surgery may be a form of AD treatment in the future.

It is important that the patient should be encouraged to be involved in normal daily activities and not to become isolated. Family support and advice is important.

CHAPTER 2

2. THE PARKINSONIAN SYNDROME.

2.1. Definition.

The Parkinsonian syndrome named after James Parkinson who first described paralysis agitans in 1817, is a disturbance of motor function. It is characterised by slowing of emotional and voluntary movement, mask- like facial expression, shuffling gait, akinesia, muscular rigidity and tremor. It may be produced by several different pathological processes involving the substantia nigra and its efferent pathways.

2.2. Signs and Symptoms.

Onset of Parkinson's disease occurs around the 60th decade and has a duration of 10 years and above. The first symptom is usually tremor or stiffness and slowness of movement. They often develop a characteristic facial expression with a widening of the palpebral apertures, infrequent blinking and staring appearance. The patient often has a stoop due to flexion of the spine. As the disease progresses the patient suffers more with rigidity, akinesia (difficulty in initiating movement), and bradykinesia (slowness with which movement is performed). This effects speech (becoming slurred and monotonous), hand movements (resulting in difficulty with fine tasks and handwriting), and reduced arm swinging on walking. They have a characteristic gait which is usually slow, shuffling, and composed of small steps. Often there is difficulty in beginning to walk, and getting out of a chair. Approximately 90% of patients suffer with depression, which is treated with drugs. Eventually the patient may develop dementia of the Alzheimer type. Death occurs usually from complications such as pneumonia, vascular disease or neoplasia. Occasionally there is a terminal stage of lethargy passing into coma.

The universally agreed four cardinal signs of Parkinson's disease are tremor at rest, rigidity, bradykinesia and loss of postural reflexes (Jankovic, 1987; Hoehn, 1992; Tanner, 1992). Bradykinesia may be manifested by a delay in the initiation and slowness of execution of a movement. An extreme degree of bradykinesia is akinesia which is a state of complete immobility. These are known as freezing attacks which may last seconds, minutes, or hours, and are most evident at the onset of gait or getting out of a chair. Tremor is one of the most frequently cited

symptom of the disease, however only half of all patients present with tremor as the initial manifestation and 15% never have tremor during the course of the illness. Tremor at rest (4-6Hz) is the most typical form although most patients also have tremor during activity (5-8Hz) which may be more disabling. The postural tremor in Parkinson's disease resembles the essential tremor and this can lead to diagnostic confusion, which may be further hindered by the fact that the two can coexist. A patients functional disability is better reflected by rigidity, which is less variable than tremor and contributes to subjective stiffness and tightness. Postural instability resulting in loss of balance during attempted propulsion and retropulsion is probably the least specific, but most disabling of all the Parkinsonian signs. The following is a list of the other signs and symptoms associated with Parkinson's disease (adapted from Jankovic, 1987; Hoehn and Yahr 1967):

Hypomimia (masked facies)
Speech disturbances
Hypophonia (speaking quietly)
Dysphagia (difficulty swallowing)
Sialorrhea (increased saliva production)
Respiratory difficulties
Loss of associated movements
Shuffling, short-step gait, festination, freezing
Micrographia (small handwriting)
Difficulty turning in bed
Difficulties with activities of daily living
Stooped posture, kyphosis, and scoliosis
Dystonia, myoclonus (clonic contractures of individual groups of mucsles),
    orofacial dyskinesia (abnormal movement of the mouth).
Muscle pain, cramps, and aching
Depression, nervousness, or other psychiatric disturbances
General fatigue
Drowsiness
Impaired visual contrast sensitivity
Visuospatial impairment
Impaired upward gaze
Impaired convergence
Oculogyric crisis (total paralysis of eye mucsles)
Impaired smooth pursuit
Impaired vestibuloocular reflex (eye position relative to head position)
Hypometric saccades

Decreased blink rate
Spontaneous and reflex blepharospasm (severe blinking)
Lid apraxia

2.2.1 Evaluation:

The assessment of Parkinson's disease is difficult because the disease is expressed differently between individuals, with differing responses to medication and variable progression. The accurate and reliable evaluation of the motor dysfunction is essential for an objective assessment of the efficacy of potentially useful drugs (Jankovic, 1987).

In assessing the motor symptoms, two approaches can be used which attempt to quantify the disability. One utilizes neurologic history and examination with subjective rating scales, subjective quantification, signs and functional disability. The second method utilizes timing of specific tasks or neurophysiological tests of particular motor disturbances (objective quantification) (Jankovic, 1987; Teravainen *et al*, 1989).

Subjective assessment:

These assessments are designed to provide numerical quantification of a patients disability from a clinical neurological examination. The usual method is assignment of scores (usually from 0 to 4: 0 = normal, 1 = mild abnormality, 2 = moderate abnormality, 3 = severe abnormality, 4 = profound disability or loss of function) (Teravainen, 1987). Probably the most widely used method of scaling is the Hoehn and Yahr scale (Hoehn and Yahr, 1967):

Stage l: Unilateral involvement only, usually with minimal or no functional impairment.

Stage ll: Bilateral or midline involvement without impairment of balance.

Stage lll: First sign of impaired righting reflexes. This is demonstrated when he is pushed from standing equilibrium with the feet together and eyes closed. Functionally the patient is somewhat restricted in his activities but may have some work potential depending upon the type of employment. Patients are physically capable of leading independent lives, and their disability is mild to moderate.

Stage lV: Fully developed Parkinsonism, severely disabling disease; the patient is still able to walk and stand unassisted but is markedly incapacitated.

Stage V: Confined to bed or wheelchair unless aided.

Other scales include the Northwestern University Disability scale, the Columbia University Disability scale, the Schwab and England scale for daily activities, the New York Rating scale and the Kings College Hospital Rating scale (Teravainen *et al*, 1987; Jankovic, 1987).

The variability of grading scales and their frequent modification by different workers has created difficulties in comparing both the results. Because of this a new scale was developed which is a combination of pre existing scales and is called the Unified Rating Scale. It grades virtually every symptom, sign and side effect that can be expected in a large population of Parkinsonian patients. It is the most comprehensive subjective scale ever introduced (Teravainen, 1987). The scale is divided into three parts: mental status, activities of daily living, and the motor scale. The highest score obtainable from these three components is 188, representing the most severe degree of disability (Hoehn, 1992).

The problem with all grading scales is that there is a significant amount of interindividual variability in assessment and the scales are not linear. Thus rating of the same patient using different scales or by different neurologists may reveal quite different results.

Objective assessment:

Most of the methods employed for objective measurement require relatively complex and expensive equipment, and they are generally restricted to sampling a fraction of the patients' symptoms and signs.

Tremor is usually recorded either by electomyography or by accelerometry. Computerised triaxial accelerometry enables measurement of frequency and amplitude of tremor. The pattern of electromyographic bursts in agonist-antagonist muscles provides a method of differential diagnosis with other kinds of tremor. Parkinsonian tremor consists of alternating bursts of electromyographic activity at a frequency of 4 - 5 cycles per second. Essential and physiological tremor have synchronous EMG bursts. Additionally Gonce and Delwaide (1984) state that following electrical stimulation applied to the radial nerve, irrespective of the timing of the cycle, the first burst of EMG activity in the extensor indicis muscle appears in Parkinson's disease always after a delay of ± 16.8 msec. In contrast, the delay in essential tremor is only 92.1 ± 6.8 msec. They find this to be a reliable and

useful test for distinguishing different tremor types. However, tremor is exceptionally variable and sensitive to psychological influences.

Electromyography has also been used in the assessment of rigidity. Recording during passive shortening of the muscle normally results in a reaction consisting of a phasic component and an inconsistant tonic component. Parkinsonian subjects regularly present this tonic component which is also abnormally intense but is much less frequently found after L-dopa treatment (Gonce and Delwaide, 1984).

Reaction time and movement times are usually used to assess hypokinesia. Certain tasks are employed such as tapping and wrist rotation. In the Purdue pegboard test small pegs are picked up and placed in holes (Teavainen *et al*, 1989). The reduction of spontaneous blinking can also be used as an assessment test. Under normal circumstances, with increased rate of electrical stimulation of the lid a reduced R2 response (the second component of the evoked response which is bilateral) results. The first component R1 (ipsilateral to the stimulated side) remains the same. In Parkinson's disease there is an absence of habituation of the blink reflex which corresponds to severity of the disease and treatment (Gonce and Delwaide, 1984). Steg et al (1989) used optoelectronic technology to measure objective motor disability in Parkinson's disease patients. This involves the use of infra red light emitting diodes fastened on various parts of the body. These markers send information on the position and movement of the body, in three dimensions, to an optoelectronic camera system, which is connected to a computer. The patient then completes a certain task (eg bending to lift a box from the floor, walking forwards with it to deposit it on a high shelf), the speed and accuracy of movements (postural, locomotor, and manual) is compared to that of a normal subject. It was found that even patients in early stages of the disease had significantly prolonged movement times compared to normal elderly subjects.

2.2.2. Diagnosis:

Accurate diagnosis of Parkinson's disease is important as it is the starting point to treatment. However diagnosis can be difficult due to the many different disease manifestations. Age of onset is variable, ranging from before 40 years (in 'young onset' Parkinson's disease) to 70 years of age. Each individual exhibits different degrees of symptomatology, some having a tremor-dominant forms of the disease, others a postural instability form. The presence and severity of symptoms differ between patients and response to treatment can be unpredictable, although improvement in symptoms following dopaminergic treatment is considered a form

of diagnosis. Post mortem examination appears the only definite way of confirming Parkinson's disease.

History:

Obtaining an accurate history from the patient is critical in making a diagnosis. Asking pointed questions such as "do you have difficulty turning in bed" can often encourage a patient to reveal symptoms not otherwise conceived as relevant. The use of the "activities of daily living" part of the Unified Parkinson Disease Rating Scale gives information about speech, salivation, swallowing, handwriting, cutting food, handling utensils, dressing hygiene, turning in bed, falling, freezing, walking, tremor, and sensory symptoms (Lieberman, 1992).

Objective assessment:

Again use of one of the rating scales is useful in making an accurate objective assessment. While talking to the patient, subtle facial masking, changes in frequency and amplitude of eye blink, and paucity of voluntary but subconscious movements can be appreciated (Lieberman, 1992). Koller (1992) suggest the following inclusion criteria for the diagnosis of Parkinson's disease:

Presence for 1 year of more of two of three of the cardinal motor signs of Parkinson's disease -
Resting or postural tremor
Bradykinesia
Rigidity
Responsiveness to levodopa therapy (at least 1000mg/d for 1 month) given -
    Degree of improvement is moderate to marked
    Duration of improvement is 1 year or more

Difficulties still remain in clinically distinguishing idiopathic Parkinson's disease from other Parkinsonian syndromes. Some features useful in making this discrimination include absence or paucity of tremor, early gait abnormalities such as freezing, and poor response of levodopa (Stacy and Jankovic, 1992). Koller (1992) developed the following exclusion criteria to aid differentiation:

Abrupt onset of symptoms
Remitting course
Step-wise progression
Neuroleptic therapy within previous year

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Exposure to any drug or toxin reported to cause Parkinsonism
History of encephalitis
Oculogyric crisis
Supranuclear downward or lateral gaze palsy
Cerebellar signs
Unexplained pyramidal signs
Lower motor neurone signs
Severe autonomic failure (causes repeated syncope)
Dementia from the onset of the disease
Postural instability with falling early in the course of the disease
Evidence of cerebrovascular disease
Unilateral dystonia associated with apraxia, cortical sensory loss

Hughes *et al* (1992) found that by using such detailed criteria for diagnosis, 93% of Parkinson's disease cases were confirmed by post-mortem examination.

Subcutaneous administration of apomorphine is also used in the diagnosis of Parkinson's disease. It can predict the responsiveness of the CNS to dopaminergic therapy with a high degree of certainty - and a positive result is indicative of Parkinson's disease. However, the disadvantages of the test include marked side-effects such as nausia, emesis, sedation and arterial hypotension.

<u>Positron Emission Tomography (PET):</u>

PET is a quantitative imaging technique employed to localize and measure physiologic and biochemical processes in the brain and other organs (Eidelberg, 1992). A subject is given a small quantity of a compound that emits positron radioactivity. The spatial and temporal distribution of the radiotracer is quantitatively studied in the course of the PET imaging study. PET techniques are used to measure local brain energetics, for example, regional metabolic rate for glucose, regional cerebral blood flow, regional metabolic rate for oxygen, for quantification of specific transport and storage processes and assessment of receptor binding kinetics.

i. PET studies of cerebral metabolism and blood flow in Parkinsonism: [^{18}F] fluoro-2-deoxyglucose (FDG) is the compound generally used for the measurement of regional metabolic rate for glucose. Results in Parkinson's disease have been variable, with some authors showing no significant difference between normals and patients (Martin *et al*, 1986), others have shown asymmetrical glucose metabolism in the basal ganglia in Parkinson's disease patients, with increased glucose

utilization contralateral to the effected limb (Martin and Calne, 1987; Eidelberg, 1992).

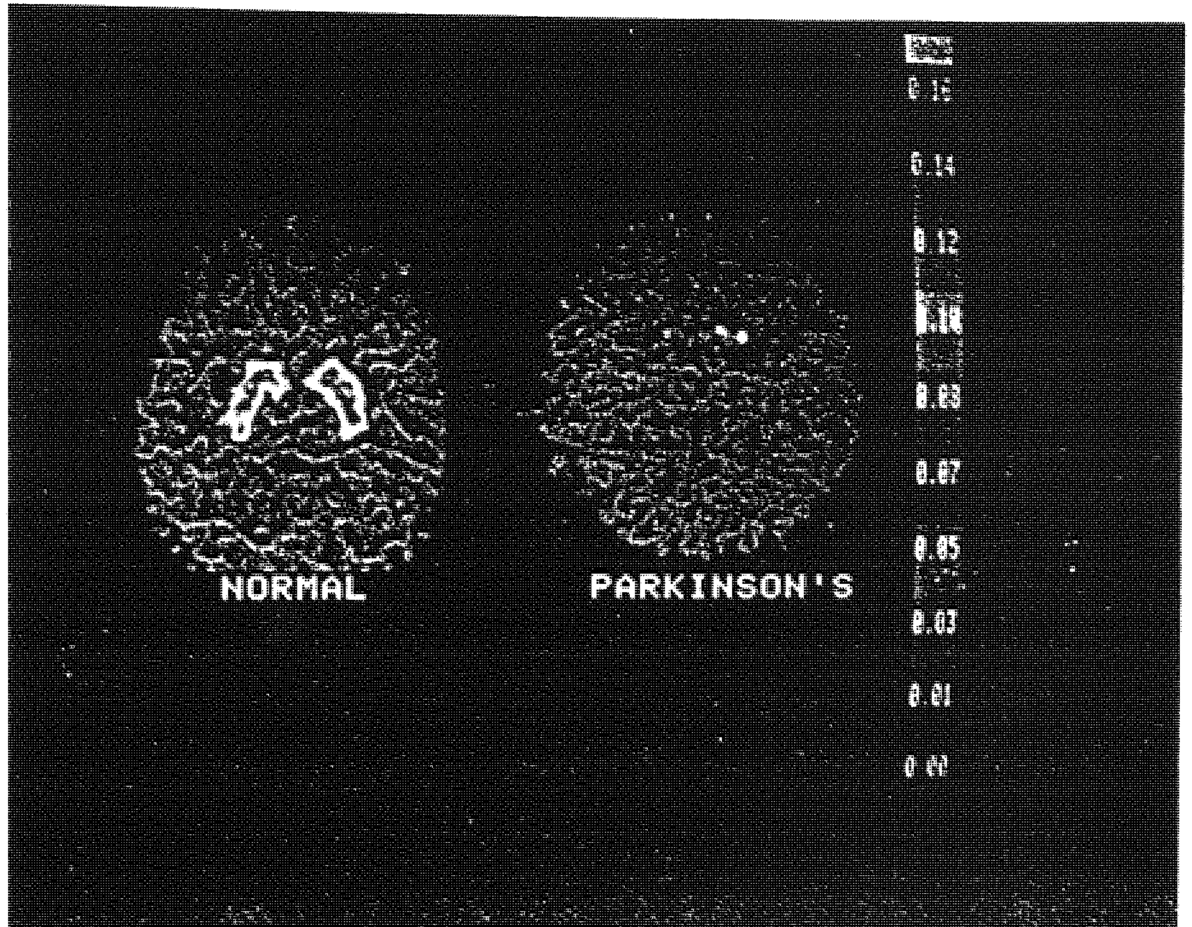
O-CO_2 is used to assess regional cerebral blood flow which is also found to be increased in the basal ganglia of Parkinson's disease patients contralateral to the effected side (Martin and Calne, 1987; Eidelberg, 1992). In bilateral Parkinsonism Walfson *et al* reported a widespread decrease in cerebral blood flow suggesting vasoconstriction due to loss of dopaminergic innervation of blood vessels (Martin and Calne, 1987).

Increased metabolic rate for oxygen using O-O_2 in the basal ganglia of Parkinson's disease patients have also been reported (Eidelberg, 1992; Martin and Calne, 1987) - although Wolfson *et al* did not find such changes.

ii. PET studies of the nigrostriatal dopamine system in Parkinsonism: ^{18}F-fluoro-L-dopa (FD) as a tracer used to examine presynaptic nigrostriatal function. The tracer is shown to accumulate in areas of the brain which are known to have high dopamine content. It has been shown that in Parkinson's disease there is a reduction is striatal FD uptake (Martin *et al*, 1986; Martin and Calne, 1987; Eidelberg, 1992). Eidelberg also found that striatal FD uptake correlates closely with bradykinesia and composite ratings of quantitative measures of disease severity and duration. Figure 2.1. gives an example of a PET scan from a normal patient and a Parkinson's disease patient - the bright areas indicate tracer uptake- and it is clear that there is a marked reduction in FD uptake in the Parkinsonian patient.

The use of [^{11}C] Methylspiperene which determines binding properties of dopamine receptors in the brain produced comparable results (Hagglund *et al*, 1986).

Figure 2.1.



PET scans of a normal (left) and Parkinson' brain. The normal brain has accumulated high levels of dopamine in the striatum; the low level of dopamine (the bright areas) in the Parkinson's brain reflects the almost complete destruction of the pathway from the substantia nigra (adapted from Martin and Calne, 1987).

Calne and Snow (1993) state that the following can be accomplished using PET in Parkinson's disease:

a. Diagnosis
b. Early detection: in view of the fact that 80% of striatal dopaminergic neurons are lost before symptoms occur - PET scan in high risk individuals should show decreased FD uptake - such cases have been reported.
c. Pathogenesis: Fluorodopa PET has demonstrated lesions of the nigrostriatal dopaminergic projections in idiopathic Parkinson's disease, progressive supranuclear palsy, multiple system atrophy, Wilson's disease, neuroacanthocytosis, MPTP Parkinsonism, petrochemical induced Parkinsonism and Guamanian Parkinsonism.
d. Natural history: Changes in FD uptake have been shown in Parkinson's disease in sequential PET scans taken over a period of 3 years.
e. Therapeutic innervation: Following fetal mesencephalic implantation PET scans have shown increased FD uptake in the region of the graft.

PET facilities are relatively unavailable and expensive and thus, as yet, can hardly be used for clinical routine.

Single Photon Emission Computer Tomography (SPECT):

SPECT is more readily available and cheaper that PET although it suffers form lower resolution. It has been shown that D_2 receptors can be measured using [^{123}I] - iodobenzamide (S(-)-IBZM) which is a ligand (benzamide derivative) with a high selectivity for D_2 receptors. It has been shown that there is no difference in (S(-)-IBZM binding between controls an Parkinson's disease patients without treatment (Brucke *et al*, 1993). However, patients receiving dopaminergic therapy have a lower binding than controls. No significant correlations between receptor binding and the clinical stage, duration of the disease, or duration of L-dopa treatment could be found.

Oertel *at al* (1993) state that visualization of postsynaptic striatal dopamine receptors with IBZM and SPECT allows one to predict the response to dopaminergic therapy in de novo Parkinsonian patients. They also suggest its use combined with apomorphine testing as a method of early diagnosis such that a patient with normal IBZM binding and a positive apomorphine test are likely to suffer from Parkinson's' disease; and a patient with reduced IBZM binding and a negative apomorphine test are not likely to be suffering from Parkinson's disease

although clinically they can not be differentiated; a patient with a normal IBZM grading but negative for the apomorphine test has an unclear diagnosis.

Magnetic Resonance Imaging (MRI):

MRI is a technique that does not involve ionizing radiation and permits direct multiplanar imaging independent of patient positioning. It is based on the magnetic properties of hydrogen nuclei and their response to externally applied magnetic fields, and the exaltation of those protons within such a field by a radiofrequency pulse. Most studies have not shown any difference in MRI scans between normals and Parkinson's disease (Martin and Calne 1987) although some have shown areas of general or frontal atrophy (O'Brien *et al*, 1990; Rutledge, 1993).

MRI is of value in excluding secondary causes of Parkinsonism, such as basal ganglia infarction, hemorrhage, calcification and hydrocephalus (Olanow, 1992).

Recently MRI has found a more important role in that it has a capacity to image iron. It has been shown that when T_2-weighted spin-echo techniques are used normal adults demonstrate well defined areas of signal attenuation or hypointensity in the globus pallidus, substantia nigra pars reticulum, red nucleus and dentate nucleus of the cerebellum that correlate with areas of ferric iron accumulation as determined by Perls' stain (O'Brien *et al*, 1990; Olanow,1992). Olanow *et al* found a marked attenuation in signal due to the presence of iron in the putamen and substantia nigra of atypical Parkinsonian patients compared to normal controls. MRI scans of the putamen were found to be normal in Parkinson' disease patients compared to patients with the atypical form of the disease. Changes in the substantia nigra were found in patients with both atypical Parkinsonism and Parkinson's disease.

It would thus seen that diagnosis of Parkinson's disease relies mainly on accurate patient questioning and objective assessment of symptoms. PET scans do have a use but are expensive. The only sure method, as yet, is by post mortem examination.

2.3. Anatomy and Physiology of the Basal Ganglia.

Parkinsonism may be caused by various pathological processes affecting the Basal ganglia of the brain.

The Basal ganglia are a group of nuclei situated deep within the substance of the cerebral hemispheres and brain stem. The nuclei involved include the caudate nucleus, putamen, globus pallidus, subthalmic nucleus and the substantia nigra. Various names are applied to different combinations of members of the basal ganglia (Fig 2.2.). The corpus striatum projects to the Thalamus which has important sensory function and is involved with the control of movement.

The striatum can be regarded as the receptive part of the corpus striatum, not only because it receives quantitatively the largest number of afferents but because these afferents come from the most diverse sources - the cerebral cortex, the thalamus and from the pars reticulata of the substantia nigra (Carpenter 1976, Fox and Rafols 1976). The striatum and substantia nigra are reciprocally connected, so also are the subthalmic nucleus and globus pallidus but in a less complete way.

The thalamus is the major site of convergence output pathways of the basal ganglia and cerebellum. The largest of these efferent bundles is the pallidothalamic projection, part of which project to the ventral lateral nucleus, which is known to exert potent drives on the motor cortex (Fox and Rafols 1976, Purpura 1976). The thalamus has thus been viewed as an "interneuronal interface" between the basal ganglia and the cerebellum on the one hand and the motor cortex on the other (Purpura 1976). Normal relations within and between the above structures must involve a coordinated functioning of different groups of intra and intersystem neurons whose transmitters may be GABA, dopamine, acetylcholine, serotonin, substance P and others (Roberts 1976).

Mc Geer and Mc Geer (1989) suggest three main types of neurotransmitter that are present in the basal ganglia:

Type I: Amino acid neurotransmitters. These are the fastest acting of the transmitters and probably serve the major input commands, and output systems of the basal ganglia. Cortex to striatum interconnections (and visa versa) involve glutamate and aspartate, so also do subthalmic nucleus to globus pallidus and subthalmic nucleus to substantia nigra neurons. Striatonigral projections, ending in the pars reticular of the substantia nigra involve GABA, so also do palidothalamic connections (Bunney and Aghajanian 1976). The substantia nigra and globus pallidus contain the highest levels of GABA and GAD (synthetic enzyme). The substantia nigra also contains some glycine innervation.

Fig 2.2. Terminology associated with the basal ganglia.

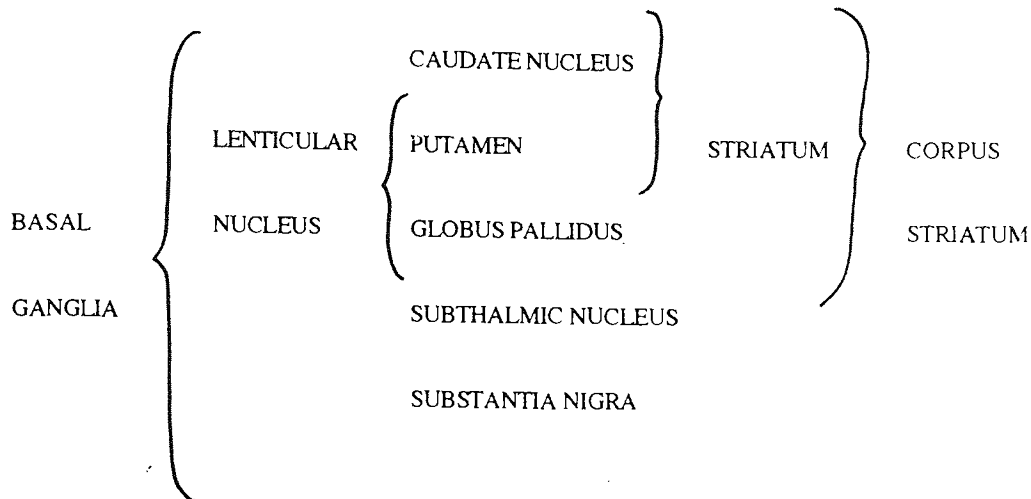


Fig 2.3. Schematic drawing of what the corpus striatum, amygdala, thalamus, and internal capsule would look like if they were all isolated from the rest of the brain.

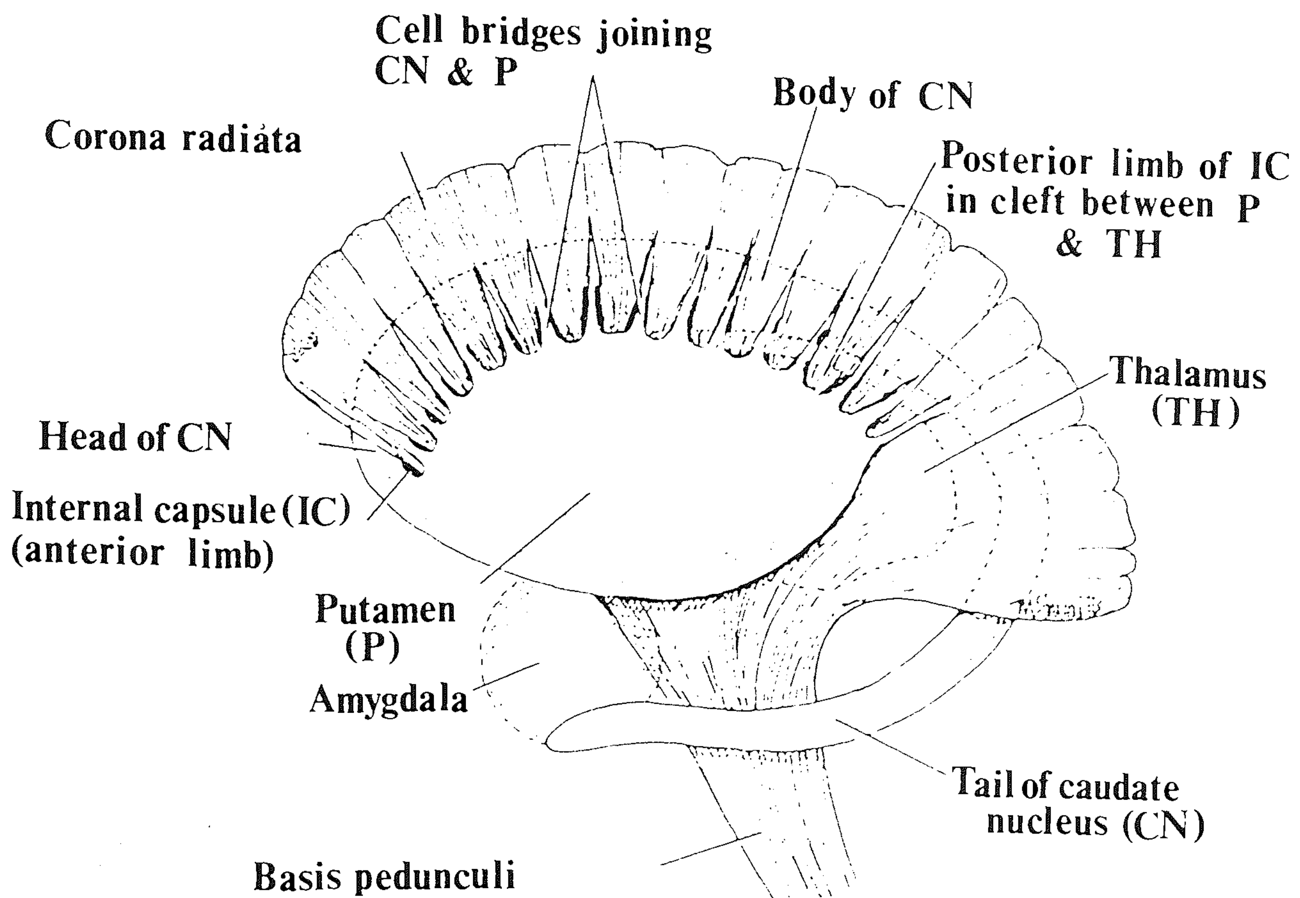


Figure 2.4 shows a schematic diagram of the main basal ganglia interconnections.

KEY:

M = Magnocellular

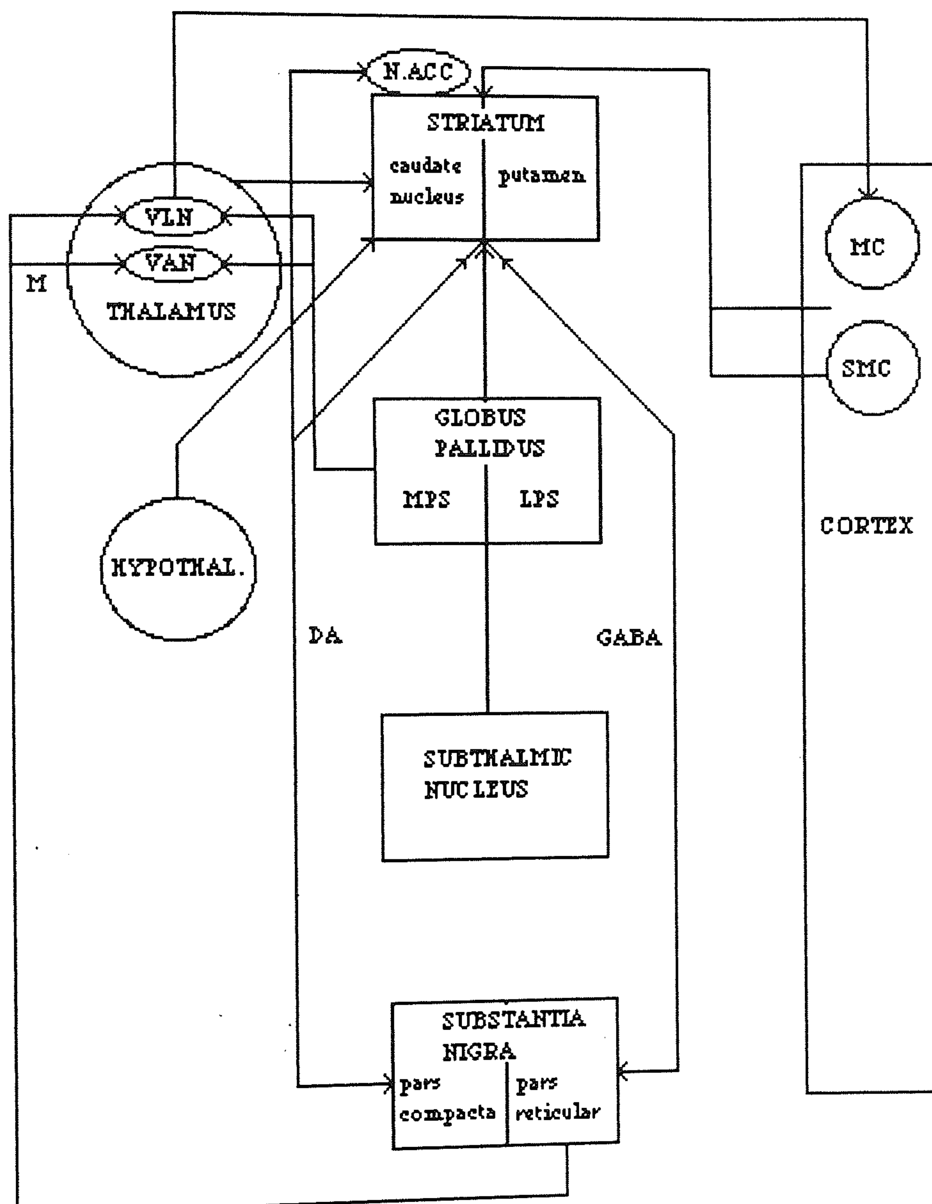
VLN = Ventral lateral nucleus

VAN = Ventral anterior nucleus

MC = Motor cortex

SMC = Sensorimotor cortex

N.ACC = Nucleus Accumens



Type II: Amine neurotransmitters. These are typically slow in onset and relatively long lasting. The physiologic actions are diverse and are frequently considered modulatory; the overall effect may be inhibitory or exitatory depending on the type of receptor and other inputs into the target neurons. Dopamine is the neurotransmitter involved in nigrostriatal transmission and is present in high concentration in the zona compacta of the substantia nigra. Caudate to putamen interneurons and globus pallidus to cortex are thought to involve cholinergic transmission. Cholinergic projections to the substantia nigra nor the presence of cholinergic interneurons have been ruled out (Bunney and Aghajanian 1976). Serotonin is present in the substantia nigra and globus pallidus and is thought to modulate the output of the basal ganglia. Transmission from the hypothalamus to striatum is thought to involve histamine.

Type III: Peptide neurotransmitters. Peptides exist in the brain in much lower concentrations than elsewhere. Their function and mode of action are as yet unknown, but apparently relatively few molecules of peptide need to be released to affect their receptors. Interneurons within the striatum contain the peptide neurotransmitters somatostatin, neuropeptide, proenkephalins, and cholecyctokinin. Striatal projections involve tachykinins, proenkephalins and prodynorphins. Proenkephalins are also present in the pars reticular of the substantia nigra, the pars compacta containing somatostatin.

There is a great deal of neurotransmitter interaction within the basal ganglia. Evidence suggests that, in the striatum, dopamine exerts an inhibitory action on cholinergic mechanisms whereas acetylcholine has, possibly by way of a feedback mechanism, an enhancing action on striatal dopaminergic mechanisms (Hornykiewicz 1976). Dopamine agonists inhibit acetylcholine release and increase acetylcholine levels in the striatum, while dopamine antagonists have the opposite effects. Such studies have been taken to support the direct innervation of cholinergic neurons of the caudate pallidium by nigral dopamine afferents (Mc Geer and Mc Geer 1989).

There also seems to be GABA - dopamine interaction at the level of the basal ganglia. It has been shown that drugs increasing GABA concentration in the brain reduce dopamine turnover in the striatum (Hornykiewicz 197). Conversely, prolonged administration of L-dopa increases the activity of the GABA synthesizing enzyme glutamic acid decarboxylase (GAD) in the striatum, which may indicate an enhancing effect of dopaminergic agents on the GABA-ergic activity. Glowinski(1990) has shown that increased dopamine release in the distal dendrites

of the substantia nigra of cats inhibits the activity of nigrothalamic cells, and this effect is associated with a decreased release of GABA in thalamic motor nuclei. Stimulated release of dopamine from proximal neurons however, while inhibiting the nigrothalamic cells, increase release of GABA in thalamic nuclei.

Another likely interrelation is that between dopamine and noradrenaline. Noradrenaline is thought to be responsible for setting the sensitivity of those neuronal systems on which dopamine acts when triggering locomotor activation. Thus inhibition of central noradrenaline activity reduces the locomotor effectiveness of dopaminergic drugs (e.g. L-dopa). The location of a noradrenalin - dopamine interaction in the CNS has not been confirmed. It is also thought that serotonin is involved in this interaction, increased brain serotonin activity inhibits locomotor activation, while decreased serotonin is fascilitatory - but the location of such interaction is again inconclusive (Hornykiewicz 1976). For dopaminergic neurons, the most powerful feedback control appears to be mediated via dopaminergic receptors (Carlsson 1976). If these receptors are blocked, the impulse generation, release, metabolism and synthesis of transmitter are stimulated in the dopaminergic neurons. Receptors involved in this feedback loop are known as autoreceptors.

2.4. Pathology of Parkinson's disease.

The main site of pathological changes associated with Parkinsonism is in the substantia nigra - resulting in damage to the dopaminergic nigrostriatal pathway. Other pathological features include (i) non-specific degenerative age related changes in other parts of the brain, (ii) a variety of other lesions elsewhere in the central nervous system (Jellinger 1986). The following discussion will mainly relate to the pathological features of idiopathic Parkinson's disease, the subtle differences found in other forms of Parkinsonisms will be discussed later.

2.4.1. Cytoskeletal Pathology.

Several types of cytoskeletal abnormalities have been found to occur in the Parkinsonian brain - these include Lewy bodies, paranucleolar Marinesco bodies, Hirano bodies, granulovacuolar degeneration and dystrophic axons.

Lewy bodies.

These cytoplasmic inclusions were first described by Lewy (1912) in cases of Parkinson's disease. They were spherical, elongated or serpiginous in shape, and in the dorsal motor nucleus of the vagus. With the Mann stain (a trichrome stain)

the inclusions were found as brilliantly red staining structures with a blue mass of cytoplasm (Forno 1986). Lewy bodies are now considered to be the principal cytoskeletal pathology of Parkinson's disease, occurring in 85% - 100% of cases, although they were also seen in various disorders and in the normal ageing brain, for example, it has been found that they occur in 5% of normal controls over the age of 30 years, in 8% - 15% of those over 65 years and in 3.6% - 11.1% in those between 60 and 100 years (Jellinger 1990, Burn *et al* 1992). They also occur in 23%-60% of patients with Alzheimer's disease (Jellinger 1990). Lewy bodies have also been found in individuals as young as 17 years in Hallervorden - Spatz disease and subacute sclerosing pan encephalitis.

In Parkinson's disease Lewy bodies occur most commonly in the substantia nigra and locus ceruleus (Forno 1986) - they are also found in the spinal cord, sympathetic ganglia and less frequently in the cerebral cortex, myenteric plexus, and adrenal medulla (Jellinger 1987, 1990).

Lewy bodies appear as single or multiple eosinophilic bodies surrounded by a less dense amorphous halo. They vary in size from 3 to 20μm (mean 9-10μm), and can be located in a nerve cell body (classical perikaryal), within nerve cell processes (intraneuronal) and extraneuronally free in the neuropil (Forno 1986, Jellinger 1990). They are composed of proteins, free fatty acids, sphinomyelin and polysaccarides, their core containing aromatic alpha - amino acids. They have a high sulfur content (indicating breakdown products of proteins and an ultrastructure of proteins) and an ultrastructure of intermediate - type filaments of diameter 8-10nm, admixed with vesicular and granular material. Constituents of Lewy bodies include all three of the neurofilament proteins, tubulin, microtubule associated protein MAP2 (particularly in the periphery). The core contains paired helical filaments and ubiquitin. They do not appear to contain actin or 200 kilokeltron which are found in neurofibrillary tangles, nor do they contain tau (Jellinger 1989, Jellinger, 1990). Ultrastructurally two types of Lewy body can be identified:

Mature or brain stem type - consisting of a central core composed of densely packed filaments and granular material, and peripheral radiation of filaments, showing immune reaction against neurofilament proteins, mainly in the core, and against ubiquitin and paired helical filaments, particularly in the periphery, while the central core reacts with monoclonal antibodies against isolated paired helical filaments. Figure 2.5 shows an electron micrograph of a Lewy body in the substantia nigra.

Early or cortex type - which are rather homogenous with random arrangement of the filaments without a marked dense core and shows diffuse reaction with antibodies to neurofilament proteins and paired helical filaments. Figure 2.6 shows an electron micrograph of a Lewy body in the hypothalamus.

Homogenous cytoplasmic hyalin inclusions or "pale bodies" are also found in the neurons of the Parkinsonian brain. They are pale areas where the cytoplasm appears devoid of normal organelles, and are composed of randomly arranged collections of 10nm filaments. These pale bodies are thought to represent early stages of Lewy body formation (Jellinger 1987, Jellinger 1989).

The role of neuromelanin in Lewy body formation has been a matter of speculation. Ultrastructuraly melanin granules in nigral and ceruleus neurons of Parkinson's diseased brain often cannot be distinguished from those of normal individuals but there can be a decrease in the very dense component of melanin. As will be described later, neuromelanin may be involved in free radical production and hence cytotoxicity and membrane decomposition.

Hirano bodies.

These are rod-shaped eosinophillic intracytoplasmic inclusions, consisting of crystaloid arrays of 6-10nm filaments of lattice-like or "herringbone" structure (Hirano 1981). They were first described in Ammon's horn of Guamanian patients with amyotrophic lateral sclerosis and Parkinsonism-dementia complex (see later). They are composed of actin, and react with tau but not with neurofilament protein and tubulin (Peterson 1988). Hirano bodies are found in the hippocampus and neocortex of normal individuals from the age of 20 years onward, increasing with age, occasionally combined with granulovacuolar degeneration, and increase numbers are seen in Parkinson's disease, Alzheimer's disease and Pick's disease (Gibson 1978, Hirano 1981).

Intracytoplasmic Eosinophilic granules.

The melanin - containing neurons of the substantia nigra and locus ceruleus in normal aged human brain, and various disorders may contain small intracytoplasmic eosinophilic granules composed of aggregates of parallel banded or twisted 8.5nm filaments (Schochet *et al* 1970), others regard them as altered mitochondria.

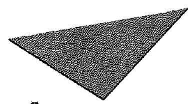


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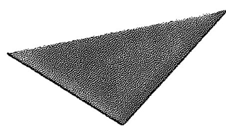
Figure 2.5. Electron micrograph of a Lewy body in the substantia nigra. x 14000. Taken from Forno 1986

Figure 2.6. Electron micrograph of a Lewy body in the hypothalamus. x4500. Taken from Forno 1986.



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Marinesco bodies.

These are intranuclear eosinophilic inclusions in pigmented neurons of the substantia nigra and locus ceruleus, found in Parkinson's disease and normal brains with increasing numbers in advancing age (Jellinger 1990). They are often multiple, and consist of 10-12nm filaments in a lattice-like arrangement. They have a peripheral ring which reacts with monoclonal antibody to paired helical filaments and ubiquitin. Their pathogenic relevance are unknown (Yuen and Baxter 1963, Leestma and Andrews 1969, Bancher *et al* 1989).

Neurofibrillary Tangles.

These intracytoplasmic lesions appear in two major forms:-

i). Alzheimer's neurofibrillary tangles - the composition of which has been described in chapter one. They are found in increased density in brains of normal aged subjects, and are particularly abundant in Alzheimer's disease, postencephalitic Parkinson's disease, Guam ALS - Parkinsonian dementia complex, and boxers dementia (Hirano 1981, Tomlinson and Corellis 1984, Yen et al 1986, Jellinger 1989). Neurofibrillary tangles involve neurons of varying transmitter specificities, including cholinergic neurons specific to the basal forebrain.

ii) Tangles in progressive supranuclear palsy differ from the above in topography and ultrastructure (Jellinger 1989). They are composed of 15-20nm straight filaments and are sometimes mixed with typical paired helical filaments. The straight filaments are thought to contain most of the antigens known to be present in paired helical filaments, and result from alternative pathways of organization of the same components, rather than being paired helical filament precursors.

Granulovacuolar degeneration and Senile plaques.

These are described in detail in chapter one as they are a common feature in the Alzheimer's disease brain. However they are also present in the elderly, increasing in number with age and thus are also present in the Parkinsonian brain.

Axonal Dytrophy and Grumelous Degeneration.

These are spheroid - like or ovoid swellings of axons and include accumulations of organelles, tubulovesicluar structures, disarranged 10nm neurofilaments, dense bodies, abnormal mitochondria, and lamellar membranes derived from the smooth

endoplasmic reticulum and have been related to disorders of axonal transport. They affect the nucleus gracilis and zona reticular of the substantia nigra of Parkinson's disease brain over the age of 50 years and may be related to the depletion of pigmented neurons in the zona compacta.

2.4.2. Neurodegeneration in Parkinson's Disease.

Dopaminergic system.

The major neurophathological alterations in Parkinson's disease as a disorder of the basal ganglia function is the loss of the melanin and dopamine - containing neurons in the zona compacta of the substantia nigra (Hornykiewicz and Kish 1986) and the ventral tegmental area (Jellinger 1987, 1989). In Parkinson's disease the substantia nigra shows a decrease in fresh volume of about 25% with loss of pigmented neurons ranging from 60%-85%, considerable reduction in nuclear nucleolar, and perikaryal volume and loss of melanin of up to 88% of controls (Jellinger 1987,1989, Gibb *et al* 1990). Graybiel *et al* (1990) found that the higher the percentage of melanized neurons in the dopaminergic cell group examined, the greater the loss of neurons in that cell group as judged by comparisons with controls. This cell loss increases with duration of disease and hence patients with young-onset Parkinson's disease show a 25% greater nigral cell loss. The degree of neuronal loss in the substantia nigra correlates with the decrease of dopamine and homovanillic acid in striatum and ventral tegmentum, and with loss of activity of tyrosine hydroxylase, the rate-limiting enzyme of catecholamine synthesis in these regions. It is generally concluded that Parkinsonian symptoms do not appear until 70 - 80% of the nigral dopamine neurons an an equivalent percentage of striatal dopamine have been lost.

Even though there is extensive destruction of the dopamine-containing innervation of the striatum in Parkinson's disease - there is very little change to structural morphology. Neither the putamen nor the caudate nucleus show any considerable reduction of their fresh volume and wet weight, nor definite loss of striatal neurons, the shrinkage of the caudate nucleus being only 7% with loss of 11% of its small neurons. Graybiel *et al* (1990) found that the fundamental division of the striatum into striosome and matrix compartments survive. This finding is of clinical significance because it suggests that much of the neuronal organization of the striatum may remain intact, and survival of these post-synaptic constituents may help to account for the success of levodopa treatment in supplementing actions of surviving dopamine containing fibres.

The globus pallidus shows a 7% reduction in its volume in post-encephalitic Parkinsonism but not in the idiopathic form of the disease. The mesolimbic system, hypothalamus and spinal cord show a considerable reduction in tyrosine hydroxylase immunoreactivity in the cell bodies and fibres. However dopamine levels in dorsal, ventral, and lateral parts of the spinal cord were found not to be different from controls suggesting that the descending dopaminergic pathways are preserved (Jellinger 1989, 1987). Reduced tyrosine hydroxylase activity and reduced dopamine and the occurrence of Lewy bodies have also been found in the adrenal medulla.

Noradrenergic system.

The main source of noradrenergic innervation of the CNS is the locus ceruleus. Fibres project from here to the whole of the neocortex and limbic forebrain (amygdala, septum and hippocampus) . A second ventral ascending pathway extends from the lower brainstem to the supra-optic and paraventricular nuclei of the hypothalamus. Damage to the locus ceruleus has been observed in normal aging, Parkinson's disease, Alzheimer's disease, depression, and degenerative disease. In most Parkinsonian syndromes there is a loss of pigmented neurones ranging from 50-80% in the locus ceruleus, whereas the capacity for protein synthesis, seems maintained. In general damage is less severe in nondemented Parkinson's disease subjects (28 -31%) than in demented ones (48 - 88%), in whom it approaches the values seen in Alzheimer's disease with a range of 25 - 90% (Jellinger 1991). In Parkinson's disease, damage to the locus ceruleus is associated with Lewy bodies in over 99% and neurofibrillary tangles in 17% of the cases.

Locus ceruleus damage results in severe loss in cortical and limbic noradrenergic innervation, with 40-75% decrease of norepinephrine, its metabolites, and related enzymes in neocortex and hippocampus. This is mainly seen in demented Parkinsonian patients with severe neuronal loss. Norepinephrine innervation to the cerebellum and spinal cord may also result from more severe involvement of the middle and caudal parts of the locus ceruleus. Degeneration of the ascending norepinephrine pathways results in its reduced input to the hypothalamus particularly in demented patients. Mental changes and depression in Parkinson's disease and Alzheimer's disease are thought to be a result of central norepinephrine deficiency (Jellinger 1991).

Cell loss in the noradrenergic dorsal vagal nucleus is thought to be as little as 5-17% in aged controls and in Parkinson's disease, but Lewy bodies are present in abundance. This region also shows a 77% loss of substance P immunoreactivity.

Serotoninergic system.

It has been reported that the dorsal raphae nucleus (which gives rise to the ascending serotononergic pathways and on to many central nervous system centres), is damaged in some Parkinsonian syndromes. Cellular loss ranges from 0 - 42% in Parkinson's disease, and is increased in cases of depression. There is a severe decrease of tyrosine hydroxylase immunoreactivity and a reduction of around 60% of $PH\text{-}8^{+}$ serotonin-sythesising neurons. Many of the remaining neurones of this nucleus contain Lewy bodies, and few show neurofibrillary tangles (this increase in cases where Alzheimer's disease is present).

Cholinergic system.

The nucleus basalis of Meynert in the substantia innominata is the main source of cholinergic innervation of the neocortex and hippocampus. It has been established for a long time that in Parkinsonism there is a marked loss of neurones (0-77%), mainly the large cholinergic neurones in the middle and posterior part of the nucleus basilis of Meynert. The extent of cell loss does not appear to correlate with age or duration of illness. It appears that the degree of loss is worse in those Parkinsonian patients suffering with dementia (50-77%) - reaching levels similar to those found in Alzheimer's disease. There is also a high incidence of Lewy bodies in this region ranging from 84-96.5%. 29-65% of cases also show neurofibrillary tangles of the Alzheimer type but with no senile palques.

Frontal cholinergic deficiency and neuronal loss in nucleus basilis of Meynert have been demonstrated in Parkinsonian patients without cognitive impairment; this may indicate that the ascending cholinergic system is already in the process of degeneration and that there may be a critical threshold level for the cholinergic deficit before dementia becomes apparent. It can be concluded that this threshold level lies at about 65 - 80% neuronal loss and/or shrinkage within the nucleus basilis of Meynert with equivalent cortical cholinergic denervation that cannot be compensated for by various mechanisms, such as increases the density of muscarinic receptors or vesicular storage of acetylcholinersterase (Jellinger 1991).

The pedunculopontine tegmental nucleus, pars compacta is a cholinergic nucleus in the dorsolateral part of the caudal mesencephalic tegmentum which receives fibres and provides major projections to the thalamus, substantia nigra zona compacta, subthalmic nucleus, stripallidum, pontine tegmentum, basal forebrain, and minor projections to widespread cortical areas. In progressive supranuclear palsy and Parkinson's disease a severe cell loss of 36 - 57% in this nucleus has been observed particularly those shown in substance P immunoreactivity. Damage to this nucleus may contribute to disorders of locomotor activities, sleeping-waking cycle, or cognitive disturbances in Parkinson's disease and related disorders (Jellinger 1991).

The Westphal-Edinger nucleus gives rise to cholinergic fibres to the ciliary ganglion regulating pupoloconstriction and is visceral subdivision of the oculomotor complex. It suffers a 54% neuronal loss in Parkinson's disease, and 2 - 3% of the cells are affected by Lewy bodies or neurofibrillary tangles (Jellinger 1991).

Peptidergic system.

Degeneration of peptidergic neuronal systems appears to be limited to comparatively small populations on the Parkinsonian brain. However the reduction of cholecyctokinin, substance B, Met-enkephalin, and Leu-enkephalin in the compacta nigrae and hippocampus are not fully explained by immunocytochemistry.

2.4.3. Neurochemistry of Parkinsonism.

Dopaminergic system.

Fig 2.7. shows the biosynthesis of Dopamine, (Birkmayer and Birkmayer, 1989). Immunocytochemical and immunofluorescence methods are used to visualize the presence of dopamine or its metabolites in brain tissue.

In the nigrostriatal system it has been shown that the activities of tyrosine hydroxylase and DOPA decarboxylase (enzymes involved in the synthesis of dopamine) are decreased in the substantia nigra (particularly the compact zone), striatum and globus pallidus of Parkinsonian patients (Hornykiewicz and Kish 1986, Agid *et al* 1987, Hornykiewicz 1989) . In these same areas there is a decrease in dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), metabolites of dopamine. The loss of dopamine within the nigrostriatal neuron

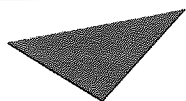
system of patients with Parkinson's disease is directly related to the main motor deficits of this disorder and the severity of symptoms is positively correlated with the degree of dopamine loss (Hornykiewicz 1989). Striatal dopamine levels differ from one patient to another, and these differences in the degree of dopamine deficiency might explain the variability in clinical pictures from one patient to another.

In the mesocorticolimbic system (nucleus accumbens, parolfactory gyrus, cingulate and entorhinal cortex, hippocampus, olfactory tubercles, frontal cortical areas, temporal cortical areas and occipital cortical areas) there are subnormal levels of DOPAC, HVA and dopamine indicating that dopamine afferents are damaged (Hornykiewicz and Kish 1986, Agid *et al* 1987, Hornykiewicz 1989, Jellinger 1991). Scatton *et al* (1983) also found a reduction in dopamine, HVA and DOPAC in the cerebral cortex.The moderate loss of dopamine in the nucleus accumbens may contribute to the motor deficits, especially akinesia in Parkinson's disease. The reduction in dopamine metabolism in some cortical areas may play a role in some of the psychic and cognitive changes seen in the disease.

In the hypothalamic system there is a reduction of dopamine concentration by 60% in the hypothalamus itself. Certain brainstem nuclei such as the locus ceruleus have reduced dopamine levels. A moderate reduction of dopamine has been reported in the dorsal and lateral horns of the lumbar spinal cord, but not the ventral horn, suggesting sparing of the descending dopaminergic system (Hornykiewicz and Kish 1986, Agid *et al* 1987). Spinal dopamine changes may contribute to motor dysfunctions and possible involvement in pain regulation.

Following degeneration of dopaminergic neurones in the striatum, there is a certain amount of compensation by the remaining neurones due to their increased activity. If less than 70% of the neurones are damaged then the compensation is sufficient to maintain normal dopamine transmission. If 70-90% of neurones are affected than there is only partial compensation and Parkinsonian symptoms occur. If more that 90% of neurones are damaged then there is very little compensation and the postsynaptic D-2 receptors become hypersensitive. This can create a problem in that the receptors are also hypersensitive to L-dopa treatment and side-effects result.

Figure 2.7 Biosynthesis of chatecholamines (from Birkmayer and Birkmayer, 1989).


Aston University

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Noradrenergic system.

Noradrenalin concentrations are 40-70% below normal in the neocortex and limbic areas - this is in correspondence with the neuronal loss in the locus ceruleus. Scatton *et al* (1983) found a marked reduction in noradrenalin in cortical regions and suggested that this may play a part in the occurrence of dementia. Subnormal levels of noradrenaline have been detected in a number of subcortical regions such as the substantia nigra, and 3-methoxy-4-hydroxyphenylglycol (the main metabolite of noradrenaline) is reduced in the CSF and spinal cord. Some patients also show reduced concentrations of noradrenaline in the hypothalamus. In the periphery the adrenal medulla of Parkinsonian patients show a reduction in tyrosine hydroxylase (Agid, 1987; Jellinger, 1991).

Serotoninergic systems.

There appears to be a reduction in serotonin concentration in the basal ganglia, hippocampus, cerebral cortex (forebrain), in some raphe nuclei, in the lumbar spinal cord and possibly in the hypothalamus. However there does not seem to be any symptoms associated with this deficit. In the caudate nucleus and frontal cortex, the levels of 5-hydroxyindole (a metabolite of serotonin and hence an indicator of serotonin metabolism) decrease, but to a lesser extent than serotonin itself, which may indicate an activation of serotonin turnover in surviving serotoninergic terminals. Dopamine transmission in the substantia nigra and striatum are under inhibitory control of the ascending serotoninergic system; thus it would seem reasonable to assume that a reduction in serotonin should increase the availability of dopamine - however there is no evidence of this (Hornykiewcz and Kish, 1986; Agid *et al*, 1987; Jellinger, 1991).

Cholinergic system.

Choline acetyl transferase (a cholinergic marker) has been found to be normal in the striatum and substantia nigra in Parkinsonian brain although some early investigations have found a decreased activity in the striatum (Hornykiewicz and Kish, 1986; Agid *et al,* 1987) . Choline acetyl transferase activity decreases in several areas of the cerebral cortex in Parkinsonian patients indicating damage to cholinergic afferents. This decreased activity is associated with lesioned areas in the nucleus basilis of Maynert. The greatest deficit is in those patients with evident intellectual impairment, suggesting that lesions of the innominatocortical cholinergic pathway may be related to dementia in Parkinson's disease. Acetylcholinesterase

(the degenerative enzyme for acetylcholine) also has a low activity in the cerebral cortex of demented patients, reflecting the nerve degeneration. There is also an increase in sensitivity of the muscarinic receptors.

Gamma-aminobutyric acid (GABA) system.

GABA levels have found to vary between normal and elevated in the putamen and decreased in the cortical areas of Parkinsonian brain. However its marker enzyme glutamic acid decarboxylase (GAD) is reduced in the striatum, substantia nigra and cerebral cortex (this may be due to the vulnerability of this enzyme to postmortem conditions)

Peptidergic systems.

Cholecystokinin-8 (CCK-8) levels decrease by 30% in the substantia nigra of Parkinsonian patients. Animal studies suggest that the peptide has an excitatory effect on nigral dopaminergic neurons and thus its deficiency may affect the expression of motor symptoms in Parkinson's disease (Agid *et al* , 1987; Jellinger, 1991).

Substance-P (SP) levels decrease by 30-40% in the substantia nigra and in the pallidum without essential changes in cortex, hippocampus striatum and hypothalamus. Since substance-P is known to have an excitatory effect on dopamine neurones, the peptide deficiency in the substantia nigra may influence dopamine dependent symptoms.

The distribution of Methionine-enkephalin (M-Enk) closely resembles that of dopamine. The dopamine neurones are surrounded by met-enkephalin containing nerve terminals - thus there is likely to be a functional relationship between the two systems. Met-enkephalin concentrations are reduced by 70% in the substantia nigra and ventral tegmental area and by 30-40% in the pallidium and putamen in the Parkinsonian brain.

Concentrations of Leucine-enkephalin follow the same distribution of M-Enk and are also reduced (by 30-40%) in the pallidum and putamen, while the substantia nigra and ventral tegmental area are unaffected.

Somatostatin (SS) concentrations in the frontal cortex and hippocampus of intellectually impaired Parkinsonian patients are reduced. This reduction seems to parallel that of choline acetyl transferase. The decrease is not found in other cortical areas, nor in the caudate nucleus or hypothalamus; although results are conflicting.

2.5. Types of Parkinsonism.

2.5.1. Degenerative Parkinsonism.

a. *Parkinson's Disease.* (Paralysis agitans, idiopathic Parkinsonism).

Parkinson's disease accounts for approximately 75 - 95% of all confirmed cases of Parkinsonism. It is characterised by anatomic lesions mainly confined to the brain stem which shows pallor of pigmented nuclei (substantia nigra and locus ceruleus) with variable unilateral and, more often, bilateral symmetric loss of melanin-containing neurons and gliosis. The ventral and caudal parts of the zona compacta nigrae, the ventral tegmental area, locus ceruleus and dorsal vagal nucleus are particularly involved. Other areas effected include the nucleus basilis of Maynert, the dorsal raphae, and the tegmental pedunculopontine nucleus, pars compacta. There is progressive degeneration of the nigrostriatal and mesocorticolimbic dopaminergic systems. Both parts lose about two thirds of their neurons, the volume of the remaining cells on the medial group seems to be better preserved. Hypothalamic dopaminergic neurons are less frequently effected and the cerebral cortex is relatively spared.

In 82 - 100% of cases, Lewy bodies are seen in many aminergic and other subcortical nuclei, spinal cord, sympathetic ganglia and, occasionally, in the cerebral cortex, the periventricular hypothalamus are relatively spared. Other pathological features commonly found at autopsy in idiopathic Parkinson's disease include Hirano bodies, granulovacular degeneration, dystrophic axons, and Alzheimer pathology, particularly in old and demented individuals (Alvord *et al,* 1974; Boller *et al,* 1979; Hakim and Mathieson, 1979; Boller, 1985; Jellinger, 1987; Jellinger, 1989).

Gerstenbrand and Werner (1990) suggest that true idiopathic Parkinson's disease can be divided into three clinically identifiable types. Firstly, classical Parkinson's disease with akinesia, rigidity and tremor (ART-type) (most fall into this group), secondly, akinetic-rigid type with little or no tremor (AR-type), thirdly, tremor-dominant type with mild akinesia and rigidity (T-type) (West 1991). A good levodopa response is usually obtained and fluctuations do not usually develop before 3-5 years in the 'classical' ART-type. AR-type often has an earlier age of onset and appears to be the most frequent type of jeuvenille disease. It tends to progress rapidly and responds poorly to levodopa, response fluctuations and abnormal involuntary movements tend to develop earlier following long-term L-

dopa treatment. Dementia is also a common feature of this type of Parkinson's disease. T-type of Parkinson's disease is less commonly associated with dementia and has the best prognosis with slower progression and less likelihood of severe disability than the other two (West 1991).

Another classification system has been suggested - type one and type two. Type one usually strikes before 60 years of age and type two after 60 years. Tremor, rigidity and bradykinesia are symptoms of both. Lewy bodies are also present in the substantia nigra of both groups. Godwin-Austin and Lowe (1987) found that males were more effected in type one, but both sexes were equally effected in type two. Type one progresses more slowly taking around 14 years from diagnosis to dependency, while type two takes around 6 years. 'On-off' attacks following treatment is more common in type one - 66% of patients experiencing such attacks compared to 11% of type two patients. However dementia is less common in type one than type two. The clinical significance of the two types of Parkinson's disease is that type one has a better prognosis, particularly with regard to dementia, and a better response to treatment. However, type one cases are more likely to develop severe dyskinetic side - effects of levodopa therapy (West 1991).

Usually onset of the disease occurs around the 60th decade and has a duration of 10 years and above. The first symptom is usually tremor or stiffness and slowness of movement. They often develop a characteristic facial expression with a widening of the palpebral apertures, infrequent blinking and staring appearance. The patient often has a stoop due to flexion of the spine. As the disease progresses the patient suffers more with rigidity, akinesia (difficulty in initiating movement), and bradykinesia (slowness with which movement is performed). This effects speech (becoming slurred and monotonous), hand movements (resulting in difficulty with fine tasks and handwriting), and reduced arm swinging on walking. They have a characteristic gait which is usually slow, shuffling, and composed of small steps. Often there is difficulty in beginning to walk, and getting out of a chair. Approximately 90% of patients suffer with depression, which is treated with drugs. Eventually the patient may develop dementia of the Alzheimer type. Death occurs usually from complications such as pneumonia, vascular disease or neoplasia. Occasionally there is a terminal stage of lethargy passing into coma.

b. *Senile Parkinsonism.*

The onset is around the age of 80 years and is of short duration (about 2 years). They are always demented and have moderate Parkinsonian symptoms (tremor, akinesia and gait disorders). At autopsy they often show Alzheimer type

neurofibrillary tangles (in the brainstem and other subcortical areas in 40%), mild damage to the substantia nigra and locus ceruleus and the appearance of Lewy bodies (Jellinger, 1987; Jellinger and Riederer, 1984; Jellinger, 1989). However it remains uncertain as to whether this is a distinct subset of Parkinsonism or a variant of Alzheimer's disease.

c. *Diffuse Lewy body disease.*

This rare disorder has been separated into three types (Kosaka *et al,* 1984):

i. type A or 'diffuse type' with the appearance of Lewy bodies in the brainstem, basal ganglia, and cerebral cortex, and severe Alzheimer lesions. It presents clinically with progressive dementia with little Parkinsonian symptoms. There is a severe depletion of cholinergic neurons in the nucleus basilis of Meynert of between 75 - 80% (Jellinger, 1991).

ii. type B or 'transitional type' with numerous Lewy bodies in the brainstem and diencephalon, but less frequent in basal ganglia and cerebral cortex. It clinically presents as Parkinson's disease.

iii. type C or 'brainstem type' with many Lewy bodies in the brainstem, but few or none in the cerebral cortex, apparently identical with idiopathic Parkinson's disease.

It remains unknown whether this disorder represents one end of a spectrum including idiopathic and atypical Parkinson's disease, presenile dementia or a combination of these disorders, or a single entity with various subtypes (Jellinger, 1987).

d. *Parkinsonian-dementia complex of Guam.*

Observed among the Chamorro people of Guam in the western Pacific, and has been reported to account for 7% of all adult deaths in that population.Until recently these Chamorro indians were more than 50 times as likely to develop Parkinson's disease than people in the United States, and they developed it at an earlier age (Ferry, 1987). It is also found among residents of the Kii Peninsula, Honshu Island, Japan; and the Auyu and Jaqai linguistic groups of Irian Jaya, Indonesia (Kisby *et al,* 1992). It presents as a combination of Parkinsonism with dementia and frequent amyotrophic lateral sclerosis. It is characterized by diffuse cortical atrophy, many Alzheimer type neurofibrillary tangles and Hirano bodies but no senile plaques (Hirano *et al,* 1961; Brody *et al,* 1971). There are few Lewy bodies present in the locus ceruleus. There is a 60 - 90% loss of the large cells in the

nucleus basilis of Meynert without decrease in cortical choline acetyltransferase activity (Jellinger, 1991). Since the 1950s the Chamorros have adopted an increasingly Western way of life, and others have emigrated, as a result fewer and fewer Guamanians have fallen victim to neurological diseases. It is thought that the cycad nut, formerly a common part of the Guamanian diet, is partly responsible (see later).

e. *Progressive supranuclear palsy.*

Progressive supranuclear palsy is a sporadic Parkinson-like disorder, first identified by Steel in 1964. It presents with ophthalmoplegia (paralysis of vertical gaze), axial dystonia, rigid akinesia, pseudobulbar palsy, speech difficulties, and dementia.The average age at onset is 58 with death occurring 2 - 12 years later. Men are more often effected than women (West, 1991). It presents with widespread neurofibrillary filament tangles different from those in Guam-parkinsonism-dementia complex and post-encephalitic Parkinsonism, and multisystem neuronal degeneration (excluding hippocampus and neocortex involvement) (Jellinger, 1987; Jellinger, 1989). There is an average 40% loss of cells in the nucleus basilis of Meynert (Jellinger, 1991). Progressive supranuclear palsy is usually initially diagnosed as Parkinson's disease but the response to antiparkinsonian medications is poor and inconsistent - no effective treatment for this disease as yet exists (West 1991).

f. *Multisystem degenerations.*

These are frequently misdiagnosed as idiopathic Parkinson's disease, despite having distinctive clinical conditions akinetic-rigid manifestations, poor or absent response to levodopa treatment and rapid progression (West , 1991). Such disorders include striatonigral degeneration, Orthostatic hyotension or Shy-Drager syndrome and Machado-Joseph disease. All include some form of nigral damage, but with or without Lewy bodies. They are not always associated with Parkinsonian symptoms (Jellinger, 1987).

2.5.2. Post-encephalitic Parkinsonism.

Encephalitis lethargica is an infection of the CNS that reached epidemic proportions in the 1920s. A patient would often present with Parkinsonian-like symptoms in the acute attack, and often Parkinsonism would develop insidiously during the succeeding 1-20yrs. With the virtual disappearance of encephalitis lethargica this form of the disease is gradually disappearing. Symptoms were very similar to the

idiopathic form of the disease but with more conspicuous rigidity and the appearance of bizarre contractures of the extremities in severe cases. Oculogyric crisis was a common complication of the disease.

Pathological signs include extensive damage to the substantia nigra and locus ceruleus, with nearly complete disappearance of all melanin cell groups and damage to other parts of the upper brain stem (Jellinger, 1989). There is a widespread occurrence of neurofibrillary tangles of the Alzheimer type in the brainstem (particularly substantia nigra, locus ceruleus and mesencephalon), hypothalamus and hippocampus, but little involvement of the neocortex (Hassler, 1938; Klaue, 1940; Greenfield and Bosanquet, 1953; Richardson, 1965; Jellinger, 1974; Ishii and Nakamura, 1981; Rail *et al,* 1981; Gibb and Lees, 1987). However the presence of Lewy bodies have not been demonstrated. The pathogenesis of Post-encephalitic Parkinsonism is unknown but as antibodies to influenza B have been demonstrated using immunofluorescence techniques, it is thought that there is some relation with a viral agent (Jellinger 1987,1989).

2.5.3. Arteriosclerotic Parkinsonism.

Clinical features resembling those of Parkinsonism may develop in the course of cerebral arteriosclerosis. Although vascular lesions may occur in typical Parkinson's disease brains, their incidence is about the same as in age-matched controls. Of the manifestations which resemble Parkinsonism the commonest are, the bodily attitude, slowness of movement, and the festinant gait. Facial immobility and tremor are rare. A study by Jellinger (1987) of autopsied Parkinson's brains revealed 7.4% to have multi-infarct atrophy, hypertensive encephalopathy, with lacunar or small infarctions in the basal ganglia and/or brainstem,with no or only mild degenerative nigral changes. Lewy bodies were present in approximately 9.3% of these cases which is twice as high as age matched controls (Jellinger, 1987). Jellinger thus suggests a combination of Parkinson's disease with cerebrovascular disorders.

2.5.4. Post-traumatic Parkinsonism.

Parkinsonism has been known to occur following physical damage to the upper brainstem, for example a bullet injury or compression from vascular lesions or raised intercranial pressure. The most well known cause is due to a boxing injury, i.e. dementia pugilistica or boxer's dementia. This presents with diffuse cortical atrophy, severe neuronal loss from locus ceruleus (around 40%) and substantia

nigra with numerous neurofibrillary filament tangles, but no senile plaques. Parkinsonism has also been observed in rare cases of tuberculoma or tumor of the brain stem (Gherardi *et al,* 1985), solid tumors causing brain stem compressions (Garcia de Yebenes *et al,* 1982), and calcification of the basal ganglia (Klawans *et al,* 1976).

2.5.5 Toxic Parkinsonism.

Parkinsonism has been known to result from intoxication by carbon monoxide, carbon disulphide and cyanide - these cause anoxic damage to the globus pallidus and/or substantia nigra.

i. Manganese:

As early as 1837, chronic exposure to manganese dust, most typically through mining, was recognised to cause neurologic injury. Other possible sources of manganese include industrial exposure and welding. Manganese is absorbed both through the lungs and gastrointestinal tract, and readily crosses the blood-brain barrier. Following high dose exposure within months workers suffer from "manganese madness" which involves behavioural changes including fatigue, insomnia, hallucinations, irritability and aggressiveness. The changes are less dramatic if the exposure is mild. After several months, Parkinsonian signs occur including propulsive gait, postural reflex impairment, bradykinesia, impaired fine coordination, sialorrhea, soft speech, and masked facies, and dystonia. If exposure ceases, symptoms stabilize or remit partially (Tanner, 1992).

Maximal pathological damage occurs in the globus pallidus, but damage can also occur in the caudate, putamen, subthalmic nucleus, frontal and parietal cortex, hypothalamus, cerebellum and substantia nigra and is thought to be a result of free radical formation of impaired mitochondrial function.

ii. Carbon disulphide:

Psychotic mood disorders in workers manufacturing inflatable rubber was attributed to carbon disulphide inhalation in 1856. It readily crosses the alveolar membrane and is quickly accumulated by lipid-rich tissues, such as the brain. Today, workers producing viscose rayon or cellophane are most likely to be exposed to carbon disulphide. Following massive continuous exposure, signs are

similar to those of manganese toxicity. Additional, subsequent signs include depression, tremor, incoordination and memory loss, peripheral neuropathy and cerebral vascular disease. Tanner (1992) suggest three possible mechanisms by which carbon disulphide may cause aminergic neurotransmitter dysfunction: (1) chelation of metals such as zinc or copper that could decrease activity of metal-dependent enzymes such as aromatic amino acid decarboxylase, the enzyme mediating the conversion of l-dopa to dopamine; (2) direct inhibition by carbon disulphide of enzymes associated with catecholamine function, such as dopamine-B-hydroxylase or monoamine oxidase; and (3) direct interaction of carbon disulphide with vitamin B6, necessary for the function of tyrosine to l-dopa and for activity of the enzyme aromatic amino acid decarboxylase.

iii. Other organic solvents:

Parkinsonism has been known to follow ingestion of large quantities of methyl alcohol usually as a substitute for ethyl alcohol. Acute toxication results in inebriation, gastrointestinal complaints, delirium and coma, followed by other nervous system injuries including blindness, Parkinsonism dystonia (due to injury to putaminal neurons) and cognitive impairment in survivors. Other solvents that have been documented as causing rare Parkinsonism include N-hexane, n-butyl keton, and carbon tetrachloride.

iv. Carbon monoxide:

Carbon monoxide is a tasteless and odourless gas that is rapidly absorbed across alveolar membrane and is one of the most common forms of suicide poisoning. Industrial exposures includes fires, automobile fuel, mining, and exposure to methylene chloride (a paint stripper metabolized to carbon monoxide). Acute toxicity is the result of carboxyhemoglobin formation thus reducing the oxygen carrying capacity of the blood. Symptoms include dizziness, headache, visual changes, alterations in conciousness, convulsions, coma and cardiorespiratory arrest.

Survivors of acute toxicity may experience delayed encephalopathy usually developing several days to weeks after recovery from the initial coma. Memory loss and personality changes and some Parkinsonian signs (though rarely the complete disease) are common sequelae. In many cases, symptoms and signs may resolve within several years, although memory and personality changes and, less

commonly, Parkinsonism may be persistent. These delayed sequelae may not be a result of hypoxia (like the acute symptoms), but alterations in cellular respiration, resulting from the interaction of carbon monoxide with other haem proteins such as the cytochromes. Others have proposed demyelination of central pathways.

The most well documented form of toxic Parkinsonism is that of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), which produces symptoms almost identical to those of idiopathic Parkinson's disease (see Chapter 3).

2.6. Epidemiology and Etiology of Parkinson's disease.

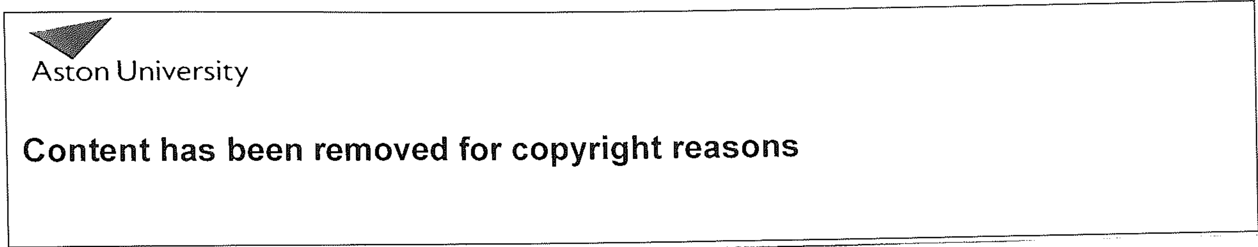
2.6.1. Epidemiology.

The underlying cause of idiopathic Parkinsonism is still unknown. Many environmental factors have been investigated such as other medical conditions, previous history of head injury, vaccinations, exposure to certain drugs or anaesthetic agents, birth order, birth weight, alcohol consumption, coffee consumption etc - but no consistent findings have resulted (Shoenberg, 1987). Parkinson's disease is estimated to affect about 100000 people in the United Kingdom. Leaving aside dementia, Parkinson's disease is the most common neurological condition to affect the elderly British population after epilepsy and cardiovascular disease. It is more common than multiple sclerosis (West 1991). Many epidemiological studies have been carried out over many years throughout the world in an attempt to establish a pattern of occurrence related to patient age, sex, home environment, childhood environment, occupation and family history. The different forms of data collection in these studies have resulted in a great deal of variability in information provided. The three main methods of data collection are mortality data, incidence data and prevalence data.

Mortality data is readily available from medical records. However, Parkinson's disease, although listed on death certificates, some other condition is often specified as the cause of death. Deaths as a result of Parkinson's disease are negligible for people under the age of 45 years, with rates steadily increasing with advancing age, reaching a peak at the age of 75 years to 84 years and then declining among the oldest age group (Shoenberg, 1987; Martilla and Rinne, 1989; West , 1991). The official death rate from Parkinson's disease per million population in England and Wales for males is 74, and for females 66. For the world, these figures are 43 and 21 respectively (West, 1991). Parkinson's disease was given as the cause of death

in England and Wales in 1988. The age and gender distribution of these deaths are given in Table 2.1 (taken from West, 1991).

Table 2.1 Recorded deaths mentioning Parkinson's disease on the death certificate; classified by age and gender (taken from West 1991, adapted from OPCS 1990).



The numbers of people dying from Parkinson's disease are likely to increase due to the increase in the number of the population surviving to old age (West, 1991).

Incidence is the number of new cases of a disorder first developed or diagnosed during a specified time interval, the data is usually obtained through special surveys and as rates for Parkinson's disease vary greatly with age - the figures must be age adjusted or age specific in any comparison. Incidence date form several studies is given in table 2.2 (taken from Tanner, 1992). Incidence rates derived from these surveys provide figures near 20 new cases per 100000 per year. After the age of 30-40 years, the incidence rates increase with age to reach a maximum at about 75 years, with a decline in the rate of new cases after that (Schoenberg, 1987).

Prevalence refers to the total number of persons with a disorder within a given population at a fixed point in time (Tanner, 1992). Rates are obtained using surveys on a particular date eg door-to-door questionnaires (Ferry, 1987; Martilla and Rinne, 1989; Svenson, 1991). Some selected prevalence rates are given in table 2.2 (taken from West 1991).

A more recent survey conducted on November 1 1987 gave a prevalence for idiopathic Parkinson's disease of 257.2 per 100000 population (Morgante *et al,* 1992).

Parkinson's disease probably occurs throughout the world, and so far no population has been reported to be totally protected against this disease (Martilla and Rinne, 1989). However, there is some evidence to suggest that the prevalence of Parkinson's disease varies between countries, and between regions. It has been suggested that Parkinson's disease is less common among Mediterranean

populations (Rosati *et al*, 1980). However Morgante *et al* (1992) found the prevalence of Parkinson's disease among a Scicillian population to be higher than that found in Bombay, India, Copiah Country Mississippi and China (Li *et al* , 1985; Shoenberg *et al* , 1985; Bharucha *et al* , 1988).

Some studies have also shown different prevalence rates among races, Parkinson's disease being more common in white races, least common among blacks and intermediate in Mediterranean and yellow races (Mutch, 1988; West, 1991; Tanner, 1992). The study in Baltimore (shown in table 2.2, Kessler 1972) found a higher prevalence among the black population compared to whites. This was also the case in Nigerian based study (Schoenberg *et al* ,1988). However the Mississippi survey revealed virtually no difference in the age-adjusted prevalence rates of Parkinson's disease among blacks and whites residing in the Copiah County (Shoenberg *et al* , 1985).

Table 2.2 Estimated incidence and prevalence of Parkinson's disease in representative community-based studies (adapted from West 1991).

Location	Publication year	PrevalencE (per 100000)	Annual Incidence (per 100000)
Rochester, MN.	1958	187	20
Carlisle, England	1966	113	12
Victoria, Australia	1966	85	-
Iceland	1967	162	16
Baltimore, MD	1972	128	-
Turku, Finland	1976	120.1	15
Aberdeen, Scotland	1986	164.2	-
San Marino	1987	152	-
Yonago, Japan	1983	80.6	10
Sardinia, Italy	1980	65.6	4.9
Northampton, U.K.	1985	108.4	-
Benghazi, Libya	1986	31.4	4.5
Rochester, MN	1984	-	20.5
Izumo City, Japan	1990	82	-

Epidemiology studies have also been used to assess the sex distribution of the disease. More commonly it would seem that both sexes are equally at risk of developing Parkinson's disease (Shoenberg, 1985; Sutcliffe *et al*, 1985; Martilla and Rinne, 1989). However in the United States and China a higher rate of Parkinson's disease prevalence has been found in males compared to females - the opposite being the case in Canada and Sicili (Li *et al* , 1985; Svenson, 1991; Morgante, 1992; Tanner, 1992).

2.6.2. Etiology.

Genetics:

There have been many studies to investigate whether Parkinson's disease is a genetically transmitted disease. The obvious way of assessing modes of inheritance is to monitor the distribution of Parkinson's disease within populations of monozygotic and dizygotic twins; this type of study has been carried out and in general it would seem that neither monozygotic or dizygotic twins pairs are concordant for Parkinson's disease (Duvoisin, 1981; Ward *et al* , 1983; Duvoisin, 1986; Marsden and Fahn, 1987; Marsden, 1987; Schoenberg *et al* , 1988; Martilla *et al* , 1988; Riederer and Lange, 1992). Thus, according to the above authors, inheritance seems to play little or no part in the etiology of the disease. However, two large kindreds of familial Parkinson's disease, studied by Maraganore and coworkers (1991) and Golbe and coworkers (1990), suggest an autosomal dominant mode of transmission of Parkinson's disease with reduced penetrance. Maraganore's group also argue against X-linked transmission because the disease is equally present in males and females.

Burn and coworkers (1992) showed a low concordance of Parkinson's disease of between 2% and 12% for both monozygote and dizygote groups. However they also evaluated uptake of ^{18}F-dopa in the putamen of twins using PET scans. They found that the asymptomatic co-twin showed a reduction in uptake of 14%, which is significantly reduced compared to normals (the uptake in the affected individuals was grossly reduced). It is possible that this could be explained by twin pairs being exposed to an environmental toxin. However, one of the twin pairs had been separated at the age of 15 years. Burn et al, therefore also suggest a possible autosomal dominant mode of inheritance with reduced penetrance (exclusively maternally transmitted and which would show similar concordances in monozygote and dizygote twins), or a multifactoral threshold model (in which some individuals

are at high risk and some at low risk, with risk being determined by a series of additive factors, both genetic and environmental) (Johnson *et al,* 1990). This model is also suggested by Vieregge and coworkers (1992), who found that the concordance rate for Parkinson's disease in monozygote twins was not higher than dizygote twins.

A perplexing finding in a Parkinsonian twin study by Eldridge and Ince (1984) was a higher rate of the disease in sibs and parents than in co-twins. They suggest that there is an in utero factor that influences the growth and survival of a cell population in the brain that is crucial for the eventual development of Parkinson's disease; that this factor is supplied unequally to the two twins, so that one twin is more at risk of developing Parkinson's disease. It is well known that twins suffer from a higher frequency of abnormalities during pregnancy and birth. The birth weight of one monozygote twin can be very much lower than the other due to chronic transfusion syndrome - however, this is not usually the case in dizygote twins (Vieregge *et al*, 1992). This would suggest that if an interuterine factor were responsible for the eventual development of Parkinson's disease, it would be more prevalent in monozygote twins than dizygote twins - which does not appear to be the case. Additionally no link has been established between Parkinson's disease and low birth weight, birth order, congenital abnormalities, or a perinatal risk factor (Vieregge *et al,* 1992).

There does seen to be a subset of Parkinsonian patients where inheritance seems to play a role. Barbeau *et al* (1984) describe two familial forms of Parkinson's disease. One is referred to as an essential tremor related Parkinsonism. Essential tremor follows a dominant pattern of inheritance. Symptoms of Parkinsonism occurs randomly within these families but with a five fold greater incidence than in the general population. Geraghty *et al* (1985) found that the prevalence of Parkinson's disease in a population of families with essential tremor was 24 fold higher than in the general population (Marsden and Fahn,1989; Breakefield *et al,* 1986). The second form of familial Parkinson's disease described by Barbeau and coworkers is an akinetic-rigid form that appears to follow an autosomal recessive mode of inheritance.

It would therefore seem that Parkinson's disease is unlikely to be strictly genetically transmitted; although a multifactorial model consisting of a combination of environmental and genetic factors, possibly on a background of normal age related

changes cannot be ruled out (Calne and Langston, 1983; Barbeau *et al*, 1985; Schoenberg, 1986; Calne, 1989; Semckuck *et al*, 1991, & 1992).

Environmental factors:

Much interest has been placed on the role of environmental or endogenous neurotoxins or a combination of the two in Parkinson's disease (Halliwell, 1989; Youdim *et al*, 1989). Damage to specific regions of the CNS remains subclinical for several decades and may result in those effected being especially prone to the consequences of age-related neuronal attrition (Calne *et al*, 1986). About 5% of nigral cells are lost each decade after the age of 50, but in the process of normal aging cells are lost predominantly from the dorsal region of the substantia nigra; the main site of cell loss in Parkinson's disease. This, combined with the fact that cell loss in Parkinson's disease occurs rather rapidly, suggests that the disease is not simply an accelerated process of normal ageing (West, 1991; Calne *et al* , 1984). The cause of the initial neuronal damage may be toxic, infectious, traumatic or uncertain, and may have occurred very early in life (Martilla and Rinne, 1989; Bernheimer *et al*, 1973).

There have been a number of studies investigating links between Parkinson's disease and childhood in a rural environment and / or drinking well water. Natural water supplies may contain chemicals used on farmland that has leached from the land. Both Rajput *et al* (1984) and Tanner *et al* (1987) found an association between young-onset Parkinsonism and rural residence, this has also been confirmed by Koller and coworkers (1990), Ho and coworkers (1989) and Wong and coworkers (1991). It has also been reported from post-mortem material that non-Parkinsonian rural residents had a lower substantia nigra cell count than urban residents of a similar age (Thiessen *et al*, 1990). However, a population-based study in Calgary by Semckuk and coworkers (1991 & 1992) found no such links (although they do suggest that there may be a dose-response relation between the duration of cumulative exposure to agricultural work and Parkinson's disease risk).

The risk of developing Parkinson's disease following exposure to herbicides and pesticides have also been investigated. The observation that MPTP causes a Parkinsonian syndrome strikingly similar to the idiopathic form - suggests that a similar compound may be present in the environment. MPP+ has been commercially marketed as a herbicide under the name of Cyperquat, and is chemically very similar to the bipyridinium herbicide paraquat (Ho *et al*, 1989). A

study in Hong Kong by Ho and coworkers where paraquat is widely used, found that subjects who previously used herbicides and pesticides had a 3 - 6 times increased risk of developing Parkinson's disease. Barbeau and colleagues (1982, 1984) also found an association between disease frequency and pesticide use (Schoenberg, 1987; Tanner, 1992). However neither Koller *et al* (1990) in a study in Kansas or Semckuck *et al* (1992) in a study in Calgary found any link between herbicide and pesticide exposure and Parkinson's disease.

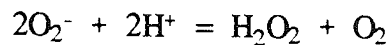
More evidence for an MPP+ type of toxicity comes from evidence that it is concentrated in mitochondria where it poisons complex I of the mitochondrial respiratory chain (Riederer and Lange, 1992). Schapira *et al* (1990) have shown that there is a complex I deficiency in the substantia nigra of idiopathic Parkinsonism. This deficiency could result from an MPTP-like substance inhibiting complex I of mitochondrial energy metabolism, or it could result from a defective gene encoding abnormal complex I proteins or a factor that regulates gene transcription (Riederer and Lange, 1992).

Heavy metals have been considered as possible toxins causing Parkinson's disease. Aquilonius and Hartvig (1986) employed pharmaceutical records of L-dopa use to identify a regional distribution of Parkinsonism in Sweden. Saw and paper mills and steel alloy industries (located in non-agricultural, non-rural areas) were prevalent in the country where most Parkinson's disease cases occurred (Koller *et al*, 1990). The fact that toxic Parkinsonism exists (as mentioned previously) and is caused by agents such as manganese - it is possible that 'idiopathic' Parkinsonism may be a result of exposure to such a toxic substance during some period of life eg chronic exposure to manganese dust during mining, carbon disulphide used as an industrial solvent, and even carbon monoxide which is a common form of poisoning (automobile fuel) (Tanner, 1992).

More evidence in favour of an environmental toxin can be found on the island of Guam where the increased incidence of Parkinson's disease has been associated with Chamarro food preparation. It is thought that the causative agent is found in cycad flour prepared from the seed kernal of "Cycas circinalis .L". Two classes of compound with neurotoxic potentials have been identified in Cycas seed: methylazoxymethanol B-D-glucoside (cycasin) and B-N-methylamino-L-alamine (BMAA). Kirby *et al* (1992) found that the highest content of cycasis was found in the flour from Umatac, the historical and current epicenter of the disease on Guam.

Free radicals:

A free radical can be defined as an atom, or group of atoms with one unpaired electron occupying an outer orbit (Calne *et al*, 1984). The diatomic oxygen molecule qualifies as a radical since it has two unpaired electrons, each located in a different orbital but both spinning in the same direction. The main free radical under consideration is superoxide O_2^- formed when the O_2 molecule accepts a single electron and is produced naturally eg during the electron transfer chain (Halliwell, 1989). The major enzyme for scavenging superoxide is superoxide dismutase which converts it into Hydrogen peroxide:-

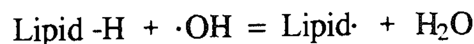


$$2O_2^- + 2H^+ = H_2O_2 + O_2$$

Other enzymes producing H_2O_2 are L-amino acid oxidase and monoamine oxidase. Hydrogen peroxide is an oxidizing agent which, unlike O_2^-, crosses cell membranes easily. It is removed by the action of catalase glutathione peroxidase within human cells. Toxicity of Hydrogen peroxide is usually mediated by formation of highly oxidizing radicals. It combines with Fe^{2+} ions to form hydroxyl radical (·OH) by the Fenton reaction:-

$$Fe^{2+} + H_2O_2 = Fe^{3+} + \cdot OH + OH^-$$

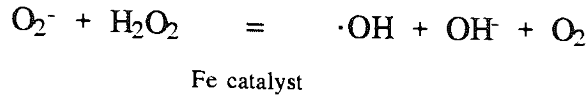
Hydroxyl radical reacts at great speed with almost every molecule found in living cells and it initiates lipid peroxidation by abstracting a hydrogen atom from a polyunsaturated fatty acid side chain in a membrane phospholipid (Halliwell, 1989).



$$\text{Lipid -H} + \cdot OH = \text{Lipid}\cdot + H_2O$$

The remaining carbon centred radical (lipid.) present in the membrane then (under aerobic conditions) reacts with oxygen to form a peroxyl radical. Peroxyl radicals then continue the chain reaction by abstracting hydrogen atoms from adjacent fatty-acid side chains. Lipid peroxidation results in the membrane function being severely disrupted, decreasing its fluidity and allowing ions such as Ca^{2+} to leak across the membrane.

The Fe^{3+} generated during the Fenton reaction can be re-reduced to Fe^{2+} by ascorbic acid or by superoxide thus accelerating the iron dependent formation of $\cdot OH$ from H_2O_2. The overall reaction is known as the Haber-Weiss reaction:-



$$O_2^- + H_2O_2 \underset{\text{Fe catalyst}}{=} \cdot OH + OH^- + O_2$$

Thus the nature of the damage done to cells by hydrogen peroxide and superoxide will be affected by the location of iron catalysis of this reaction within the cells.

Thus Parkinson's disease may be the result of :-

i. an environmental factor causing cell injury resulting in the release of iron which accelerates free radical reactions. However studies using MPTP have shown that although this toxic substance causes nerodegeneration, it does not alter the iron content of the caudate nucleus or substantia nigra - neither does it cause lipid peroxidation.

ii. Oxidative deamination of dopamine by monoamine oxidase is the main catabolic pathway for dopamine within dopamine nerve terminals. Cohen (1988) has suggested that an accelerated turnover of dopamine in Parkinson's disease leading to increased hydrogen peroxide formation may provoke an oxidant stress within surviving dopamine terminals and accelerate their destruction. (The prolonged therapy by L-dopa may also relate to increased superoxide formation) (Halliwell, 1989). Once injury sufficient to cause cell death has occurred - it cannot be repaired. The high metabolic rate of CNS cells results in an increased speed in toxic reactions. The surviving nigral cells will increase their activity in an attempt to maintain dopamine production thus increasing the speed of free radical production further.

iii. An increased amount of iron will drive the Fenton reaction at an increased rate. The highest concentration of iron in the brain is found in the pallidium and substantia nigra, and this level has found to be increased in patients with Parkinson's disease (Hirsch *et al*, 1989; Halliwell, 1989; Youdim, 1989; Riederer *et al*, 1989). The increased amount of iron in the substantia nigra of Parkinsonian brains could result from either increased uptake or decreased elimination of iron - however, no evidence is, as yet, available.

iv. In normal circumstances iron is stored in its inactivated form. In the substantia nigra, globus pallidus, ventral pallidum and caudate nucleus about 70% of the iron is bound to melanin. Hirsch *et al* (1989) have demonstrated the greater vulnerability of the pigmented cells in Parkinson's disease. Usually melanin acts as a radical scavenger, however it now seems possible that melanin participates in neurodegeneration (Youdim, 1989). In 1988 Pilas and coworkers demonstrated that with low concentrations of Fe^{2+}, melanin decreased the yield of $\cdot OH$ due to the binding of Fe^{2+} to the melanin. However, if the predominant form of iron is Fe^{3+} then melanin increases the rate of $\cdot OH$ production (Youdim, 1989).

v. a functional reduction in any of the oxygen radical scavenger systems such as glutathione, glutathione peroxidase, superoxide dismutase and ascorbate (known to be present in relatively high concentrations in the basal ganglia) could theoretically be highly damaging to the dopamine neurone (Youdim *et al*, 1989) - as it may push the hydrogen peroxide to interact with increased Fe^{2+} and drive the formation of $\cdot OH$ thus producing more Fe^{3+} and continue the chain reaction. Youdim and coworkers have shown that the ratio of Fe^{2+} to Fe^{3+} in the substantia nigra of controls is 3:1, but this ratio changes to 1:1 in advanced Parkinson's disease.

Disease and Trauma:

Ever since the pandemic of encephalitis lethargica - much interest has been placed on the relation between infection and Parkinson's disease. Similarly due to the existence of boxer's dementia (see previously) links between idiopathic Parkinsonism and a history of head injury has been investigated.

It is apparent that several viruses can infect the nervous system to produce acute transient tremor, rigidity and masking of facial expression. These include measles, varicella, polivirus, Cacsackie virus, Equine encephalitis and Japanese B encephalitis. However, there is no good evidence to indicate that any viral infection other than encephalitis lethargica will produce progressive Parkinsonian deficits (Calne *et al*, 1984). It has been postulated that Parkinson's disease may be the result of an unconventional or slow virus infection - however, since it has not proved possible to transmit Parkinson's disease from the brain of patients to any other species tested up to the present time, the results are not promising (Calne *et al*, 1984).

Barbeau and Pourcher (1982) found a relationship between diabetes mellitis and Parkinson's disease; a study by Ho and coworkers in 1989, however could find no such relationship. Fazzini, Fleming and Fahn (1990) found increased cerebrospinal fluid antibodies to coronavirus in persons with Parkinson's disease (Tanner, 1992), and Mattock *et al* (1988) found a link with interuterine influenza (analyzing birth years compared to influenza endemics).

There have been reports that bacterial involvement of the nervous system for example with Treponema pallidum, occasionally resulted in a Parkinsonian syndrome, but there is no evidence to implicate this type of infection as a cause for Parkinson's disease. Kessler (1972, 1 & 11) found that arteriosclerosis and prostate diseases were more prevalent in patients with Parkinson's disease, but heart diseases, stroke, and peptic ulcer were less prevalent in male cases, whereas in female cases, encephalitis was more frequent but diabetes was less frequent (Kondo, 1984). Martilla and Rinne (1976) found no link with heart disease or stroke. Kondo also showed that the prevalence of malignant neoplasms in autopsied cases was more that twice as common as in control autopsies.

There seems little doubt that certain types of trauma can induce a syndrome resembling, but clinically distinct from Parkinson's disease, but there is no good evidence to implicate trauma in the vast majority of patients (Calne *et al*, 1984). Bharucha and coworkers (1986), Tanner *et al* (1987), and Duloney *et al* (1990) all found an association between head trauma and Parkinson's disease (Tanner, 1992). Riederer and Lange (1992) state that people with Parkinson's disease are more likely to give a history of head trauma, but compared to the general population, diseased patients are more likely to remember such a history in the hope of finding a cause to their condition.

Life-style:

The notion of premorbid behaviour characteristics is based on the assumption that initially levels of dopamine are reduced sufficiently to produce a change in personality but not to produce any problems with movement. A study by Duvoisin *et al* (1981) on monozygote twins found a higher incidence of smoking and alcoholism in co-twins which may represent an early behavioural expression of the disease. They indicated a personality difference dating back to adolescence in 7 out of 12 twins, with the effected twin being described as more "nervous", "quieter", "introverted" and "serious", and the co-twin being more "outgoing" and

"confident". These behavioural differences have been confirmed by Ogawa *et al* (1984), Kondo (1984), Golbe *et al* (1986), Sagar (1991) and West (1991). While Ogawa and coworkers state that smoking and personality are independent risk factors, Sagar believes that the personality types who tend not to smoke are also of the personality type more at risk from Parkinson's disease and *visa versa* (Marttila and Rinne 1989).

A link with increased alcohol intake was not confirmed by Ho *et al* (1989). Stress was among the earliest proposed causes of Parkinson's disease. Laboratory studies suggest that stress-produced changes in central dopamine systems could theoretically contribute to the development of Parkinsonism (Tanner, 1992). Links with dietry habits have been investigated, Marttila and Rinne (1989) have reviewed these studies and state that some suggest that patients with Parkinson's disease dislike green vegetables but prefer nuts, salad oils and plums!

Protective factors:

Due to the inverse relationship between smoking and Parkinson's disease - it has been suggested that a compound in cigarette smoke ameliorates, delays or prevents Parkinson's disease. Nicotine, like MPTP is a close analogue of a nicotine derivative present in cigarette smoke 4-phenylpyridine. Golbe *et al* (1986) suggest the following supposed anti-Parkinsonian effects of smoking:-

i. the hypothesis that the reducing activity of the carbon monoxide in cigarette smoke might neutralize some of the delaterious oxidative effects of the free radicals produced in the substantia nigra as a by-product of dopamine synthesis.

ii. the speculation that nicotine may be degraded to nicotinic acid, which may, in turn 'displace' the equilibrium between tryptophan and tyrosine so as to increase the elaboration of DOPA.

iii. the observations that nicotine stimulates nigral cell firing and striatal dopamine turnover.

However, if smoking were a protection against Parkinson's disease - there should be a dose - response relationship, which does not seem to be the case.

Tanner (1992) suggest that dietry intake of factors that interfere with the pathogenic mechanisms underlying Parkinson's disease might prevent disease development, for example, if oxidative mechanisms are involved in the pathogenesis of Parkinson's disease intake of antioxidant vitamins may be protective.

In summary it would seem that Parkinson's disease is a result of genetic susceptibility to environmental neurotoxins, the identity of which is unknown but exposure to it may have occurred early in life. Once toxic injury has damaged the dopamine producing cells their increased activity encourages a chain reaction of free radical production culminating in neuronal self destruction.

2.7. Treatment of Parkinson's Disease.

Treatment of Parkinson's disease is based on the replenishment of the neurotransmitter dopamine which is significantly reduced in the disease. One has to be aware of the main steps of biosynthesis of dopamine and its breakdown to understand the therapeutic approach to its treatment (see figure 2.7 at the beginning of this chapter).

2.7.1. L-Dopa.

The most successful pharmacologic strategy in the treatment of Parkinson's disease is the use of L-dopa (3,4-dihydroxyphenylalanine). This neutral aromatic amino acid came to be used as a precursor to dopamine because it was found to be actively transported into the brain and decarboxylated to dopamine (dopamine itself is effectively excluded from transport). Under natural circumstances L-dopa is found systemically and in the human brain only in trace amounts. L-dopa undergoes rapid conversion to dopamine because it is an intermediate between hydroxylation of L-tyrosine and the decarboxylation step yielding dopamine, and as this step is not a rate-limiting process L-dopa does not accumulate (Le Witt, 1989,1992). L-dopa can be highly effective at reversing virtually all of the positive (e.g. resting tremor, dystonia, rigidity) and negative features of Parkinsonism (e.g. bradykinesia, dysphagia, decreased dexterity, mask-like facies, drooling, and impaired gait, posture, and balance). Depending particularly on the goals, adverse effects, and long-term strategies of therapy, there is a wide range of what can be defined as 'optimal' dose of L-dopa. Following the initial clinical experiences with L-dopa, clinicians were advised to use maximally tolerated L-dopa, increasing the dose until

side effects appeared or until a satisfactory level of improvement occurred. Typical regimes of L-dopa involved a starting dose of 500mg given in 3 -4 doses daily and increasing over 4 -8 weeks to a maximum of 8 g/day.

Absorption of L-dopa occurs primarily in the proximal small intestine. The rate of drug delivery to the duodenum from the stomach appears to be a major determinant of uptake. Since no significant absorption and only minimal metabolism of L-dopa occurs in the stomach, factors inhibiting release of gastric content to the small intestine can have a major influence on the rate of absorption. During the initial systemic distribution of absorbed L-dopa, there is rapid first-pass metabolism through the liver and transfer to other systemic compartments. After systemic distribution, skeletal muscle serves as an important peripheral storage reservoir for L-dopa. No significant metabolism is known to occur in muscle. Uptake of L-dopa by erythrocytes occurs, and red cells possibly metabolize L-dopa to 3-0-methyldopa. At the interface of the vasculature and the brain is a sodium-dependent active transport system for neutral amino acids, by which L-dopa is taken up (Le Witt, 1989; Wooten, 1987).

There are two main problems with the use of L-dopa - peripheral side effects and central side effects. Much of the orally administered L-dopa will undergo conversion to dopamine peripherally before reaching the brain due to the abundant systemic L-aromatic amino acid decarboxylase (AAAD) activity. This results in peripheral adverse effects of dopamine including vomiting and hypotension (Fahn, 1989; Le Witt, 1989). The combined use of L-dopa plus a decarboxylase inhibitor (such as carbidopa in sinemet and benserazide in madopar) has improved this situation remarkably. These combinations have been shown to be considerably more effective than L-dopa alone - although it does not increase the 'duration' of clinical effect, permeability into the brain, or antiparkinsonian potency of L-dopa. The tactic behind this combination therapy was the inhibition of dopamine formation from L-dopa in the periphery of the body, yielding a higher amount of L-dopa reaching the brain (Fahn, 1989; Birkmayer and Birkmayer, 1989 (1 & ll)). A very important point is the ratio of the combination of L-dopa and decarboxylase inhibitor since overhigh levels of dopamine produce new side-effects such as vivid dreams, anxiety, hyperkinesia, hallucinations, and delusions.

Another peripheral side effect is the possible involvement of L-dopa in the formation of melanomas. Skin melanin utilizes dopa generated by tyrosinase from its precursor tyrosine. In the formation of skin melanin, dopa is converted to

dopaquinonone, again by the same enzyme, tyrosinase. L-dopa used in the treatment of Parkinsonism could theroretically be used in the metabolism of melanomas (Fahn, 1989). Other side effects include sweating, respiratory distress, hypersexuality, constipation, and pain.

The second, and more problematic, adverse effect of L-dopa following its long term use include the 'on-off' phenomenon. This is described as the initial and dramatic situation noticed by patients when the beneficial response to the drug was suddenly terminated, like a light switch being turned off. The beneficial response could turn on again just as quickly (Hardie *et al*, 1984, Hardie, 1987; Fahn, 1989; Sage and Mark, 1992). This condition occurs in about 10% of patients after 6 years of L-dopa treatment. A more prominent phenomenon is the gradual fading of benefit of the drug as the duration of the dose is prolonged, occurring approximately 2-3 hours after taking a dose of L-dopa. Patients feel as though their medication is wearing off - hence the term 'wearing-off' effect (or 'end-of-dose' deterioration). With continued use of L-dopa other adverse effects become noticeable including peak-dose chorea, peak-dose dystonia, dystonia occurring during the 'off' phase, and freezing (when the patient is transiently immobile as if stuck to the ground). Numerous reasons have been suggested to explain these complications:

(i) AAAD in the basal ganglia, which is needed to convert L-dopa to dopamine, might become significantly reduced in Parkinson's disease. However there is no significant reduction of monoamine oxidase and only a 25% decrease in catechol-0-methyltransferase. This results in a reduction in the conversion of L-dopa to dopamine but continued conversion of L-dopa to its metabolites such as 3-0-methyldopa. This situation becomes more marked as the disease continues.

(ii) As previously mentioned a patient must lose about 80% of his or her substantia nigra pars compacta neurons before symptoms occur. It has been suggested that a new-onset patient may have some remaining hyperactive neurons in this region that are still able to take up dopamine derived from exogenously administered L-dopa. These neurons are then able to release dopamine as the brain L-dopa levels are decreasing. In this way, the remaining substantia nigra neurons are able to buffer the effects of changing plasma L-dopa levels such that the clinical effects outlasts the plasma L-dopa levels. With further loss of substantia nigra neurons, the duration of beneficial clinical response lessens with decreased ability of the brain to buffer dopamine levels. The brain levels of dopamine become more dependent on brain L-dopa levels, which in turn are dependent on plasma L-dopa levels. Since

the plasma half-life of L-dopa is between 1 and 2 hours less frequent oral dosing of L-dopa will result in fluctuating plasma levels and therefore, fluctuating clinical control of symptoms (Hardie, 1989; Montgomery, 1992).

(iii) Changes also might occur in the post synaptic dopamine receptor, associated with continued loss of presynaptic elements, continued exposure to L-dopa or both. Patients who show motor fluctuations have a lower plasma L-dopa threshold than those patients whose duration of response is longer, suggesting changes in the physiologic response of the receptors. It is speculated that the receptors become hypersensitive.

(iv) Ideally, dopamine replacement therapy mimics the precise influence of substantia nigra dopaminergic neurons on neurons of the caudate nucleus, and putamen - and these neurons are not only spatially but temporally specific in their action. The individual dopamine neurons dynamically modulate their activity such that dopamine release is controlled over milliseconds and not hours as in the case of orally administered L-dopa. It is unlikely that pharmacalogic applications of L-dopa over a period of hours will fully restore the localized and dynamic modulation of neuonal activity that is necessary for normal generation of movement (Montgomery, 1992).

A possible solution to the 'on-off' and 'wearing-off' phenomena is to reduce the inter-dose interval. The ultimate in this respect is continuous release of L-dopa. There have been studies in the development of oral controlled release forms of sinemet and madopar. Early studies revealed that controlled release Sinemet required around 3 times as much daily L-dopa intake and although clinical responses in the morning was improved in some patients, fluctuations or other functional disabilities were not aided by this delayed release preparation. Further studies revealed more 'on' time and fewer 'off' periods (Le Witt, 1987). A study by Wolters *et al* (1993) comparing continuous release sinemet to oral doses revealed an increased clinical efficacy especially for bradykinesia and rigidity when using the controlled release form. The sustained release preparation of madopar makes use of a gelatin capsule which is transformed in the stomach to a mucous body delivering both constituents by diffusion through a hydrated layer. Trials comparing continuous release with conventional madopar have shown that six of ten patients had a reduction in end-of-dose and other types of motor fluctuations - but increased daily amounts of L-dopa were required. A discussion by Koller (1992) states that the advantages of controlled release medication includes a delay of

L-dopa complications, a reduction in the total number of doses taken per day, a reduction in the amount of off time, reduced severity of off periods, improved nocturnal mobility and sleep pattern, reduction in dyskinesias, reduction in off period dystonia, and increased effectiveness of response. The disadvantages include lack of kick in effect, increase in dyskinesias, increase in sleep disturbances, decrease in effectiveness of response. Intravenous infusions of L-dopa have been studied and have been found to be successful in the short tern in all cases - however its impractical mode of delivery is its one major limitation (Mouradin *et al,* 1990; Sage and Mark, 1992). Duodenal and jejunal L-dopa delivery takes advantage of the presence of the neutral amino acid carier system present in the small intestine, eliminates the variability introduced by erratic gastric emptying, and achieves plasma L-dopa concentrations and clinical responded similarly steady to those seen with intravenous routes. Patient experience the advantages - for up to 4 years (to date). The large volumes of L-dopa required due to its water insolubility is one of the main disadvantages (Sage and Mark, 1992).

<u>2.7.2 Dopamine agonists.</u>

Synthetic dopamine agonists are drugs that directly stimulate dopamine receptors and have been developed in an attempt to address some of the motor fluctuations associated with long term L-dopa use. They act by directly stimulating the post synaptic dopamine receptors of the striatum and thus they are independent from enzymatic conversion of dopamine. They also lower the turnover rate of dopamine and therefore could theoretically generate less hydrogen peroxide and free radicals and help to protect dopaminergic cells (Clough *et al*, 1984; Goezt and Diedrich, 1992; Riederer *et al*, 1993). The most widely used dopamine agonists include bromocriptine, pergolide, apomorphine and lisuride

<u>*Bromocriptine:*</u>

Bromocriptine mesylate is an ergot alkaloid with potent D2 receptor antagonistic effect. It is absorbed rapidly from the gastrointestinal system and has a plasma half life of 7 hours (approximately four times that of L-dopa).

In de novo patients bromocriptine monotherapy results in similar improvements in symptoms to L-dopa monotherapy (Van der Drift, 1986) or L-dopa plus carbidopa (Gawel *et al*, 1986). However response to bromocriptine is not as long lasting and usually the addition of L-dopa is required (Olsson *et al*, 1990, Goetz and Diederich,

1992). However Rinne (1986) found that patients benefited less than with L-dopa although there were fewer fluctuations in disability. Stern and Lees (1986) found that de novo patients sustained benefit from bromocriptine for at least one year; two of their patients continued to take the drug successfully for 10 years.

Numerous studies suggest that combinations of bromocriptine and L-dopa results in efficacy similar to or superior to L-dopa alone. Most studies including that by Olsson (1990) state that without a decrease in clinical efficacy, there is a lower need for L-dopa in patients also treated with bromocriptine - and these benefits have been found to continue over five years (Van der Drift, 1986; Riederer *et al*, 1990; Goetz and Diederich, 1992). Given last thing at night bromocriptine has been found to improve early morning akinesia (Lindvall and Olsson, 1986). However Jansen and Meerwaldt (1986) found that the effect of bromocriptine in patients with advanced Parkinson's disease deteriorated to pre-drug levels after 6 years.

Pergolide:

Pergolide mesylate is considered approximately 10 times more potent than bromocriptine; the usual total daily dose is 1 to 4mg. It is a semisynthetic ergoline derivative. It has a longer half life than bromocriptine, reaching peak concentration in the plasma within 1 to 3 hours, and a single dose is cleared completely from the system within 7 days.

There have not been many studies involving this drug. However it would seem that in combination with L-dopa, pergolide provides more 'on' time in Parkinson's disease patients experiencing motor fluctuations (Jankovic and Orman, 1986; Olanow and Alberts, 1986; Tanner *et al*, 1986). The effectivety of its action reduces and stabilizes at around 6 months of use. However its advantageous effects have been shown to continue over 2-4 years (Tanner *et al*, 1986; Goetz and Diederich, 1992).

Apomorphine:

Apomorphine has both D1 and D2 receptor agonist functions and is highly lipophilic. Its action starts after 5-15 mins, reaches its maximum after 30 mins, and lasts for 90-120 mins. Studies have shown that when injected during an 'off' period, apomorphines fast action can effectively convert this state to an 'on' condition (Clough *et al*, 1984; Quinn, 1990; Frankel *et al*, 1990; Goezt and

Diederich, 1992). Frankel also showed that intermittent doses given throughout the day using a penject system reduced the number of 'off' hours in the day from 6 - 9 hours to 2 - 9 hours over 13 months. Continuous infusion of apomorphine (via minipump) has also been shown to reduce the number of 'off' hours during the day and to reduce the requirement of L-dopa (Frankel, 1990; Stocchi *et al*, 1993; Poewe *et al*, 1993). However, due to the side effects of nausia and hypotension, the peripheral antagonist domperidone is also required throughout the day. Also all patients on continuous infusion treatment develop nodules at the needle insertion site that are often painful.

Lisuride:

Lisuride is a hydrophilic semisynthetic ergot alkaloid with selective D2 receptor and serotoninergic functions. When given orally, its plasma half-life is 1.5 to 2 hours, and consequently its action lasts only for 3 hours. On a milligram basis, it is 10 to 20 times more potent than bromocriptine.

Rinne (1986, 1989) showed that when used as monotherapy in de novo patients in a 4 year study, it caused fewer end of dose fluctuation and peak-dose dyskinesias than L-dopa but also less overall improvement. However in combination with L-dopa improvement in clinical symptoms was the same as L-dopa alone with the addition of reduced end of dose fluctuations. Similar results were found by Rabey *et al* (1990), this group also note that lisuride was preferable to L-dopa in the management of 'off' episodes and dyskinesias. They also state that at low doses lisuride was still a potent dopamine agonsit after long-term follow up, suggesting the possible potentiation of its effects after chronic administration (unlike bromocriptine and pergolide).

Due to its solubility, lisuride is well suited to intravenous or subcutaneous applications using a mini-infusion pump - although, like apomorphine, nodules develop at the point of entry. Results have indicated reduced 'off periods of up to 100% and decreased L-dopa requirements (Luquin *et al*, 1986; Rabey *et al*, 1986; Goetz and Diederich, 1992).

PHNO:

(+)-4-propyl-9-hydroxynaphthoxazine is a potent D2 agonist without any D1 activity and is structurally unrelated to the ergoline or apomorphine classes. It is a

new dopamine agonist which has mild antiparkinsonian effects as oral monotherapy and is still in its experimental stages (Goetz and Diederich, 1992). A study by Coleman *et al* (1990) assessed the effect of nasogastric and intravenous infusions of PHNO on 8 patients with Parkinson's disease taking conventional dopaminergic medication and experiencing 'on-off' fluctuations. All patients switched 'on' in response to PHNO - the time spent 'on' increased with higher doses. The dose of nasogastric PHNO required to achieve therapeutic blood levels were about sixty-fold higher that those required for intravenous routes.

All dopamine agonists have side effects, some of which include confusion, nausia, visual distortions, drowsiness, visual hallucinations, psychotic episodes, agitation, depression and insomnia. Pergolide can potentially cause hepatotoxicity and pleural thickening.

2.7.3. MAO Inhibitors.

Monoamine oxidase is the major enzyme for degrading monoamines. It is located in the outer mitochondrial membrane and exists in A and B forms. Dopamine is a substrate for both subtypes but MAO-B is thought to be the more important as it is the dominant form in the human striatum (Olanow 1993). Much of the current interest in MAO-B inhibitors in Parkinson's disease centres on the possibility that they may have neuroprotective effects and slow disease progression. This is based on the hypothesis that they can block the oxidation of an MPTP-like protoxin or diminish free radical formation generated from the oxidative metabolism of dopamine. As previously mentioned the neuronal damage underlying MPTP Parkinsonism is dependent on the oxidation of MPTP to MPP^+ in a reaction catalysed by MAO-B. Therefore if an MPTP-like compound contributes to the etiology of Parkinson's disease, MAO-B inhibitors might have neuroprotective effects. MAO-B inhibitors may also diminish oxidant stress consequent to the MAO-B inhibition of dopamine as hydrogen peroxide is formed as a result of dopamine oxidation.

MAO-B inhibitors used early in the course of therapy may also protect against the development of the adverse effects associated with L-dopa therapy. The early administration of agents that provide sustained stimulation of brain dopamine receptors might more closely mirror the tonic stimulation of dopamine receptors and prevent receptor damage.

The most widely used MAO-B inhibitor is selegiline (or deprenyl). This was developed by Knoll et al in 1965 and was based on the structure of methamphetamine (Tetrud and Langston 1992). One of the major advantages of selegiline is that it does not induce the "cheese effect" which is a side effect of other MAO inhibitors resulting in episodes of life-theatening hypertensive crisis potentiated by the injestion of foods high in tyramine such as cheese, red wine, chocolate and yeast products (Tetrud and Langston 1992).

The selectivity of selegiline for MAO-B has been shown in post mortem studies in Parkinsonian patients who took the drug 6 days before death. Riederer and coworkers (1993) showed MAO-B to be almost totally inhibited in the brains compared to controls, whilst MAO-A was much less so. Dopamine levels were substantially increased (Sandler and Glover, 1989). Selegiline is claimed to increase the firing rate of nigrostriatal dopamine neurons and to increase the rate of dopamine utilization in the striatum. In addition, selegiline has been shown to protect dopaminergic neurons from the toxic effects of the highly selective neurotoxins 6-hydroxydopamine and MPTP in experimental animals (Elizan *et al*, 1990; Sandler and Glover, 1989; Heinonen and Rinne, 1989; Tetrud and Langston, 1992). A report by Rinne *et al* suggested that neuropathologic examination of post mortem brain from Parkinson's disease patients taking selegiline compared to an age matched patient group not taking the drug shows a significantly higher neuronal cell count and lower number of Lewy bodies in the medial region of the substantia nigra in the selegiline treated group (Tetrud and Langston, 1992).

Selegiline, used in selective inhibitory dosage (5-20 mg/day) appears to be very safe. It has now been administered to thousands of Parkinsonian patients with marked untoward effects or drug interaction since 1974. As an adjunct to L-dopa, it can increase both magnitude and the duration of levodopa effects (Le Witt, 1992). It helps the reduce end-of-dose fluctuations, early morning dystonia, dose-related off period dystonia, dose-related freezing episodes and random oscillations (Heinonen and Rinne, 1987).

A number of studies have shown that the addition of selegiline to L-dopa therapy improves the wearing off syndrome - although there is no improvement in peak clinical response when optimal levels of L-dopa are used (Teychenne and Parker, 1989; Chouza *et al*, 1989; Fornadi and Ulm, 1990; Csanda and Tarczy, 1993). It has also been stated that the response to 'wearing off' fluctuations is better than that to 'on-off' fluctuations, although patients receiving selegiline tend to have longer

'on' periods (Chouza *et al*, 1989). Przuntek and Kuhn (1989, 1990) also showed an improvement in Parkinsonian symptoms in patients having the disease for a period of one years duration, when taking L-dopa and selegiline compared to L-dopa alone. However a study by Elizan *et al* in 1990, failed to show any benefit of selegiline in 200 Parkinson's disease patients experiencing L-dopa side-effects.

The use of selegiline as monotherapy in de novo patients has been studied, some authors have found that Parkinsonian symptoms improve when taking the drug compared to a placebo, and delays the requirement for L-dopa initiation (Myllyla *et al*, 1989; Siverstsen *et al*, 1989), although Yahr *et al* (1989) could find no evidence of this.It has also been suggested that selegiline slows the progression of Parkinson's disease (Shoulson, 1989; Fornadi and Ulm,1990; Csanda and Tarczy, 1993), but this is also disputed by Elizan *et al* (1990) and Yahr *et al* (1989).

Side effects of selegiline include dyskinesias, nausia, hallucinations, insomnia, dryness of the mouth, confusion, anxiety and hypotension. Most side effects reflect an overdosage of L-dopa and can usually be managed by reducing the daily dose of L-dopa (Heinonen and Rinne, 1989; Le Witt, 1992; Chouza *et al*, 1989).

2.7.4 Anticholinergics.

Anticholinergic drugs remained the only effective medical therapy for Parkinson's disease for almost 100 years. Ordentein (1967) first discovered their antiparkinsonian effects when tinctures of deadly nightshade were used to control excessive drooling and salivation. Today the most commonly used drugs are orphenadrine hydrochloride (disipal) and benzhexol (artane) - benztropine (cogentin) and procyclidine (kemadrin) are also used. Benztropine is similar to benzhexol but is excreted more slowly. Both procyclidine and benztropine may be given parenterally and are effective emergency treatments for acute drug induced dystonic reactions, which may be severe. Most have a duration of effect of 1 - 6 hours with a peak in clinical activity at approximately 2 - 4 hours (Lang and Blair, 1989).

Anticholinergics are less effective than L-dopa in the treatment of idiopathic Parkinson's disease although they are a useful supplement to its action. Patients with mild symptoms (particularly tremor or rigidity) are usually treated with anticholinergics although some benefit can be obtained in all stages of the disease. Many neurologists utilize these drugs initially in hopes of delaying the need for L-

dopa due to the long-term drug induced motor fluctuations of the latter. These drugs also reduce the symptoms of drug-induced Parkinsonism as seen, for example, with antipsychotic drugs.

The precise mechanism of action of anticholinergic drugs in not entirely clear but is thought to be based on the inhibitory effect nigral dopamine neurons have on striatal cholinergic interneurons. The reduction in dopamine activity as a result of diseased nigral cells is thought to lead to increased acetylcholine activity. This disequilibrium between striatal dopamine and acetylcholine activities can be normalized by the action of anticholinergics.

Most anticholinergics produce a slight to moderate improvement is disability of 10 - 25% when used alone. Unfortunately akinesia responds poorly, if at all. They slow gastric motility and thus may delay L-dopa reaching its absorption sites in the small bowel. Over 60% of patients taking a combination of L-dopa and long-term anticholinergics are unable to tolerate anticholinergic withdrawal and abrupt withdrawal may result in marked exacerbation of Parkinsonian symptoms (possibly as a result of receptor hypersensitivity).

Beneficial peripheral side effects of anticholinergics include improved sialorrhea and urinary function. More unfortunate peripheral side effects include impotence, gingivitis, impairment of accommodation, risk of closed angle glaucoma, gastro intestinal disturbances, and less commonly tachycardia and hypersensitivity. Central side effects are common and include dyskinesias and dizziness, the most serious are changes in mental activity and psychiatric disturbances. Nishyama *et al* (1993) describe 5 cases of Parkinson's disease on long term anticholinergic medication who developed dementia which gradually recovered following anticholinergic drug withdrawal. These represent major limiting factors to their usage especially in the elderly and in those with moderate to severe pre-existing cognitive impairment.

2.7.5 Surgical Techniques.

Thalamotomy surgery:

Thalamotomy surgery has been one of the most commonly used surgical techniques in the treatment of Parkinson's disease. Cooper (1969) was one of the first to use this as a technique in the treatment of Parkinsonian tremor and dystonia. It has been

found that discrete, well localized stereotactic lesions in the nucleus ventrolateralis of the thalamus or in the corresponding area subthalmica can abolish pathological tremor. It tends to be most successful for dystonia of the limbs compared to involvement of axial musculature. Initially chemicals were used to create lesions, but cryotherapy provides a more accurate and safer method. Surgeons are using sophisticated computerized guided placement of the operating probe, and refined neurophysiological techniques to locate the target accurately (Fahn and Marsden, 1987). Struppler *et al* (1993) have also noticed the following improvements in symptoms:

1. Rigidity is reduced and there is more spontaneous muscle activity.
2. Normal maximal voluntary force in proximal as well as distal muscles, rapid movements and phasic stretch reflexes remain unchanged and rapid movements are usually more synchronized.
3. There is no deficiency in coordination such as ataxia, dysdiadochokinesia, and dysmetria, and no lack of initiation of movement.

An alternative form of surgery was completed by Pollack *et al* (1993) who instead of creating thalamic lesions, used thalamic electrical stimulation to control movement. During thalamotomy surgery, acute thalamic electrical stimulation is often used in order to control the location of the electrode around the target. When the target is reached tremor can be considerably suppressed. A 2.3mm diameter electrode was inserted under local anaesthesia through a burr hole. Then a programable stimulator was implanted under general anaesthesia in the subclavicar regions. The frequency of the stimulator could be altered by the patient to reach maximal beneficial effect (usually around 130Hz). Post operatively patients experienced initial deterioration. Patients then experienced a sustained relief from tremor (over 5years) as well as reduced rigidity, pain and induced dyskinesias but akinesia was not. L-dopa therapy was continued in all but two patients but doses were reduced by more than 30% in one third of patients.

Transplant Surgery:

As the symptoms of Parkinson's disease are a result of a reduction in dopaminergic neurons, it is apparent that replacement of dopamine producing cells should provide lasting relief, and should prevent the motor fluctuations caused as a result of varying dopamine concentration. Attempts have been made to use dopamine producing cells of the adrenal medulla and from fetal mesencephalic tissue implants.

Adrenal Medulla implants:

The adrenal medulla is embryologically related to neuronal tissue and its chromaffin cells synthesise and secrete epinephrine and its precursors norepinephrine and dopamine. Autografts reduce the risks of graft rejection and avoid ethical problems associated with the use of fetal tissue. Addition of nerve growth factor increased cell survival and enhances the fibre outgrowth in the host striatum.

Transplantation surgery of adrenal medulla tissue into striatum and ventricle of 6-hydroxydopamine lesioned rats resulted in improvement in apomorphine induced rotational abnormalities, although no improvement in spontaneous behaviour has been noted (Lindvall and Bjorklund , 1989). Post mortem studies did not reveal much cell survival (Shults, 1992).

Studies have also been carried out on MPTP treated monkeys. Adrenal medulla tissue has been implanted by stereotactic (involving the injection of a suspension of tissue into the striatum through a long cannula entering the brain though a small bore hole in the skull) and open surgical techniques. Fiandaca and colleagues (1988) reported minimal survival of chromaffin cells, although survival was noted by Kordower et al (1991) (Shults, 1992). Plunkett *et al* (1990) did not find any improvement in apomorphine induced rotation, but reports by Watts *et al* and Kopin *et al* (1993) have noted such improvements but only up to three months post-operatively (Lindvall and Bjorklund , 1989; Shults, 1992; Kopin *et al*, 1993).

Transplantation of tissue from Parkinson's disease patients' own adrenal medulla began in 1982 by a Swedish group - using stereotactic surgery into the caudate nucleus. However none of these patients experienced a sustained significant benefit from the procedure (Sladek and Shoulson, 1988; Lindvall and Bjorklund, 1989; Burns, 1990; Shults, 1992). Two studies were carried out in 1987 - one by Madrazo and coworkers (1987) and the other by Lindvall *et al.* (1989, 1990) The first used a transcortical open approach in which several large fragments of adrenal tissue were placed in a cavity in the head of the right caudate nucleus. They noted a significant improvement in their Parkinson's disease patients over one year, with reduction in tremor, rigidity and akinesia both during on and off periods, this was accompanied by reduced daily intake of L-dopa medication. However there were some side effects and post-operative complications. Although the procedure was replicated by others in the United States - the same dramatic improvement in condition has not been reported. The study by Lindvall *et al* using a stereotactic

technique also report reduced rigidity and increased percent of 'on' time in their two patients.

The method of open surgery was also carried out by Lieberman *et al (1989)* and Koller *et al* (1990) and they both note post operative complications including cerebral infarction, cerebral haemorrhage and mortality (Lindvall *et al* 1989, 1990; Koller, 1990). About 50% of patients experience moderately positive results from surgery. In those patients who died, post-mortem examination did not reveal chromaffin cell survival.

Although some benefit has been described using adrenal medulla transplantation surgery, the post-operative complications do not justify its use as a routine form of anti-Parkinsonian treatment.

Fetal Mesencephalic Tissue Transplants:

Transplantation of fetal dopaminergic neurons is a rat model of Parkinson's disease in 1979 raised hopes of this type of surgery being used in man. Studies on rodents have revealed that the procedure results in an attenuation in apomorphine induced rotation over extended periods of time. Post-mortem examinations have also revealed survival of the dopaminergic neurons and synapse formation between host striatum axons and graft neurons (Lindvall and Bjorklund , 1989; Dymecki *et al*, 1990; Shults, 1992). The transplanted cells have also been shown to produce dopamine. From these studies a number of variables crucial for graft cell survival have been identified. These include the age of the donor tissue, the age of the recipient, rapid vascularization of the transplanted tissue, and immunological protection (Shults 1992). A method of transplantation of previously collected and subsequently frozen rat fetal tissue has been developed by Sauer *et al* (1992).

Non human primates have also been used to demonstrate the beneficial effect of fetal tissue implantation on MPTP induced Parkinsonism. Both stereotactic and open surgical techniques have been used. Behavioural improvements have been noted in most cases (Bjorklund and Kindvall, 1989; Shults, 1992; Kopin, 1993; Freed *et al*, 1993). Post-mortem studies have confirmed survival of the fetal tissue and fibre growth (Kopin, 1993). A 15 month follow up study by Widner *et al* (1993) on MPTP treated monkeys receiving 7 to 9 gestational week old fetus implants (using a stereotactic technique) provided evidence for continued improvements in functional status with a reduction in rigidity and akinesia, reduced

bradykinesia, resolution of freezing episodes and improved walking. A doubling of fluorodopa uptake was also noted on a PET scan.

Following the relative success of fetal implants in monkeys, the technique has been developed for use in human Parkinson's disease patients. Donor tissue is obtained from natural abortions following suction surgery. Suspensions of cells from the ventral mesencephalon are used from 7 to 9 gestational week old fetuses. Two studies have been carried out by Lindvall and colleagues (1989, 1990), in the second a superior method of stereotactic implanatation into the putamen using a smaller diameter cannula resulting in virtually all of the tissue being used. Patients experienced reduced 'off' time. Reduced rigidity and reduced time to perform certain tasks. These improvements persisted for at least one year. PET scan also revealed increased uptake of fluorodopa in the region of the graft (Lindvall and Bjorklund, 1989; Lindvall et al, 1989, 1990; Shults, 1992). In the United Kingdom Hitchcock and co-workers have reported on transplant surgery in 12 Parkinsonian patients and state that although L-dopa medication was continued post-operatively, the daily dose was reduced. Patients were said to show a moderate but definite improvement (Hitchcock *et al*, 1988; Shults, 1992).

Freed *et al* (1993) used a technique that they initially developed on monkeys on four Parkinson's disease patients. They also used a stereotactic technique of implantation of tissue that was matched for ABO blood group in order to reduce immunological complications. They also developed a tissue extrusion method by which a single mesencephalon piece can be made into a strand of up to 10 cm long - this helped to conserve tissue and ensure maximum amounts of tissue is delivered to the striatum. Three out of the four patients showed improvements in symptoms six weeks after surgery - they were able to reduce medication (Shults, 1992; Freed *et al*, 1993). In all studies there were very few post-operative complications.

This technique appears quite successful although a number of points have to be taken into account. A number of ethical questions have been asked about the use of human fetal tissue is transplant surgery. Only 10% of the implanted cells are thought to survive - and although this should be sufficient - an improved survival rate would be beneficial. The long term survival of graft tissue is unknown as the disease process that initially caused the Parkinson's disease may ultimately attack the graft tissue.

2.8. Links between Alzheimer's disease and Parkinson's disease.

As mentioned earlier in this chapter, dementia occurs in the later stages of many Parkinsonian patients. Estimates of prevalence of dementia among PD patients range from 0-93% (reviews by Growden and Corkin, 1986; Biggins *et al*, 1992; Midham *et al*, 1993). The large variation largely results from the different methods of defining, assessing and recognising dementia between the different authors. Midham and colleagues and Biggins and colleagues conducted a longitudinal study over 54 months assessing cognition, mood and disability in a cohort of patients with PD and a matched control group. They found a cumulative incidence of dementia of 19% over 54 months. It was demonstrated that those who developed dementia were older at onset of PD, and had a lower initial performance score on the dementia scales used (Wechsler Adult Intelligence scale and Mini Mental State examination). A study by Portin and Rinde (1980) over 8-10 years, found that 70% of their study group showed a significant deterioration of cognitive function over time. The severity grade of this deterioration varied from mild to moderate to severe, and approximately half of the deteriorated patients were evaluated as clinically demented. This group also demonstrated that the demented patients tended to be older, showed more hypokinesia, more often had clinical sign of arteriosclerosis, developed PD later, and responded less well to levodopa than PD patients with no dementia.

Due to the high incidence of dementia in PD patients and that patients with Alzheimer's disease of an advanced stage exhibit extrapyramidal and Parkinsonian signs, it has been suggested that these two diseases co-exist (Mayeux *et al*, 1985; Chui *et al*, 1985; Tyrell and Rassor, 1989; Morris *et al*, 1989; Hofman *et al*, 1989). Post mortem studies have shown that senile plaques and neurofibrillary tangles exist in the brains of Parkinsonian patients, and that Lewy bodies exist in the brains of patients with Alzheimer's disease (Boller, 1980; Forno, 1991; Arai *et al*, 1992; Duyckaerts *et al*, 1993). In addition, neuronal loss in the nucleus basilis of Meynert has been demonstrated in both diseases (reviewed by Whitehouse, 1986). Korozyn *et al*, (1986) found that there was a slowing of the alpha frequency of the EEG in PD patients similar to that found in AD, and also that the CT scan of PD patients with dementia demonstrated sulcal enlargement and ventricular dilation.

Evidence of a genetic link between the two diseases in certain circumstances has also been demonstrated. Gimenez-Roldan *et al* (1986) present a study of a family in which four members died at advanced age from a dementing illness identical to AD,

and in two of the patients, PD was also diagnosed. The links between AD and PD in the population of Guam has already been discussed. The difference between the AD found in the Guamanian population and that in the general population is the lack of extracellular deposition of Beta amyloid in the former (Perl, 1991). Vieregge *et al*, (1991) have shown that extrapyramidal sign of PD may be a feature of advanced Down's syndrome and these signs were only encountered in demented Down's patients.

However, it must not be assumed that all cases of dementia existing with PD is of the Alzheimer type. Studies have shown that there are cases in which PD patients exhibiting signs of cognitive impairment have not demonstrated a deterioration, and some have shown an improvement,in their mental state scores over 12 months. While it is expected that AD patients demonstrate a progressive deterioration every 6 months (Growden and Corkin, 1986). In addition differences have been shown in language and memory function. Patients with AD tend to exhibit more pervasive deficits in naming spontaneous verbalization, and word generation capacity. They are also more impaired on delayed recall tasks and recognition (Levin, *et al*, 1992). It has been suggested that some forms of mild dementia in PD may be subcortical in origin, and that those exhibiting subcotical and cortical involvement may reflect an Alzheimer type pathology.

CHAPTER 3.

3. A DRUG INDUCED MODEL FOR PARKINSON'S DISEASE AND ALZHEIMER'S DISEASE.

3.1 Parkinsonism.

The neurotoxin 1-methyl-4-Phenyl-1,2,3,6-tetrahydropyridine (MPTP) was first synthesized in 1947 by Ziering *et al* as a possible therapeutic agent for Parkinsonism. However, when given to non-human primates, they became rigid, and unable to move and eventually died. 6 humans were given the compound and 2 subsequently died, after which it was abandoned. In 1976 a young student was synthesizing and abusing MPTP (1-methyl-4-propionoxypiperidine) as a heroin substitute. Following the production of a 'sloppy batch' he developed Parkinsonian symptoms and died 2 years later. Post-mortem studies on his brain revealed cell loss limited to the substantia nigra. This case was followed by numerous others in the USA.

All of the patients suffering with this induced Parkinsonian syndrome exhibit all of the clinical features of the disease which gives support to the suggestion that all of the motor deficits are due to substantia nigra damage.

Hadjiconstantinou *et al* (1988) however states that MPTP effects other dopaminergic systems as well as the locus ceoruleus and substantia nigra. Dementia does not seem to occur, which is compatible with the suggestion that dementia especially memory loss may be secondary to the involvement of the cholinergic system. Patients respond well to L-dopa therapy but exhibit on-off and wearing off syndromes early on in the course of treatment (Langston, 1987).

MPTP has since been used in animals (particularly primates) as a model for Parkinson's disease (Chiueh *et al*, 1986; Kopin, 1986; Langston, 1987; Albanese *et al*, 1990). The only major difference between MPTP induced Parkinsonism and the idiopathic form of the disease is the fact that Lewy bodies do not seem to be present in the brain of the MPTP Parkinsonian brain. However Tetrud and Langston (1989) showed eosinophilic intraneuronal inclusion bodies similar to Lewy bodies in the brain of an adult squirrel monkey injected with MPTP. They suggested that these inclusions are an immature form of Lewy body. They also established that older monkeys are more susceptible to the disease.

It is thought that MPP+, a metabolite of MPTP , is the toxic agent. It is generally thought that MPP+ , which is structurally similar to dopamine, is taken up into the dopaminergic nerve terminal by the dopamine uptake system and causes cell damage by interrupting mitochondrial NADH dehydrogenase metabolism (Tetrud and Langston, 1989).

Certain antipsychotic agents such as Haloperidol (which is a post-synaptic dopamine antagonist), are known to have side-effects that mimic post-encephalic or idiopathic Parkinsonism (Baldessarini and Tarsy, 1980, Jankovic, 1987). Symptoms include bradykinesia, shuffling gait, facial inexpressiveness, muscular rigidity, and variable degrees of tremor. The British National Formulary include Parkinsonism as a cautionary side-effect for haloperidol and other antipsychotic drugs.

3.2 Alzheimer's disease.

Hyoscine hydrobromide is a muscarinic cholinergic antagonist, the effects of which are powerful centrally and less powerful peripherally than those of the related alkaloid atropine (Morrison and Reilly, 1987). As described in chapter 1, Acetylcholine is a neurotransmitter that is found to be significantly reduced in Alzheimer's disease. Various studies have been undertaken to establish whether anticholinergic drugs have a detrimental effect on memory and other cognitive function.

In 1969, Berger and Stein demonstrated learning deficits following hyoscine administration. Crow and Grove-White (1973) demonstrated that word learning and number-colour association tests were effected by the administration of 0.4mg of hyoscine to 12 young volunteers, the drug did not effect scanning tests. They also found that 0.6mg of atropine had no effect on any of the tests. Drachman and Leavitt (1974) showed that young people receiving 1.0 mg of hyoscine hydrobromide administered subcutaneously resulted in memory disturbances which were quite similar to changes in elderly people. They found that the 'storage' of new information was particularly compromised during drug administration. Drachman (1977) also demonstrated that physostigmine, an anticholinesterase drug, reversed the effects of hyoscine.

Ridley and colleagues (1984) showed that administration of hyoscine to marmosets, just before or after a new learning task, spared previously stored material but

apparently impaired new learning by blocking the encoding of information into long-term memory.

Hopelman and Corn (1988) used various tests to show the effect of intravenous infusions of 0.4mg and 0.2mg of hyoscine on young healthy normals compared to a saline placebo. The results showed that short term memory and visuospatial tests were effected but long-established sematic knowledge was not. They state that cholinergic depletion could indeed produce an anterograde amnesia consistent with the pattern seen in Alzheimer's disease. However it seems unlikely that cholinergic depletion could account for the full range of deficits seen in Alzheimer's disease.

Sunderland *et al* (1988) completed a similar study using hyoscine hydrobromide (0.1, 0.25 and 0.5mg) intravenous infusions on young normals, Alzheimer patients and age matched normals. Once again the drug effected cognitive function particularly in the older age group (and Alzheimer group) indicating that there is an increased sensitivity to cholinergic blockade with age.

It would seem therefore that Hyoscine hydrobromide may be used as a model for Alzheimer's disease, at least in terms of cholinergic deficit. Antimuscarinics cannot be used to mimic all the deficits known to occur in Alzheimer's disease because the drugs produce an "acute, short-lasting blockade of cholinergic receptors that are primarily postsynaptic while Alzheimer's disease is a chronic, slowly progressing, irreversible disorder that involves, in addition to the changes in presynaptic cholinergic function, substantial pathology of many other neurotransmitter systems" (Fibiger 1991).

CHAPTER 4.

4. THE VISUAL PATHWAY.

4.1 Anatomy of the visual pathway.

Introduction.

The visual pathway is the route by which complicated visual information is transmitted in coded form to the visual areas of the brain where it is analysed. Figure 4.1 shows a schematic representation of the visual pathway from retina to visual cortex. Light enters the eyes where it is transformed into electrical information in the retina and sent down the optic nerves. The two optic nerves meet at the chiasma where partial decussation takes place. From here, the visual pathway can be divided into two sections, a geniculate pathway and a non-geniculate pathway. The former involves the transmission of fibres to the primary visual cortex via the lateral geniculate nucleus (LGN) and optic radiations. The latter involves the transmission of fibres to the association areas of the visual cortex via the superior colliculus (SC).

4.1.1 Retina.

The retina of vertibrates is a thin sheet of neural tissue which lines the back of the eye interposed between the choroid and vitreous (Ruskell, 1988; Rowe, 1991). It is a derivative of ectoderm arising from the diancephalon during early embryosis and is considered to be an extension of the central nervous system (Brecha, 1983). Its function is to transduce light into biologically meaningful signals, process these signals and subsequently transmit this visual information as electrical impulses to the brain.

Morphologically, the retina is organized into 10 major layers (as first reported by Cajal, 1893). The layers and membranes are numbered conventionally form the outermost layer (adjacent to the choroio capillaris (CC) and basal membrane (BM)) as follows: (1) retinal pigment epithelium (RPE), (2) receptor cell layer (separated into outer segment (OS) and inner segment (IS)), (3) outer limiting membrane (OLM), (4) outer nuclear layer (ONL), (5) outer plexiform layer (OPL), (6) inner nuclear layer (INL), (7) inner plexiform layer (IPL), (8) ganglion cell layer (GCL),

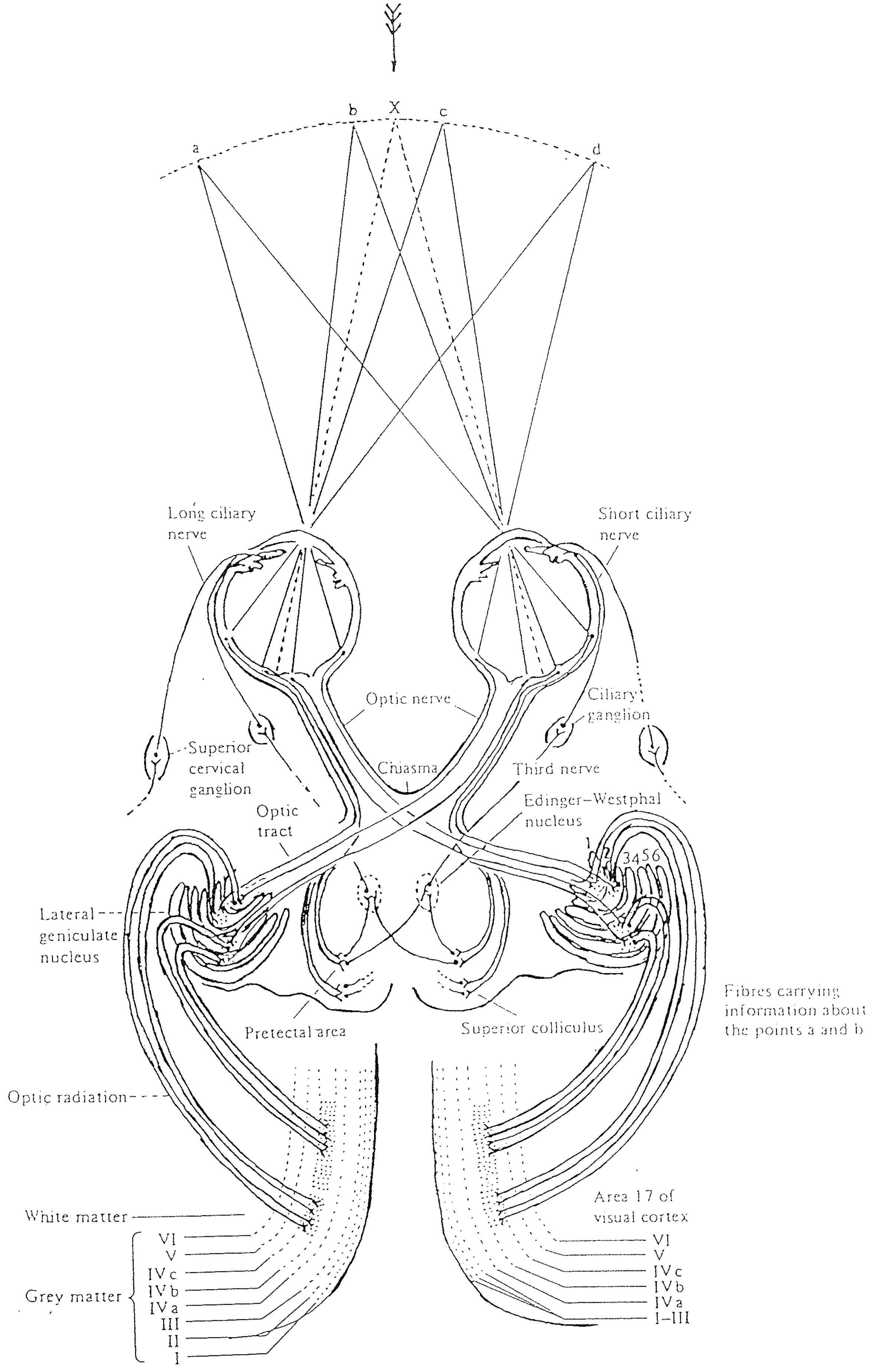


Figure 4.1. Diagram of the visual pathway adapted from Willmer 1982.

(9) optic fibre layer (OFL), (10) inner limiting membrane (ILM). These layers are shown diagramatically in figure 4.2.

The pigment epithelium is a single layer of cells that is firmly attached to the choroid, but its attachment to the neural retinal is weak and vulnerable. Anteriorly, the retina is continuous with the ciliary epithelium at the ora serrata and posterior with the optic nerve, the attachments at these locations are very strong. Six cell types are to be found within the layers of the neural retina, these include photoreceptors, horizontal cells, bipolar cells, amacrine cells, interplexiform cells and ganglion cells. Besides the nerve cells there are numerous neurological cells for example those giving rise to the radial fibres of Muller, which act as supporting and insulating structures.

The RPE is a pigmented layer that provides a selective barrier which actively transports nutrients to the neural retina from the chorio capillaris and removes debris and other waste products. Its association with the receptor cells is via finger-like villi which surround the outer segments. It also absorbs any stray light that has failed to bleach the receptor, thus preventing back scattering and degradation of the retinal image.

The photoreceptors are the light sensitive elements of the retina and consist of rods and cones. There is an estimated 110 to 125 million rods and nearly 6 to 7 million cones in the human retina - thus rods outnumber the cones by about 20:1 overall, but they have quite different topographical distribution (Ruskell, 1988; Rowe,1991). The density of cones reaches a peak in the fovea which has an average diameter of 350 μm and is the location of highest visual acuity. Rods are absent at the fovea and reach peak density within a radius of 4 - 5 mm (or 20° of visual angle). The density of both cell types decrease with eccentricity (Davson, 1990; Rowe, 1991; Kaplan *et al*, 1991). Three types of cones exist in the primate retina, the red-sensitive (or L-cones) with maximum absorption near 566 nm, the green-sensitive (or M-cones) with a maximum absorption mean 535 nm and blue-sensitive (or S-cones) with a maximum absorption near 500 nm.

The structure of rods and cones are similar and are made up of an outer segment containing photopigments within an array of discs, and an inner segment containing many mitochondria, Golgi apparatus and microtubules. The outer and inner segments make up the receptor cell layer of the retina. In rods the outer and inner segments are separated by a distinct cilium, in cones the cilium is much shorter such that in the foveal region particularly it is effectively absent. The discs of the outer segment in cones are made up from infoldings of the plasma membrane, but in rods they are not continuous with the plasma membrane except at the base of the outer

segment where they are formed, and they migrate from the base to the tip of the outer segment.

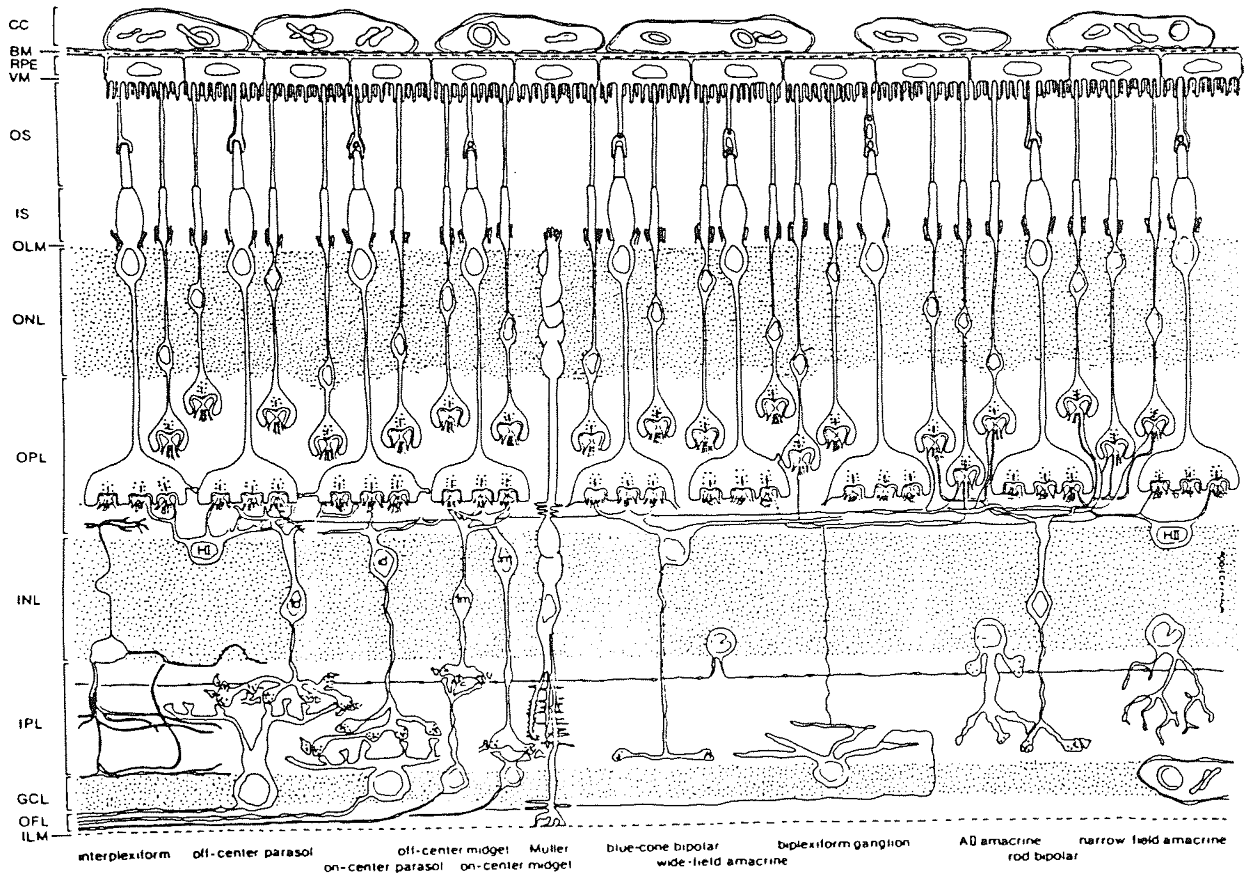


Figure 4.2. Diagramatical representation of the 10 retinal layers Adapted from Rowe 1991.

The photoreceptors traverse the outer limiting membrane which is made up of Muller cell terminals. The cell bodies of the photoreceptors then become the outer nuclear layer (ONL). The outer plexiform layer (OPL) is made up of rod spherules and cone pedicles which are synaptic terminals. In this region the photoreceptors transmit visual information to bipolar cells and horizontal cells. Each cone pedicle presents as a wide, flat synaptic surface on which can be seen a number of prominent invaginations. Each invagination is occupied by a bipolar cell process, flanked by two horizontal cell processes. Additional bipolar processes are to be found on the flat surface of the pedicle. Each rod spherule has a single large invagination containing up to five central bipolar cell processes and two horizontal cell processes situated laterally. Horizontal cells are also connected to one another.

The INL contains the cell bodies of a number of cells including bipolar cells, horizontal cells and amacrine cells. Seven varieties of bipolar cells exist in the primate retina, these are rod bipolars, flat and invaginating midget bipolars, flat and invaginating diffuse bipolars (Polyak, 1957), giant bistratified bipolars and S-cell associated bipolars (Kaplan *et al*, 1991). In the primate fovea many bipolar cells contact only a single cone and are usually termed midget bipolar cells. This one-to-one relationship of cones and bipolars is not maintained away from the fovea in man. Bipolars which contact many cones are generally labelled as diffuse bipolars. Giant bistratified bipolars contact about 20 cones through wide cleft basal functions and stratify at two distinct levels of the IPL. Rod bipolar cells constitute a single class and they have the broadest spread of up to 45 dendrites which invaginate a similar number of rod spherules.

Horizontal cells provide lateral spread of visual signals across the retina. There are thought to be two types in the primate retina, H1 and H2 cells (Boycott, 1988; Kaplan *et al*, 1991). H2 cells have larger dendritic trees than H1 cells (in monkey at 25° from the fovea, H2 dendritic fields are between 1.5 and 2 times greater than H1) and they make sparse contact with cones. H1 cell axons contact a large number of rods.

The IPL constitutes the functional connection between first and second order neurons in the retina and contain bipolar cell, amacrine cell, interplexiform cell and ganglion cell dendrites. The term amacrine cell has come to refer to those cells which receive their synaptic input entirely from bipolar cells of other amacrine cells in the IPL, and whose synaptic output can be directed at bipolar cells, other

amacrine cells or ganglion cells at the level of the IPL, and in some cases to bipolar cell and/or horizontal cell processes of the OPL (Rowe, 1991).

About 25 types of amacrine cells have been described all having different morphology and cytochemistry. Amongst these are the AII cells, GABA containing amacrines, dopamine containing amacrines, neuropeptide containing amacrines and starburst amacrines (Kaplan *et al* , 1991; Rowe, 1991). They transmit visual information to the ganglion cells, in addition to their contribution to lateral processing. It is suggested that they contribute to the generation of the surround response of ganglion cells (Kaplan *et al,* 1991).

Interplexiform cells have processes that emanate from the IPL, traverse the INL and ramify in the OPL and are thought to be a subset of the amacrine cells. They provide a feedback pathway - carrying information from the amacrine cells back to the distal neurons such as bipolars, other amacrines and receptor cells. It bas been suggested that they are involved in the modification of the receptive field structure following dark adaption (Mongel and Dowling, 1987).

The thickness of the IPL varies across the retina from 18 µm to 36µm and is completely absent at the foveal region. A fine capillary network is present within this layer providing nutrients to the inner retinal layers.

The ganglion cell layer contains the cell bodies of the ganglion cells. This layer also varies in thickness across the retina - being at its thickest (70 - 80 µm) around the macular region where it is 8 - 10 cells deep, and becomes thinner in the periphery where it eventually becomes a single cell layer. The average human retina contains 1.07 million ganglion cells (Curcio and Allen 1990). The cell density in the nasal retina is 3 times greater than that found in the temporal retina for eccentricities above 3mm (Curcio and Allen, 1990; Kaplan *et al,* 1991). Curcio and Allen found that in human retina the highest density of ganglion cells averaged 35100 cells/mm^2 and was found about 1mm from the foveal centre. They also found that the ganglion cell density was about 15% higher in nasal retina than at equivalent temporal eccentricities up to 2mm from the fovea. Along the nasal horizontal meridian there is a high concentration of ganglion cells known as the visual streak. They also found that the superior retina from 4mm to the ora serrata has an average 60% more ganglion cells than corresponding eccentricities in inferior retina.Visual resolution measured physiologically is also greater on the nasal retina compared to the temporal retina. The ganglion cell bodies are absent at the fovea but are pushed

aside to the perifoveal region. It is the firing pattern and spatial sampling characteristics of these cells that ultimately limit the resolution of the retinal output and are responsible for the encoding of our visual world due to the convergence of information through receptors and bipolars. There are a number of different classes of ganglion cell which will be discussed in detail later in this chapter.

The axons of the ganglion cells form the nerve fibre layer which pass towards the optic disc to form the optic nerve. This layer is thickest at the disc margin and thinnest at the fovea. The axons are unmyelinated until they reach the optic nerve where myelination begins at the lamina cribrosa. No fibres cross the horizontal meridian of the retina, such that superior fibres enter the disc superiorly and inferior fibres inferiorly, this arrangement continues into the distal region of the optic nerve. This NFL also contains a vascular system.

4.1.2. The Optic Nerve, Chiasm and Tracts.

The optic nerve is made up of approximately 1 million axons of the retinal ganglion cells and conducts them to the optic chiasm. The full length of the nerve is approximately 50mm and is made up of 4 sections: intraocular (1mm), intraorbital (20 -30mm), intracanicular (6mm) and intracranial (3 - 16mm). It is surrounded in a meningeal sheath consisting of a thin pia mater, arachnoid layer and finally dura mater which is continuous with the periosteum of the orbit. The nerve fibres within the optic nerve vary in diameter from 0.2 to 2.0 μm and are surrounded by a thin insulating myelin sheath until they reach the scleral canal where it is lost. In man, the myelin can occasionally continue into the retina for a short distance.

The chiasm is formed by the junction of the two optic nerves. It lies slightly above the diaphragm sella which is a thick endothelial-lined tissue continuous with the dural lining of the cranial cavity forming the roof of the hypophyseal fossa. It has a height of approximately 3 - 5mm and width of around 13 mm. Two internal carotid arteries flank the chiasm on the point of contribution to the arterial circle of Willis. Within this structure, the nerve fibres from the temporal hemiretinas occupy lateral positions and continue into the ipsilateral optic tract. In primates, fibres from the nasal hemiretinas decussate in the chiasm and continue into the contralateral optic tract. Macular fibres are dispersed throughout most of the chiasm although they are substantially located in the central region; half of them undergo decussation such that half of the macular fibres from each optic nerve are represented in the optic tracts.

The degree of decussation varies between species and is reprasentative of their degree of binocular vision. Thus in animals with laterally positioned eyes such as the guinea pig most of the nerve fibres decussate in the chiasm, and animals with frontally directed eyes have about equal numbers of crossed and uncrossed fibres (Davson, 1990).

Most of the fibres from the chiasm continue into the optic tracts, but a few leave it dorsally to enter the bilateral suprachiasmatic nuclei as the retinohypothalamic pathway. The optic tracts pass laterally and posteriorly, skirting the body of the hypothalamus and terminate in the lateral geniculate nucleus. However, approximately 20% of fibres leave the tract in the superior brachium and head towards the pregeniculate, the pretectal nucleus, the superior colliculus, the pulvinar and the accessory optic nuclei (Cogan, 1972; Ruskell, 1988; Harrington, 1990).

4.1.3. The Non-geniculate Pathway.

4.1.3.1. Suprachiasmatic nuclei (hypothalamus).

These nuclei lie just above the optic chiasm and just lateral to the third ventricle (Rodieck, 1979). Each nucleus receives a bilateral projection of retinal fibres, as well as inputs from the ventral lateral geniculate nucleus and other non visual areas. The nucleus is an important pacemaker for the generation of circadian rhythms and the diurnal cycle of light intensity conveyed by the visual input is used to synchronise this rhythm (Schwartz and Gainer, 1977).

4.1.3.2. Accessory Optic Nuclei.

These are a bilateral array of three terminal nuclei located in the midbrain near the mesodiencephalic border. Fibres leave the optic tract at the level of the brachium as the superior and inferior accessory optic tracts. The inferior fasciculus terminates in the dorsal portion of the medial terminal nucleus (MTN) which is situated in the basal surface of the midbrain ventral to the red nucleus and slightly rostral to the emergence of the third cranial nerve. The superior fasciculus is larger and more diffuse and terminates in the basal portion of the MTN, and the dorsal and lateral terminal nuclei (DTN and LTN).

The LTN is found posterior and dorsal to the MTN in a position ventro-medial to the medial geniculate body along the lateral surface of the brain. The DTN is located at the anterior-lateral edge of the superior colliculus in close proximity to the dorso-lateral pretectum (Rodieck, 1979; Davson, 1990; Grasse and Cynader, 1991).

Input to the accessory optic system of cats arises primarily from the contralateral retina and ipsilateral visual cortex. Efferent fibres have been shown to terminate in the inferior olive which in turn projects to the flocculus of the cerebellum and on to the vestibular and occulomoter nuclei (Grasse and Cynader, 1991). Cells of this system are also thought to be direction and velocity specific. Thus it has been suggested that the accessory optic system may influence eye movements, vestibulocular reflex, optokinetic nystagmus and control of interfering eye movements during smooth pursuit.

4.1.3.3. The Pretectum.

The pretectal region is a complex collection of cells that lie just rostral to the superior colliculus where the midbrain fuses with the thalamus. There appear to be about seven nuclear subdivisions in mammals including the nucleus of the optic tract (NOT), the olivary pretectal nucleus (PO), and the posterior pretectal nucleus (PP). These three nuclei are thought to receive bilateral retinal inputs from the brachial fibres as well as inputs from the superior colliculus and ventral lateral geniculate nucleus (Rodieck, 1979). Fibres pass form the pretectum to the Edinger-Westphal nucleus and on to the ciliary ganglion with the III rd nerve fibres. Post ganglionic fibres innervate the smooth muscle of the pupillary sphincter thus mediating the pupillary light reflex.

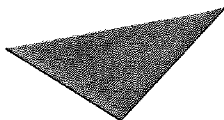
4.1.3.4. Superior Colliculus.

The superior colliculus appears as a large protuberance on the midbrain and is composed of seven alternating fibrous and cellular laminae. Functionally it is separated into two layers - the superficial layer made up of laminae I - III namely the stratum zonale, superior grey and optic grey, and the deep layer made up of laminae IV - VII namely the intermediate grey, intermediate white, deep grey and deep white (Rodieck, 1979; Wurtz and Albano, 1980; Davson, 1990; Rhoades *et al,* 1991; Stein and Meredith, 1991).

The superficial layers are the visual centres receiving retinal input from the optic tract as well as input from the visual cortex. Axons of retinal ganglion cells enter the superior colliculus bilaterally to terminate chiefly within the upper portion of the striatum griseum superficiale. The deeper layers have very little direct retinal input but receive afferents from acoustic and somatosensory systems as well as some visual cortex input (primarily from extrastriate regions). It is thought that the deeper layers are involved in the coordination of visual and motor activity.

Table 4.1 gives a list of the afferent and efferent connections of the superficial layers (from Wurtz and Albano, 1980). In cat and monkey there is an extensive direct ipsilateral retinal input to most areas of the superior colliculus to represent only the contralateral hemifield (the nasal hemifield of the contralateral eye and the temporal hemiretina of the ipsilateral eye), with a substantial degree of binocular convergence on individual cells (Stein and Meredith, 1991). The projection from the striate cortex arises from layer V and terminates for the most part in the ipsilateral superior colliculus.

Table 4.1.Connections of the superficial layers of the superior colliculus (from Wurtz and Albano, 1980)



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Afferent and efferent connections to the deeper layers are given in table 4.2 (from Wurtz and Albano, 1991). It can be seen that there are an overwhelming number of

projections. The connections indicated by an asterisks are those that have been confirmed in cat. The corticotectal projections are diffuse and do not terminate within a single lamina although striate and prestriate areas tend to terminate more dorsally than the more remote cortical areas. There are also extensive projections from extrastriate cortex and central lateral geniculate nucleus. The projections from the pars reticulata of the substantia nigra has an inhibitory influence and is important in the eye movement related discharges of collicular neurons (Rhoades *et al,* 1991).

As can be seen from table 4.2 the efferent connections of the intermediate and deep layers are organised into four pathways: ascending, descending ipsilateral, descending contralateral and commissural. Projections to the cerebellum may provide pathways linking the superior colliculus with visual-oculomotor regions of the cerebellar cortex - these include the dorsolateral pontine nuclei, regions of the pontine reticular formation, and subnucleus B of the medial accessory nuclei of the inferior olive.

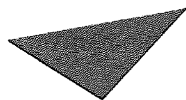
Thus the superior colliculus is involved in evoking eye movements, eye and head orientation and ocular centring movements whether in response to visual, auditory or somatic stimuli. Visual stimulation is provided largely by the visual cortex. and a balance between visual cortex and superior colliculus must be maintained in order to support normal visually guided behaviour.

4.1.3.5 The Pulvinar Nuclei.

In primates the pulvinar complex is a nuclear mass located medial and caudal to the dorsal lateral geniculate nucleus in the posterior dorsal region of the thalamus (Rodieck, 1979; Davson, 1990; Garey *et al,* 1991). It has a close connection with the LGNd and various cortical areas including acoustic, visual, and somatosensory area, thus suggesting an important role in processing visual information. In rodents it is known as the lateral posterior nucleus, and in cats, the lateral posterior pulvinar nuclear complex. The size and differentiation of this complex increases markedly as one ascends the phylogenic scale; a similar expansion occurs in occipital, temporal and parietal area. The largest thalamic nucleus is in humans, and is thought to pay a role in higher integrative functions (Chalupa, 1991).

The lateral posterior pulvinar complex of cats has been the subject of a number of classifications. It is composed of small and medium sized neurones separated into

Table 4.2 Connections of the intermediate and deep layers of the superior colliculus (from Wurtz and albano, 1980), (* confirmed in cats).



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bands by the axons of the optic tract and dorsal thalamic radiations which traverse it. Updyke (1983) described it as having a core consisting of four zones appearing as parallel slabs when viewed coronally. From lateral to medial these zones are called the pulvinar nucleus, the lateral zone of the lateral posterior nucleus (LPl), the interadjacent zone (LPi) and the medial zone (LPm). The LPl is further divided into caudal (LPl-c) and rostral parts (LPl-r). LPl-c has interconnections with the area 17 and 18 of the visual cortex as well as numerous other extrastriate visual areas. This area is also thought to receive a weak projection from the superior colliculus. The LPi lies between the ventromedial border of the LPl and the dorsomedial borders of the LPm and the suprageniculate nucleus. It has a highly complex representation of the contralateral hemifield and has reciprocal interconnections with a number of cortical association areas. The main subcortical afferents to this region arise from the deeper tier of the stratum griseum superficiale in the superior colliculus. The LPm is located at the medial margin of the LP complex and has reciprocal connections with the anterior ectosylvian area and insular cortex.

Graybiel (1972) however subdivided the cat LP-complex into three zones: the pulvinar proper receiving its major input from the pretectum, the lateral portion of the LP, considered the striate recipient zone because it is the only subdivision innervated by projections from areas 17 and 18 and the medial LP, the principal tectorecipient region receiving input from the cells in the superficial layers of the superior colliculus.

The pulvinar complex of primates is conventionally divided into four parts: an inferior part located ventrally between the medial and lateral geniculate nuclei, and separated from the main body of the pulvinar by the brachium of the superior colliculus; a lateral part that extends along the external medullary lamina forming the caudolateral border of the thalamus; a medial part that composes the medial half of the pulvinar; and an anterior part that is really the rostromedial portion of the medial pulvinar, that extends between the ventral posteriolateral and centromedian nuclei.

The inferior part of the primate pulvinar complex is further organized into three nuclei: a large, central nucleus (PIc), a medial nucleus (PIm) and a posterior nucleus (PIp); all are strongly reciprocally interconnected with different visual cortical areas. Plc and Plm receive projections from areas V1 and V2 and MT, and projecting to layers l, ll and lll of V1, and layers l, lll and lV of area V2 (Davson, 1990; Garey *et al*, 1991). PIc contains a precise map of the contralateral visual hemifield and is also thought to receive projections from the superior colliculus

(Garey *et al*, 1991). A direct retinal pathway to this region remains a subject of debate. Plm receives its major source of afferents from the extrastriate areas particularly MT and the non-visual insular cortex, although it does have an input from the primary visual cortex. This nucleus also contains a rough retinotopic map of the contralateral visual hemifield. The Plp nucleus is small and does not appear to be retinotopically organized. It receives its main projection from the superior colliculus. The only cortical projections it receives are located rostral to MT.

The lateral part of the pulvinar can be divided into a lateral nucleus (PLl) and a medial nucleus (PLm). The former nucleus is thought to contain a precise map of the contralateral visual hemifield, and receives projections from areas V1, V2 and V4 of the visual cortex (Davson, 1990; Garey *et al,* 1991). The PL also projects to layers l,ll,and lll of the striate cortex and to many extrastriate areas.The PLm nucleus does not seen to be retinotopically organized, and receives inputs from the thalamic reticular nucleus and the claustrum and from a number of extrastriate visual areas excluding areas V1 and V2. The targets of the PLm nucleus are not yet known.

The medial part of the pulvinar is interconneted with the deep layers of the superior colliculus, frontal eye fields, (area 8) limbic and insular cortices and the amygdaloid nuclear complex (Davson, 1990; Garey *et al* 1991). The anterior part of the pulvinar is strongly interconnected with the parietal cortex.

4.1.4. The Geniculate Pathway.

4.1.4.1. Dorsal Lateral Geniculate Nucleus (LGNd).

The LGNd is one of the nuclear complexes of the posterior part of the dorsal thalamus (Garey *et al* ,1991). In the cat it is located dorsolaterally and is separated from the dorsal thalamus by a medial ramus of the optic tract. In primates it is a relatively large nucleus situated in the ventrolateral part of the dorsal thalamus - again the optic tracts separate it from the rest of the thalamus. In cat and primates, the LGNd is a laminated structure, in the cat there are three main cellular layers, originally named A1, A, and the C complex (Guilley 1969). A diagram of the laminated structure is shown in figure 4.3. Layers A1 and A are the most superficial layers, the most dorsal of which being A and the most ventral A1. Layer A receives retinal input from the contralateral eye and layer A1 from the ipsilateral eye (Thurma, 1928; Davson, 1990; Garey *et al,* 1991). The C complex is the most

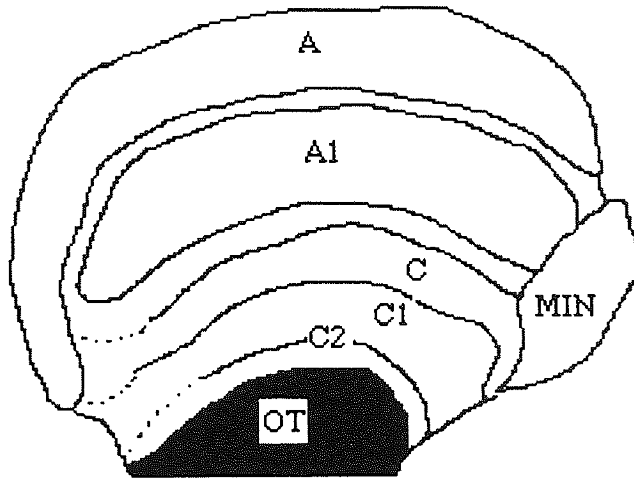
ventral layer and lies adjacent to the optic tracts. It is subdivided cytologically into three laminations which are visibly indistinct (Rodieck, 1979). Lamina C1 receives ipsilateral retinal input, while lamina C2 receives contralateral retinal input. Just dorsal to the optic tract, there is a smaller lamina C3 which does not receive any retinal input at all. Finally there is a Medial Interlaminar Nucleus (MIN) which is distinct from the other laminae, it lies medially and receives retinal input from ipsilateral and contralateral eyes (Davson, 1990; Garey *et al,* 1991).

In Old World monkeys, Chimpanzees and humans, the LGNd is basically a six layered inverted conical structure. The main layers are numbered 1 - 6 starting at the dorsal hilum and terminating at the dorsal surface. Layers 1 and 2 are magnocellular and layers 3 - 6 are parvocellular (Ruskell, 1988; Garey *et al,* 1991; Kaplan *et al,* 1991). This laminar organisation is shown diagramatically in figure 4.3. In addition to these layers are the interlaminar cell zones or intercalated layers which are located between magnocellular laminae 1 and 2, and between magnocellular layer 2 and parvocellular layer 3. A further layer the 'superficial' of 'S' layer is located close to the pial surface of the thalamus. These additional layers contain small to medium sized cells and are thus called konicocellular regions, and are thought to receive their retinal input from a class or classes of ganglion cells which do not project to the main laminae (Garey et al, 1991; Casagrande and Norton, 1991).

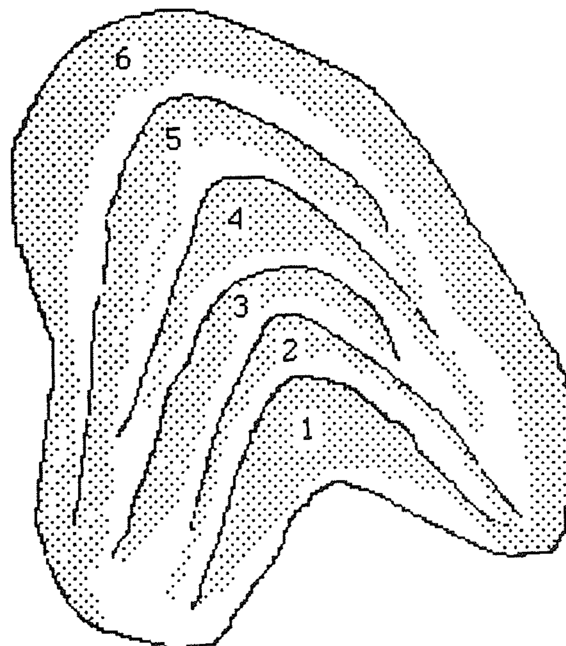
In man, the lamina pattern is far more complex and up to 8 layers have been distinguished - 6 of which appear to be subdivisions of the basic parvocellular layers. The posterior part of the nucleus contains the most parvocellular duplication as this region represents the foveal region.

In primates axons from the two eyes remain segregated in the LGNd. In Old World monkeys layers 1, 4 and 6 were found to receive axons from the contralateral retina while layers 2, 3, and 5 receive axons from the ipsilateral retina (Davson, 1990; Garey *et al,* 1991; Kaplan *et al,* 1991).

Figure 4.3.
Drawing of cat LGN, showing laminations as seen in a frontal section through the rostral third (adapted from Davson, 1990).



Drawing of old world monkey LGN showing laminations 1-6, as seen in a coronal section (adapted from Garey et al, 1991).



The LGNd of all mammals receives axons from the visual cortex - this projection provides a substantial proportion of extraretinal afferents. In macaque this corticogeniculate projection originates in the striate cortex while in cats the projection originates from various visual areas. In cats area 17 (striate cortex, area 1V) projects to the entire LGNd complex (the A laminae, the C complex and the MIN); area 19 (parastriate cortex, area V3) terminates in the parvocellular C laminae and MIN (Rodieck, 1979; Davson, 1990; Garey *et al*, 1991).

In the macaque monkey, most of the projections from area 17 terminate in the parvocellular and magnocellular laminae, while those from area 18 and the middle temporal visual area (MT) innervate the interlaminar areas, the magnocellular laminae and the S laminae. The cortical projection from area 17 is a significant pathway and may well contribute many more synapses to the LGNd cells than do retinal axons (Casagrande and Norton, 1991). In all mammals studied so far, this corticogeniculate pathway is topographically organized.

A restricted proportion of afferents to the LGNd originates in the superior colliculus. In cats this colliculogeniculate projection originates from the striatum griseum superficiale and terminates exclusively in the parvocellular C laminae. In primates, the konicocellular intercalated layers and S layers are the site of termination of such axons (De Lima and Singer, 1983; Garey *et al*, 1991; Casagrande and Norton, 1991).

Other afferents to the LGNd originate in the parabigeminal nucleus which is a small aggregate of cells near the lateral edge of the midbrain tegmentum which receives its principal projection from the superior colliculus. These afferents are thought to terminate in parvocellular and magnocellular layers as well as the S lamina and interlaminar zones.

A further small projection originates in 2 of the pretectal nuclei namely the olivary pretectal nucleus and the nucleus of the optic tract - and terminate primarily but not exclusively in the parvocellular layers. Other brainstem nuclei that innervate the LGNd include the pedunculopontine and lateral tegmental nuclei of the midbrain and the locus coeruleus

4.1.4.2. The Pregeniculate nucleus / Ventral Lateral Geniculate Nucleus (LGNv).

The pregeniculate nucleus of primates is a part of the ventral thalamus and is located dorsal to the LGNd and separated from it by a bundle (circumgeniculate nucleus) that contains geniculocortical and corticogeniculate axons and is thought to be analogous the the ventral lateral geniculate nucleus of non-primates (Rodieck, 1979; Garey *et al,* 1991). It seems to play a role in brightness discrimination and in the pupillary light reflex. It is thought to be a visuomotor integration centre and is involved in ambient rather than focal vision.

The LGNv of cats receive a cortical projection mainly from areas 18, 19, and 21 and from several areas along the lateral suprasylvian sulcus. It also receives input from the superior colliculus, the ipsilateral and contralateral pretectal complex, the contralateral LGNv, and possibly from the dentate interpositus complex of the cerebellum (Davson, 1990; Garey et al, 1991). Axons from the LGNv of cats are thought to project to the ipsilateral superior colliculus, contralateral LGNv, ipsilateral anterior pretectal nucleus, nucleus of the optic tract, and ipsilateral and contralateral suprachiasmatic nucleus of the hypothalamus as well as to both the ipsilateral and contralateral nucleus centralis, the ipsilateral pulvinar and nucleus lateralis posterior, zona incerta and thalamic reticular nucleus in the ventral thalamus and the paramedian zone of the pontine grey matter (Rodieck, 1979, Davson, 1990; Garey *et al,* 1991).

The pregeniculate nucleus of the primate has a bilaminar structure. The ventral lamina, located close to the LGNd, is thought to receive a substantial input from the contralateral retina and a small input from the ipsilateral retina. The dorsal lamina does not receive retinal input. The other connections of this nucleus are comparable to those of non-primates.

4.1.4.3. The Perigeniculate / Thalamic Reticular Nuclei.

The perigeniculate nucleus of the cat and other carnivores and its presumed homologue, the visual segments of the thalamic reticular nucleus of primates and rodents consists of a thin sheet of cells embedded in the thalamic radiation on the rostral and lateral surfaces of the dorsal thalamus (Garey *et al,* 1991). Geniculocortical axons traverse this nuclear mass and form terminal collaterals in these nuclei resulting in them having a topographic representation of the contralateral visual field. The nuclei also receive another major input from layer IV

of the visual cortex, as well as inputs from the parabrachial nucleus in the brainstem, laterodorsal tegmental nucleus periaqueductal grey, pretectum locus coerulus raphe nuclei and nucleus cuneifromis. In cat the thalamic reticular nucleus receives projections from the substantia nigra pars reticulata. These nuclei project back to the A lamina of the LGNd and are thought to have an inhibitory influence.

4.1.4.4. The Optic Radiations.

Visual information pass from the LGNd to the visual cortex as the optic radiations. These fibres emerge dorsolaterally from the LGNd as the optic peduncle and then fan out into a thin, vertically oriented band that sweeps around the wall of the posterior horn of the lateral ventricle before terminating on the lateral surface of both the temporal and occipital horns of the lateral ventricle. However, the band is twisted as it expands from the peduncle with inferior fibres looping forwards into the lateral lobe of the brain, skirting the inferior horn of the lateral ventricle, before turning back sharply - this looping forwards is known as the loop of Meyer.

4.1.4.5. The Visual Cortex.

The visual cortex of all primates are remarkably similar. It is situated on both sides of the calcarine fissure on the medial aspect of the occipital lobe, extending for a short distance onto the occipital pole (Valverde, 1991). The cortex is made up of a number of visual areas that are interconnected in a semi-hierarchial manner (Kaas and Krubitzer, 1991). The largest of these is situated at or near the posterior pole of the hemisphere and is described by a number of terms such as the striate cortex, Brodmann's area 17, visual area 1 (Vl), and primary visual cortex. It is the location of powerful direct input from the LGNd and is the principal cortical recipient of visual input (Van Essen, 1979; Ruskell, 1988). Surrounding this area are a number of additional areas involved in a higher or more abstract level of analysis and are known as the extrastriate visual cortex, prestriate cortex, circumstriate cortex, association areas, Brodman's area 18 and 19, secondary visual cortex, or visual areas 2 and 3. The numbers, positions and nomenclature of these extrastriate areas vary slightly between species.

In New World monkeys (eg Owl monkey) visual area 2 (V2) almost completely encircles the striate cortex. Immediately adjacent to V2 is a belt of cortex known as the "third tier" which contains at least five visual representations including the medial (M), dorsomedial (DM), dorsolateral (DL), dorsointermedial and entorhial

zones. An additional visual representation, the middle temporal area (MT) has been found in a region anterior to the third tier (Van Essen 1979, Kaas and Krubitzer, 1991; Sereno and Allman 1991). There are also visual projection targets in the superior temporal region (such as the middle superior temporal area (MST) and the fundal area of the superior temporal sulcus (FST)) and in the temporal parietal region. At least three regions of frontal cortex have visual or visuomotor function including the frontal eye fields (FEF), the rostral part of the supplementary motor area (E-SMA), and the frontal ventral area (FV).

In Old World monkeys (eg Macaque monkey) the occipital lobe has a greatly expanded surface area associated with a more elaborate pattern of convolutions, and an increased number of visual areas. Within Brodmann's area 18 there are at least four visual representations including V2, V3, V4, and V3A. Within area 19 only one well defined area has been identified and is probably equivalent to the MT area of New World monkeys. Visually receptive areas also exist in the temporal and parietal lobes (area 20, 21 and 7), frontal eye field, and supplementary motor area.

In humans Positron Emission Tomography has been used to monitor cortical activity and it has been suggested that human visual areas V1 and V2 are organized quite similarly to those of other primates. There is also an area that is ellipsoidal in shape and is heavily myelinated and is situated in a dorsolateral occipital sulcus that may correspond to human visual area MT, although it is three to four times the size of the equivalent area in macaque. Figure 4.4 shows a preliminary map of the visual cortical area of human (Sereno and Allman, 1991).

The sensory visual cortex of primates is divided into layers corresponding to the distribution of certain cell populations revealed by Nissl stain. In 1905 Brodmann (1905) adopted a six layered cortex, numbered l to Vl in roman numerals, while Cajal (1911) developed a nine layered cortex using Golgi stain. These layers were as follows: 1. plexiform (cell deficient), 2. small pyramids, 3. medium pyramids, 4. large stellates, 5. small stellates, 6. small pyramids, 7. giant pyramids, 8. medium pyramids, 9. fusiform or triangular cells. Figure 4.5 gives a comparison between the two layered systems (Davson, 1990; Henry, 1991).

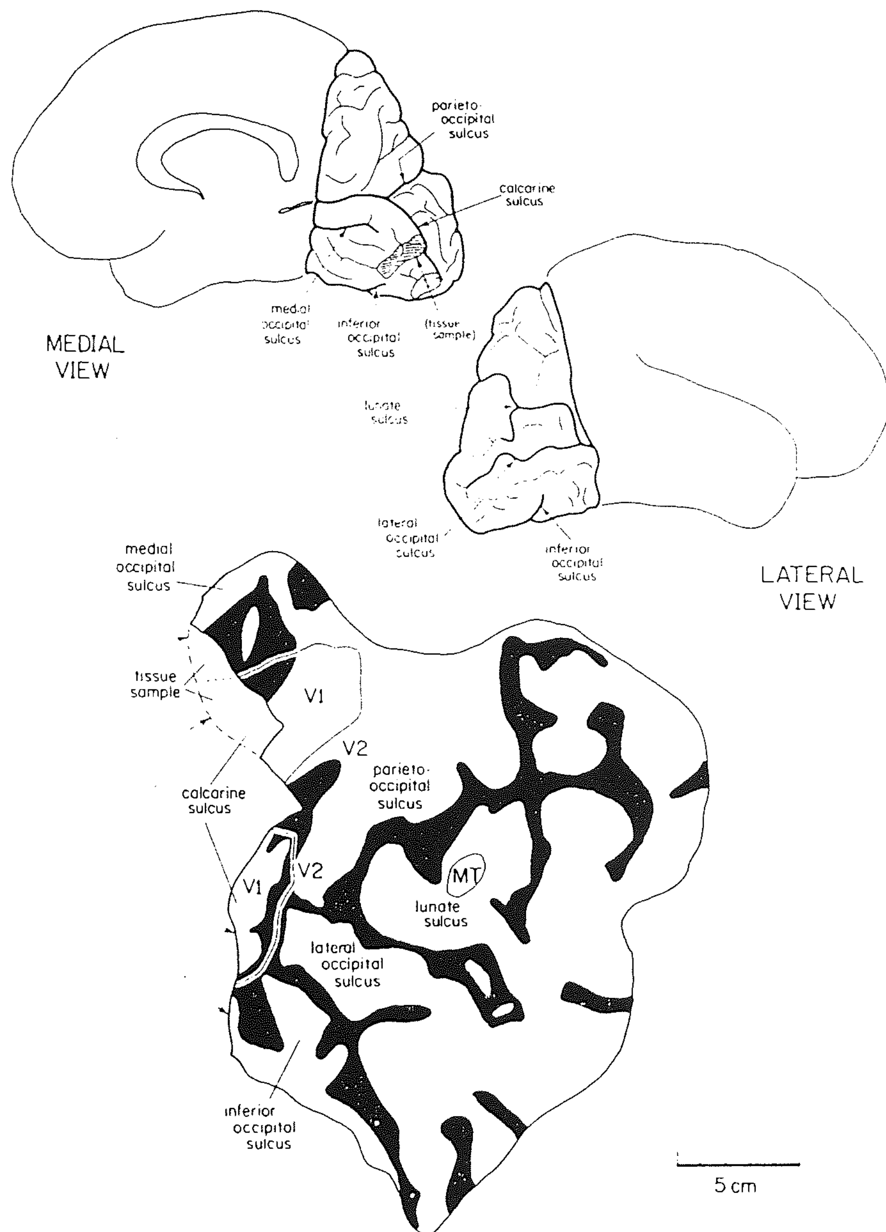


Figure 4.4 Visual cortical areas in the human (preliminary). A left occipital lobe was physically flattened, sectioned parallel to the cortical laminae, and stained for myelin. The exposed crown of the gyri are coloured black in the diagram of the flat cortex. The myelin stain clearly revealed V1 as well as an elliptical, densely myelinated area located in a dorsolateral sulcus that may correspond to area MT. Abbreviations: MT, middle temporal; V1, striate cortex; V2, second visual area. (Adapted from Sereno and Allman, 1991).

Figure 4.5. Schemes of lamination of the primate visual cortex (adapted from Henry, 1991).

	CAJAL (1911)	BRODMANN (1905)	
plexiform	I	I	molecular layer
small pyramids	II	II	external granular
		III	external pyramidal
medium pyramids	III		
		A	
		B	
		IV	inner granular
large stellates	IV	Cå	
small stellates	V	Cß	
small pyramids	VI	A	
		V	inner pyramidal
giant pyramids	VII	B	
medium pyramids	VIII	A	
		VI	polymorph layer
fusiform cells	IX	B	

Layer IV of the primary visual cortex, or inner granular layer is the main site of monosynaptic termination of the thalamic input. This layer contains a whitish horizontal band called the stria of Gennari, that corresponds to subdivision lVB. This band is not thought to contain any direct input from thalamic neurons, rather it is made up of horizontal fibres which are collaterals of descending axons of cells located more superficially, as well as from cells located within lVB. It also contains ascending ramifications of spiny stellate cells located in layer lVC.

The lighter appearance of the Nissl stain of this layer is thought to be due to the long horizontal dendrites of the large pyramidal and stellate cells residing in this sublayer (Davson, 1990; Valverde, 1991). Others state that the white line of Gennari is due to terminating fibres of the optic radiations retaining their myelin (Ruskell, 1988).

It can be seen from the above that two main class of cell exists in the visual cortex, the pyramidal and stellate cells, differentiated by the length of axon and shape of cell body. Pyramidal cells have the longer axons and, as the name suggests, the cell body is shaped like a pyramid, the apex of which is directed towards the cortical surface and gives rise to a single dendrite, while its base gives rise to a number of radial dendrites. The cell bodies of these cells lie in layers lll, lV and V, they are the main thalamocortical recipients and they project to cortical and subcortical sites (Valverde, 1991). Stellate cells have a more rounded cell body from which arise an array of dendrites in a star-shaped configuration. These cells can have smooth dendrites, a small number of spines (sparsely spinous), or have a density of spines approaching that of most pyramidal cells (spinous cells). Stellate cells are found almost exclusively in layer lV and ramify locally to form intracortical connections - it has been suggested that they link simple to complex cells in other cortical areas.

Further aspects of cortical organisation have been revealed using cytochrome oxidase (CO), the activity of which varies in different regions, reducing in areas of reduced neuronal activity. In primates, a tangential section through sublayers ll and lll of the primary visual cortex reveals a two-dimensional array of round-to-oval blobs forming parallel rows 0.5mm apart, which correspond with ocular dominance columns. Areas between these blobs are known as interblob regions. CO blobs are also distinguished by having more widespread intrinsic connections than interblob regions. Cytochrome oxidase also reveals a system of light and dark bands in visual area ll, the CO dark bands being thicker than the CO light bands. It is thought that

the blob regions of V1 project to the dark bands of V2, and the interblob regions project to the light bands of V2.

Afferent and efferent projections to and from the visual cortex are numerous and complicated. In addition to the LGNd, the cortex receives inputs from an array of subcortical structures such as the locus coeruleus, lateral hypothalamus, nucleus basalis of Meynert, claustrum, nucleus basalis lateralis amygdalae, pulvinar, medial interlaminar nucleus and others.

The primary visual cortex receives its main input from the LGNd, the afferents of which terminate in layers lVA and lVC. Afferents from the parvocellular layers of the LGNd terminate largely in the lower part of sublayer lVA and in lVC, and more specifically in blob and interblob regions. Magnocellular input tends to reside in the upper part of sublayer lVA (Van Essen, 1979; Davson, 1990; Kaas and Krubitzer, 1991; Van Essen *et al*, 1991; Valverde, 1991). Sublayer Vl contains a small number of terminals from both systems. Axons arising from the interlaminar and S-layers of the LGNd are thought to terminate in sulayers lll, lVA and l (Valverde, 1991). The striate cortex also receives direct input from the pulvinar, principally to sublayer l. Efferent projections from the primary visual cortex include a prominent pathway to the LGNd arising from sublayer lV (Van Essen, 1979) those from the upper part of this sublayer projecting to the P divisions of the LGN, and those from the lower part to the M divisions (Davson, 1990). Sublayer V send projections to the superior colliculus and to the pulvinar. From this principal recipient zone of the visual cortex visual information is transferred to extrastriate areas for further processing.

Visual area 2 receives direct cortico-cortico input from V1, the parvocellular blob stream terminates in thin stripes, the parvocellular interblob stream terminates in the interstripe region, and the magnocellular stream terminates in the thick stripes (Van Essen *et al*, 1991). The thicker bands then project on to V3 and the MT area, and the interbands and thinner dark bands to the DL (or V4) area (Kaas and Krubitzer, 1991; Sereno and Allman, 1991, Van Essen *et al*, 1991). V2 also receives a direct projection from the superior colliculus (Davson, 1990), as well as a possible direct input from the LGN (although this remains inconclusive). V2 sends reciprocals back to V1 that terminate mainly in sublayer l but also in layer lV (Van Essen, 1979). Area MT and M of New-World monkeys, and their possible equivalents, V3

and MT of Old-World monkeys, also receive direct input from the primary visual cortex as well as from V2.

Areas V2 and V3 then project on to areas DL and DM of New-World monkeys and V4 and V3A of Old World monkeys (Van Essen, 1979, Kaas and Krubitzer, 1991). From MT, fibres continue on to the MST, FST and posterior parietal cortex, and from V4 to the inferotemporal cortex (Desimone *et al*, 1985).This somewhat simplified pattern of interconnections is shown schematically in figure 4.6. Reciprocal fibres from layer lV of the extrastriate visual areas project back to the LGNd, and those from layer V to the superior colliculus and pulvinar (Van Essen, 1979).

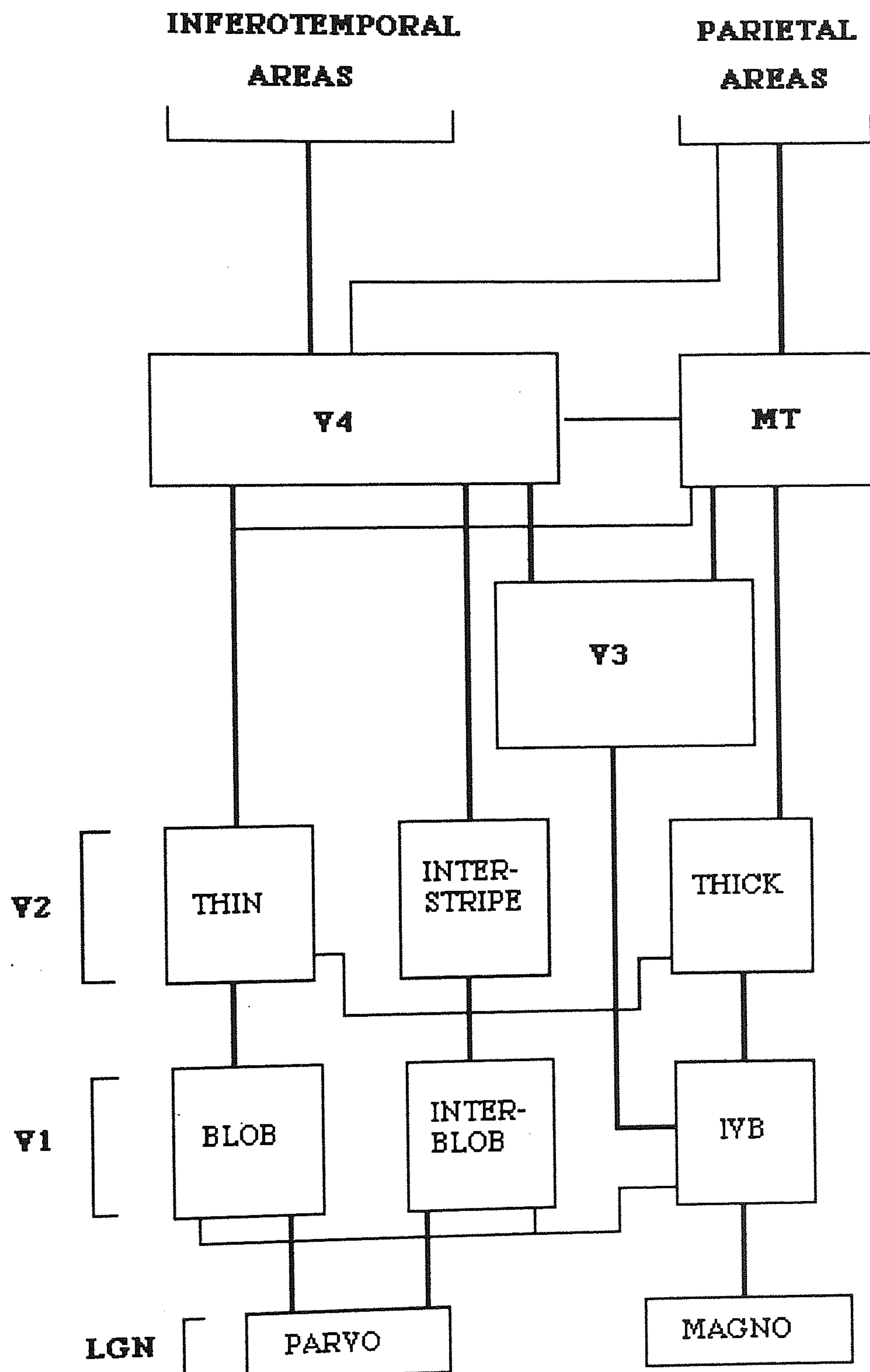
4.2 Neurophysiology of the Visual Pathway.

4.2.1. Retina.

The retina is the complicated structure which transforms the light energy that enters the eye into electical energy that is transmitted along the visual pathway. Our visual world is extremely complicated and variable, containing images of various spatial frequencies, contrasts, colours, and movement which alter depending on levels of illumination. It is thus impossible for a one-to-one relationship, such that each visual stimulus is related to a single cortical cell, to exist. Instead, the visual information is transmitted in a coded format. This coding begins at the retina.

Light enters the eye, and is absorbed by the outer segments of the photoreceptors. These cells are designed to capture light as they exhibit the property of total internal reflection such that light entering within the critical angle is trapped there and guided down the length of the cylinder (Rowe, 1991). Within the outer segment the light encounters photopigment molecules which are isomerized to create an electical impulse. The spatial sampling ability of the photoreceptors is dependent upon their optical separation and this is usually determined by the physical dimensions of the inner segment. Thus this is the first filtering stage of the visual pathway, and all the information available to the organism is present in the output of this photoreceptor array. There are three types of cones which are responsible for colour vision (there are L long wavelength cones, M medium wavelength cones and S short wavelength cones) although rods are likely to make some contribution (Dow, 1991).

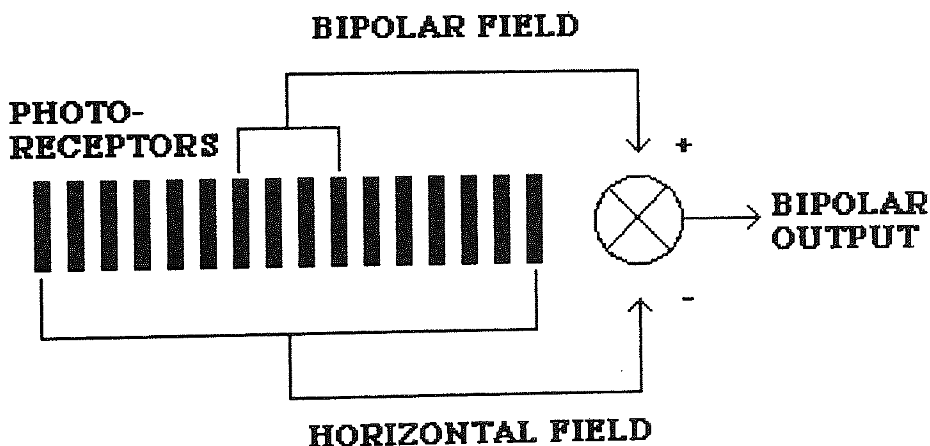
Figure 4.6
Schematic diagram to show the hierarchial arrangement of interconnections in the visual cortex (adapted from Van Essen et al, 1991).



From the photoreceptors, the information interacts with that from horizontal cells and converges upon the bipolars. A single bipolar cell will contact a number of photoreceptors over a narrow region, and also an horizontal cell which itself contacts photoreceptors over a wider region (figure 4.7).

The bipolar cell output is the difference in activity between the narrow central region of photoreceptors and that over a broader region governed by the horizontal cell connections (Rowe, 1991). These two components comprise the receptive field of the bipolar cells. This results in the signal generated by the bipolar cell being related to local contrast rather than local illumination - this is known as 'predictive coding'. It means that an estimate of the signal to be expected at a point on the retina is subtracted from the amplitude of the actual signal at that point. The area over which the estimate is made is governed by the horizontal cell connection ie the receptive field surround.

Figure 4.7. Diagram to represent the overall output of a bipolar cell (adapted from Werblin, 1991).



It has been shown that there are two functionally different bipolar cells - ON centre cells and OFF centre cells. The ON cells are thus named because they depolarize in response to light falling in the central region of their receptive field, the OFF centre cells depolarize to a light OFF stimulus in the central region of the receptive field (Werblin *et al*, 1991; Nguyen-Legros, 1988). This difference in response is thought to be dependent upon the cells' response to the release of a neurotransmitter (probably glutamate). The ON-centre cell is inhibited by the transmitter, so a decrease in the amount of transmitter released will disinhibit and excite the cell. The OFF-centre cell is however, excited by the transmitter so a decrease in the amount

would inhibit the cell. The surround regions of these cells are thought to be antagonistic to their centre and this is thought to be mediated by the horizontal cells, although the exact synaptic mechanisms have not yet been established (Rowe, 1991). The horizontal cells are inhibitory interneurons and are thought to exert their effects either by feeding back onto the receptors or by antagonizing directly the bipolar cells or both (Cohen and Dowling, 1982; Dowling, 1990).

These ON and OFF bipolar cells are segregated by their position of termination within the inner plexiform layer. The outer half (sublamina a) receives the OFF bipolars, and the inner half (sublamina b) receives the ON bipolars (Kaplan *et al*, 1991; Werblin *et al*, 1991). In the foveal region the midget bipolar cells receive their central input from a single cone. It is therefore likely that there are separate classes of Long wavelength ON and Long wavelength OFF centre bipolar cells as well as M ON and M OFF centre cells. The S system may be slightly different as S cones have their peak distribution at an eccentricity of about 1° and are less common than L and M cones (Dow, 1991).

The bipolar cell receptive field alters depending on the state of light or dark adaption - the inhibitory surround having a reduced effect in the dark. This is thought to be mediated by the action of interplexiform cells on the horizontal cells (Cohen and Dowling, 1983; Nguyen-Legros, 1988; Dowling,1990).

The first quantitative investigation of a ganglion cell receptive field from the mammalian retina was reported by Kuffler (1953), in the cat, although the concept of the receptive field was originally put forward by Hartline (1940) in the bull frog. Using small spots of light to stimulate the ganglion cells, Kuffler's main finding were:

(a) The receptive fields is not homogeneous, but rather is made up of several concentric sub-regions, each with its own characteristic response to light onset or offset.

(b) Stimulation of the peripheral region of the receptive field yielded a response that was opposite of the response elicited by stimulation of the central region. Thus if central stimulation produced an ON discharge, then peripheral stimulation produced an OFF discharge and visa versa.

(c) Stimulation of the region between the centre and periphery produced mixed responses (ON-OFF).

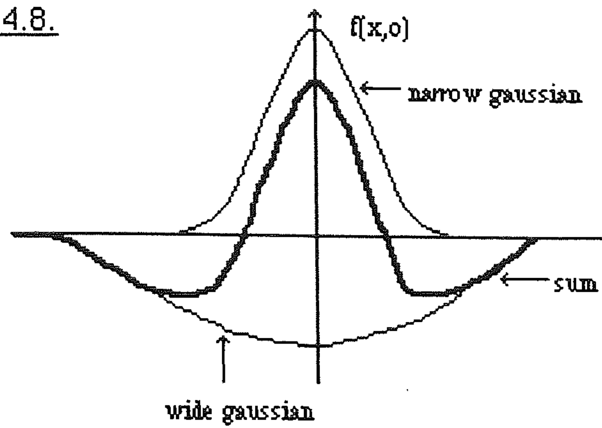
(d) Stimulation of both central region and the periphery elicited a response that was smaller than the response to stimulation of either region by itself.
This last statement suggests that the response from the centre and surround are summed. These receptive fields are known as circularly symmetric and can be quantified using Rodieck's difference of gaussians model (Rodieck, 1965), which states that the response at any point in the receptive field would be just the arithmetic sum of the contributions from the centre and surround (shown diagramatically in figure 4.8).

This model can only be used if the receptive field is linear which is not always the case in ganglion cells. Kuffler also described a basic distinction among ganglion cells - these being ON-centre and OFF-centre (figure 4.8)

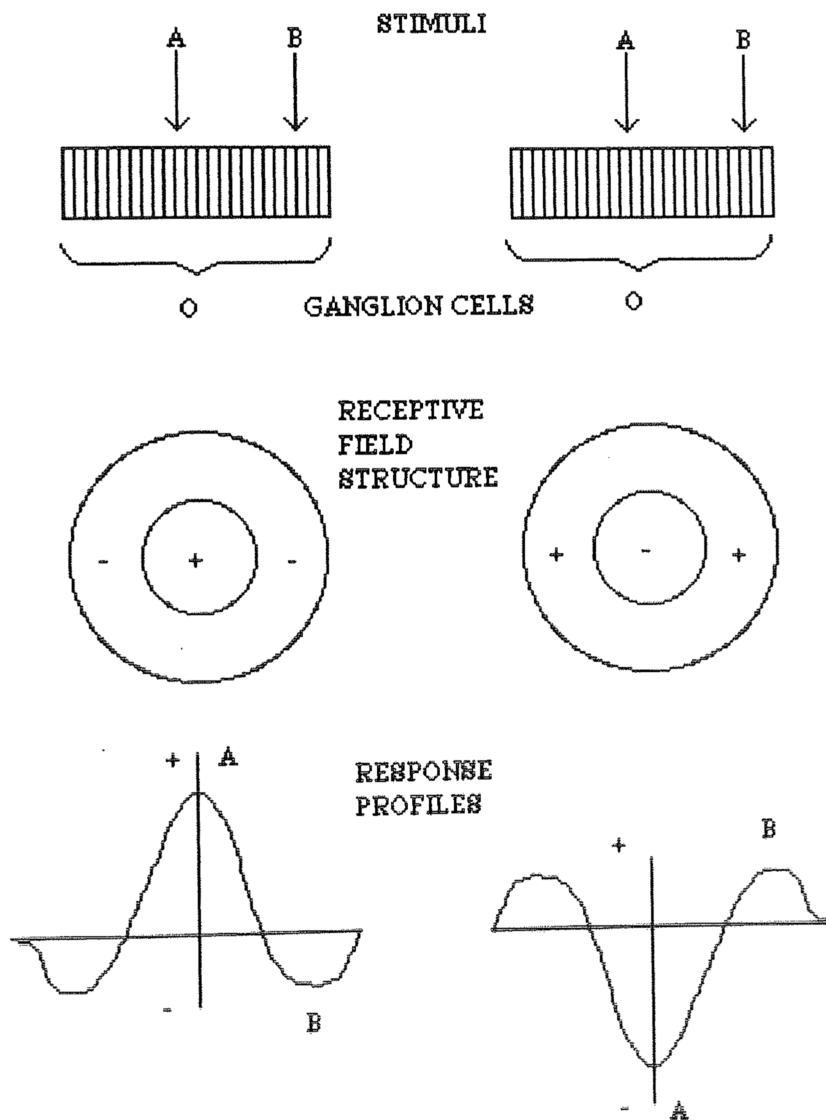
ON cells give excitatory firing to stimuli brighter than the background and show inhibition to stimuli darker than the background at the receptive field center. Similarly OFF cells will give excitatory firing to stimuli darker than the background and show inhibition to stimuli brighter than the background at the receptive field centre (Ikeda and Robbins, 1988; Dowling. 1990). Maximum excitiation of an ON-centre ganglion cell will occur when a spot of light fills the central region. A larger spot of light will produce a lower response if it impinges on the surround region due to lateral inhibition, filling the whole of the receptive field gives the lowest response (Gilchrist, 1988). Non-linear receptive fields have also been described in the cat retina - but remain unconfirmed in primates - such as cells with no antagonistic surround (sluggish cells), 'local edge detectors', direction selective cells, 'suppressed by contrast units' and colour opponent units in monkey (Lennie 1980).

Colour opponent cells are the most common type in the foveal region - they receive their central input exclusively from a single class of cones (L, M or S) and their surround input from a different cone class (or classes). There are L ON centre cells with M OFF surrounds, M ON centre cells with L OFF surrounds, M OFF centre cells with L ON surrounds, and L OFF centre cells with M ON surrounds. There are also S ON centre cells with either M or L M OFF surrounds (Dow, 1991).

Figure 4.8.

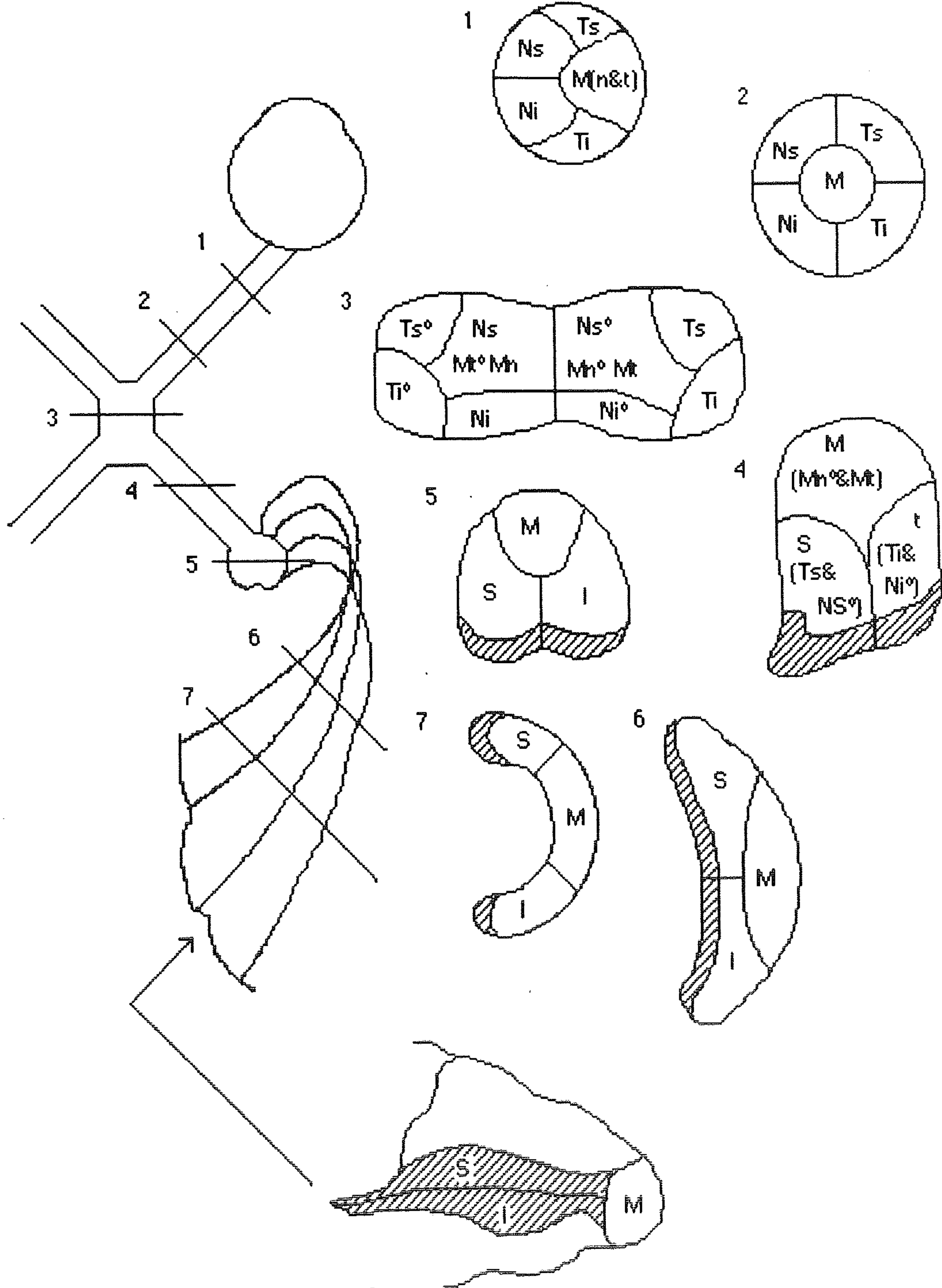


Graphical representation to show the principal of the difference of gaussians (adapted from Kaplan, 1991).



Digram to show the ON and OFF receptive fields of ganglion cells, (adapted from Gilchrist, 1988).

Figure 4.9. Diagram to show the position of nerve fibres from the retina to cortex (M = macular fibres, T = temporal, N = nasal, S = superior, I = inferior, ° = equivalent fibres from left eye); (adapted from Ruskell, 1988).



As the output of bipolar cells vary with the state of light adaption - so also do the receptive fields of ganglion cells. Under scotopic conditions the surround mechanism becomes less effective at inhibiting the central region such that the overall response is dominated by the central region (Werblin *et al*, 1991). Under these conditions the spectral sensitivity of the central region also alters with responses becoming more rod-like. Receptive field sizes also alter with retinal eccentricity - they are smallest in the foveal region and gradually increase in diameter with increasing eccentricity.

Amacrine cell input to ganglion cells may contribute to antagonistic surround mechanisms and may also impart more complex properties to the ganglion cell receptive fields, such as orientation selectivity (Dowling, 1990).

Thus the receptive field characteristics of ganglion cells are the result of a complex set of transformations within the retina, these being a system of summation and convergence of visual information from photoreceptor, through bipolars to the ganglion cells. Together, this system reduces the signal to noise ratio and increases retinal sensitivity. The visual information passing from the ganglion cells down the nerve fibres is also topographically organised such that fibres from the superior retina enter the optic nerve head superiorly, nasal fibres enter the optic nerve head nasally and macula fibres enter temporally. There is a rotation of fibres before they enter the optic chiasm such that the macula fibres enter it centrally. However, the fibres remain segregated throughout the visual pathway (figure 4.9).

4.2.2. Lateral Geniculate Nucleus.

The LGN is generally regarded as a relay station where a group of cells receives input from the retina and sends connections to the cortex. Most of the cells of the LGN are thus relay cells, although up to 25% are interneurons and do not send axons out of the nucleus (Casagrande and Norton, 1991; Kaplan, 1991).

Geniculate cells behave in a similar way to retinal ganglion cells in having concentrically organized receptive fields. The properties of these receptive fields resemble their retinal input eg ON-centre retinal ganglion cells produce ON-centre LGN cells (Casagrande and Norton, 1991). The receptive field centre size is also maintained in the LGN cells representing the central retina having smaller receptive field sizes - with increasing eccentricity the receptive field centre sizes also increases. Those with the smallest receptive fields are found in the parvocellular

layers (Lennie, 1980). Most of the cells of the parvocellular layers are spectrally opponent (although up to 25% are not) (Wiesel and Hubel, 1966; Lennie, 1980). Parvocellular cells fall into two major categories red/green and yellow/blue showing either L/M opposition or S opposition to one or both of the two cone types. The magnocellular layers have mainly spatially though not spectrally opponent receptive fields (although a very small number which are seldom encountered have rather crude colour - opponency) and have only ON centre receptive fields (Lennie, 1980). Cells of the magnocellular layers tend to have larger receptive fields.

It has also been found that the receptive fields centres of many LGN cells in cats and primates are actually somewhat elliptical in shape (Cleland and Enroth - Cugell, 1968; Irvin *et al,* 1986; Casagrande and Norton, 1991). This may be a continuation from the retina and is thought to represent the first step in setting up the orientation selectivity found in many visual cortical neurons.

It has been suggested that in macaque ON and OFF centres are segregated within the LGN, ON centre cell occupying parvocellular layers 5 and 6 and OFF centre cells in parvocellular layers 3 and 4 (Wiesel and Hubel, 1966; Schiller and Malpeli, 1978; Kaplan *et al,* 1991; Garey *et al,* 1991). However, more recently, this has been shown to be only a mild bias (Kaplan and Shapley, 1982; Derrington and Lennie, 1984).

Due to the presence of interneurons and input from other areas of the brain - the LGN cannot merely be a relay station. The visual information is modified as it passes through the structure eg many retinal spikes do not always produce an LGN relay spike. This is the result of the action of inhibitory circuits and other non-retinal inputs. These inhibitory circuits include a feed forward circuit through the LGN interneurons and a feedback circuit (from the reticular nucleus) (Casagrande and Norton, 1991). Non retinal inputs include (taken from Casagrande and Norton):

1. Diffuse global neuromodulatory control from noradrenergic and serotonergic brainstem pathways.
2. More specific non-retinotopic control through several different cholinergic brainstem pathways.
3. Focal excitatory control through visuotopically organized connection from cortex, superior colliculus, pretectum, and other non-retinal visual areas.

Each geniculate layer contains a precise retinotopic map of the contralateral visual field. In monkey, the upper visual field projects inferio-laterally while the lower field projects supero-medially. The representation of zero vertical meridian of the visual field is located caudally, with peripheral field representations located rostrally in the nucleus. The fovea projects to the caudal pole of the LGN (Connolly and Van Essen, 1984). The area occupied by the foveal projection is wedge-shaped and proportionally much greater than that devoted to the periphery. This 'over-representation' of central visual field is known as the magnification factor, and is mainly due to the high density of ganglion cells representing the foveal region. Connolly and Van Essen also suggest that there is more emphasis on central vision in parvocellular layers than magnocellular layers - although this was disputed by Livingstone and Hubel (1988).

4.2.3. Superior Colliculus.

Electrophysiological techniques have been used to assess the receptive field properties of the superior colliculus. A detailed study by Cyander and Berman (1971) on macaque monkey using electrode penetration into the superior colliculus resulted in being able to divide the responses from superficial, intermediate and deep layers. They found that superficial cells had a centre and surround organisation very similar to that of ganglion cells but the surround region could inhibit the activation of the central region but could not elicit a response itself. These cells responded well to moving slits of any orientation, to concave, convex, serrated, and flat tongues, and also to small circles, annuli, ellipsoids, and other irregular shapes. Some cells showed little specificity to stimulus size while others responded best to stimuli smaller than the central region. They found that most cells in this region responded better to moving stimuli than to those just flashed on. Optimal speed of target was 0.5 - 30°/sec and an optimal diameter of light spot of 30' to 1.3°. They showed no direction selectivity.

A study by Humphrey (1968) also revealed cells that responded best to moving stimuli (5 - 10°/sec), although they found no clear differentiation with depth of electrode penetration. A review by Wurtz and Albano (1980) also states that superficial cells respond briskly to visual stimuli and are not fussy about stimulus size, shape, direction or speed of movement (responding well to speeds as slow as 5°/sec and as high as 600 - 900°/sec). This review also states that the corticotectal cells of the superficial superior colliculus show weak orientation specificity, weak

directional specificity, and are binocular with complex type receptive fields (also Rhoades *et al* 1991).

Schiller and Malpelli (1977) describe their cells as being broad-band (ie showing no colour opponency), having receptive fields similar to the equivalent ganglion cell, and rarely encountered cells showing a lack of colour sensitivity, relatively slow conduction velocity, some of which having very little or no surround inhibition.

With deeper penetration into the superior colliculus the receptive fields become larger (Humphrey, 1968; Cyander and Berman, 1971; Schiller and Malpelli, 1977; Wurtz and Albano, 1980; Rhodes *et al,* 1991). In the intermediate layers, Cyander and Berman found cells having receptive fields whose central region was circular, ellipsoid or approximately rectangular. They had lower spontaneous activity and gave a weaker response on repeated stimulation. These cells were also insensitive to stimulus detail, shape of orientation. They were found to respond best to novel stimuli moving through the receptive field or appearing suddenly within the field. They also found one class of cell that responded better to flashing stimuli than to smooth movement. Wurtz and Albano state that most of the cells of the deeper layers are involved in the initiation of eye movements. Some of these cells discharge before saccadic eye movements to a visual target.

A review by Rhoades and colleagues (1991) indicates that many of the cells of the deeper layers receive indirect cortical input as ablation of the visual cortex has little effect on the superficial layers. The deep layers according to Cyander and Berman contain cells that respond well to large dark objects, that are binocularly driven, give weaker responses on repeated stimulation and have larger receptive fields than the more superficial layers.

Humphrey states that the receptive fields of units recorded in one penetration lay in the same part of the visual field, indicating columnar organisation - however this still remains inconclusive.

Like the LGN, the retina is mapped onto the superior colliculus. The more nasal portions of the visual field (temporal retina) are mapped rostrally in the colliculus, and the upper, lower, and temporal fields are mapped in the medial, lateral and caudal superior colliculus. In macaques, the vertical meridian is represented most rostrally and successively more temporal parts of the visual fields are represented

more caudally. Additionally, the area centralis has a higher collicular magnification factor that the peripheral retina.

4.2.4. Visual Cortex.

The cells of the visual cortex can also be classified according to their receptive field properties. The original classification was made by Hubel and Wiesel (1968). They found cells in layer IV that had concentric receptive fields that received input from one eye and which responded to a spot of light. They receive direct input from the dLGN cells. They also found cells with ON and OFF receptive fields, as before, but this time the receptive fields were found to be elongated so that they were maximally stimulated by a bar of light and were called 'simple cells'. Simple cells are found mainly in layer IV of the visual cortex but are also found in the deeper layers (Hubel and Wiesel, 1968; Lennie, 1980; Zeki, 1993). These simple cells are orientation specific, the response being markedly reduced when the stimulus orientation differs by 10° or 20° from the optimum and completely absent when it differs by 90°. It is thought that the elongated receptive field arrangement is the result of input from several centre surround antagonistic cells of the LGN arranged in a row (Zeki, 1993).These cells may also show specificity to spatial frequency, velocity and direction of movement (Orban, 1991).

The second class of cortical cells are the 'complex cells' which have larger receptive fields and are thought the be the result of convergence of a number of simple cells (Lennie, 1980; Henry, 1991; Zeki. 1993). This results in both ON and OFF responses to be obtained from every part of the receptive field with no distinct antagonistic ON and OFF region. Their optimal stimulus is usually an edge or slit of the appropriate orientation often moving in a particular direction and smaller that the receptive field (Lennie, 1980). They receive input from both eyes and are thus binocular. They are found in greatest numbers in Lamina V of the visual cortex (Henry, 1991).

Table 4.3 gives a summary of the differences between simple and complex cells (adapted from Nelson 1988).

Cells with more complicated receptive fields have been described and were known as hypercomplex cells, and are usually found in the association areas.Like simple and complex cells they respond to lines of a specific orientation but the length of the

line is of importance. They are now referred to as 'end inhibited' or 'end stopped' cells.

Table 4.3. Differences between simple and complex cells.

SIMPLE	COMPLEX
Separate ON/OFF areas	Mixed
Separate response areas to the light edge / dark edge of a moving bar.	Mixed
Small receptive field.	Large
No spontaneous discharge.	Action potentials emitted in the absence of visual stimulation.
Response summates as stimulus length and width are increased, up to full size of RF.	Response saturates when stimulus is still smaller than RF
Sensitive to stimulus position within RF.	Phase insensitivity.
Linear. frequency	Non-linear, saturating, doubling.
Sharp orientation tuning.	Less sharp.
Tend to be stellate cells, tend to be local to cortex.	Tend to be pyramidal cells, tend to project out of one cortical area.
Tend to receive primary or second-synapse visual input in striate cortex.	Tend to occur later in the information processing chain.

Colour selective cells are known to exist in the visual cortex. Some of which show 'double opponency' which means both spatial and chromatic selectivity. Colour selectivity cells exist in simple, complex and end inhibited classes. It is thought that cells showing colour opponency are not orientation specific, while achromatic cells are orientation specific.

The visual cortex is also thought to have a columnar organisation. This was first suggested by Hubel and Wiesel (1977) who used electrode penetrations in cat and macaque cortex. A perpendicular penetration in area Vl encountered cells that responded to the same orientation and all cells were activated by one eye only or dominated by that eye.Thus the cells seemed to be arranged in columns, referred to as orientation and ocular dominance columns (Gilbert et al, 1991; Valverde, 1991; Le Vay and Nelson, 1991; Zeki, 1993). The receptive fields of cells encountered in a perpendicular penetration also occupy the same retinal position (although with a small amount of scatter). The complete area represented by one penetration is known as the total aggregate receptive field and will be smaller at the fovea compared to the periphery. An oblique electrode penetration revealed that the orientation specificity of successive cells changed systematically while the eye preference would remain the same and then change suddenly to the other eye.

A tangential penetration encounters cells whose receptive fields represents areas of the retina adjacent to each other. These receptive fields overlap each other and a 2mm penetration represents a functionally separate area of retina. The same amount of electrode penetration will encounter cells whose orientation specificity has rotated by 180°, and all the varying degrees of ocular dominance will be represented twice. These ocular dominance columns have been demonstrated in monocular post mortem human cortical area 17 using silver and Golgi staining methods. The columnar organisation of the visual cortex is shown schematically in figure 4.10. (Zeki, 1993).

As a result of this columnar organisation, the visual cortex contains a detailed map of the retina. The right visual cortex receives projections from the right temporal retina and left nasal retina. In each striate cortex, the superior retina is represented in the upper lip of the calcarine fissure, while the inferior retina is represented in the lower lip. Central vision (5°) is represented at the pole of the occipital pole, more peripheral visual field projects to positions deeper into the fissure. The upper and lower octants adjoining the vertical meridian of the visual field are represented on

the lower and upper medial surfaces of the cortex. The lips of the fissure represent the 45° and 135° meridians. This is shown diagramatically in figure 4.11.

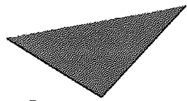


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Figure 4.10. Schematic diagram to show the orientation and ocular dominance columns in area Vl of the monkey visual cortex (from Zeki, 1993).

4.3. Parallel Pathways.

For the last 25 years it has become evident that the visual system is arranged into functionally separate pathways. The distinction begins in the retina with the existence of different sub-classes of retinal ganglion cells. These cells can be differentiated by their anatomical, physiological, and psychophysical properties. From the retina, this distribution is maintained through the LGN to the visual cortex.

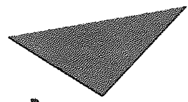

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Figure 4.11.

Projection of the right visual field on the left visual cortex in humans (from Brindley 1970)

4.3.1. Anatomical Properties.

The existence of parallel pathways was made evident by Enroth-Cugell and Robson (1966) who demonstrated that cat retinal ganglion cells could be physiologically separated into X and Y cells. Later, an additional cell type, W-cells were added to the classification (Stone and Fukuda, 1974). Cat retinal ganglion cells have also been morphologically classified. Boycott and Wassle (1974) distinguished four types of cells (alpha, beta, gamma and epsilon) by Golgi stain (Lennie, 1980; Stone, 1983). Alpha cells have large somata, thick axons and large dendritic fields and are thought to correspond to the Y cells. Beta cells have medium sized somata and axons and very small dendritic trees and are thought to correspond to the X cells. Gamma cells have the smallest somas and axons, but large, sparse dendritic trees and may correspond to the 'W' cells - although this still remains uncertain (Lennie, 1980; Stone, 1983; Shapley and Perry, 1986; Karten *et al*, 1990; Rowe, 1991). At any retinal eccentricity, alpha cells have a dendritic tree two to three times larger than those of beta cells, and the dendritic tree of both types increase steadily with eccentricity, so that the smallest alpha cells in the vicinity of the area centralis are very similar to the largest peripherally located beta cells. Cleland and colleagues (1975) found that alpha cells represented 3 - 4% of ganglion cells everywhere except in the central area where the proportion drops to about 2%. In areas 14° from the central area, it has been suggested that the ratio of cell numbers of gamma-, beta-, and alpha- cells is 38:55:7, whereas in the central area the proportion of gamma cells still constitutes approximately 40% of the population while the proportion of supposed beta cells rises to nearly 50% at the expense of alpha cells (Lennie, 1980).

The larger alpha cells of cat retina project via axons of large calibre and distinct arbor morphology to the larger cells of laminas A, A1,C and MIN of the dLGN. The medium sized beta cells with confined dendrites project via axons of intermediate calibre and distinct, restricted arbor morphology to medium sized LGN cells in laminas A1, A, C and MIN. A few X (or beta) cells also project to other midbrain areas but are unlikely to project to the superior colliculus, while many Y (alpha) cells project to the superior colliculus (Stone, 1983). The W cells (gamma) are projected mainly to the superior colliculus, with some input to layer C of the dLGN, medial interlaminar nucleus and pulvinar (Stone, 1983; Garey *et al,* 1991).

Two distinct types of ganglion cells have been identified in primate retina which may correspond to cat alpha and beta cells. They have referred to by various forms of nomenclature such as parasol and midget cells by Rodieck (1985), A and B cells by Leventhal and colleagues (1981), or Palpha and Pbeta by Perry and Cowey (1981) (Stone,1983; Rowe, 1991; Kaplan, 1991).More recently they have been named as M cells (as they project to the magnocellular layers of the dLGN) and P cells (as they project to the parvocellular layers of the dLGN). A further class of cell which are neither M or P and have been described as 'rarely encountered' cells or C and E cells and may be the equivalent of the W or sluggish cells of the cat. These project to the superior colliculus, pretectum and konicocellular dLGN (Wurtz and Albano, 1980; Stone, 1983; Garey *et al*, 1991). The P cells represent about 80% of the total retinal ganglion cells, M cells account for 10% and the C or E cells make up the remaining 10%.

P cells have small soma diameters, small dendritic fields and medium sized axons. M cells have large soma with medium sized dendritic fields and large axons. W-like cells have small soma, large dendritic fields and small axons (Bassi and Lehmkuhle, 1990; Kaplan *et al,* 1991; Kaplan, 1991).

P cells are distributed throughout the retina with a relatively high density in the fovea, M cells are evenly distributed over the retina and are present in the foveal pit - although they are buried deep in the pile of ganglion cells (Kaplan *et al* 1991).The size of both M and P cells increase in size with eccentricity such that a peripheral P cell can have the equivalent size as a central M cell (Bassi and Lehmkuhle, 1990). The dendritic tree size of M cells increases in size with eccentricity. That of the P cells remain constant within the central 10° - beyond this it increases and becomes variable. These properties are shown schematically in figure 4.12.

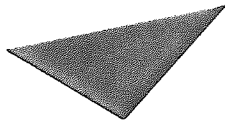
The superior colliculus receives direct retinal input - Hofmann demonstrated that two direct retinotectal projections could be distinguished in the cat: a fast direct pathway composed of retinal Y cells and a slower direct pathway composed of retinal W-cells. These two direct pathways terminate in the stratum griseum superficiale (the W cell input being more superficial than the Y input). A third pathway, referred to as the Y indirect pathway, projects via select Y cell rich laminae of the LGN to standard and special complex cells of striate cortex and area 18 and from these to terminate in the stratum griseum superficiale of the ipsilateral superior colliculus. A Y cell input has also been shown in the upper portions of the deep laminae (Wurtz and Albano, 1980; Stone, 1983; Rhoades *et al,* 1991; Stein

and Meredith, 1991). Most authors have not demonstrated an X-cell input to the superior colliculus (Fukuda and Stone, 1974; Leventhal *et al*, 1985), but some (Cleland and Levick, 1974; Sawai et al, 1985) have shown that a small proportion of the cat's X-cells project to the superior colliculus. In macaque Leventhal and colleagues (1981) showed that very large ganglion cells (A type) and smaller ganglion cells with widespread but very thin dendrites (C type) project to the superior colliculus. Additionally electophysiological studies of Schiller and Malpeli (1977) on Rhesus monkey superior colliculus identified two groups of cells - broad band cells (M) and rarely encountered cells (W-like cells).

Most of the neurons of the LGN are relay cells receiving information from the retina and transmitting it onwards to the visual cortex. Thus the X and Y divisions of the retina remain in the LGN. Likewise in primate P cells of the retina are relayed within the parvocellular layer of the LGN and the M cells of the retina are relayed within the magnocellular layers.

From the LGN the X cells of the cat project to area 17 of the visual cortex, particularly to layers 4C and 6 (Stone, 1983, Garey *et al,* 1991). Y cells of the cat project from the MIN strongly to area 18, probably also to area 17 and to the suprasylvian gyrus, and perhaps to area 19; while the Y cells of laminae A, A1 and C project to areas 17 and 18 (Stone, 1983), with main Y cell projection to area 18, their projection to area 17 remains controversial (Garey *et al* 1991).It has been suggested that the X and Y terminals remain segregated within the layer lV of the cortex such that Y cells terminate in the upper part of layer lV (sublayer lVab) and the lower part of layer lll, while X-type geniculate afferents terminate in the lower part of layer lV (sublayer lVc), (Valverde, 1991) However this segregation has been severely challenged. Although most W cells project to the superior colliculus, some also project to areas 17, 18 and 19 (mainly 19) of the visual cortex and to the lateral suprasylvian gyrus (Lennie, 1980; Stone, 1983).

Figure 4.12. Schematic diagram to show the distribution of M and P cells over the retina. The size of the characters represents the relative size of their dendritic fields (from Bassi and Lahmkuhle, 1990).



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In monkey the P cells of the dLGN project to layer lVA and lVC beta of the striate visual cortex, which projects diffusely to the blobs and interblobs of layer lll. M cells of the dLGN project to layer lVCalpha, to layer lVB, and to the blobs of layer lll (Stone, 1983; Bassi and Lehmkuhle, 1990; Garey *et al,* 1991; Kaas and Krubitzer, 1991; Valverde, 1991). From layer lll the P cell project to extrastriate areas including the pale stripes of area 18. From area 18 they proceed to the dorsal lateral area, and to the caudal portion of the temporal cortex. The M cells project from layer lVB directly to the middle temporal area and indirectly via the thin stripe region of area 18 (Bassi and Lehmkuhle, 1990). This pathway is shown schematically in figure 4.13.(see also figure 4.6).

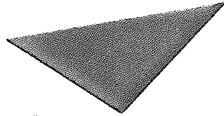
Thus there appears to be three processing streams within the visual cortex, the parvo-blob stream (P-B), the parvo-interblob stream (P-iB), and the magno stream (M) (Van Essen *et al,* 1991). The M stream is highly direction selective, with some cells being selective for orientation and disparity, but few selective for wavelength. The P-iB stream has cells that are orientation selective, wavelength selective and responsive to binocular disparity. The P-B stream has many wavelength selective cells, but fewer orentation and direction selective cells (Van Essen *et al,* 1991). Gilbert et al (1991) found that the majority of cells in the blob regions were colour specific, with individual blobs specializing in particular colour opponency: red/green or blue/yellow.

4.3.2.Physiological Properties.

Physiological classification of retinal ganglion cells have evolved from experiments involving intracellular recordings monitoring the response of single cells to sinusoidal patterns of varying spatial frequencies, temporal frequencies and contrasts. The first distinction was made by Enroth-Cugell and Robson on cats in 1966 who used sinusoidal gratings to show that in some cells the response to a bright bar over one part of the receptive field of that cell could be cancelled out by a dark bar in another part of the receptive field, thus showing linear summation - these cells they called X cells. Other cells, namely Y cells did not show this effect, thus illustrating non linear summation. For circularly symmetric receptive fields therefore, X cells were able to show a 'null' position, which is the position of a sinusoidal grating over a receptive field that results in no response because the response from the centre can been completely cancelled by the response from the surround (this is illustrated in figure 4.14). A 'null' position could not be found for Y cells. Figure 4.14 also shows that Y cells responded to the grating at twice the rate of stimulation (Lennie, 1980; Stone, 1983; Shapley and Perry, 1986; Kaplan, 1991).

Cleland and coworkers (1971) distinguished two types of ganglion cell in terms of their temporal characteristics. They found that both cell types, namely 'sustained' and 'transient' showed a sharp increase in discharge rate corresponding to the onset of the stimulus, but whereas the sustained type maintained the response for the duration of the stimulus presentation, the transient cells' response rapidly returned to resting level. These cells are likely to correspond to X and Y cells respectively (Lennie, 1980, Stone, 1983; Kaplan, 1991).

Figure 4.13



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Schematic of striate and extrastriate cortex. Horizontal hatching denotes areas related to M-cell pathway,vertical hatching related to P-cell pathway, cross hatching is overlap between the two systems. A: Tangential schematic showing layers of striate cortex. I-VI refer to layers within cortex, blobs/interblobs refer to staining with cytochrome oxidase. B: Schematic of area VII (stripes are not drawn to scale). This insert is a representation of the three types of cytochrome oxidase staining patterns found in VII, as well as their associated pathways: thick stripes = M-pathway; thin stripes = M- and P- pathway; pale stripes = P- pathway. C: Schematic of brain: PP = posterior parietal,, DL = dorsal lateral, MT = middle temporal, ST = superior temporal, IT = inferotemporal.(From Bassi and Lehmkuhle, 1990).

A third type of ganglion cell, the W cell has also been described which project to the superior colliculus. They are a heterogenous group of cells with large receptive fields and slow conduction velocity.

Since these discoveries in cat, similar investigations have been carried out in monkey. This was first done by Gouras (1969) who described 'tonic' and 'phasic' cells in rhesus monkey - the tonic cells responded to the stimulus for as long as it remained on, while the phasic cells responded only to the onset or offset of the stimulus. The tonic cells were also found to be colour opponent while the phasic cells were not. Following the anatomical segregation of ganglion cells into A and B or Palpha and Pbeta - these cells were physiologically segregated into M (magnocellular projecting) and P (parvocellular projecting) cells. A group of cells projecting to the superior colliculus and comparable to the cat W cell have also been distinguished. They have large receptive fields, low spontaneous activity, slow conducting axons and are known as rarely encountered cells or W-like cells (Stone, 1983).

Although the tonic and phasic cells can be compared to the X and Y cells of the cat, it has been shown that the similarities between cat and monkey cell groupings is only partial. This is partly due to the fact that the primate is diurnal and has a cone-dominated retina while the cat is nocturnal and has a rod-dominated retina. Therefore the primate retina has a mechanism more involved in the analysis of colour. The differences between cat and monkey will become evident within this chapter.

4.3.2.1. Receptive Fields.

As previously mentioned the receptive fields of X and Y cells consist of a roughly concentric centre and surround mechanism (this is also true for some but not all W cells). There is general agreement that at any retinal location, X cells have the smallest receptive field centre regions of the three classes, while the Y cells and W cells have the larger receptive fields (Lennie, 1980; Stone, 1983; Kaplan. 1991).

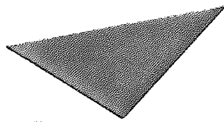

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Figure 4.14. X and Y cells' responses to the appearance and disappearance of a fine sine-wave grating at four different positions within their receptive fields. (a) Average response of an X-OFF cell, showing strong responses at 0° and 180° spatial phase (indicated on the right), but no response at 90° ar 270° (the so-called 'null points'). The position of the grating with respect to the receptive field centre are illustrated in the right column. (b) The average response of a Y-ON cell, showing a frequency-doubled response at all four grating positions: the cell discharged in response to the appearance and disappearance of the grating. The horizontal bars indicate 1.1s (From Enroth-Cugell and Robson, 1966).

It has been suggested that in the central retina of cat, the receptive field centre size of X cells is about 0.5° or less, while those of Y cells is about 1°, and that at any one eccentricity the centre diameters of Y cells are between 2 and 3 times those of X cells. The smaller receptive field size of X cells and their higher concentration around the area centralis has been interpreted as evidence that these cells are involved in high spatial resolution. In all three cell groups there is a trend for the receptive field centre size to increase with retinal eccentricity while there is no systematic increase in surround size. This is less marked for W cells.

Studies have also indicated that the diameters of the surround region in Y cells was rather similar to the diameter of the centre region, whereas in X cells the centre was substantially smaller than the surround. This has an important implication with regard to the response of these two cell types to large stimuli : X-cells will respond only weakly to such stimuli, whereas Y cells will respond more vigorously.

In monkey M and P cells have roughly circularly, concentrically arranged receptive fields (Bassi and Lehmkuhle, 1990). De Monasterio and Gouras (1975) have also shown that in monkeys the receptive field diameters of P ganglion cells are smaller than M cells. They reported that the smallest P receptive fields had diameters of approximately 0.01° with an average of 0.03°, while the average M receptive field had a diameter of 0.06°. It was later established by Derrington and Lennie (1984) that the radius of the central region of an average M cell is 2 - 3 times larger than the smallest P cell (Kaplan *et al*, 1991) making their area 4 - 9 times larger (Kaplan, 1991). As in cats the receptive field size of M and P ganglion cells increase with retinal eccentricity (Bassi and Lehmkuhle,1990).

4.3.2.2. Contrast Sensitivity and Contrast Gain.

Contrast Sensitivity is a measure of spatial visual performance and is based on the fact that contrast is the basic requirement of edge detection. The amount of contrast needed for a grating to be just detectable is called the contrast threshold and its reciprocal is the contrast sensitivity. Contrast can be defined by the Rayleigh-Michelson equation:

$$C\% = 100 \text{ X } (Lmin-Lmax) / (Lmin+Lmax)$$

(where Lmin and Lmax are the minimum and maximum luminance levels within the stimulus and C is contrast expressed as a %).

Derrington and Lennie (1984), Kaplan and Shapley (1986) and Shapley and Perry (1986) have measured the sensitivity of retinal ganglion cells to contrast. They found that on average M cells were 8-10 times more sensitive to luminance contrast than P cells (Kaplan et al, 1991; Bassi and Lehmkuhle, 1991, Kaplan, 1991). This is shown graphically in figure 4.15 which shows data adapted from Kaplan and Shapleys results (1986) illustrating the average response versus contrast functions for a sample of 8 M cells and 28P cells recorded from one rhesus monkey.

From this figure it can also be seen that the rate of increase in response with increasing contrast is greater for M cells - i.e. they have a greater contrast gain. Additionally the figure demonstrates that the responses of the P cells are linearly related to contrast and do not saturate at high contrast, while the M cells' response saturates above 10-15% (Kaplan *et al,* 1991; Kaplan, 1991). However the response amplitude of the M cells still increase beyond contrasts of 10-15% though at a lower rate, such that their contrast gain is lower at high contrasts than at low contrasts.

The higher contrast gain of M cells compared to P cells persists even when coloured gratings are used instead of black and white. Under these conditions the contrast gain of the P cells increase but still fail to reach the level of that achieved by the M cells. There have been a number of explanations for this difference in contrast gain such as (l) Pcells are less sensitive because their receptive field is smaller, (ll) Pcells are less sensitive because of mutual cancellation of cone signals (lll) P cells are less sensitive because they have restricted wavelength specific cone input compared to M cells - these are described in detail in a review by Kaplan *et al* (1991).

Light adaption is a major factor in determining the contrast sensitivity of a neuron. It has been found that as retinal illumination is reduced the contrast gain declines. As M cells have a contrast gain that is roughly 8-10 times that of P cells, they can continue to function even when the retinal illumination declines to the scotopic level. P cells, on the other hand, cannot detect visual patterns under scotopic conditions. Additionally it was found that the M cell's response versus contrast function became linear at low light levels, such that it looked very similar the response function of P cells under high luminance levels (Purpura *et al,* 1988).

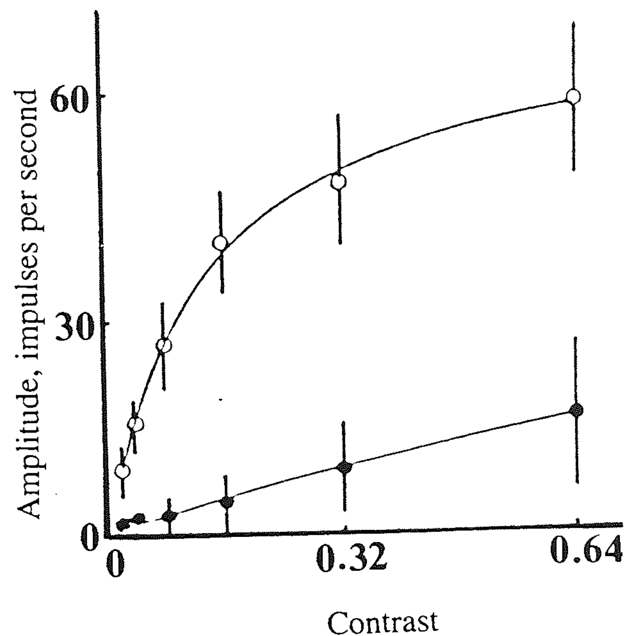

Figure 4.15 The average response vs contrast functions for a sample of 28P cells (filled circles) and 8M cells (empty circles), recorded in one rhesus monkey.The cells' activity was monitored at the LGN in the form of S potentials. The stimuli were sine-wave gratings, drifting on a (white) CRTA at a rate of 4Hz, and their spatial frequency was adjusted to be optimal for each cell. The error bars represent ±1 SD.

This large difference in contrast gain between M and P cells provide a clear distinguishing feature and Kaplan and coworkers suggest that it can be used as a means for the selective stimulation of one cell population without perturbing the other. Thus the use low contrast stimuli would bias the input to the cortex in favour of contribution from the M cell population, and minimize the response from the P cell population.

4.3.2.3. Spatial Resolution.

As the receptive field of P cells are smaller than those of M cells, it has often been stated that the M system is a low resolution, low acuity system and the P system is the carrier of information about fine detail. However,as stated by Kaplan and coworkers (1991), the ability of a neuron to respond to a fine pattern is determined by the product of the receptive field area and the peak point sensitivity, and is limited by the noise level in the system. It is found that given a high enough contrast sensitivity, a large detector can respond to fine detail at least as well as a small detector. This suggests that the M system can resolve fine detail as well as the P system. However, this also depends on the level of background noise. As the P system has a much higher number of cells - the resulting summed cortical response should have a reduced noise level, giving the P system the advantage particularly at the fovea. This higher sampling density also results in the P system being superior in stimulus 'recognition'. Thus it is generally accepted that M cells are about 10 times more sensitive than P cells to spatial frequencies lower than 1cpd and P cells are more responsive than M cells at high spatial frequencies (> 10cpd) (Bassi and Lehmkhule, 1990).

From these results it seems that spatial frequency alone does not provide us with an effective means of selectively stimulating the M or P pathway - but may be used in addition to other characteristics.

4.3.2.4. Chromatic Sensitivity.

Colour vision begins at the photoreceptor level. It has been established for some years that there are three cone types containing different photopigments. These cones are sensitive to different wavelengths of light. The L cones (long-wavelength sensitive) are maximally responsive to a wavelength of about 565nm, M cones (middle-wavelength sensitive) are maximally responsive to a wavelength of about 535nm and S cones (short-wavelength sensitive) are maximally responsive to a wavelength of about 420nm. The sum of the absorbances of the three cones provides a measure of our total visual sensitivity in daylight (photopic sensitivity). The absorbance of the rods provides a measure of our visual sensitivity at night (scotopic sensitivity). While photopic sensitivity results from the summing of the signals from three cones (or possibly from two cones), chromatic sensitivity is thought to be due to subtraction of cone signals from one another (Kaplan *et al*,

1991; Dow, 1992; Kaplan, 1991). Given three types of cones, there are 12 possible subtractive combinations. However, the great majority of cells (approx 85%) receive input from only M and L cones (either +M-L, or +L-M). Some cells receive input from S cells, opposed by a combination of the other two (+L+M-S, -L-M+S).

As mentioned previously, On and OFF centre / surround opponency begins at the bipolar cell level, and it is likely that there are separate classes of LON and LOFF centre bipolar cells as well as MON and MOFF centre bipolars in the primate retina. The S system may be slightly different as S cones are more sparsely distributed particularly in the foveola.

This spectral opponency continues at the ganglion cell level. The earliest distinction was made by Wiesel and Hubel (1966) who described four types of ganglion cell: Type l cells have concentric centre surround receptive fields with a colour opponent organisation, type ll cells have colour but not spatially opponent receptive fields, type lll cells have spatially but not colour opponent receptive fields, and finally type lV cells have 'on-centre' colour opponent receptive fields (Lennie, 1980). Wiesel and Hubel also suggested that the centre of the receptive field received input from one cone type while the surround received input from on opponent single cone type. However, evidence has shown that the horizontal cells that are responsible for the surround mechanism are not cone specific. It has therefore been suggested that more than one cone type feeds the surround region, and that the surround response is determined by the cone type which forms the majority in the surround region (Kaplan *et al*, 1991; Shapley *et al*, 1991; Kaplan, 1991). It is thought that the majority of P cells tend to be type l, but some are type ll and lll, whereas the M cells tend to be type lll and a few type lV. De Monasterio and Gouras (1975) have also demonstrated that the P cells are mainly colour opponent and that M cells are achromatic. The chromatic sensitivity of the P cells have also been demonstrated using lesion studies (Merigan, 1989,1991; Merigan and Eskin, 1986; Merigan and Maunsell, 1990; Schiller *et al,* 1990; Schiller, 1991; Lynch *et al*, 1992; which will be described in more detail in section 4.3.2.6) as well as with psychophysical and electrophysiological techniques (reviewed by Kaplan et al, 1991, Kaplan, 1991; Dow, 1991).

Additional evidence to suggest that the P pathway is responsible for colour vision is provided by the fact that in man the ability to see a full range of colour is restricted to central vision (where there is a higher proportion of P cells). Colour sensation can be elicited from the peripheral retina with the use of large stimuli, but it remains

impossible to elicit perception of saturated colours and particularly saturated greens. It has been suggested from experiments on monkey that the P cells in the central 1.6mm (8°) have small constant dendritic trees and are colour opponent. Those outside 1.6mm have a gradually increasing dendritic tree size and are thought to be hidden opponent cells dominated by red cone input (Shapley and Perry, 1986).

The M cells are largely broad band. Their spectral sensitivity corresponds closely to the overall luminosity function of the eye. As the luminosity function is thought to be derived from the summation of L+M cones, it suggests that both cone types provide input to the centre and surround of the M cells. However, the M cell system is not totally colour blind due to the non-linear contribution of the L and M cones to the surround. It has been shown that a residual response still remains even if an isoluminant stimulus is used - this response is reduced if the stimulus is restricted to the centre of the receptive field (thus reducing surround contribution). The 'rarely encountered' cells or 'W' like cells usually lack colour selectivity (Schiller and Malpeli, 1977). Thus, as mentioned previously, the superior colliculus is insensitive to colour.

The use of an isoluminant chromatic stimulus thus provides a useful method of preferentially activating the parvocellular pathway, particularly if the stimulus is restricted to the central retina around the fovea.

4.3.2.5. Temporal Characteristics.

Ganglion cells can be classified according to their temporal characteristics. Enroth-Cugell and Robson (1966) and later Cleland *et al* (1971) describe two types of cat ganglion cell - one group of cells responded with a discharge modulated about a steady mean, while the other responded to gratings of high spatial frequencies with an increase in steady discharge. These groups almost certainly correspond, respectively, to X and Y cells, but Cleland preferred to call them 'sustained' and 'transient'. This sustained / transient distinction seems to be much more apparent at high contrast than at low (Shapley and Perry, 1986).

This temporal differentiation can also be applied to the M and P pathway of primates and the distinction was first made by Gouras (1969) who described them as phasic and tonic. Conduction time, temporal resolution, visual latency and response duration are four response measures used to indicate the temporal differences between M and P cells (Bassi and Lehmkuhule, 1990).

The conduction velocity of an axon is largely dependent upon axon diameter and hence the amount of myelination. The M pathway is more thickly myelinated (large axon diameter) and conducts more quickly than P cells which are more thinly myelinated. Ogden and Miller (1966) describe two groups of fibres in the rhesus macaque having conduction velocities of 8 and 4 m/sec. Griffin and Burke (1974) also describe two groups of nerves in the cynamologus monkey (M.inis) with much higher velocities of 22 and 11m/sec. The 'phasic' and 'tonic' cells of Gouras had conduction velocities of 3.8 m/sec and 1.8 m/sec respectively. Schiller and Malpeli (1977) reported that the extraretinal portion of the axons of M cells of rhesus macaque had a mean conduction velocity of 22m/sec and of P cells was 12.9m/sec. However, this difference in conduction speed is probably insignificant to the overall processing speed of the visual system due to other synaptic connections at the LGN and Visual Cortex. Bassi and Lehmkuhule state that the difference in orthodromic latencies of M and P pathways to electical stimulation of the optic chiasm, measured at the geniculate, is only 1-2msec.

This difference in conduction velocity has also been noted in the cat X and Y system. The average conduction velocity of X axons between optic nerve and chiasm is about 18m/sec. The estimated average velocity of Y axons is more variable, and values of between 30 and 70 msec have been reported. The cat W cells have small axons and have slow conduction velocities (Shapley and Perry, 1986; Lennie, 1980). Schiller and Malpeli recorded responses from rarely encountered cells in rhesus macaque - they also describe then as having slow conduction velocities.

The temporal resolution of M and P cells describe their capacity to resolve stimuli modulated at high temporal rates and is often described as the critical flicker fusion (CFF). In cat Fukada (1971) has shown that cells with higher conduction velocities could follow flicker to higher temporal frequencies than slow conducting neurons (Lennie, 1980; Stone, 1983). Derrington and Lennie (1984) and Marrocco (1976) among others have demonstrated that M cells of monkey have a higher CFF than P cells. The M pathway has been shown to have a temporal resolution of up to 50 Hz and the P pathway up to 30Hz (Bassi and Lehmkuhle 1990). Psychophysical studies have shown that the human observer is maximally sensitive to a luminance modulation of 10Hz - while if isoluminant chromatic modulation is used the visual system becomes more sensitive to low temporal frequencies, the response falling off rapidly at frequencies above 5Hz. At low spatial frequencies the temporal

resolution of the M cell is far superior to the P pathway; for higher spatial frequencies, the temporal difference diminishes.

The visual latency has been shown to differ between M and P cells. Marrocco (1976) reported in macaque that those cells with the shorter conduction velocities (M cells) also had shorter visual latencies. M cells have a visual latency about 10 - 15 msec shorter than P cells.

The response duration of different types of cells was one of the first methods of differentiating them - with the 'sustained' and 'transient' cells in the cat of Cleland *et al* (1971), and the 'phasic' and 'tonic' cells of Gouras (1969) in monkey. Thus X cells continue to respond for the duration of the stimulus and Y cells elicit a burst of activity at stimulus onset that subsequently falls to baseline levels of responding during the stimulus presentation.

Tonic and phasic cells exist within the W cell group - but most cells are tonic. One group have been called 'luminance' units (Fukuda, 1971) which give extremely tonic responses to standing contrast stimuli. There is also a monotonic relationship between their ongoing firing rate and ambient illumination that may mediate their role in the monitoring of ambient illumination , e.g. for the control of pupil size (Stone, 1983).

It is suggested that P cells of primate correspond the sustained cells and M cells to transient cells - however, this differentiation is not clear-cut as response duration is influenced by various other stimulus conditions such as size, spatial frequency, adaption level and colour. Following dark adaption M and P cells become more sustained, conversely in high levels of light adaption they become more transient.

The temporal characteristics of M and P cells do not provide an ideal method of pathway differentiation - however - the use of a low spatial frequency, low contrast stimulus of high temporal modulation should preferentially stimulate the M pathway (but would not completely silence the P pathway).

4.3.2.6. Lateral Geniculate Nucleus.

Much of the information regarding magnocellular and parvocellular parallel pathways was obtained from the laminar organisation of the dLGN of primates in which the two classes of cells are segregated.

It has been shown that the medium sized ganglion cells - the X cells of cat and P cells of macaque project to the medium sized cells or parvocellular layer of the LGN. The larger ganglion cells - the Y cells of cat and M cells of macaque project to the large cells or magnocellular layer of the LGN. The small ganglion cells (usually W-like cells) project to the small LGN cells of cat or koniocellular or S laminae of primate. The physiological properties of these cells are similar to their retinal ganglion cell counterparts.

The parvocellular cells have relatively small receptive fields and thus high spatial resolution and low contrast sensitivity. They are also more sensitive to lower temporal modulation (10 Hz in macaque). LGN cells generally give more transient responses to flashed visual stimuli than do their retinal counterparts, but P cells are more sustained than M cells (Casagrande and Norton, 1991). The parvocellular layers of the LGN have been shown to carry chromatic information. Wiesel and Hubel (1966) identified 3 classes of cells within the parvocellular layers of rhesus monkey. The majority were Type 1 defined as those showing chromatic opponency between receptive field centre and surround under light adapted conditions. The most common subclass of Type 1 cells was red/green opponent. The second group, Type ll, was defined as lacking spatial centre / surround organisation but having opponent colour responses to green and blue cones throughout the receptive field. Type lll cells were distinguished by receptive fields that were ON or OFF in the centre with spatially opponent surrounds. However, the centre and surround showed the same spectral sensitivities. In the dark adapted state Wiesel and Hubel found that only some Type 1 and Type lll parvocellular cells showed clear evidence of rod input. No rod input could be shown for the two Type ll cells examined scotopically. Since this study there have been various others (Derrington *et al,* 1984; Purpura *et al*, 1988) that confirm that P cells are mainly responsible for the transmission of colour information.

Magnocellular cells of the LGN have larger receptive fields than parvocellular cells and thus have a higher contrast sensitivity function. The temporal contrast sensitivity function of M and P LGN cells have been shown to broadly overlap (Derrington and Lennie, 1984) although, in general M cells were found to be more sensitive to stimuli modulated at higher frequencies (20Hz). In primates M cells respond better to rapid movement of objects appropriate to activate the surround of the receptive field than to P cells. As mentioned above M cells are not thought to be responsible for the transmission of chromatic information. The study by Wiesel and

Hubel (1966) found that M cells were mainly of Type lll, and some were of Type lV (having ON centres with large dominant OFF surrounds that were particularly sensitive to long wavelengths and had broad non-opponent spectral sensitivities). They found no evidence of rod input to these Type lV cells. Purpura and colleagues (1988), however, found that there was more rod input to magnocellular compared to parvocellular cells and that the M LGN cells may thus be more important for conveying spatial contrast information under mesopic or scotopic conditions and that the P cells are responsible for vision under photopic conditions.

The W-like cells of the LGN are the least studied cells and their physiological characteristics are as those of retinal W-like cells. Generally these cells have large receptive field centre diameters, low maintained activities, slow conduction velocities and slow visual onset latencies. Most of the non-standard cells reported in the LGN appear to belong to this category. The spatial contrast sensitivity function (CSF) profiles of W or W-like cells of cat and Galago have been shown to be quite distinctive. In anaesthetized Galagos the majority of W-like cells do not respond well enough to grating stimuli to measure a CSF. Those that do respond exhibit average high spatial frequency cut-offs and contrast sensitivities that are intermediate between the parvocellular and magnocellular groups (Norton *et al*, 1988). In cats W cells have been shown to have some chromatic properties.

4.3.2.7. Lesion Studies.

The physiological role of M and P pathways have been demonstrated by using lesions to destroy selective regions of the LGN or retina. Merigan and Maunsell (1990) used ibotenic-acid lesions in magnocellular layer 1 of the LGN of macaque monkey to show that contrast sensitivity at low spatial frequencies, and possibly at high temporal frequencies, depends on the integrity of the M pathway. They also illustrated that neither high contrast flicker resolution nor luminance contrast sensitivity at low temporal frequencies is dependent on the M pathway through the LGN. Ibotenic-acid lesions to parvocellular layers 3 and 5 caused a localized reduction in acuity of about a factor of four - while the M layer lesion did not decrease visual acuity (Merigan, 1991). They also showed that P lesions reduced the sensitivity to a slow onset stationary grating of moderate spatial frequency (2 cpd) while a lesion to the M layers had no effect.

Acrylamide lesions of the P retinal ganglion cells resulted in a large reduction in contrast sensitivity at high spatial as well as low temporal frequencies - these

lesions had no effect on high temporal, low spatial frequency stimuli or on flicker resolution thresholds for unpatterned stimuli (Merigan and Eskin, 1986). These lesions also resulted in a larger reduction in visual acuity compared to ibotenic acid lesions, but did not effect vernier acuity or form discrimination (Lynch et al, 1992). Additionally acrylamide and ibotenic acid induced lesions involving the P pathway had a devastating effect on chromatic sensitivity, M pathway lesions did not (Merigan, 1989; Merigan, 1991). Merigan (1991) also showed that M cell lesions (of the LGN) reduced the contrast thresholds for detection and direction discrimination as the velocity was changed from 1 to 20 deg/sec.

Schiller and colleagues (Schiller, 1991; Schiller *et al,* 1990) also used ibotenic acid injections to create lesions in either the parvocellular or magnocellular portions of the rhesus monkey LGN. They found that P lesions abolished the capacity for discriminating colour differences but do not interfere with the capacity to 'see' stimuli on the basis of wavelength differences - magnocellular lesions have no effect on colour discrimination. At high spatial frequencies they found that pattern, shape and texture form vision were severely compromised following P LGN lesion (less pronounced with low spatial frequency stimuli) M lesions had no effect on these tasks. Lesions to either M or P cells had no effect on the detection or the discrimination of low spatial frequency stimuli on the basis of luminance difference alone. This suggests that luminance information from low spatial frequency stimuli can be processed by both the colour-opponent and broad-band systems. Parvocellular LGN lesions were also found to produce major deficits to fine but not coarse static stereopsis to random dot stereograms. Magnocellular lesions produced significant deficits in the detection of both monochromatic and heterochromatic flicker at high frequencies indicating that the temporal limits of flicker perception are set by the broad-band system.

4.3.3.Psychophysical Properties.

Evidence for the existence of parallel pathways has been provided from many psychophysical experiments. Tolhurst (1973) measured the contrast sensitivity function (CSF) to both stationary and modulated sinusoidal stimuli following adaption to a sinusoidal wave of a particular spatial frequency and modulation frequency. The experiments described provided evidence for a 'division of spatial frequency selective channels into two classes: movement - dependent channels which respond only to temporally modulated changing stimuli, and movement - independent channels which respond to both stationary and moving gratings'. It

was found that for the perception of movement - excitation of the movement - dependent channels was essential; the movement - independent channels would respond to moving stimuli, but if they were stimulated alone, the stimuli would appear stationary. The movement - independent channels were found to be scarce at low spatial frequencies while the movement - dependent channels were very sensitive at these spatial frequencies and were also found at higher frequencies. Additionally it was found that if the stimulus was turned on and off at low temporal frequencies the stimulus appeared to be stationary at low contrast, while at low spatial frequencies, the temporal modulation was the most notable feature of the stimulus. The author compared the movement - dependent channels to the Y cells of the cat and the movement - independent channels to the X cells.

Kulikowski and Tolhurst (1972) provided additional evidence using a flickering stimulus to show two distinct detection thresholds: at one contrast, the temporal character becomes evident, and at the second contrast, the spatial structure becomes distinct. They termed the neurons responsible for flicker detection as movement - analysers and those mediating pattern recognition as form - analysers. They demonstrated that the movement analysers responded optimally to patterns which were temporally modulated at about 5-6Hz. They were optimally responsive to gratings of about 2 cpd and there was little low spatial frequency attenuation, the highest spatial frequency to which they responded was about 30 cpd. The form analysers showed no low frequency cut off in the temporal frequency domain and were most responsive to stationary stimuli. The optimal spatial frequency was about 3.5 cpd and the low spatial frequency cut off was pronounced; the maximum detectable spatial frequency was about 50 cpd. They responded to moving stimuli, but if they were exited alone no movement was perceived. Bodis-Wollner and Hendley (1979) also used adaption techniques to show that the detection of contrast modulation of a grating at different spatial frequencies was due to the interaction of two mechanisms: one responding to the steady and the other to the modulated component of the same grating pattern.

Lee *et al* (1990) used the method of adjustment (i.e. increasing or decreasing the contrast until the stimulus is "just" seen) to measure the temporal contrast sensitivity to luminance or chromatic modulation and compared the results to physiological experiment on M and P ganglion cells of macaque monkey. They found that for luminance modulation, contrast sensitivity curves for phasic (M) cells resembled the psychophysical data. In both, the curves were band-passed at high levels of retinal illuminance becoming more low pass as retinal illuminance was decreased. The

tonic - cell (P) sensitivity to chromatic modulation also resembled the psychophysical data. Both sets of curves were predominantly low pass in shape and the sensitivity decreased with the retinal illuminance level. They also demonstrated a notch - at approximately 10Hz in the chromatic - contrast sensitivity function which they state is due to participation of the M pathway in detection.

4.3.4. Summary

From the results of anatomical, physiological and psychophysical studies is has been established that parallel pathways exist in the cat, monkey and human visual system. In cat it is suggested that these pathways are represented by the X cells, Y cells and W cells which are though to be responsible for high-resolution pattern vision, movement vision and ambient vision respectively (Stone, 1983). The category of 'ambient' vision is drawn from studies of the visual capacity which remains after destruction of the areas of the cerebral cortex to which X and Y cells project (for examples in humans see Spehlmann *et al* 1977, Celesia *at al* 1991). This remaining vision may be served partly by the Y cell system, but the W cell system is the most likely candidate.

In primate, it was originally suggested that P cells were functionally similar to X cells and M cells were similar to Y cells. More recently it has been found that cells projecting to the parvocellular layers (P cells) of the LGN are X like since they have linear spatial summation. However, cells projecting to the magnocellular layers (M cells) are of two types: approximately 75% of them are also X like but 25% are Y like (Shapley and Perry, 1986; Kaplan *et al*, 1991; Kaplan, 1991). Part of this proposal is that the monkey P cell group has no exact functional equivalent in the cat, and is involved mainly in chromatic information processing.

Thus it is agreed that the M cells are involved in the analysis of movement but their high gain and high sensitivity are probably important for pattern perception at low contrasts at low to intermediate spatial frequencies. The high sampling density (particularly at the fovea) and small receptive field size of the P cells result in them extending the dynamic range of vision at high contrast levels where the M cell responses will saturate. Additionally the P cells are involved in colour analysis.

The following lists the properties of the magnocellular and parvocellular systems:

CHARACTERISTICS OF MAGNOCELLULAR SYSTEM:

1. Larger ganglion cells of the retina.

2. 10% of total population of ganglion cell.

3. Present in equal concentrations throughout the retina - including foveal region.

4. Dendritic field increases in diameter rapidly with eccentricity.

5. 75% have X type response, 25% have Y type response.

6. Phasic response.

7. Very little colour opponency (broad band) - no response to isoluminance.

8. Sensitivity to luminance contrast is 8-10 times higher than P cells - response increases rapidly to 10-15% and then saturates.

9. Higher conduction velocity - optimal temporal frequency 8-14Hz.

10. Spatial resolution similar to P cells.

11. Pattern vision at scotopic levels.

CHARACTERISTICS OF PARVOCELLULAR SYSTEM:

1. Smaller cells.

2. 80% of total cell population.

3. Present in higher concentrations in the foveal region - in the central 2.5 deg there are 35 times as many Pcells to Mcells.

4. Field size increases beyond 10 deg but becomes variable.

5. X type of response.

6. Tonic response.

7. Show colour opponency.

8. Response to contrast increases linearly and does not saturate.

9. Lower conduction velocity - optimal temporal frequency 4Hz.(Purpura *et al*,1988)

10. Spatial resolution as M-cell - but due to higher sampling density performance at very high spatial frequencies is better particularly when recognition of pattern is necessary.

11. No pattern vision at scotopic levels.

4.4. Neurotransmitters of the Visual Pathway.

Neurotransmitters are chemicals that are involved in the transmission of an impulse from one neuron to another. The chemical is released from the presynaptic neuron on the arrival of an electrical impulse. The chemical then diffuses accross the synaptic gap to reach the post-synaptic neuron where the impulse is once again set off. Neuromodulators act on post-synaptic cells by activating intracellular enzyme systems and affecting post-synaptic cells via biochemical mechanisms. Neuromodulators alter various aspects of neuronal function and they appear to act over relatively long periods of time. There are many neurotransmitters and neuromodulators involved in the transmission of visual information along the visual pathway. The neurotransmitters of the visual pathway are tabulated in table 4.4. As mentioned in chapters 1 and 2, a depletion of neurotransmitters dopamine and acetylcholine are found in Parkinson's disease and Alzheimer's disease respectively and I shall be concentrating this review on these two chemicals.

TABLE 4.4. Neurotransmitters of the visual pathway.

LOCATION	NEUROTRANSMTTERS	REFERENCES
RETINA		
Photoreceptors	Glutamate	Iuvone, 1986
	Aspartate	Dowling, 1990
	Kainic acid (KA)	Redburn, 1988

	Quisqualic acid (QA)	Ehinger, 1983
	N-methyl-D-aspartic acid	
	(NMDA)	
	2-amino-4-phosphorous	
	butyrals (APB)	
	Taurine	
	Melatonin	
	Serotonin	
	5-Hydroxytryptamine (5-HT)	
Horizontal cells	Gama-Aminobutyric acid	Cohen + Dowling, 1983
	(GABA)	Ehinger, 1983
	Dopamine	Dowling, 1986
		Shigematsu +Yamada 1988
		Rowe, 1991
Bipolar cells	Aspartate	Mariani, 1989
	Glutamate	Rowe, 1991
	Decarboxylic acid	Redburn, 1988
	Glycine	Kaplan, 1991
	GABA	
Amacrine cells	Acetylcholine	Ehinger, 1983
	GABA	Dowling, 1990
	Glycine	Masland + Tauchi, 1986
	Dopamine	Mariani, 1988
	Adrenaline	Osborne + Ghazi, 1988
	Noradrenaline	Rowe, 1991
	Serotonin	
	5-HT	
	Aspartate	
	Glutamate	
	Enkephalin	
	Substance P	
	Glucagon	
	Somatostatin	
	Neurostatin	
	Choelcystokinin	

Interplexiform cells	Dopamine	Cohen + Dowling, 1983
	Glycine (goldfish)	Rowe, 1991
	GABA (cats)	Ehinger, 1983
	Substance P?	Dowling, 1986
	Somatostatin?	Dowling, 1990
		Frederick et al, 1982
		Mariani, 1989
Ganglion cells	Glutamate (pigeon, rat cat)	Iuvone, 1986
		Mariani, 1989
	Aspartate	Ehinger, 1983
	Acetylcholine (frogs)	Karten et al, 1990
	Enkephalin (frog)	
	Substance P (frog, chick rabbit)	
	Choelecystokinin (frog, pigeon)	
	Dopamine (cat, pigeon)	
	Bombesin (frog)	
	Serotonin (chicken)	
LGN	Acetylcholine	Mc Cormick, 1989
	GABA	Fitzpatrick + Raczkowski, 1991
	Glutamate	
	Aspartate	De Lima + Singer 1987
	Noradrenaline	
	Serotonin	Casagrande + Norton, 1991
	5-HT	
		Hallanger et al, 1987
		Shute + Lewis, 1967
SUPERIOR COLLICULUS	Acetylcholine	De Lima + Singer, 1987
		Fitzpatrick + Raczkowski 1991
		Shute + Lewis, 1967
VISUAL CORTEX	GABA	Henry, 1991
	5-HT	Fitzpatrick + Raczhowski,

Noradrenaline	1991
Somatostatin	Houser et al, 1983
Serotonin	Aoki + Kabak, 1992
Glutamate	Dykes, 1990
Aspartate	Spehlmann, 1971
Acetylcholine	Sillito + Zeki, 1983

4.4.1. Dopamine.

In chapter 2, Parkinson's disease was described as a disease that is a result of destruction of the cells of the substantia nigra that are responsible for the production of dopamine. Dopamine is also known to be present in the visual pathway - particularly in the retina where it acts as a neuromodulator.

Light microscopy using formaldehyde induced histofluorescence, autoradiography or immunohistochemistry and electron microscopy using 5-6-dihydroxytryptamine labelling have been used to identify dopamine in the retina. There are at least two types of neuron that contain dopamine - the interamacrine cell (whose processes ramify only within the inner plexiform layer) and interplexiform cells (which extend processes widely in both inner and outer plexiform layers - they receive synapses from amacrine cells and end on horizontal cells in the outer plexiform layer), (Frederick et al, 1982; Ehinger, 1983; Brecha, 1983; Iuvone, 1986; Nguyen-Legros, 1988). A large number of different animal species have now been investigated and it seems safe to conclude that all vertebrates have catecholamine containing neurons in the retina (Ehinger, 1983). Frederick and coworkers (1982) used ^{3}H-dopamine labelling to identify dopaminergic interamacrine and interplexiform cells in humans.

Dopamine is synthesised from tyrosine in two steps. The first is a rate limiting step and is the hydroxylation of tyrosine to L-DOPA using the enzyme tyrosine hydroxylase. The L-DOPA is then decarboxylated by DOPA decarboxylase. Light increases the release and turnover of retinal dopamine and increases the levels of the dopamine metabolites 3,4-dihydroxy-phenylacetic acid (DOPAC) and homovanillic acid (HVA) (Ehinger, 1983; Iuvone, 1986). Kramer (1971) found that flashes of light increased the release of ^{3}H-dopamine in the perfused cat retina. Dopamine is at least part broken down by monoamine oxidase.

There are two types of dopaminergic receptors in the retina D1 and D2. D1 receptors are involved in mediating the activation of the enzyme adenylate cyclase in response to dopaminergic agonists. D2 receptors are not linked to adenylate cyclase but are activated by nanomolar concentration of agonists eg dopamine or apomorphine and are blocked by sulpiride, domperidone and metodopramide (Ehinger, 1983; Iuvone, 1986). D1 receptors are to be found on horizontal cells where the interplexiform cells interact. Some D2 receptors can be found in the retina associated with dopaminergic autoreceptors (where dopamine neurons make synaptic contact onto themselves or each other).

Dopamine has two principal effects on horizontal cells: (a) it reduces the light responsiveness of the cell, and (b) it uncouples the electrical functions between cells. This was shown using carp retina following superfusion of the retina with dopamine - the response of the cell to a spot of light (indicating cell coupling) increased, and the response to full-field illumination decreased (indicating light responsiveness) (Dowling, 1990). Additionally Cohen and Dowling (1982) showed that by destroying the terminals of the interplexiform cells in the carp retina (using an injection of 6-hydroxy-dopamine) increased the receptive field sizes of the horizontal cells due to increased coupling between adjacent cells. They speculate that "dopamine released from the interplexiform cells increased cyclic AMP levels within the horizontal cells and the cyclic AMP modifies the coupling between adjacent cells, thus altering the size of the horizontal cell receptive field" (Cohen and Dowling, 1983; Dowling, 1986).

Overall, the action of dopamine on horizontal cells is to diminish the effectiveness of the cell in mediating lateral inhibitory effects responsible for the antagonistic surround of bipolar cell receptive fields. It is also speculated that interplexiform cells and/or dopamine play a role in the regulation and strength of lateral inhibition and centre/surround antagonism in the retina as a function of adaptive states. This is supported by the high dopamine turnover during light stimulation, and by the known reduction in effectiveness of the surround mechanism in the dark (Ehinger, 1983; Dowling, 1986; Iuvone, 1986; Shigematsu and Yamada, 1988; Boycott, 1988; Nguyen-Legros, 1988; Dowling, 1990).

Dopaminergic amacrine cells in primate retina have been reported to have a distribution which parallel that of rods (Davis and Niemeyer, 1986), but more recent data indicate that their highest density occurs in the central retina, not at the ring of high density which surrounds the fovea (Rowe, 1991).

To summarize " the interplexiform cells and dopamine appear to modulate horizontal cell activity as a function of the light history of the retina. In the light and in short-term darkness, the interplexiform cells are turned off and horizontal cells function maximally. In prolonged darkness, the interplexiform cells become active, releasing dopamine, which depresses horizontal cell activity. Thus lateral inhibition and surround antagonism are reduced under these conditions, making the retina a better photodetector, but, presumably, at the expense of visual acuity" (Dowling, 1990).

There is very little evidence that dopamine is a transmitter involved in the processing of visual information in the dLGN. Certainly monoamines are present, such as serotonin and noradrenalin but these are not retinothalamic projections - serotonic projections arise from the dorsal raphae and noradrenergic neurons from the locus coeruleus (De Lima and Singer, 1987; Mc Cormick, 1989; Casagrande and Norton, 1991; Fitzpatrick and Raczkowski, 1991).

Dopminergic innervation of the cortex appears to be primarily restricted to frontal and limbic areas (Moore and Bloome, 1978) although there is widespread innervation to all cortical regions by noradrenergic and serotoninergic fibres. However, Tork and Turner (1981) and Phillipson and colleagues (1987) found dopamine in area Vl, although its function is uncertain. An experiment by Troscianko and Calvert (1992) in which Parkinsonian patients showed a failure in their parallel search mechanisms, which they state to be due to an abnormality in the inferotemporal region of the brain indicates that dopamine may have a role to play in visual attentional processes in this region.

4.4.2. Acetylcholine.

Acetylcholine is a neurotransmitter found extensively in the autonomic nervous system, and central nervous system. As mentioned in chapter 1 in Alzheimer's disease it's production is severely effected.

Histochemical (for cholinesterase), autoradigraphic (for 3H-acetylcholine) and immunochemical (for choline acetylcholinesterase ChAT) techniques have been used to identify ACh and ChAT in the retinas of most vertebrates. The results of these studies indicate that the cholinergic synapses are located in the inner plexiform layers and inner nuclear layer - principally within the amacrine cells (Brecha, 1983;

Puro, 1985; Iuvone, 1986; Masland and Tauchi, 1986). Choline uptake has been located in the photoreceptors where it is converted to choline-containing phospholipids. Choline has also been located in the ganglion cell layer, however as these cells do not degenerate following optic nerve section and cannot be labelled by retrograde transport of marker molecules - they are known as displaced amacrine cells or starburst cells (due to their distinctive dendrite branching pattern) (Masland and Tauchi, 1986). Choilnergic amacrine cells can also be identified using 4,6-diamidino-2-phenylindole which is fluorescent dye. Using this technique it has been shown that the dendritic tree of these neurons is narrow and dense in the central retina, it becomes wider and less dense , in an orderly progression, towards the periphery (Masland and Tauchi, 1986).

The inner plexiform layer also contains both nicotinic and muscarinic acetylcholine receptors (Puro, 1985; Masland and Tauchi, 1986). The ratio of nicotinic to muscarinic receptors is markedly different in the retinas of various species with a tendency during evolution towards a relative increase in muscarinic receptors in the vertebrate retina.

Acetylcholine is released in response to light (Puro, 1985; Iuvone, 1986; Mariani, 1989). Flashing light produces a large increase in the rate of acetylcholine release, while steady light does not - thus ACh release is produced more effectively by rapid changes in illumination (Masland and Tauchi, 1986). These authors also state that there is a response to onset of the stimulus and a second response to the offset of the stimulus (in rabbit) - and suggest that these responses come from displaced and conventionally placed cholinergic amacrine cells respectively. A detailed study was conducted by Ariel and Dow who have analysed the effects of cholinergic drugs on the activity of rabbit ganglion cells *in vivo*. They found that :

1. physostigmine did not affect the receptive field properties of ganglion cells,
2. the X cells and Y cells increased their spontaneous activity, but generally not their light evoked responses after injection of physostigmine - the investigators speculate that the spontaneous activity of the X and Y and large field ganglion cells is regulated by a tonic cholinergic input that is minimally driven by light,
3. with physostigmine, the sluggish (W) and the more complex cells (ganglion cells with orientation, local edge or direction sensitivity) had proportionately greater increases in their light - evoked responses than in their spontaneous rate - the investigators suggest that these ganglion cells receive transient, light driven, excitatory, cholinergic input.

It seems therefore that cholinergic effects on ganglion cells are mediated via a variety of functionally different pathways. Some ganglion cells have receptors that are directly excited by cholinergic input. Other ganglion cells appear to lack cholinergic receptors but can be excited indirectly by cholinergic neurons. Although amacrine cells are probably involved in the modification and organisation of ganglion cell receptive fields, the cholinergic amacrine cells do not appear to play a significant role in this aspect of visual processing. Rather, cholinergic input to ganglion cells generally increases the rate of spontaneous activity or the number of action potentials in light evoked responses (Puro, 1985).

Cholinergic projections to the dLGN arise from distinct populations of neurons in the mesencephalic and pontine reticular formation, specifically the pedunculopontine tegmentum, as well as from the parabigeminal nucleus (a compact nucleus on the lateral edge of the midbrain tegmentum that is composed entirely of cholinergic neurons) (Shute and Lewis, 1967; De Lima and Singer, 1986; Hallanger *et al,* 1987; Mc Cormick, 1989; Fitzpatrick and Raczkowski, 1991). Projections from the pedunculopontine tegmentum terminate throughout the dLGN although their density is not uniform - in the cat, the cell layers are more richly innervated than the interlaminar zones and layers A, A1 and C have a greater density than the parvocellular layers (Fitzpatrick and Raczkowski, 1991).

The transmission of visual signals in the dLGN is modulated in a state-dependent way by these non retinal afferents. These modulatory effects vary with the level of arousal. For example, during sleep or drowsiness, neurons in the dLGN are relatively unresponsive to visual stimuli and they fire bursts of action potentials that are unrelated to the activity of their retinal afferents; by contrast, during wakefulness, dLGN neurones are highly responsive to visual stimuli and they exhibit single spike discharges that mimic closely the activity of retinal afferents (Fitzpatrick and Raczkowski, 1991). This is illustrated by the state of the EEG compared to the thalamic activity. When thalamic neurones exhibit burst activity the EEG is synchronized and when these neurones exhibit single spike activity the EEG is desynchronized (Mc Cormick, 1989). Activation of the cholinergic system can result in many of the changes that occur during arousal e.g. stimulation of the cells in the pedunculopontine tegmentum facilitates the transmission of information through the geniculate and these effects are blocked by the administration of cholinergic antagonists.

The pedunculopontine tegmentum and dorsolateral tegmentum are also the source of cholinergic projections to the deeper layers of the superior colliculus (De Lima and Singer, 1986; Fitzpatrick and Raczkowski, 1991). The superficial layers of the superior colliculus are supplied by reticular - like neurones containing acetylcholinesterase and cholinesterase situated in the striatum griseum intermediate (Shute and Lewis, 1967).

Shute and Lewis also showed that the central supra-optic decussation (nerve fibres that decussate at the chiasm of rat that turn medially, cross the medial geniculate body to enter the deep pretectal nucleus) are also cholinergic. There is very little evidence of a cholinergic retinogeniculate pathway or geniculo-cortical cholinergic pathway (Shute and Lewis, 1967; Bigl and Schober, 1977).

It is well established that acetylcholine is a major neurotransmitter present in the cerebral cortex (Parnavelas and Mc Donald, 1983; Houser *et al*, 1983) however its role in the visual cortex remains uncertain. The visual cortex receives cholinergic projections from the basal forebrain area (Aoki and Kabak, 1992), comprising the nucleus basilis of Meynert (Fizpatrick and Raczkowski, 1991) which are part of the mesencephalic reticular formation.. Cholinergic fibres, identified using choline acetyltransferase are distributed throughout the visual cortex although muscarinic receptors have been found to be densest in the outermost layers l through lll with a gap in layers V and Vl (Dykes, 1990) with nicotinic binding sites being specific to layer lV (Prusky *et al*, 1987). It is unclear whether the primary visual cortex receives direct cholinergic input from the LGN. Bigle and Schober (1977) found an unchanged choline acetyltransferase activity of the visual cortex after lesions affecting the whole LGN. Additionally they found that ablation of the visual cortex did not diminish the choline acetyltransferase activity of sub cortical visual centres. Thus the cortical neurones which project to the dLGN and superior colliculus are also non-cholinergic. Spehlmann *et al* (1971) measured the effect of electrically applied acetylcholine on the spontaneous firing rate of cortical cells, to the electrical stimulation of the optic radiations and mesencephalic reticular fibres (MRF), and the retinal flash stimulation. They found that acetylcholine increased the spontaneous firing rate of approximately 20% of neurones studied (while atropine produced a mild decrease in firing rate). Acetylcholine facilitated the radiation responses in only about 10% of neurons tested, and less than half of the neurons responded to flash stimulation - although acetylcholine did facilitate this response minimally. However, acetylcholine application resulted in a marked facilitation of response of 30% of visual cortex neurones to electical stimulation of the MRF.

Electrophoretically applied atropine diminished the excitatory effect of reticular stimulation in many neurons.

Sillito and Kemp (1983) examined the influence of iontopheritically applied acetylcholine on the receptive field properties of cells in the visual cortex of cats. They found the response of 61% of cells well facilitated by acetylcholine and 31% of cells were depressed. Those that were facilitated by acetylcholine were observed in laminae ll - Vl and those depressed by acetylcholine in ll - lV. There was no obvious distinction in laminar distribution of the simple cells facilitated or depressed by acetylcholine, but complex cells inhibited by acetylcholine were restricted to lamina lll and the upper part of lamina lV, those facilitated by acetylcholine were distributed through laminae ll - Vl. However, this group found that in those cells facilitated by acetylcholine, the application of the neurotransmitter was only effective in increasing the visual response to optimal stimuli of the cell (i.e.orientation specificity etc) but not to non-specific stimuli such as a diffuse flash (as used by Spehlmann) (Mc Cormick 1989). They speculated that this action of acetylcholine is comparable to the effects of arousal or may reflect the operation of the intrinsic cortical neuronal mechanisms processing the visual input. They also state (as do others) that the action of acetylcholine is slow - indicating a neuromodulatory effect.

4.5. The Visual System in Alzheimer's disease and Parkinson's disease.

4.5.1. Alzheimer's disease.

4.5.1.1 Physiology.

It has been shown that histological and pathological changes do occur in cortical, retinal and optic nerve regions of the visual pathway in Alzheimer's disease.

Post-mortem studies have shown that NFTs are present in the large pyramidal cells of the hippocampus and of layers lll and V of the association areas (areas 18 and 20) of the cerebral cortex - but are absent from the geniculostriate up to and including area 17 (primary visual cortex) (Katz and Rimmer, 1989; Schlotterer *et al*, 1983; Lewis *et al*, 1987). SPs were found to be more uniformly distributed throughout the visual cortex.

Hinton et al (1986) examined post-mortem sections of optic nerves taken from Alzheimer's disease patients. They found that there was a 15-80% depletion in axons, particularly those of larger diameter, and that the remaining axons were not packed in a tight annular fashion but interspersed with an increased amount of glia. They also examined the retina of some of these patients and found that there was a diminution of the ganglion cells and that the remaining ganglion cells showed signs of degeneration. No NFTs or SPs were found. Syed and co-workers (1993) also found significantly lower numbers of larger diameter axons in the optic nerves of 5 post-mortem AD patients. Sadun and Bassi (1990) also examined the retinae of Alzheimer patients and found a reduction in ganglion cells of the inner layers, particularly those of diameters over 40 micrometers. Certain other ganglion cells showed signs of degeneration, with swelling and microvascularization. They also found a 50% depletion in optic nerve axons.

Benson (1982) used positron emission scanning to measure the cortical metabolic activity in Alzheimer patients and elderly controls. The cerebral metabolic activity of the Alzheimer patients fell well below the cerebral metabolic activity of age-matched normals.

Fundus examinations early on in the course of the disease do not show any abnormalities. However as the disease progresses there is evidence of increasing disc pallor and ultimately atrophy can occur. Kiyosawa and co-workers (1989) found no abnormality in the optic disc of patients with AD even in patients complaining of visual disturbances.

4.5.1.2. Psychophysics.

Visual symptoms are often one of the presenting features of Alzheimer's disease. Patients often complain of an inability to read, being unable to follow lines of print, of bumping into things and misreaching for objects (Sadun and Bassi,1990; Katz and Rimmer,1989; Kiyosawa *et al,* 1989).

Visual acuity has been assessed and has been found to be normal in the early stages of the disease, although the patient may have difficulty in maintaining fixation. As the disease progresses fixation becomes difficult and eventually visual acuity is impaired. At this stage VA is difficult to assess but measurements of 20/100-20/400 were stated by Sadun and Bassi. Kiyosawa et al (1988) found that in their AD patients complaining of visual disturbances had normal visual acuities. If backward masking is used while the patient is attempting to recognise a letter then further

difficulties arise. If a patterned mask is used (as opposed to a flash of light) then the patient takes longer to recognise the letter (Schlotterer *et al*, 1983). It was suggested that this was due to the involvement in the association areas when a patterned mask is used.

Colour vision was assessed by Sadun and Bassi using AO test and Farnsworth-Munsell tests, and was found to be impaired. This may be due to damage to the inner retinal layers and optic nerve. Visual fields were also tested and were found to be normal. Kiyosawa et al (1989) found that AD patients could arrange D15 tiles with relatively few errors, however they were unable to read ishihara isochromatic plates even though they were capable of colour naming tasks - they suggest that these observations could imply that colour information is available at the striate cortical level, but a defect may be present in using colour information to recognize forms.

Contrast sensitivity measurements have revealed contrasting results. Schlotterer et al (1983), and Wright et al (Wright, 1985; Wright and Richardson, 1986; Wright *et al*, 1984; Wright *et al*, 1986) could not find any difference in contrast sensitivity compared to age matched normals. Sadun and Bassi found that severe Alzheimer's patients showed a depression in contrast sensitivity over all spatial frequencies. Morrison and Reilly (1988) monitored the topical instillation of 0.025% hyoscine hydrobromide eyedrops on the contrast sensitivity function in man. It was found that the drug had a deleterious action on contrast sensitivity specific to patterns of 2 - 5 c/deg, while leaving higher spatial frequencies essentially unaffected, and was present irrespective of whether the grating pattern was stationary or phase-reversed.

Minor visual field defects such as mild constriction and hemianopia have been reported in AD patients. Stereopsis has also been found to be abnormal (Kiyosawa et al, 1989).

4.5.1.3 Visuospatial results.

Changes in ocular motility occur with increasing severity of Alzheimer's disease. Fixation becomes more difficult, saccadic latencies increase, decreased saccadic velocities, inaccurate saccades, reduced performance during smooth pursuit movements, and abnormal scanpaths during visual scanning. Kiyosawa et al (1989) reported delayed onset of saccades, hypometric saccades, and defective smooth pursuit in AD patients.

Mendez and colleagues (1990) measured visual object recognition, face recognition, complex form recognition, figure-ground analysis, visual synthesis,.and spatial localization in patients with AD. All of these complex visual tasks were found to be significantly abnormal and they suggest deficits to higher visual areas in this disease. However, all of these responses can be markedly affected by the cooperation ability of the patient.

From the above it seems reasonable to suggested that AD results in a magnocellular deficit in the visual pathway. Certainly the apparent reduction in large ganglion cells and large diameter optic nerve axons corresponds to such a deficit. A magnocellular deficit would also result in loss in high-temporal resolution, but would not effect visual acuity or colour vision (Bassi, 1990).

4.5.2. Parkinson's Disease.

4.5.2.1. Physiology.

As Parkinson's disease is a result of dopamine depletion in the substantia nigra it would be of interest to establish whether these deficits are also apparent in the dopaminergic mechanisms of the retina. This task was undertaken by Nguyen-Legros (1988) who used TH- immunohistochemical techniques on post-mortem retinae of 5 Parkinsonian patients and compared the results to those from a normal population. Results showed that a degenerative process with massive neuronal loss, identical to that found in the substantia nigra, does not occur in the retina of the Parkinsonian patients. Whereas the peripheral neurons seemed to remain normal, those of the central retina were distorted both in their perikarya and dendrites. The reduction in dopamine innervation was especially visible in the central area, where dopamine processes surround the foveola. These aspects do suggest a degenerative process in dopaminergic neurons.

Hadjiconstantiou (1988) showed that direct administration of MPTP to the eye of a mouse revealed reduction of retinal dopamine and DOPAC. Histofluorescence revealed a loss of amacrine cells and their terminals. This adds to the evidence that Parkinson's disease may well effect the retina.

4.5.2.2. Psychophysical results.

Contrast sensitivity has been measured in Parkinsonian patients by increasing the contrast of a grating until it becomes visible. This is done for gratings of numerous spatial frequencies so that a graph illustrating the change in contrast sensitivity with spatial frequency can be produced. Bodis-Wollner and colleagues (Bodis-Wollner, 1988; Bodis-Wollner, 1990; Bodis-Wollner and Onofrj, 1986; Bodis-Wollner *et al,* 1984; Bodis-Wollner *et al,* 1987) found that, when compared to normals, the bandwidth of the contrast sensitivity function was narrowed for Parkinsonian patients, and the 'peak' was shifted such that low frequency inhibition was less apparent or completely absent (Fig. 4.16).

The contrast sensitivity was also measured under periods of 'on' and 'off' to establish the effect of dopamine on the function. It was found that dopamine increased the responses (increased amplitude) to spatial frequencies of 4cpd and attenuates responses below 2 cpd. Domenici et al (1985) also measured the effect of L-dopa administration on the contrast sensitivity function in patients with Parkinson's disease and found that it improved sensitivity to the high spatial frequency gratings. These data suggest that dopamine is involved in low frequency attenuation and medium and high frequency amplification in human vision (Bodis-Wollner 1988).

The spatiotemporal function was also measured using various spatial frequency gratings alternating at either 1Hz or 8Hz. In normals the increase in modulation rate increases the sensitivity to the low spatial frequency gratings, this is known as the 'sensitivity gain'. It was found that the Parkinsonian patients showed very little or no sensitivity gain.

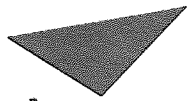

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Fig 4.16. Spatial contrast to a 4° field is presented a a function of spatial frequency for the mean normal curve (open triangles) for each eye of a 60 year old PD patient (right eye as open circle, left eye as closed circles), and for each eye of a 51 year old PD patient (right eye open square, left eye as a closed square). Taken from Bodis-Wollner (1988).

These changes imply that spatial and temporal tuning function are altered in the process of visual signals in the CNS in PD. One of the prime candidate sites for altered spatiotemporal processing in PD is the retina.

Bulens et al (1986, 1989) found rather more eratic results for contrast sensitivity in Parkinsonian patients, with results ranging from high spatial frequency losses to low spatial frequency losses to notch defects. They also state that the defects were not related to severity of disease.

Regan (1988) found a reduced contrast sensitivity to low spatial frequency gratings, and a certain amount of orientation selectivity to vertical gratings (this would suggest cortical involvement). Visual fields were also measured and no abnormality was detected.

In all of the above experiments visual acuity was measured at 6/9 (or better) in all patients. Colour vision has been assessed in Parkinsonian patients using isochromatic plates by Kupersmith et al (1982) and was found to be normal.

4.5.2.3. Visuospatial results

Visuospatial ability has been defined as a "group of complex behaviours derived from several elementary functions including visual analysis and synthesis, facial recognition, judgment of direction, orientation and distance, constructional praxis, and spatial attention" (Levin et al, 1990, 1991). Utilizing various tests to investigate the above, it was found that patients with PD did not perform as well as the control group. Even when factors such as motor speed and manual dexterity were controlled, visuospatal deficits remained, and were progressive and related to disease duration. Additionally, visuospatial deficits were worse in PD patients suffering from dementia.

Troscianko and Calvert (1992) investigated visual search (the ability to identify a target which is different in some way from other elements in the scene) in patients with Parkinson's disease. It has been suggested that visual search utilizes both a fast autonomic "preconscious" mechanism (parallel search) and a slower "conscious" process (serial search). The above study found that PD patients had no trouble in detecting a single target bar in a sea of distractors when its position was known (thus the visibility of the bar in PD was normal). However when the task was transformed into a search task the PD patients had a slower reaction time and appeared to be using a serial search mechanism. They suggest that dopamine may

have a role to play in visual attentional processes in the infero-temporal area of the brain.

It is difficult to speculate whether the above visual deficits can be attributed to a specific parvocellular or magnocellular loss. However if one takes the electrophysiology results into account (see chapter 5) it seems to indicate that Parkinson's disease patients experience more difficulties with high spatial frequency stimuli of high contrast, thus indicating a parvocellular deficit.

CHAPTER 5.

5. ELECTROPHYSIOLOGY.

Electrophysiological methods can be used to study any organ, to provide information about the neurophysiology and hence, functional integrity of that organ. The tecniques involve the measurement of electrical signals resulting from electrochemical events occuring within the structure in question. In the visual system the first electrochemical event occurs within the photoreceptors of the retina where the visual environment is transformed into an electrical impulse. Further electrophysiological events occur within the retina, lateral genicuate nucleus, superior colliculus and visual cortex - each of which can be measured, some more easily than others. The electroretinogram is a measurement of the mass electrical response of the retina when it is stimulated by light, the visual evoked cortical potential is a measure of cortical activity; each are relatively easy to record as non-invasive electrodes can be placed near to the active site.

5.1. Visual Evoked Potentials (VEP).

The visual evoked potential (VEP) is defined as an electrical response of the nervous system elicited by visual stimulation of the sensory nerves (Spehlmann 1985). The response is generated within the visual cortex. Babel *et al* (1977) described the sequence of events in a simplified manner. They explain that the signal enters the primary visual cortex (layer lV) and is amplified as it is relayed to the type ll Golgi cells. These then activate the pyramidal and large stellate cells which depolarize the pyramidal cells in layers V and Vl. The overall effect of this is a post-synaptic depolarization current which is recorded on the cortical surface as a positive wave. More recently a dipole model has gained acceptance. The cells believed to generate the VEP are arranged in parallel with each other, perpendicular to the surface of the cortex such that they can be considered as a sheet of generators. Thus the foveal area of the visual cortex can be represented by a single equivalent dipole radial to the scalp, and the cortical areas represented within the sulci can be represented by an equivalent dipole tangential to the scalp (Spekreijse, 1991; Drasdo and Thompson, 1992). Due to the symmetrical arrangement of the striate cortex, the potentials from the upper and lower or right and left half field stimulation will be of opposite polarity since the equivlalent dipole direction is perpendicular to the cortical surface (Spekreijse *et al,* 1977). Magnetometry can be used to measure the magnetic fields generated mainly by the tangential dipoles.

The stimulus can be a flash of light or a patterned stimulus (gratings or checkerboards) that are presented using a counterphased modulation or onset/offset modulation. If the repetition rate is less than 4 per second, the individual components of the VEP can be separately identified in the 'transient' VEP waveform. At faster rates, the components merge together to give an oscillating signal, known as a 'steady-state' VEP. The steady state technique is rapid, but information about the individual components is lost.

5.1.1. Recording Techniques.

The electrical signals that constitute the VEP are minute and thus specisalized equipment and averaging techniques are required in order to distinguish them from the background brain activity. Electrodes are required that can be placed in close association with the scalp and provide as little resistance as possible to the signal. Electrophysiological tecniques are inolved with the measurement of the potential difference between two electrodes and thus amplifiers are required to measure this potential difference.

5.1.1.1. Electrodes.

The most commonly used electrode in the measurement of the VEP is the silver-silver chloride 'stick-on' electrode, which is the standard electrode used in the measurement of the electroencephalogram. This electrode consists of a small dished silver cup, with a narrow flange (complete diameter = 1cm) and the lead soldered to a tag on one side. The complete electrode is coated in silver chloride. It is attached to the scalp either using collodion adhesive (a non-toxic glue) which is applied to the rim of the electrode and dried using a stream of air from an air gun; or using a 2.5 cm strip of Blenderm tape over the electrode and the hair holding the electrode firmly in place. There is a small hole in the cupped part of the electrode through

electrode jelly fills the dead space between the electrode and the skin of the scalp. This electrolyte penetrates the skin, aided by firstly preparing the skin by lightly scrubbing with Ominiprep to remove dirt and superficial dead cells, to ensure low electrode-skin resistance. As a general rule the resistance between two electrodes shoule be equal or less than 5 k-ohms.

The placement of the electrodes is important, so that the VEP can be repeatable. Measurements are taken from bony landmarks which are present on all skulls. The inion is the long ridge just above the base of the skull (just below the visual cortex)

used to locate the cortex, the nasion is a position just above the nose used to indicate the midline, and the two cochas which are the preauricular depressions just in front and toward the top of the outer ears, used to indicate the lateral midline. From these landmarks the other measurements can be taken. The most commonly used system on which studies have been performed is the International 10-20 system, which used these bony landmarks. The electrode locations are percentages of the measurement distances between these landmarks - these are shown in figures 5.1 - 5.3.

Figure 5.1. Frontal view of the skull with the lateral locations of the 10-20 system. The division of the line between the right and left preauricular depressions and the percent distances between temporal (T3 and T4), central (C3 and C4), and vertex (Cz) electrodes are shown (from Harding 1991).

Figure 5.2. Superior view of the skull with the circumference location of the 10-20 system. The divisions are made from the frontal pole to the occiput, and percent distances are given to the left fromtal (F1), and the frontal (F7), midposterior-temporal (T5), and the occipital (O1) electrodes, (from Harding, 1991).

Figure 5.3. Location of electrodes using 10-20 system. Lateral view of the skull showing divisions of the line from nasion to inion and the percent distances between the frontal pole (Fp) and the frontal (F), central (C), parietal (P), and occipital (O) electrodes (from Harding 1991).

Figure 5.1

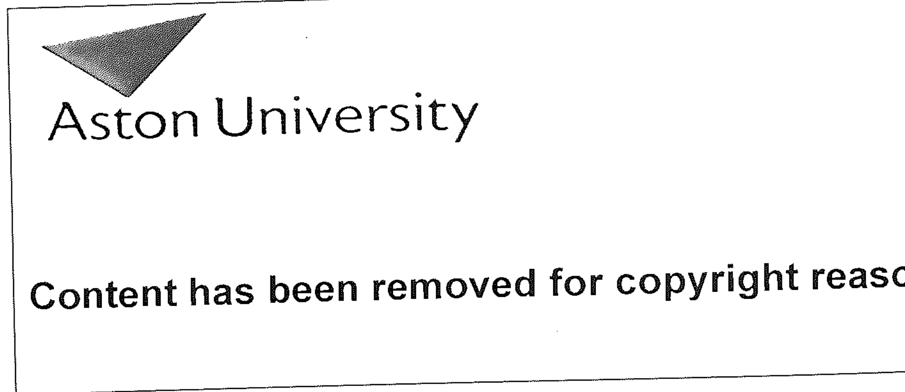


Figure 5.2.

Figure 5.3.

5.1.1.2. Amplifiers.

As mentioned, the VEP is very small and thus a system of preamplifiers and amplifiers is required to increase the voltage of the signal and to filter out any unwanted electrical activity (Odom, 1991). For all amplifiers used in electrophysiology there are always two inputs, that is, the amplifier amplifies the potential difference between a pair of electrodes. Conventionally, one input is known as the black lead and the other as the white lead - if the black lead is negative with respect to the white lead there is an upward deflection of the trace (EEG convention). There are two type of electrode linkage, known as 'reference' and 'bipolar' recording.

In reference recording, one electrode is considered the 'active' electrode (black lead) is placed over the source of the signal - in this case the visual cortex (O1, Oz, O2), and the 'reference' electrode (white lead) is placed over some relatively inactive site. The position of the reference in VEPs has been the subject of much debate, as the definition of a reference point is difficult to fulfill. Thus a point is chosen which is relatively inactive in terms of the visual evoked potential but is not so far forward as to be affected by other electrophysiological artifacts such as eye movements. A midfrontal point (Fz) or linked rolandic electrodes (C3, C4) provides a good compromise.

If more than one channel is used then a common reference may be used, such that for example two acitve electrodes (say O1 and O2) are both referred to a midfrontal electrode (say Fz). In this situation the relative amplitude of different active sites may be compared in relation to the same reference electrode. Additionally, any signal arising from the reference electrode will appear in the same phase and be of the same amplitude in all channels. The use of Fz as a common reference should also be used with caution as it has been show that it is highly active, not with the VEP, but by a signal of opposite polarity that occurs almost simultaneously with the major positive component of the VEP (Harding, 1991).

Other forms of reference include the average reference technique in which the amplifyer will record the potential difference between the selected active electrode and the average of all the other electrodes on the head; and the noncephalic reference in which the reference electrode is placed on the body and is therefore unlikely to be influenced by any cephalic activity. A disadvantage of the latter is that the ECG can cause problematic artefacts that are dependent on the posture and build of the patient.

Under bipolar recording, both electrodes are assumed to be active, and successive channels or amplifiers are connected to a chain of electrodes. As the amplifier records the potential difference between each pair of electrodes in succession, changes of opposite polarity and equal amplitude at the two sites will produce the same signal. This system is useful in locating the source of signal which is the electrode that produces opposite phase signals is adjacent channels.

5.1.1.3. Signal enhancement systems.

Over the years there have been many methods of enhancing time locked signals such as superimposition techniques. Today time locked signal-processing is usually completed using an averager. An averager is a computer which is connected to both the amplifiers and to the stimulus generator. Following signal generation, the resulting signal from each successive time interval is stored within cells of memory. When the trigger is repeated, the contents of each cell are recalled, a new voltage level is added, and the entire value is stored. At the end of N such cycles, the value in each cell is divided by N, so the contents represents the average. The signal contains both noise, which is random, and the signal which is time locked to the stimulus. Thus as the averaging continues the amplitude of the noise will reduce while that of the time locked signal is relatively enhanced - this signal-to-noise ratio is enlarged by the square root of N.

5.1.2. Wave Morphology and Source Derivativion.

The most commonly used VEPs clinically are the flash and pattern initiated responses. The VEP induced by a patterned stimulus is caused by the visual content of that pattern, particularly the change in luminosity at the border between the dark and light regions. The VEP induced by a flash of light is due to the changes if luminance only.

5.1.2.1. Flash VEP.

Flash stimulation is normally performed using a xenon gas discharge tube in either a parabolic reflector or in a ganzfeld stimulator (Harding, 1990; Harding and Wright, 1986). The flash VEP consists of a series of deflections referred to as components whose description depends on amplitude, polarity and/or latency. The system of nomenclature described by Harding (1974), will be adopted in this report where each component is described by a letter according to its polarity (P or N), followed by a sequential numbering system. Figure 5.4 shows a schematic diagram of a flash VEP with the various components identified. N1 occurs around 30ms, P1

at 55ms, N2 at 75ms, P2 at around 110ms, N3 at 140ms, P3 at 175ms and N4 at around 220ms (Harding, 1991). The earlier components appear to be the most variable, being succeptible to recording parameters and physiological variables.The most consistent component appearing is the major positive or P2 occurring at about 95-120 msec.

It is generally accepted that the flash VEP is distributed widely over the visual cortex and reflects the integrity of the central retina, and that the P2 component is probably generated from the central 5° of vision. This is largely due to the large area of cortex representing the macular region (Drasdo, 1977; Drasdo, 1983; Harding, 1991). It has also been suggested that the earlier components of the flash VEP (N1, P1, N2) are generated in the striate cortex (17), while the later components including P2 are generated in the association areas (18 and 19) (Spekreijse *et al*, 1977; Regan & Spekreijse, 1986; Wright, *et al*, 1987; Harding, 1991). Further evidence for this was provided by Spehmann *et al* (1977) and Celesia *et al* (1991) who found that patients who were cortically blind had a preserved flash VEP and suggest that this was due to the activity of an extrageniculate pathway terminating in the association areas i.e. the tectal-association area pathway.

Figure 5.4. Schematic diagram of a VEP to flash stimulation.

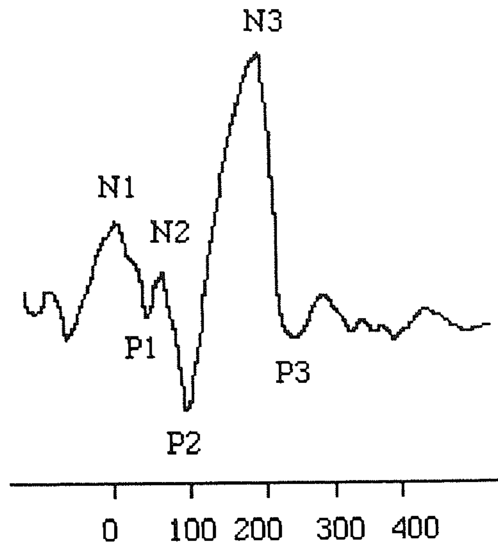


Figure 5.5. Schematic diagram of a VEP to pattern reversal stimulation

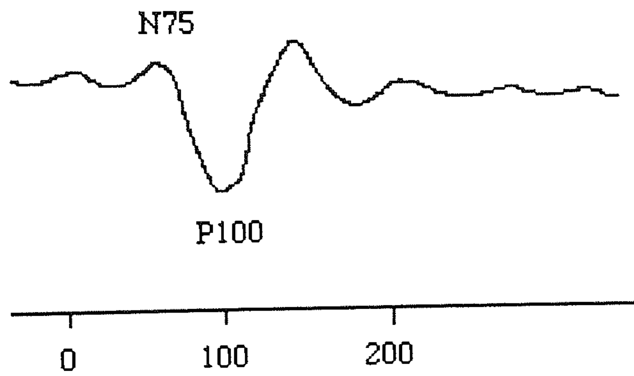
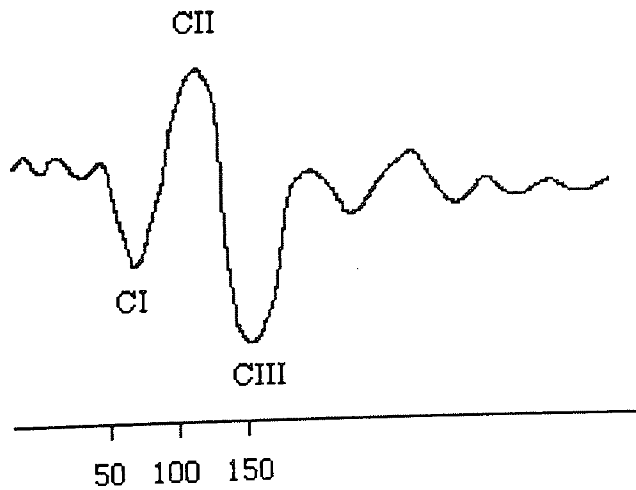


Figure 5.6. Schematic diagram of a VEP to a pattern onset/offset stimulus



5.1.2.2. Pattern Reversal VEP.

The stimulus or pattern reversal VEP usually consists of a black and white checkerboard pattern or grating (although chromatic patterns can be used) reversing at a constant rate with no overall change in luminance. These stimuli can be produced on a CRT screen or using optical systems based on a slide projector. The major problems with CRT - based stimulators are the presence of scan -lines, limited resolution and an inability to produce a real 'black'. Resolution is determined by the beam spot size, the video bandwidth of the amplifiers, and the number of horizontal scan lines in the raster. Additionally one complete cycle of the frame frequency is required to build up the entire pattern - this may induce variability in the response latency if fixation wanders from the centre of the screen to the edge or corner. The pattern element size in a grating pattern is specified by the 'spatial frequency' (f), which is the number of sinusoidally modulated dark and light bars subtended in an angle of 1° at the eye. The width (w) of a bar, or band of a grating, can be calculated (in min of arc) by the formula:

$$w = 60 / 2f$$

where w is in min of arc and f is the spatial frequency in cycles per degree (cpd). The fundamental spatial frequency of a check pattern can be expressed as:

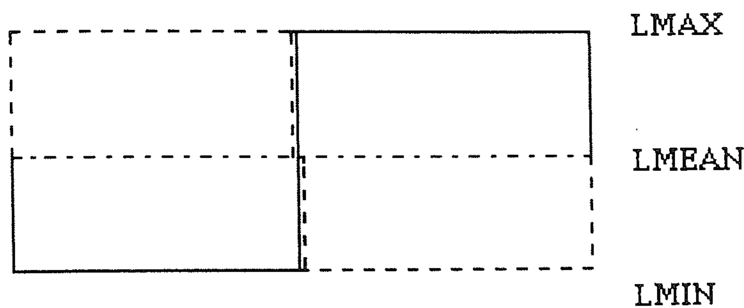
$$f = 60 / 1.4w$$

where f is measured in cpd and w is the width of a single check in min of arc. The contrast (C) of the pattern is the luminance difference of adjacent dark and light bands and is described by:

$$C = Lmax - Lmin / Lmax + Lmin$$

When using the pattern reversal mode of presentation the pattern is constantly visible and the visual cortex is stimulated by the black and white pattern elements changing place. The luminance profile of the stimulus is shown in figure 5.7.and a schematic diagram of the resulting VEP is shown in figure 5.5.

Figure 5.7.Luninance profile of pattern reversal stimulus.



The waveform consists of a predominant positive componenet occurring consistently around 100msec latency and hence is known as the P100. Preceeding this major positive is a negative component known as N75 and following the P100 is another negative component known as the N145.

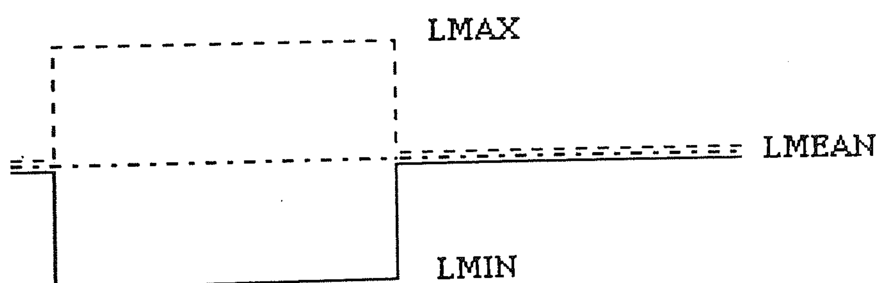
The P100 deflection is almost certainly the result of postsynaptic changes in the soma-dendrite polarization of primary visual cortex neurons (Wright et al, 1987; Edwards and Drasdo, 1988; Bodis-Wollner *et al*, 1990; Maffei and Fiorentini, 1990). It has been suggested that the pattern reveral VEP to a sinusoidal grating is generated in the simple cells of the cortex, while the response to a checkerboard is generated in both simple and complex cells (Maffei and Fiorentini, 1990). The respose to full field stimulation is maximal at the Oz electrode which is above the foveal region of the visual cortex (Harding, 1991). However it has been found that if half-field stimulation is used the source of the P100 becomes more confusing. If large check are used within a large half field the maximal response occurs over the ipsilateral visual cortex. This depends upon the position of the active and reference electrode and the size of stimulus size and field size. As the check size is reduced (less than 15' of visual angle) and the field size is reduced (less than 10° visual angle) the response apparantly swings over to the contralateral side (Harding *et al*, 1980; Clement *et al*, 1984; Flanagan and Harding, 1986; Harding, 1988). A suggested explanation for this, is that although the major positivity is generated by the visual cortex contralateral to the stimulating field, the major positivity appears at the midline and ipsilateral electrodes are positioned maximally for a radial source due to their orientation with respect to the midline. The contralateral electrodes see the source as tangential and therefore do not receive a clear signal (Barret *et al*, 1976). With a large stimulating field the response is represented for a further distance down the calcarine fissure, and by reducing the field size to 3-4° the response would be restricted to the classical surface of the visual cortex.

Lehmann et al (1977) used upper and lower field stimulation to establish the source of the P100. Using lower half-field stimulation they found a positive component at 103ms. Upper half-field stimulation revealed a negativity at 103ms and a positivity at 146ms. They state that this latency difference may be due to a higher receptor density and hence visual acuity in the superior hemi retina. This study was confirmed by Flanagan and Harding (1986) who also found an increase in latency with upper half field stimulation. This latter study states that source derivation reveal a source located at Oz irrespective of whether upper or lower hemiretina were stimulated.

5.1.2.3. Pattern onset/offset VEP.

The stimulus for a pattern onset/offset VEP consists of a black and white checkerboard or grating disappearing into a grey background of equal luminance. The luminace profile of this stimulus is shown in figure 5.8, and the resulting waveform in figure 5.6. The components which are present are usually referred to as C1 (positive at 72 ms), CII (negative at 105 ms) and CIII (positive at 155 ms) (Jeffrey, 1977). Unlike the pattern reversal and flash response, this waveform is ususally presented with positive up, although for this thesis I have used positive down.

Figure 5.8. Luminance profile of pattern onset-offset stimulus.



These components are often differently affected by different stimulus and subjective parameters. The CII and possibly the CIII component appear to represent the response of the visual cortex to the pattern detail of the stimulus (e.g edges) and is easily the most sensitive to defocusing - this is known as the 'contour' response. C1 and probably the off components seem to respond to transient changes in contrast - and is known as the 'contrast' response.

By using arrays of electrodes about the occipital region of the scalp attempts have been made to localize the source of these components. The use of upper and lower

half-field stimulation produces results very similar to those found using pattern reversal stimulation. Lower field stimulation results in Cl and Cll components localized about 2 - 5cm above the inion. Upper half-field stimulation results in the same components but of opposite polarity localized about 5 - 10cm above the inion, (Jeffreys and Axford, 1972).

The use of right and left half field have been used to asses the horizontal distribution of the VEP over the visual cortex. The Cl component consistently appears over the hemisphere contralateral to the half-field stimulated. However there is uncertainty as to whether this component is present when small foveal stimuli are used. Jeffreys and Axford (1972 i,ii) and Jeffreys (1980) could not find such a response when they used a 2° field. However, Drasdo (1980), when using 12' checks in a 2.5° field and electrode positions in positions slightly lower than the previous authors, could elecit a Cl response from laterally placed electrodes. He suggests that using these stimulus parameters the Cl component is originating in area 18 and19. At the same time a negative transient is maximal at the midline electrode (C0). When smaller check are used (4') the Cl component could be seen at the midline and hence becomes more striate in origin (corresponding to areas 17, 18 and 19). Drasdo believes that the disappearance from the midlin of the Cl component when larger check are used is due to its coincidence with a negative transient of C0, and that C0 is the result of interaction of Cl and Cll.

The cortical origin of the remaining components remains inconclusive, with striatal and area 17 being suggested for Cll and extrastriate areas for Clll (Jeffreys 1977). Ossenblok and Spekreijse (1991) also suggest that CI and CIII have a mainly extrastriate origin, and CII, a striate origin.

5.1.2.4. Steady State VEP.

As previously mentioned steady state VEP results from a patterned stimulus reversing at temporal frequencies above 4Hz, such that the individual components merge together. The stimulus may be regarded as the sum of a steady grating and a counterphase grating of the same spatial frequency. The counterphase grating is modulated sinusoidally in time (Bodis-Wollner *et al* 1990). A characteristic property of steady-state pattern reversal VEP is the fact that their waveform has a temporal frequency that corresponds to the second harmonic of contrast alternation (up to temporal frequencies of 10-20 reversals/sec). In the visual cortex this is a property of complex cells (Maffei.and Fiorentini, 1990), although this does not mean to say that simple cells do not respond to such a stimulus. In the case of phase-reversed sinusoidal gratings the cortical simple cells respond with a modulation of their

discharge corresponding to the fundamental temporal frequency of the stimulus. Fast fourier analysis used to describe the wave in term of its amplitude and phase, the amplitude is often specified as the percentage power of a particular frequency in the waveform

5.1.3. Normative data.

In all diagnostic VEP investigations it is important that the limits of normality for latency and amplitude and the normal range of intraocular variation be known for each age band. It is essential that these parameters are established in each laboratory due to the variations in latency and amplitude resulting from the use of different recording equipment. At least 10 normal subjects from each decade are required to establish statistically acceptable means and standard deviations. Latencies falling outside 2.5 standard deviations of the norm are considered abnormal (Harding, 1991). There are a number of factors that can effect the latency and amplitude of the VEP:

5.1.3.1. Age.

Most studies of the flash VEP over the normal population have shown that the latency of the P2 component increases with age (Dustman *et al*, 1977; Cosi *et al*, 1982; Harding, 1982; Wright *et al*, 1985) (Table 5.1). Harding (1982) also showed that the amplitude of the P2 component is high in childhood and slowly decreases and stabilizes with age, and that the P2 latency gradually increases from the age of 20 years onwards. This increase in P2 latency with age cannot be due to optical factors such as pupil size as this would only account for a 3- to 4- ms increase in the latency (Harding, 1991). The P1 component of the flash VEP shows a marked increase in amplitude with age particularly in the 60 to 70 year age group.

There have been a number of studies on the effect of age on the P100 component of the pattern reversal VEP and most have noted an increase in latency with age. Halliday and co-workers (1982) provide a short review. They quote studies by Celesia and Daly (1977) who noted a linear increase in latency with age with a slope of approximately 0.18 msec/year over the age of 50 to 65 with a progressive increase thereafter; Shaw and Cant (1980) who found an increase in latency from the fifth decade onward and Stockard *et al* (1979) who found no significant effect of age on the P100 latency in the 20 - 25 year age group, but in the sixth decade they found that this component increased in variance but not in mean latency. Halliday's group found a significant increase in latency with age for females only,

they also showed that the increase in latency with age is dependent on check size - being more pronounced with smaller checks, this has also been noted by other authors (Celesia and Daly, 1977; Sokol and Moskowitz, 1981; Wright *et al*, 1985). Here at Aston, Harding (1982) and Wright *et al* (1985) found only a 3msec increase in P100 latency with age using a 56' check (as shown in table 5.1). Amplitude of the P100 component tends to be higher in the under 25 year old age group and shows litle significant changes during the rest of the age span (Celesia and Daly, 1977, Halliday *et al*, 1982, Harding, 1991).

Table 5.1 Normal values for VEP latency throughout the adult life span (Table shows mean ± one standard deviation).

Decades (yr)	Flash P2 Component Latency (ms)	Pattern-reversal P100 (56' check) Latency (ms)	Pattern-Onset Cll (56' check) Latency (ms)
10-19	114.50 ± 9.84	108.56 ± 10.9	‡
20-29	120.75 ± 10.99	101.78 ± 7.64	98.0 ± 14.0
30-39	121.70 ± 7.8	106.78 ± 4.91	99.0 ± 4.6
40-49	126.80 ± 11.26	104.60 ± 5.15	102.9 ± 9.95
50-59	122.50 ± 15.45	102.89 ± 6.75	105.6 ± 13.1
60-60	127.28 ± 11.28	109.22 ± 10.45	110.5 ± 9.8
70-79	134.25 ± 12.72	111.00 ± 8.7	116.4 ± 9.2

(‡ Patten onset data not available due to ambiguity of waveform).

There have not been as many studies on the pattern onset/offset VEP because this technique is used less often in clinical studies. Most have shown greater variability of the Cl, Cll, and ClII latencies, particularly in the younger age group (Wright *et al*, 1985; Harding,1990; Harding, 1991).

In the study undertaken at Aston, measurements were also taken of the monocualar variation in latency as it is often required to compare the affected eye with the fellow eye in clinical diagnosis. These values are shown in table 5.2 where it can be seen that there is very little variation for any group throughout the age ranges. The pattern reversal VEP showed particular consistency between the ages of 30 and 60 years.

Table 5.2. Normal values for mean monocular latency variation. (Table shows mean ± one standard deviation).

Decades (yr)	Flash P2 (ms)	Pattern Reversal P100 (ms)	Pattern Onset CII (ms)
10-19	5.50 ± 1.87	6.30 ± 4.81	-
20-29	5.40 ± 3.55	6.70 ± 6.49	6.50 ± 3.87
30-39	5.50 ± 5.42	2.45 ± 1.62	4.25 ± 3.39
40-49	5.30 ± 4.04	3.55 ± 2.14	4.40 ± 2.51
50-59	4.65 ± 2.98	2.10 ± 1.58	3.85 ± 4.43
60-69	4.60 ± 4.55	5.40 ± 6.83	2.42 ± 1.36
70-79	5.00 ± 3.72	7.05 ± 5.98	4.20 ± 3.90

Adachi-Usami *et al* (1988) studied the effect of age on the pattern VEP to various temporal frequencies ranging from 1Hz to 22Hz. They found that the maximal amplitudes shift toward lower frequencies with age except for the 30-39 years. In this age group they found an attenuation in amplitude when using temporal frequencies less than 10 reversals/sec. They also found that unlike in older age groups, the 0-9 year age group showed to peaks, one at 3 reversal/sec and one at 10 reversal per sec.

5.1.3.2. Sex.

Using checkerboard pattern reversal stimulation both Stockard *et al* (1979) and Halliday *et al* (1982) found a small but significant difference in latency of the P100 component between males and females. In both cases the latency was shorter for women and may be related to the smaller average head size and skull thickness women and their higher deep body temerature (Halliday, *et al*, 1982).

5.1.3.3. Retinal Blur.

There have been a number of studies assessing the effect of optical blur on the VEP (Uren *et al*, 1979; Sokol and Moskowitz, 1981; Harding and Wright, 1986; Wright, 1983).The use of optical lenses have shown that the latency of the flash P2 component remains unaltered as would be expected as it is a diffuse stimulus. The pattern reversal P100 latency however becomes increasingly delayed with increasing blur. This is more pronounced when smaller checks are used. In her PhD thesis Wright (1983) shows that a 3D blur increases the P100 latency by

around 4.5ms when 56' checks are used and by 20.4ms when 14' checks are used. When pattern onset stimulation is used there are extremely pronounced increases in latency of the Cll component even at relatively low amounts of blur (Harding and Wright, 1986; Wright, 1983) These results are graphically represented in figure 5.9. Sokol and Moskowitz showed that similar delays in latency can result from cycloplegia, this means that if a subject does not accommodate correctly onto the stimulus then an increased latency can result. This group also showed that if an astigmatic blur is used, then a delay only occurs if the cylinder is placed at 90° or 180°, oblique angles did not effect the latency. The above authors also note a corresponding reduction in amplitude with increasing retinal blur, particularly when small checks are used.

As retinal blur can have such a detrimental effect on the pattern reversal VEP it is important that the clinican monitors the patients compliance. Uren *et al* (1979) measured the VEP while the subject performed several tasks, these included 1. performing regular saccadic movements around the periphery of the stimulus, 2. fixing on the corner of the screen so that the stimulus was only in the upper temporal quadrant of the visual field for each eye, 3. performing a mental task while fixing on the central fixation target (e.g. adding up numbers from one to one hundred), and 4. fixing on a target about 40cm from the subject in line with the stimulus (to simulate voluntary defocusing). In all conditions the P100 latency was delayed although minimally in situation 3., and maximally in condition 2. The amplitude was also reduced in all cases except for condition 3 when the subject had to perform a mental task.

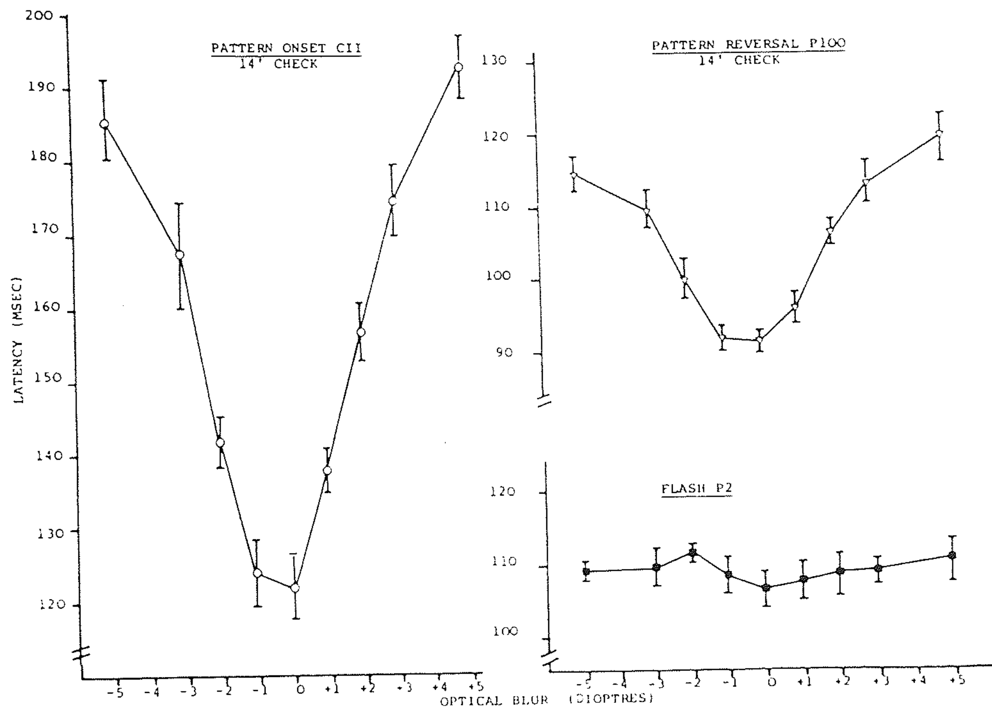


Figure 5.9. Effect of defocusing on the pattern onset CII component, pattern reversal P100 component and the flash P2 component.

5.1.3.5. Stimulus Parameters.

Other stimulus parameters also determine the latency and amplitude of the VEP, - these include stimulus size, field size, contrast and luminance. A study by Torok et al (1992) which involved measuring the pattern reversal and pattern onset offset VEP to checkerboards of various spatial frequencies resulted in a spatial frequency tuning curve. The optimal spatial frequency (i.e that which produced the largest amplitude) for both stimulus conditions was 2.5 cycles per degree (cpd) with the amplitude reducing at higher and lower spatial frequencies. This study also confirmed the results found by others that the latency of the P100 and CII component increases with increasing spatial frequency (Halliday, 1982; Harding, 1992). A review by Bodis-Wollner *et al* (1990) states that optimal check sizes for the generation of a pattern reversal VEPs have been measured at 10 min and15 min of arc, and 5cpd. This reduction in amplitude and increase in latency with increasing spatial frequency is thought to be due to the optical degradation of the pattern as it passes through the optics of the eye thus creating a blurred retinal image.

The size of the visual field of the stimulus has an effect on the amplitude of the pattern VEP. Restricting the pattern to a very small field of 2.5° results in a reduced amplitude VEP as only the foveal region is stimulated. Increasing the field to 10-15° will increase the amplitde as the parafoveal region is also being stimulated. Beyond this, there is no appreciable increase in amplitude as the VEP response is dominated by foveal organization due to the cortical magnification of this region (Bodis-Wollner *et al*, 1990). The latency of the VEP is unaffected by field size.

The pattern VEP is also effected by the sharpness, brightness and contrast of the stimulus (Halliday *et al*, 1982). As the overall luminance of the pattern decreases the latency of the VEP increases and amplitude decreases. There is an increase in amplitude as the contrast of the stimulus is increased from low levels until saturation is reached, after which there is no further increase (Harding, 1991).

The latency and amplitude of the flash P2 component is affected by the intensity of the stimulus, although these variations are usually only found around the absolute threshold. It has been found that a 6-log-unit attenuation is necessary before any increase in latency of the flash VEP is observed. As the intensity is increased from threshold there is an initial decrease in latency, any further increase in intensity does not result in a further reduction in latency since the stimulus in now markedly suprathreshold (Harding, 1991).

5.2 The Electroretinogram (ERG).

The electroretinogram is used to measure the global electrical activity of the retina in response to changes in illumination (Nguyen-Legros, 1988) and represents the algebraic summation of all the potentials developed in a variety of retinal layers and cells. Due to this retinal activity the cornea becomes positive compared to the posterior pole. By modifying the stimulus parameters and recording conditions one can stimulate different cells of the retina.

5.2.1. Recording Techniques.

As with VEPs the measurement of the ERG involves measuring the potential difference between two electrodes then amplfying and averaging the response. In order to obtain an ERG one electrode has to be placed either in contact with or close to the cornea and the other in a position near to the posterior portion of the eye.

5.2.1.2. Electrodes.

Electrodes that are used as the active electrode and thus have to be in close proximity to the cornea include contact electrodes, gold foil electrodes, DTL (Dawson Trick and Litzkow) fibre electrodes and skin electrodes. The reference electrode is usually a skin electrode placed at the outer canthus. Much of the artefacts of ERG recording can be traced to the electrode particularly the active corneal electrode - these include polarization and electrode slippage and movement. It is important that both the active and reference electrodes are made of the same metalic type as this results in the potential difference between the two electrodes being close to zero (although slight impurities in the metal and surface contamination can alter this potential difference slightly). A review by Coupland (1991) describes the different electrodes available in detail.

Contact lens electrodes are the recommended standard for clinical recordings because of their ability to give reliable and reproducible recordings - the most commonly used being the Burian-Allen and Henkes assemblies. The Burian-Allen assembly consists of a large speculum that holds the eyelids open and contacts the sclera. A spring assembly holds a small clear corneal contact lens against the corenea - a circular silver wire around the circumference of which acts as the active electrode. This type of electrode is very uncomfortable and requires corneal anaesthesia, and is not tolerated well by children. It can cause rare corneal and conjunctival abraisions.

The Henkes electrode consists of a glass contact lens that maintains electrical contact with the surface of the cornea through a dome or cup filled with isotonic saline and methylcellulose. Good corneal contact is ensured through suction creating a vacuum. It has however the same problems with tolerance.

Improvement in comfort has been achieved using a soft contact lens placed underneath the hard lens to act as a cushion - however, anaesthesia is still required. Soft contact lenses have also been used as electrodes. This usually consists of a fine gold or platinum wire sandwiched between two soft contact lenses. This form of contact lens electrode is not very stable and requires frequent rehydration.

Due to the discomfort associated with contact lens electrodes - other forms of electrodes have been developed. The most widely used of these is the gold foil electrode (GFE) which consists of a polyethylene film (Mylar) strip to which gold foil is applied. It is a very flexible electrode - the end of which is bent over and inserted into the lower fornix so that is just touches the corneal margin - the rest of the electrode rests on the cheek. A junction wire is connected to the gold foil electrode and leads to an insulated standard electrode wire. This type of electrode does not interfere with the optics of the eye and hence is ideal for the measurement of pattern ERGs. It is also well tolerated by children. The disadvantages are that it can be blinked out, it can stimulate tearing, it can fall out of the fornix of elderly patients with lax lids and it produces an ERG with a slightly smaller amplitude than the contact lens electrodes.

The DTL electrode developed by Dawson, Trick and Litzkow (1979) overcomes many of the problems assoiciated with ERG electrodes. The original electrode was based upon an extremely low mass conductive thread consisting of a 2cm length of spun nylon fibres impregnated with silver. This fibre floats in the tear film and makes contact with the cornea - the other end is electrically coupled to a standard insulated electrical wire. The loosely spun conductive fibres are woven between the spread strans of the tip of a piece of 24-guage copper electronic 'hook-up' wire with vinyl insulation. After the conductive thread is woven into the strands the joint is covered with epoxy resin. This type of electrode can be autoclaved or gas-sterilized without changing the resistance.

Thompson and Drasdo (1987) designed a holder for the DTL fibre so that it can be disposed of after use - this is useful to prevent transmission of eye infections. The holder is constructed from a 5cm length of 0.5mm diameter silver wire. A contact plug is soldered to one end and the soldered joint is enveloped in a small blob of

epoxy resin. A length of 'Perisil' (silicone elastomer on glass sleeving, 0.5mm) sleeving is passed over the wire and embedded in the epoxy resin, which is then allowed to cure. The sleeving is cut flush with the distal end of the silver wire and is retracted until 1cm of wire protrudes which is then bent over to form a hook. The DTL fibre is wound around the angle of the hook and the sleeving is then released which springs back to secure the wire (shown diagramatically in figure 5.10). This is the arrangement currently used at Aston and was used in the ERG study described later in this thesis.

In order to record the ERG, the holder is attached to the subject's temple such that the hook is in close to the outer canthus. The subject is then asked to look upwards while the fibre is draped accross the sclera such that it floats on the tear film and the other end is secured close to the nasal canthus with a small piece of Blenderm surgical tape. When the subject then looks straight ahead the fibre maintains a reasonably constant position with respect to the cornea and is prevented from drifting deep into the lower fornix - this arrangement is illustrated in figure 5.11. Corneal damage during blinking and lateral eye movements is prevented by the DTL fibre being spiralled and hence extensible such that it will stretch and return to its original position. The reference electrode is a silver-silver chloride skin electrode attached to the skin with tape approximately 1cm form the outer canthus. The ground electrode is a skin electrode usually placed on the forehead.

The amplitude of the ERG recorded in this way is slightly reduced compared to the contact lens electrodes (Dawson *et al*, 1982) - but is far superior in terms of comfort and is well tolerated by children. It is not blinked out of the eye - although the blink action and the resulting fibre movement can induce large amplitude blink artefacts. If this becomes a problem, the averaging should be paused while the subject is allowed to blink for a few seconds, then continue recording while the subject stares at the stimulus without blinking. This type of electrode is also useful for recording pattern ERGs as it does not interfere with the optics of the eye.

Figure 5.10. Construction of holder for DTL electrode.

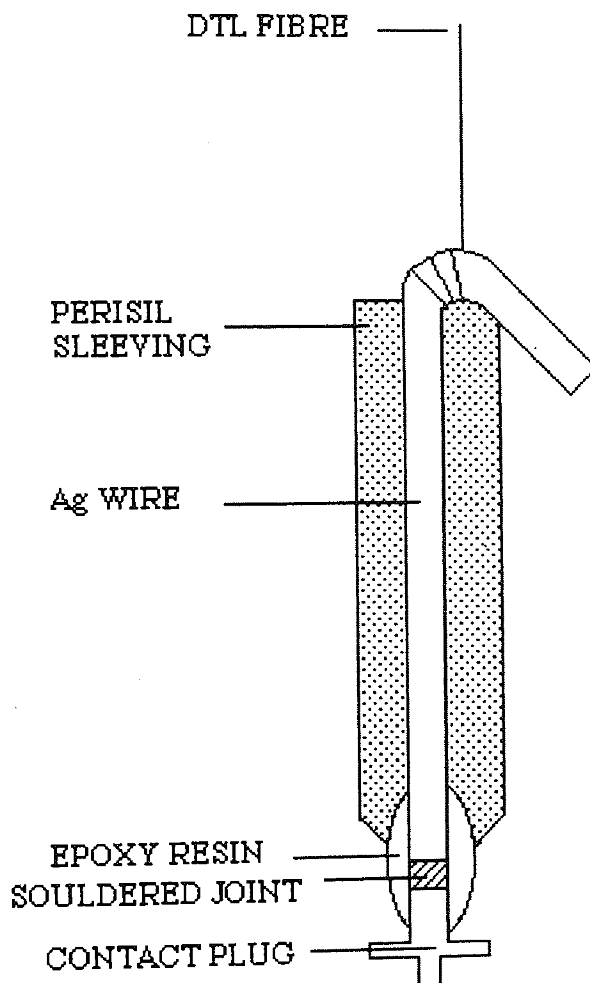
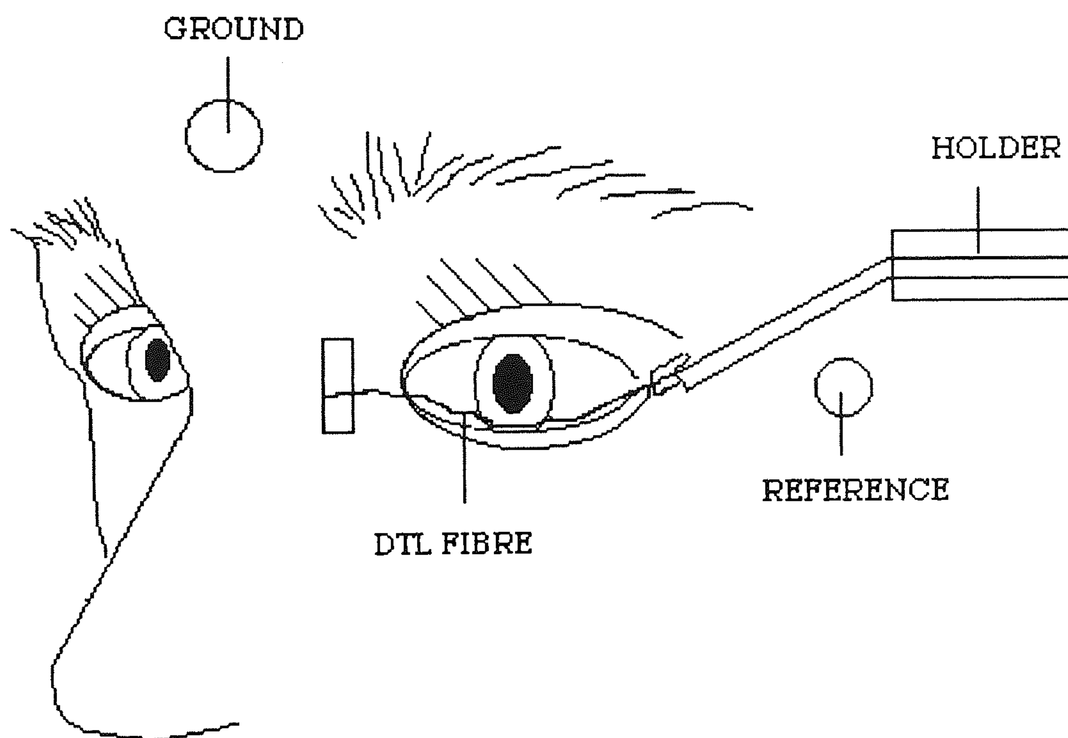


Figure 5.11. Schematic diagram of DTL and holder position.



Skin electrodes can also be used as the active electrode if placed either at the inner canthus or on the cheek directly beneath the cornea in its central position. This type of recording is obviously the most comfortable and is well tolerated by infants and children. The amplitude of the ERG is reduced compared to the other active electrodes described above - and the signals produced are also noisier, less reliable and more variable (Rubinstein and Harding, 1981).

5.2.1.2. Amplifiers and Signal Enhancement Systems

The amplifiers and signal enhancement systems used in the measurement of ERG s are much the same as those for the VEP described in sections 5.1.1.2. and 5.1.1.3.

5.2.2. Wave Morphology and Source Derivation.

Depending on the stimulus used and the general lighting conditions three types of ERG can be described - the photopic ERG, scotopic ERG and the pattern ERG.

5.2.2.1. The Photopic ERG.

This was the first type of ERG recorded in humans by Kahn and Lowenstein in 1924. The stimulus is a series of flashing lights presented at a rate of about 2 per second in light adapted conditions. The intensity of the light effects the latency and amplitude of the ERG. If a strobe light is used subtending 20° only the central 2.5% of retina is stimulated, the remaining retina is stmulated by scattered light thus reducing the amplitude and increasing the latency of the resonse (Drasdo, 1983). Thus Ganzfeldt stimulation is generally used. This consists of full field bowl stimulator consisting of a plastic sphere with an inner matt white surface provides a large diffuse stimulus. Diffusing goggles or contact lenses produce similar although less uniform effects.

The flash stimulated ERG results in an initial negative deflection known as the a wave (occuring at around 12ms after the impact of light on the retina), followed by a much larger positive deflection called the b wave (maximal at around 30ms). The c wave is a slower positive deflection beginning after about 200ms seen when the stimulus is prolonged. Finally, a few seconds after the stimulus ceases, an 'off' effect begins to develop, this is the d wave. Under certain conditions (usually when a flash of high intensity is used) small wavelets can be seen on the rising limb of the b wave, these are known as the oscillatory potentials, the first one ocurring at 20ms followed by three or four peaks at 7ms intervals. A typical photopic ERG is illustrated schematically in figure 5.12.

The leading edge of the a wave is thought to represent photoreceptor activity and has two components from the cones (a1) and the rods (a2). The b wave has been related to activities in the bipolar cells, Muller cells and indirectly rods and cones (Babel *et al*, 1977; Drasdo, 1983; Harding, 1988; Newman and Frishman, 1991) and Gottlob *et al*, (1985) suggest that amacrine cells also participate. The b wave also has early and late features - the early features predominate under light adapted conditions and the late features under dark adaption. The oscillatory potentials are all thought to be generated in the same retinal location. It is thought that they originate in the outer layers of the retina particularly the amacrine cells (Drasdo, 1983; Karwoski and Kawasaki, 1991). The c wave is thought to consist of two components one generated in the Muller cells and the other in the pigment epithelium (Griff, 1991). The origin of the d wave remains inconclusive but is thought to be largely produced by the positive going offset of the late receptor potential (Fishman and Karwoski 1991).

A cone dominated ERG can be obtained by light adapting the eye and using rapid (30Hz) white or red flashes against a blue background illumination designed to saturate the rod receptors. In addition rod receptors cannot follow above 16Hz.

5.2.2.2. The Scotopic ERG.

This is also a light evoked response but this time the eye has been dark adapted. Ideally the eye should be dark adapted for around 25mins and then a single flash of light used to generate the ERG. The resulting wave is dominated by the b wave which has an amplitude almost twice that of the photopic ERG and is much more rounded. An example of such a wave is shown in figure 5.13. A rod dominated ERG can be achieved by using a blue stimulating light.

Figure 5.12. Schematic diagram of Photopic ERG

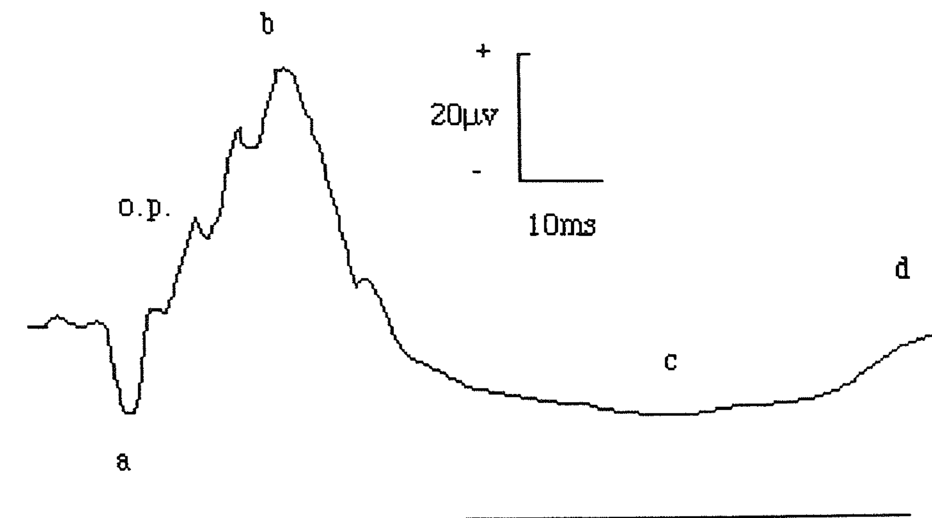


Figure 5.13. Schematic diagram of Scotopic ERG

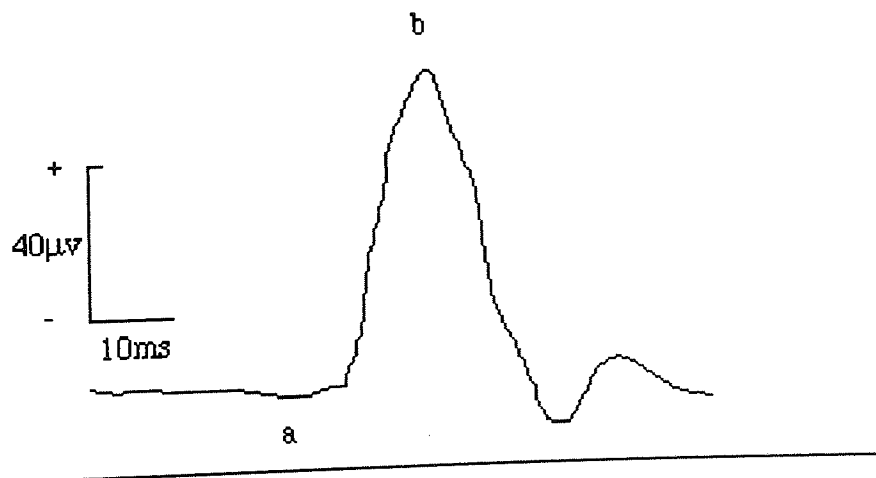


Figure 5.14. Schematic diagram of pattern reversal ERG

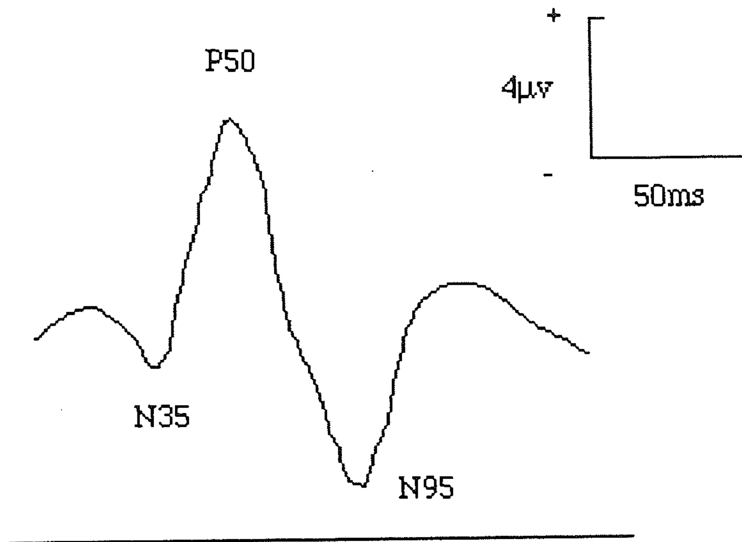
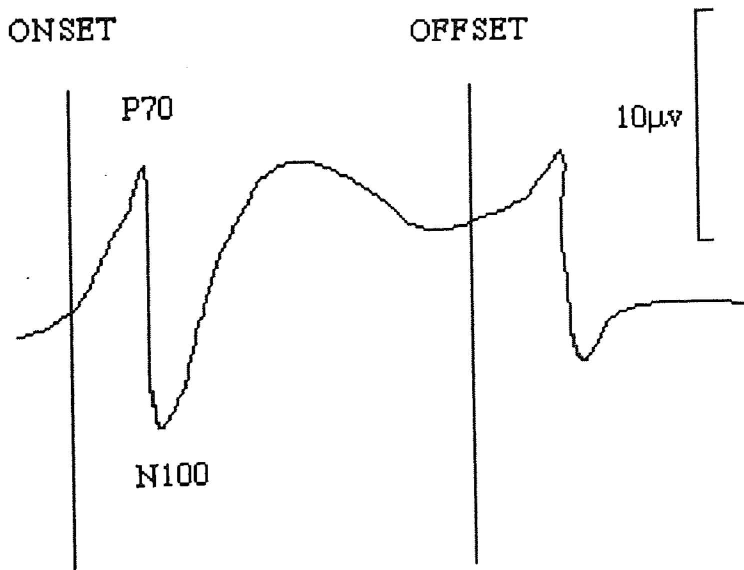


Figure 5.15. Schematic diagram of pattern onset/offset ERG



5.2.2.3. The Pattern ERG.

The pattern ERG can be evoked by using either checkerboards or gratings that are counterphased or presented with an on/off modulation. The amount of light entering the eye during stimulation remains the same but the region of the retina onto which the stimulus falls is subject to repetitve changes in illumination. As the stimulus changes from dark to light at a particular location, an 'on' ERG is generated (as would be acheived using a pattern onset technique), as the stimulus changes from light to dark at that location an 'off' ERG is generated (as would be achieved using a pattern offset technique). Thus the pattern reversal ERG is thought to be the sum of these waveforms. The pattern ERG is not merely the response to the local changes in illumination, part of it is generated is due to the presence of the pattern itself (Berninger and Arden, 1991). The waveform to pattern reversal stimulation consists of negative component at around 35ms (N35) followed by a positive component at around 50ms (P50) and a further negative component at around 95ms (N75), shown diagramatically in figure 5.14.

The pattern onset offset ERG had a similar waveform to the above, consisting of an initical negative, followed by a positive, followed by a negative component corresponding to the onset of the stimulus. In additiion there is a further response corresponding to the offset of the stimulus (see figure 5.15).

It has been established for some years following animal experimentation and clinical research that the ganglion cells of the retina are responsible for generating the pattern ERG. It has been shown that in both cats and primates, that following optic nerve section the pattern ERG is lost while the photopic ERG remains (Maffei and Fiorentini, 1981; Maffei *et al*, 1985). As mentioned previously the pattern ERG is made up of a luminance response and a pattern specific resonse which may be generated in different cells of the retina. Drasdo *et al* (1987, 1990) and Thompson and Drasdo (1987) devised a method of separating these two components. Pattern onset ERGs were obtained from three contiguous zones of the retina that provided a central field of 5.1° radius, a mid-peripheral field of 5.6-12.6° annular radii, and a peripheral field of 12.3-26.3 annular radii using a vertical grating of spatial frequency ranging from 0.14 to 20cpd. The areas of the zones were calculated to contain the same densitiy of ganglion cells. It was assumed that the lowest spatial frequency used, generated a luminance only response as one square covered the whole of the area investigated, (this response was called the retinal illumination response or RIR). Additionally as the spatial frequency of the grating increases the effective contrast is reduced due to the optics of the eye degenerating the retinal

image. This factor was calculated for each spatial frequency used. The ERGs recorded in each retinal zone were corrected for the eye's optical imperfections and the RIR subtracted from the result to produce a pattern specific response (PSR). Comparisons of the profiles of peak amplitudes for each zone and change in histology across the retina gave some support to a theory for the origin of these signals. The RIR appeared to correspond to the distribution of the inner nuclear layer, whereas the PSR corresponded to the distrbution of the ganglion cell layer.

Steady state pattern ERG can be measured if the temporal frequency of stimulus presentation is increased (around 8Hz) such that the response waveforms merge The resulting waveform has a negative - positive - negative sinusoidal morphology and the peaks are usually labelled according to polarity and latency. The amplitude is commonly measured from peak to peak. Using fast fourier transform (FFT), it is found that most of the energy is at the second harmonic frequency (16Hz) (Hull and Thompson, 1988; Maffei and Fiorentini, 1990). The peak-to-peak amplitude of the second harmonic is considered the retinal response to the pattern, while that of the fundamental is a response to overall changes in retinal illumination.

5.2.3. Normative Data.

There have been relatively few studies to assess normative data for the ERG - this is largely because the amplitude of the ERG can be affected by the type electrode used. Thus it is necessary for normative data to be obtained at each laboratory using standard repeatable conditions.

5.2.3.1. Age.

There have been few studies on the effect of age on the ERG. Celesia *et al* (1986), Trick (1987) and Hull and Drasdo (1989) all noted reduced amplitude of both positive and negative components of the pattern ERG. Celesia *et al* and Hull and Drasdo also note an increased latency with age, but Trick does not. The latency change could be due to decreased pupil size and reduced media transparency thus reducing the retinal illumination. The reduction in amplitude could also be due to these factors in addition to possible retinal ganglion cell loss with age.

5.2.3.2. Pupil Size.

As the amplitude of the photopic and scotopic ERG is dependent on the amount of retina illuminated, a reduced pupil size will reduce retinal illumination and hence reduce the amplitude. For this reason some clinicians choose to dilate the pupils before the recording (Harding, 1988). Berninger (1986) found a significant

reduction in latency of the N95 component and a highly significant increase in latency for both the P50 and N95 components of the pattern ERG in artificially miosed pupils. No difference was found for dilated pupils.

5.2.3.3. Stimulus Parameters.

Spatial frequency of the stimulus affects the latency and amplitude of the pattern ERG. Thompson and Drasdo (1989) noted an increase in latency of the pattern onset response with increasing spatial frequency and a corresponding decrease in amplitude. Torok *et al* (1992) noted a gradual increase in latency of the b wave pattern reversal and pattern onset and offset response with increasing spatial frequency. They also noted a corresponding decrease in amplitude for the pattern reversal b wave and pattern offset response but not for the onset response. These effects are thought to be due to the increased effects of optical degradation of the patterns of high spatial frequency thus reducing their contrast.

The above study by Thompson and Drasdo (1989) also noted a decrease in amplitude of the ERG as the contrast of the stimulus is reduced particularly when high spatial frequencies are used. They found that reducing contrast had no effect on the latency. If contrast and spatial frequency reduce the amplitude of the pattern ERG one would expect that retinal blur caused by defocus would have a similar effect - a review by Berninger and Arden (1991) confirm this.

As it is thought that the pattern ERG is generated in the ganglion cell layer one would expect the spatial frequency tuning function to be band passed due to the centre surround organisation of these cells. However the above studies did not show such an effect. This may be due to the luminance response of the ERG contaminating the result and concealing any low spatial frequency attenuation. By subtracting the RIR from the ERG Drasdo and Thompson (1989) revealed a more band passed result.

5.3. Electrophysiology of Parkinson's disease and Alzheimer's disease.

5.3.1. Electrophysiology and Parkinson's Disease.

5.3.1.1. Visual Evoked Potentials.

VEP s have been measured in patients with Parkinson's diesese for some years with varying results. It seems that the type of stimulus used, spatial frequency of

the stimulus and whether the patients are taking medication are important considerations. The most common trend seems to be a delay to the pattern reversal VEP, particularly if vertical gratings are used (Bodis-Wollner and Yahr, 1978; Bodis-Wollner and Hendley, 1979; Bodis-Wollner *et al,* 1984; Bodis-Wollner, 1985, 1990; Onofrj, 1986, Marx *et al*, 1986; Bhaskar, 1986; Pierelli *et al*, 1988). Appart from the study by Marx and collegues all of the patients had been withdrawn from medication or had not yet embarked on treatment - in most cases P100 latencies reduced when dopaminergic medication was resumed or initiated (the study by Bhaskar is an exception).When checkerboards are used as a stimulus, the results are more variable. Some studies have shown a delayed P100 component (Gawel *et al*, 1981; Solazzo, 1985; Bhaskar, 1986; Gottlob *et al*, 1987; Ellis *et al*, 1988; Calzetti, 1990; Henderson, 1992) - in all patients not taking medication. Where measured, only Solazzo (1985) and Bhaskar (1986) noted an improvement in latency with the initiation of treatment. The others showed no improvement with medication. Henderson (1992) revealed a delay to the P100 component in patients taking L-dopa that improved slightly following fetal mesencephalon implantation surgery. Other authors have not observed such a delay to the P100 component of the pattern reversal VEP to a checkerboard stimulus (Ehle, 1982; Dinner *et al*, 1985; Nightingale *et al*, 1986). However in all these studies all patients were taking dopaminergic medication.

In some cases the delay was dependent on spatial frequency of the checkerboard, the delay being more pronounced with increased spatial frequency of stimulus (Onofrj,1986; Pierelli *et al*, 1988; Calzetti, 1990; Bodis-Wollner and Yahr, 1978; Bodis-Wollner and Hendley, 1979; Bodis-Wollner *et al,* 1984; Bodis-Wollner, 1985, 1990). In others the delay was more pronounced with increaseing contrast of the grating (Gottlob *et al*, 1987), or with increasing duration of the disease (Sollazzo, 1985; Marx *et al*, 1986). Some authors (Gawel *et al*, 1987; Pierelli *et al*, 1988; Calzetti, 1990; Kupersmith, 1982) also illustrate an accompanying reduction in amplitude of the P100 component which also tended to recover with administration of L-dopa. The remaining studies did not indicate any change in amplitude, or even an increase in amplitude (Ehle, 1982; Marx *et al*, 1986).

Steady state VEPs to patterned stimuli have also been studied. Bodis-Wollner (1990) and Marx *et al* (1986) used a grating with an on-off modulation (at around 4 and 8Hz). The VEP contained power at the input frequency and at harmonically related frequencies. When analysing the first and second harmonic they found that the amplitudes were similar between groups (i.e. patients and controls) but there were differences in phase indicating an abnormality in visual processing in

Parkinson's disease patients. Calzetti (1990) used a checkerboard counterphasing at 4 and 8 Hz, and measured the peak to peak amplitudes of the second harmonics - which were found to be reduced in Parkinson's disease patients compared to normals.

Pattern VEPs have also been measured in monkeys following the instillation of MPTP (Bodis-Wollner, 1988; Ghilardi *et al*, 1985, 1988). Results revealed an increased latency of the P100 component and a reduction in amplitude that were spatial frequency dependent. These effects recovered to normal following treatment with sinemet. Pattern VEPs have also been studied in normal human volunteers following administration of haloperidol (Onofrj, 1986; Stanzione *et al*, 1991). Both found an increased latency of the P100 component (although not statistically significant in the latter study) compared to pre-drug conditions. Stanzione *et al* (1991) measured the pattern VEP to gratings in young normal humans following oral administration of haloperidol and also reported an increased latency of the P100 component - although not statistically significant.

There does not seem to be as much information on the flash VEP in Parkinson's disease. A report by Yaar (1980) indicates that no change in flash VEP could be detected, either before or after L-dopa treatment. However Van Duijn *et al* (1985), found that haloperidol increased the latency of both flash and pattern VEP.

5.3.1.2. Electroretinograms

The electroretinogram has been measured in patients with Parkinson's disease, with varying results. Ellis *et al*, (1987, 1988) found that the photopic ERG had a delayed and reduced amplitude b wave, and a reduction in amplitude of the oscillatory potentials. The scotopic and flicker ERG also had a reduced b wave amplitude. These results were found to improve following L-dopa administration. Jaffe *et al* (1987) also revealed a delayed b wave when isolating the blue cone response only, but with no alteration in amplitude. They also showed an enhancement of the light adapted a wave response following L-dopa infusion. Gottlob (1985, 1987) and Nightingale *et al* (1986) could not find such a change in latency whether patients were taking medication or not, although Gottlob does state that a reduction in amplitude b wave could be shown as well as a reduction in oscillatory potential amplitude. Iudice *et al* (1980) measured the scotopic ERG in Parkinson's disease before, 3 days after, and 3 months after L-dopa and carbidopa treatment. They found no significant change in b wave amplitude compared to controls.

The ERG to a patterned stimulus has also been measured - some using checks (Nightingale *et al*, 1986; Gottlob *et al*, 1987; Calzetti *et al*, 1990; Henderson *et al*, 1992) and others have used gratings (Pierelli *et al*, 1988). In patients not taking medication Pierelli and coworkers and Calzetti found an increase in b wave latency (particularly to high spatial frequencies) but no change in amplitude - treatment has been shown to improve latency. Gottlob and coworkers (1987) found decreased b wave amplitude but no change in latency in all patients whether they were taking medication or not. Nightingale *et al* (1986) and Henderson *et al* (1992) found decreased b wave amplitudes in all their parkinson's disease patients taking medication. The latter group showed an improvement in 2 of their patients following fetal mesencephalon implant surgery.

Gilhardi *et al* (1985. 1988) measured pattern ERGs in monkeys following MPTP administration and found an increase in b wave latency and a reduction in its amplitude. Bodis-Wollner also found a reduction in b wave amplitude under similar conditions, particularly with higher spatial frequency patterns. Following oral administration of haloperidol in young normal humans, Stanzione *et al* (1991) noted a delayed b wave of the pattern ERG to grating stimuli. Vaclav and Balik (1978) measured the scotopic ERG in normal volunteers before and after the oral administration of thioridazine or a placebo. Thioridazine is a neuroleptic with antidopaminergic properties and is well tolerated by experimental subjects. Administration of the drug resulted in an increased a and b wave latency and a reduction in b wave amplitude. Perossini and Fornaro (1990) found that perphenazine and haloperidol (dopamine inhibitors) reduced the scotopic b wave amplitude; while levodopa in combination with carbidopa, nomifensine, and bromocriptine (potentiators of dopamine transmission) increased the scotopic b wave amplitude; and impiramine and diazepan (having no effect on dopamine transmission) had no effect on this component.

Although the results are somewhat variable, it would seem that the b wave of the ERG, particularly to a patterned stimulus of high spatial frequency, is effected by a depletion in dopamine.

In the case of Parkinson's disease it is a possibility that either striatal or extrastriatal catecholaminergic pathways affect the VEP, or the delay could be induced by depleted dopaminergic transmission within the retina as suggested by the ERG alterations.

5.3.2. Electrophysiology and Alzheimer's Disease.

5.3.2.1. Visual Evoked Potentials.

VEPs were first measured in patients suffering from AD or senile dementia of the Alzheimer type (SDAT) by Visser *et al* in 1976 who reported a delay in the flash components occurring after 100ms. Since that time much of the work has been completed in this department by Harding, (1988, 1990), Harding *et al*, (1981, 1984, 1985), Wright *et al* (1984, 1985, 1986) and Orwin *et al* (1986) starting with a study of 12 patients with AD in 1981. It has been repeatedly shown that AD patients show a delay in latency of the P2 component of the flash VEP, co-existing with a normal P100 of the pattern reversal VEP. The P2 - P100 latency difference was found to be around 52ms. The amplitudes of the components did not seem to be effected. Other studies have confirmed these findings (Danesi *et al.* 1985; Katz et al, 1989; Philpot *et al* 1990; Coburn *et al*, 1991; Sloan *et al*, 1992), with the addition that the delay increases with severity of the disease.

Reports exist which claim that the flash P2 components is not significantly altered in AD patients compared to normals (Coben *et al*, 1983; Berg *et al*, 1984; Pollock *et al*, 1989; Ray *et al*, 1991). Although Coben and Berg suggest delays in the P100 and later components of the pattern evoked VEP. Visser *et al* , (1976, 1985) have also noted an increased latency of the later components of the pattern VEP and a reduction in amplitude of the earlier peaks (P100). Smith and coworkers (1990) measured the pattern onset VEP in patients with AD and found a delayed CI component of slightly reduced amplitude but a normal CII component.

Celesia *et al* (1993) measured the steady state VEP to square wave gratings in patients with AD. They calculated the power spectrum of the second and fourth harmonic and measured the association of activity between occipital, temporal, parietal and central regions by intra and inter-hemispheric coherence and phase. They found less evoked activity of the fourth harmonic at O1 and O2 in the AD patients. AD patients also showed statistically significant phase despersion at O1-P3 and O2-P4 not seen in control groups.

Flash and pattern VEPs have also been measured in patients with other forms of dementia. Ruessman and Beneicke (1991) found that the latency of the flash P2 component in a group of patients with dementia was not significantly different from control subjects. Huisman and coworkers (1987) measured the pattern VEP in demented patients with non-organic brain disorders or korsakow psychosis and

they found that in the demented patients all of the components had slightly larger amplitudes and the late peaks (N130, P165, N220) were delayed compared to normals. Cosi *et al* (1982) measured the flash VEP in patients with cerebral atrophy either with or without dementia. They found that all patients had a delayed N2 and P2 component - those of the demented group being longer. Straumanis and collegues (1964) measured flash VEP on patients with chronic brain syndrome associated with cerebral arteriosclerosis and found that the later components beyond 100 ms were delayed. The flash VEP has also been measured in patients with Down's syndrome (Crapper *et al*, 1975) and only in patients showing signs of dementia were the late components absent.

Studies have also been conducted comparing the VEP in patients with AD to those in patients exhibiting other forms of dementia. There have been a number of studies comparing VEPs in ADs to patients with multi-infarct dementia (MID) (Wright and Furlong, 1988; Engedal *et al*, 1989; Sloan *et al*, 1992). Both forms of dementia revealed delayed flash P2 and normal flash P1 and pattern reversal P100 components compared to normal controls and in some cases to other forms of dementia - the AD patients usually showing the largest P2 delay. Coburn *et al* (1991) measured pattern VEP and flash VEPs in AD patients, patients with other dementias and normals - they found that only the AD group showed a delayed flash component, all other components were of normal latency. Aguglia *et al* (1991) found delayed flash P2 and normal flash N1, P1 and N2 components but delayed flash P2 components in both AD patients and in patients with Creutzfeldt-Jakob disease - pattern reversal VEPs were not measured. Care has to be taken however to carefully diagnostically separate patients with MID from those with AD this has not been done in some studies (e.g. Wright and Harding, 1988)

Harding *et al* (1984) and Harding and Wright (1986) postulated that the delay in the flash P2 component was due to the fact that it was transmitted via a superior colliculus - association area pathway which is cholinergic.The effects of hyoscine hydrobromide (scopolamine) on the flash and pattern VEP of normal subjects has been used to test this theory. Bajalan *et al*, (1986) measured the flash and pattern VEP before and after a subcutaneous injection of 0.6 mg hyoscine hydrobromide (or scopolamine) on 10 young normal subjects. The results showed a significant increase in latency of the flash response but with no change to the pattern response. A similar test was completed by Gilles *et al* in 1989 with addition of administration of the drug to older subjects, patients with SDAT and patients with major depressive disorders. A delayed P2 was noted in all cases, with increasing latency with age. The drug had a drastic effect on the P2 component of the Alzheimer

patients, but no effect on the P100 component of the pattern reversal VEP in any group. Sannita *et al* (1988) measured the pattern reveral VEP in young healthy volunteers before and after an intramuscular injection of hyoscine hydrobromide (0.25mg, 0.50mg, or 0.75mg). A decreased latency of the N75 component and increased latency of the N175 component was noted, but only when the 0.75mg dose was used. Ray *et al* (1991) measured the flash and pattern VEPs in patients with AD, and healthy young, middle aged and elderly subjects before and after treatment with hyoscine hydrobromide (0.002, 0.004, 0.007 mg/kg i.m). They found that the flash P2 component only increased in lateny in the youngest age group following drug administration, and that the P100 component of the pattern VEP was delayed in all groups following drug administration. There was no significant difference in amplitude in any group. Neither Sloan *et al* (1991) or Gilles *et al* (1993) found any detrimental effect of hyoscine hydrobromide on the flash VEP in young healthy subjects, although Gilles *et al* found that the drug increased the latency of the P50 and N150 and decreased the latency of the P100 component of the pattern reversal VEP. Finally, Smith and coworkers (1990) found that 1.2 mg of hyoscine hydrobromide administered to young volunteers increased the latency and decreased the amplitude of the CI component of the pattern onset VEP, but had no significant effect on the CII component.

5.3.2.2. Electroretinograms.

To date there does not seem to have been much research into the effect of Alzheimer's disease on the ERG. Katz *et al* (1989) report that AD has no effect on the latency or amplitude of the photopic ERG a or b wave compared to normals - although a reduced amplitude b wave of the pattern ERG was noted. Trick et al, (1988) measured the pattern ERG to a checkerboard stimulus reversing at 4 or 16 reversals per second. They found that the peak to peak amplitude was reduced in patients with AD - but only when the 16 reversals per second stimulus was used This would suggest an abnormality at the inner plexiform layer of the retina or a ganglion cell abnormality. In this latter study as an amplitude reduction was only evident when the high temporal frequency was used - this suggests that only the magnocellular ganglion cells are effected by the disease. This would be compatible with the pathological changes observed by Hinton *et al* (1986) and Basi *et al* (1987) in the optic nerves and retina of AD patients.

From the above studies of VEPs and ERGs in Alzheimer's disease and Parkinson's disease it would seem that deficits in the neurotransmitters dopamine and acetylcholine has quite different effects of the visual pathway. Alzheimer's disease

and the accompanying acetylcholine deficit results in an anomaly in the transmission of the flash VEP, which is the ultimate low spatial frequency stimulus, and to checkerboards reversing at high temporal frequencies when measuring the ERG. This may be the result of a neurotransmitter deficit involving the association areas of the visual cortex as mentioned above and/or reduction of the large ganglion cells of the retina and optic nerve. Parkinson's disease, and the accompanying dopamine deficit seems to effect the transmission of patterned stimuli both when measuring the VEP and ERG, particularly when high spatial frequencies are used. This is likely to be due to a reduction in the neurotransmitter at a retinal level. From what we know about the parallel organisation of the visual pathway one could speculate that these two diseases effect different parts of that pathway - Alzheimer's disease having its maximal effect on the magnocellular pathway and Parkinson's disease having its maximal effect on the parvocellular pathway. If one could design stimuli that could preferentially stimulate these pathways, and then measure the VEPs and ERGs in patients with AD and PD then it would be possible to gain information about the function of the neurotransmitters involved in addition to designing a useful clinical tool for the diagnosis and monitoring of these patients.

5.4. The use of Electrophysiology to Demonstrate Parallel Pathways.

For some years there has been much interest in the division of the visual system into transient and sustained, X and Y or magnocellular and parvocellular parallel pathways. Electrophysiology has been used as a tool to an attempt to illustrate their existence. The stimuli used have been based on human and animal psychophysical studies as well as intra and extracellular recordings in animals. Invariably they are based on the assumption that the magnocellular system is maximally responsive to low contrast, achromatic, high temporal frequency, low spatial frequency stimuli, and that the parvocellular system is maximally responsive to high contrast, chromatic, low temporal frequency and high spatial frequency stimuli.

Perhaps the most sensitive method of isolating the parvocellular pathway is to use chromatic stimuli. In this case red and green checkerboards and gratings have been used. It is important that the two colours are matched in luminance (i.e. isoluminant) otherwise a luminance response will be evoked from the magnocellular pathway. Isoluminance can be measured objectively by using a photometer or subjectively. Subjective measures of isoluminance usually involves the use of heterochromatic flicker photometry. This is based on the principle that the parvocellular chromatic channel is not as sensitive to motion as the magnocellular luminance pathway. Thus if a red/green grating is flickered at high frequency

(15hz) then, if there are luminance cues the flickering will be visible, however if the stimulus only contained chromatic cues the flickering would seem minimal. To measure subjective isoluminace the person is allowed to adjust the luminance level of the red or green components of the stimulus until minimum flicker is perceived (Murray *et al*, 1987). VEPs can also be used to establish the point of isoluminance. Kulikowsi, (1991) found that the amplitude of the VEP was minimal when a red/green grating was presented at isoluminance compared to when it was presented with slight increases or decreases in luminance of the red or green components.

Pattern reversal and pattern onset and offset VEP have been measured using isoluminant stimuli and compared to achromatic stimuli. It is thought that the response to an on/off modulated grating results in a VEP whose amplitude is proportional to the contrast of the stimulus, while the response to a reversing grating contains both contrast and motion detection (Kulikowski, 1991). This has been illustrated in the morphology of the VEP waveforms to chromatic and achromatic, reversing and on/off modulated grating stimuli (Murray *et al*, 1987; Berninger *et al*, 1989; Murray and Parry, 1989). They found that when on/off modulation was used an achromatic grating produced a positive component at around 130ms, an isoluminant red/green grating however resulted in a negative component at the same latency, particularly for higher spatial frequencies. The responses to chromatic and achromatic reversing VEP were of similar morphology. Murray *et al* (1987) used the appearance of this negativity using pattern onset to determine the position of isoluminance. That is, by changing the luminance ratios of the red and green away from isoluminance the negativity was replaced by a positive component. They also showed that this change in wave morphology at isomuninance was not as convincing when low spatial frequencies were used, or when checkerboards were used. A study by Paulus *et al* (1986), measuring VEPs to unstructured red or green stimuli, appearing onto an equally bright yellow field, found an N87 component that only occurred for these chromatic stimuli. They also noted that the later P120 was of minimal amplitude at isoluminance and increased in amplitude with luminance increments and decrements. They state that the X cells respond to both colour and to chromatic and achromatic boarders. These studies suggest that a chromatic pattern onset offset stimulus is preferable to a reversing stimulus (which has motion cues) for parvocellular stimulation.

Chromatic stimuli have also been used to evoke ERGs (Berninger *et al*, 1989; Korth and Horn, 1992). Berninger *et al* (1989) found that the ERGs to isoluminant red/green square wave gratings were very small and surface negative. A blue/yellow pattern produced no response. When luminance contrast was used a

typical pattern ERG resulted. Korth and Horn also used square wave gratings presented in onset-offset mode, and found that at the isoluminance point the red/green colour contrast patterns produced responses of large amplitude and long peak times, while luminance contrast patterns were of smaller amptitude but of shorter peak times. The amplitude of the chromatic ERG increased with increasing retinal illumination The discrepancy between these two authors is thought to be due to the higher overall luminance used by the latter group.

The different temporal sensitivities of magnocellular and parvocellular pathways have been annalysed using steady state VEPs. Strasburger *et al* (1993) measured the spatial frequency tuning function of the VEP elicited by an 8Hz contrast reversal and 8 and 16Hz pattern on/off grating stimulation. The reversing stimulus resulted in a function that contained a notch of reduced amplitude VEP and phase reversal at around 4cpd. They suggest that this is the result of the transition between phasic and tonic pathways. The phasic pathway responding at the lower spatial frequencies and the tonic pathway at the higher spatial frequencies - between 2 and 6 cpd both systems are in operation such that there signals cancel out. The 16Hz on/off stimulus resulted in a spatial frequency tuning curve that was comparable to that obtained from psychophysical measures, without a notch and maximal sensitivity occuring in the middle of the spatial frequecny range. They state that pattern onset stimulation is a less efficient stimulator of the transient system and results in a spatial tuning function governed by a single mechanism. As 16Hz is believed to be beyond the peak of the transient system's temporal sensitivity function it does not bring an advantage to the spatial frequency tuning function.

Nelson and Sieple (1991) measured the contrast modulation threshold of a 4cpd grating modulated at 1.5Hz (sustained) and a 1cpd grating modulated at 20Hz (transient) by retrieving VEPS while the amount of modulation impressed upon a standing contrast was swept, so that fluctuations in contrast were initially small and gradually became and observable flicker. Thresholds for temporal modulation of contrast increased with standing contrast under sustained conditions but not under transient conditions. The sustained system showed contrast gain control and acted like a spatial contrast detector. Under the transient conditions there was little change in increment thresholds up to about 20% standing contrast. Within this range the system acted as a detector of local luminance change since the same absolute change in luminance was required for detection of all standing contrasts. Beyond this range, sensitivity to contrast modulation decreased, although never to the level seen under sustained conditions.

Bobak *et al* (1984, 1988) measured the contrast sensitivity function of the steady state VEP to a 6cpd grating modulated at 7.5Hz (on/off) using a contrast range of 1.7% to 27.5% (0.15log unit steps), and compared the results to psychophysical pattern and flicker thresholds. They annalysed the amplitude and phase of the first and second harmonic of the wave. They found a double limb function relating VEP amplitude to contrast, the slope of the two functions being similar, the second limb beginning above 13.8% contrast. The shape of the response function was similar for the fundamental and second harmonic components, the fundamental being parallel to the second harmonic but larger in amplitude. They believe that this double-limbed function is due to the existence of two groups of neurons, one sensitve to low and the other sensitive to high contrast. They also found that the regression line of the fundamental function (used to estimate the VEP threashold) corresponded to the psychophysical pattern threshold, and that the second harmonic VEP threshold corresponded to the psychophysical flicker threshold.

It therefore seems reasonable to suggest that VEPs and ERGs could be used to preferentially stimulate the magnocellular and parvocellular pathways. In the following experimental chapters, I will describe how the temporal and chromatic aspects of the stimuli can be manipulated further to provide better differentiation of the two pathways.

CHAPTER 6.

6. DEVELOPMENT OF STIMULI FOR VEPS AND ERGS THAT PREFERENTIALLY ACTIVATE MAGNOCELLULAR AND PARVOCELLULAR PATHWAYS.

From the properties of the M and P pathways described in chapter 4 and from previous psychophysical and electrophysiological studies used to demonstrate their existence, the spatial frequency, temporal frequency, contrast and chromaticity of patterned stimuli have been manipulated in an attempt to preferentially stimulate the M and P pathways. In addition it was necessary to ensure that the stimuli were robust enough to be used in a clinical environment as they were later to be used to evoke VEPs and ERGs in patients with Alzheimer's disease and Parkinson's disease.

6.1. Experiments to design stimuli that preferentially stimulate the magnocellular pathway.

Introduction

It has been established that the magnocellular pathway responds to low spatial frequency patterns of high temporal frequency. Additionally this pathway is thought to demonstrate high gain at low contrast levels - with the response increasing with increasing contrast up to levels of about 15% before saturation (Chapter 4). If this is true, then when using a low spatial frequency checkerboard counterphasing at a high temporal frequency, by increasing the contrast of the stimulus in small increments, the amplitude of the VEPs or ERGs should increase correspondingly until saturation point is reached.

EXPERIMENT 1.

Effect of increasing contrast on the amplitude of the steady state VEP.

Instrumentation.

Visual evoked potentials were recorded using the Nicolet Pathfinder II electrodiagnostic system. The bandpass of the system was 0.5 to 70Hz. The patterned stimuli were generated using a VSG 2/1 grating generator developed by Cambridge Research Systems and displayed on a CRT with 14 bit luminance resolution (E120 Flexscan 9080i 16 inch colour monitor) at a frame rate of 70Hz, with 624 pixels and 878 lines, using standard rastar technique. The gamma-corrected display was linear up to 90% contrast. The display screen had a mean luminance of 50 cd/m^2 and was 22.5cm vertical by 30cm horizontal. A square wave pulse was used to trigger the pathfinder.

Silver-silver chloride electrodes were attached to the scalp using Blenderm tape and the interelectrode impedence was maintained at 5K-ohms or less. The electrode montage used was OZ referred to FZ, O1 referred to FZ and C3, and O2 referred to FZ and C4, CZ acted as ground (in accordance to the methodology described in chapter 5). All recordings were taken in dim illumination.

Stimulus.

A black and white checkerboard pattern was generated using the VSG and displayed on the CRT. The spatial frequency of the checks were 73', and they were counterphased at a temporal frequency of 6Hz. The stimulus was presented within a 4°17' X 5°42' field. The contrast of the pattern was increased from 5% to 85% in 5% increments.

Subjects.

8 healthy subjects volunteerd to take part in this study. All were students at the Vision Sciences department and were relatively experienced in taking part in electrophysiological studies. They were all aged between 18 and 27 years and had corrected visual acuity of 6/5. They had no history of any ophthalmological disease.

Procedure.

On arrival the visual acuity of each subject was noted and they were optically corrected for the designated viewing distance. VEPs were measured monocularly. The subject was asked to fixate on a small spot in the centre of the CRT screen. 50 sweeps were averaged at each contrast level, and the recording was repeated. To prevent fatigue from effecting the results, the contrast levels were chosen randomly rather than increasing the contrast progressively from 5% upwards

Results.

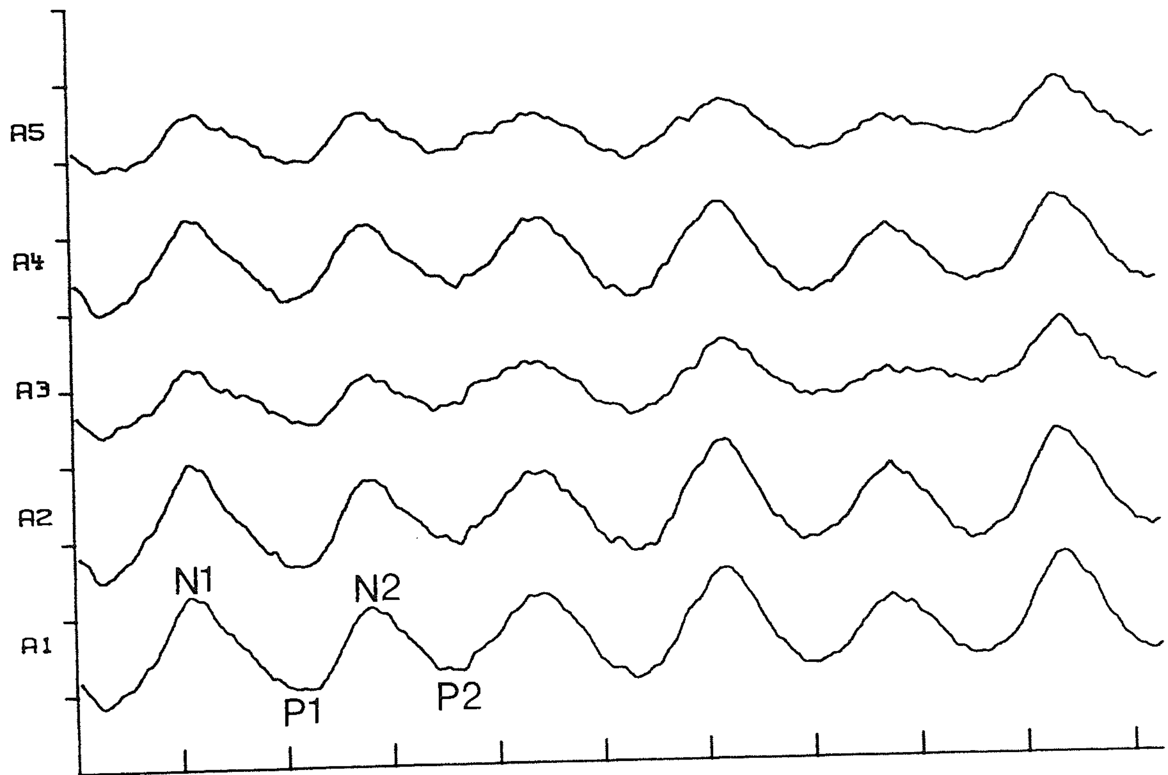
The VEP appeared with a sinusolidal morphology with 6 peaks being present within a 500ms time window. This means that the VEP represented the second harmonic (12HZ) of the input frequency. An example of such a response is shown in figure 6.1.

Channels Oz-Fz and O1-C3 were used for annalysis. The peak to peak amplitude of the first (N1 {approx. 50ms}-P1 {approx. 100ms}) and second (N2 {approx. 140ms}-P2 {approx. 175ms}) component were measured at each contrast level. The mean amplitude and standard deviation were then calculated. These data are presented in tables A1 - A4 of appendix 1. The results are shown graphically in figure 6.2.

It can be seen that the amplitude of the response increases rapidly up to a contrast level of around 25% after which the curve levels out representing saturation. This saturation appears more marked for the O1-C3 channel.

The Pathfinder II also has software facilities to present the power spectra of the waveform and also to calculate the % power of the second harmonic frequency in the waveform. The individual results and mean % power and standard deviation are shown in tables A5 and A6 of appendix 1. These data are graphically represented in figure 6.3.

Figure 6.1. Example of a steady state VEP to a 73' check counterphasing at 6Hz (85%) contrast.



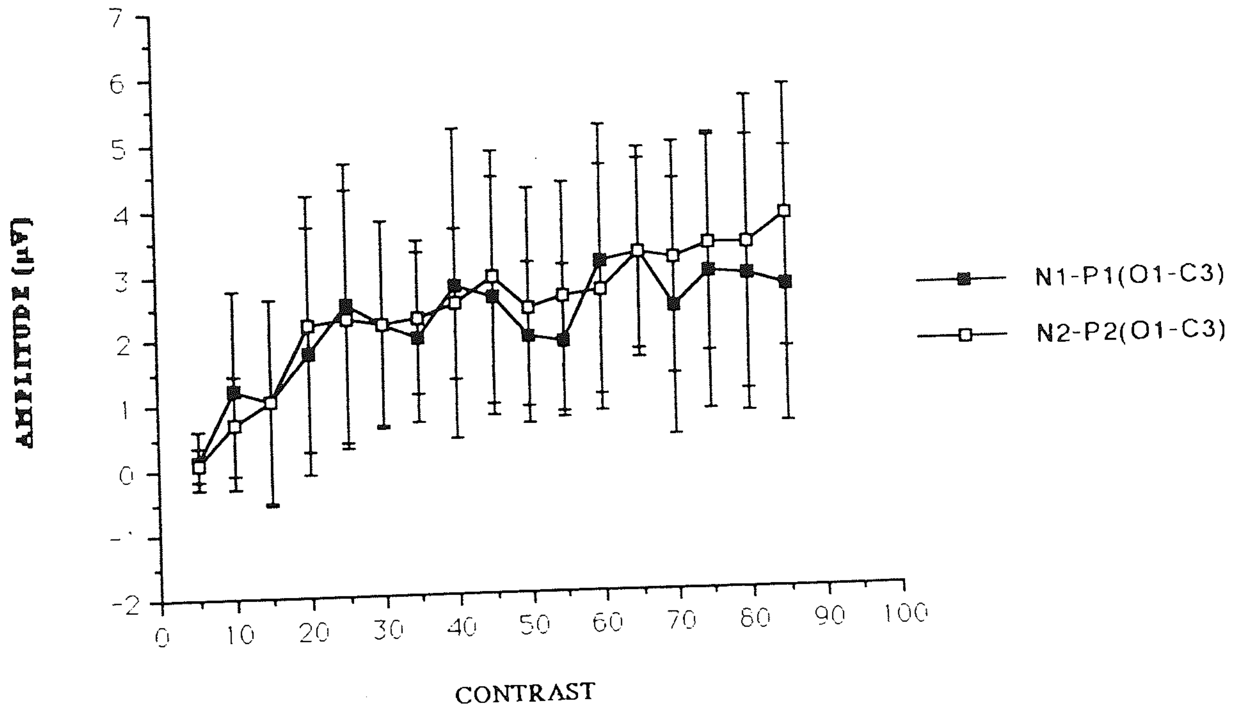
ms/div = 50.00

μv/div = 7.50

A2 (O1-Fz)		A2 (O2-Fz)	
N1	52.00	N1	57.00
P1	103.00	P1	112.00
N2	137.00	N2	138.00
P2	181.00	P2	169.00
N1-P1	18.14	N1-P1	5.41
N2-P2	6.40	N2-P2	3.72

Figure 6.2.

GRAPH SHOWING CHANGE IN AMPLITUDE OF STEADY STATE VEP WITH CONTRAST (O1-C3)



GRAPH SHOWING CHANGE IN AMPLITUDE OF THE STEADY STATE VEP WITH CONTRAST (OZ FZ).

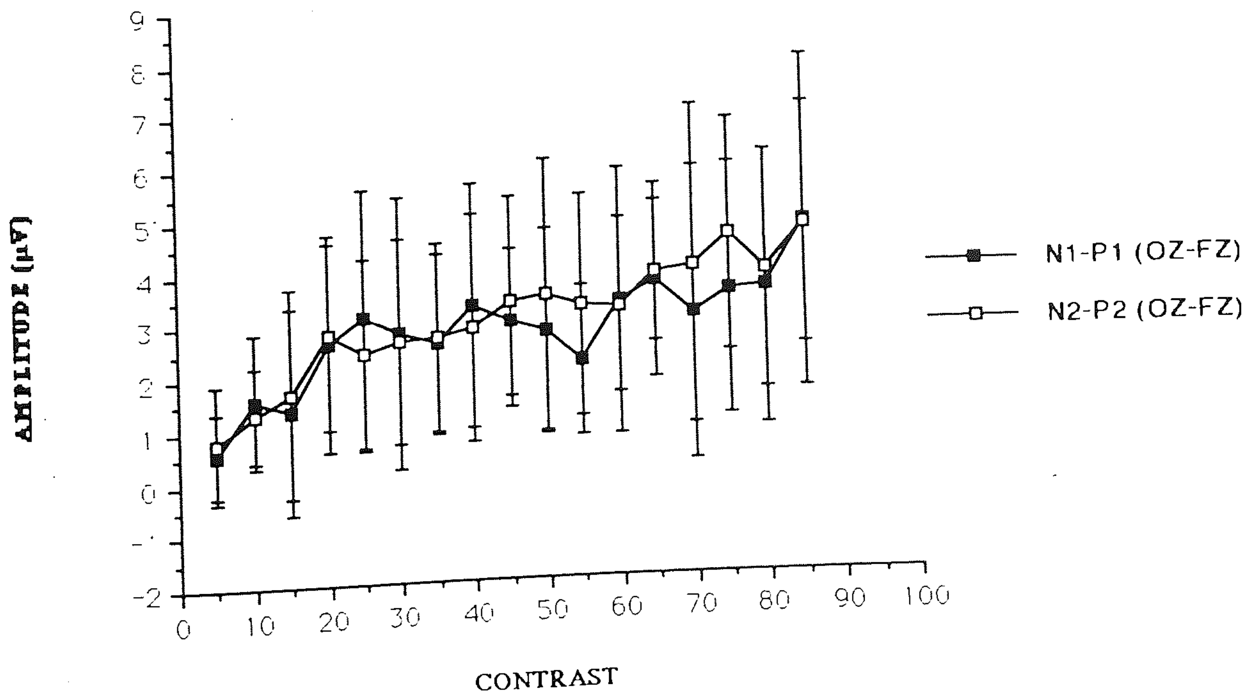
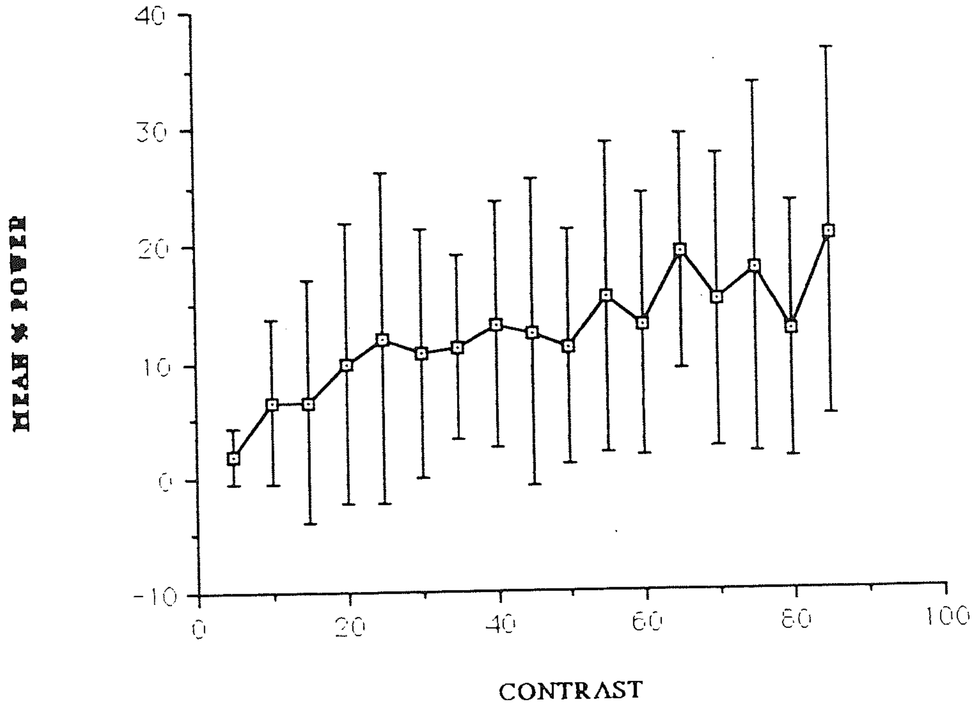
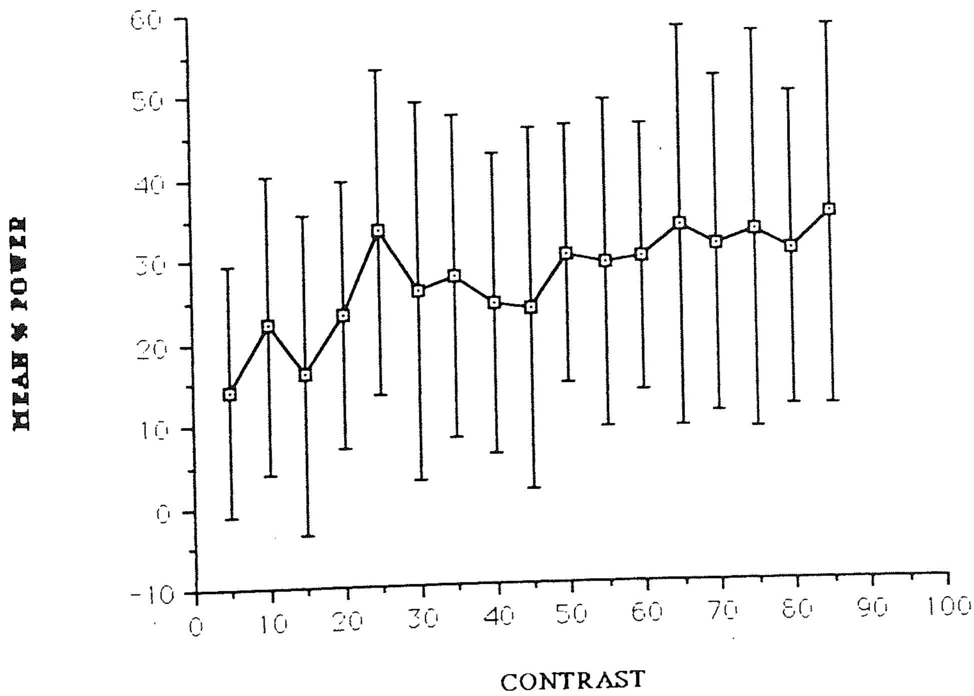


Figure 6.3.





Once again the % power increases as the contrast increases up to levels of 25% after which the response saturates. This saturation is again more marked for the O1-C3 channel.

Discussion.

These data indicate that the use of a checkerboard counterphasing at high frequency results in a saturation of the amplitude of the response as the contrast of the stimulus is increased above about the 25% level. This may well be due to the checkerboard stimulating the magnocellular pathway only. It is difficulat to explain why the Oz-Fz channel shows less saturation. It is possible that the negativity known to exist in the frontal region of the brain may continue to increase in amplitude as the contrast of the stimulus in increased, thus effecting the overall response when an Fz reference is used. Alternatively, since the superior colliculus - association area pathway is magnocellular, the distribution of this response may be more lateral than that usually associated with pattern reversal.

In order to decide on the stimulus to use for future work on patients with Alzheimer's disease and Parkinson's disease, it was necessary to chose a contrast that produced the largest response and yet least likely to stimulate the parvocellular pathway. A contrast of 30% was considered optimal as it lies just beyond the point of saturation.

EXPERIMENT 2.

Effect of increasing contrast on the amplitude of the steady state ERG.

Instrumentation.

Electroretinograms were also recorded using the Nicolet Pathfinder II electrodiagnostic system. The bandpass of the system was 0.5 to 30Hz. The patterned stimuli were generated using the same system as of the VEP study above. A square wave pulse was used to trigger the pathfinder.

DTL electrodes were used as the acitve electrodes and were referred to silver-silver choride electrodes at the outer canthus. The methodology for electrode attachment

described in section 5.2.1.2 of chapter 5 used by Thompson and Drasdo (1987) was utilized. All recordings were taken in dim illumination.

Stimulus.

A black and white checkerboard pattern was generated using the VSG and displayed on the CRT. The spatial frequency of the checks were 2°22', and they were counterphased at a temporal frequency of 6Hz or 8Hz. The stimulus was presented within a 19°5' X 24°46' field. The contrast of the pattern was increased from 5% to 85% in 5% increments.

Subjects.

14 healthy subjects volunteerd to take part in this study. All were students at the vision sciences department and were relatively experienced in taking part in electrophysiological studies. They were all aged between 18 and 27 years and had corrected visual acuity of 6/5. They had no history of any ophthalmological disease.

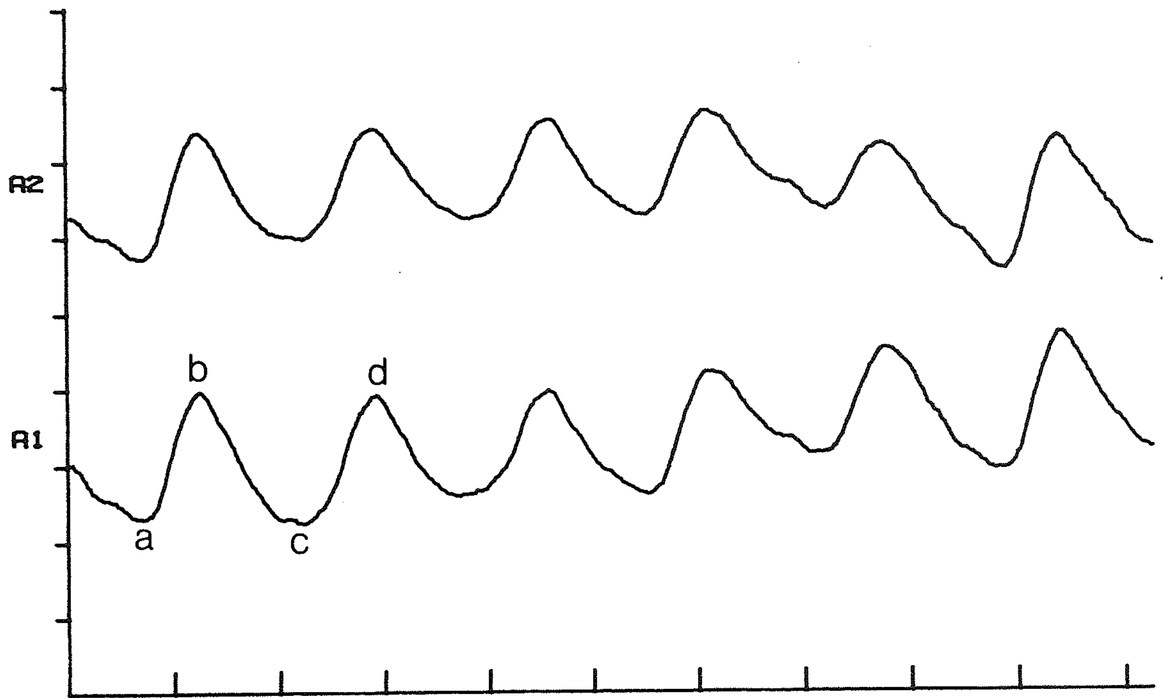
Procedure.

On arrival the visual acuity of each subject was noted and they were optically corrected for the designated viewing distance. ERGs were measured binocularly. 8 subjects were presented with a checkerboard chounterphased at 6Hz and 6 subjects were presented with a checkerboard counterphasing at 8Hz. The subject was asked to fixate on a small spot in the centre of the CRT screen, and asked to keep blinking to a minimum. 150 sweeps were averaged at each contrast level, and the recording was repeated. To prevent fatigue from effecting the results,the contrast levels were chosen randomly rather than increasing the contrast progressively from 5% upwards

Results.

The ERG to the 6Hz counterphasing checkerboard also appeared as a sinusoidal waveform with 6 peaks appearing within a 500ms time window. However, in this case the peaks were not as uniform as those found in the VEP - they were not equidistant appart. This arhythmical morphology may be due to the influence of the blink reflex. An example of such a response is shown in figure 6.4.

Figure 6.4. Example of a steady state ERG to a 2°22' check counterphasing at 6Hz (85% contrast).



ms/div = 50.00

μv/div = 3.75

A1 (left eye)		A2 (right eye)	
a	33.00	a	33.00
b	60.00	b	59.00
c	107.00	c	107.00
d	144.00	d	143.00
a-b	6.31	a-b	6.25
c-d	6.34	c-d	5.47

The peak to peak amplitude of the first two components (a-b and c-d) were measured for each eye. The data for each individual and mean and standard deviations are given in tables A7 to A10 of appendix 1. A graph showing the change in amplidue with contrast is shown in figure 6.5.

It can be seen that there is a rapid increase in the amplitude of the response up to contrast levels of 30% followed by a flattening of the curve up to a contrast level of 70%. After this there is a second increase in the amplitude.

The results for a checkerboard counterphasing at 8Hz are similar. The individual results are given in tables A11-A14 of appendix 1 and are shown graphically in figure 6.6. The graph shows a curve very similar to that shown above using a 6Hz frequency, although not as marked.

It was found that when the fast fourier transform software of the Pathfinder was used to calculate the % power of the second harmonic frequency in the waveform, the result was often 0%. This is probably due to the arhythmical nature of the waveform such that the frequency could not be identified.

Discussion.

Once again, the use of a checkerboard counterphasing at high temporal frequency appears to evoke a magnocellular response. However, the ERG does not appear to provide the same quality of isolation as the VEP. This is not surprising since the pattern ERG is a combined luminance and pattern respose. This is probably one of the reasons why there is a sudden increase in amplitude at high contrast levels - the distinctive edges of the checkerboards could be influencing the response by stimulating the parvocellular pathway. Alternatively there could be an additional luminance response due to lack of linearity of the CRT at these contrast levels. Thus, although magnocellular pathway isolation is not to be expected when using the ERG, it is important to use a low contrast as well as a high temporal frequency.

Figure 6.5.

GRAPH SHOWING CHANGE IN AMPLITUDE OF THE 6HZ ERG WITH CONTRAST

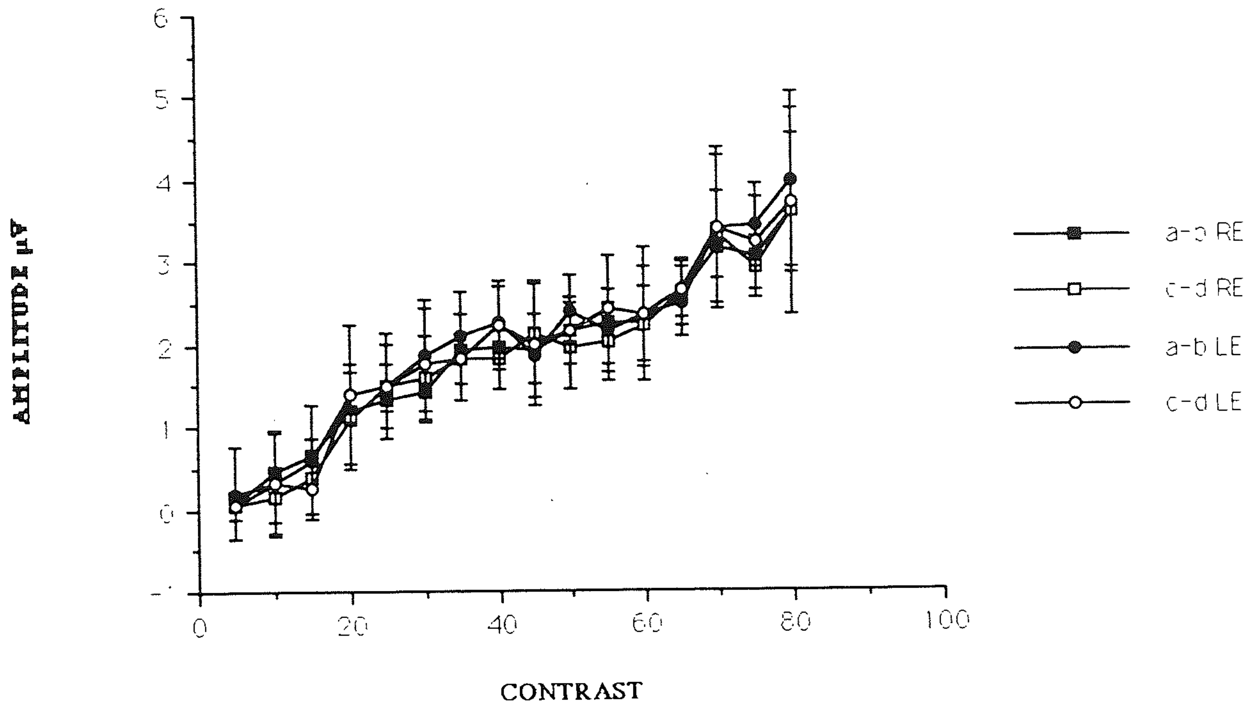
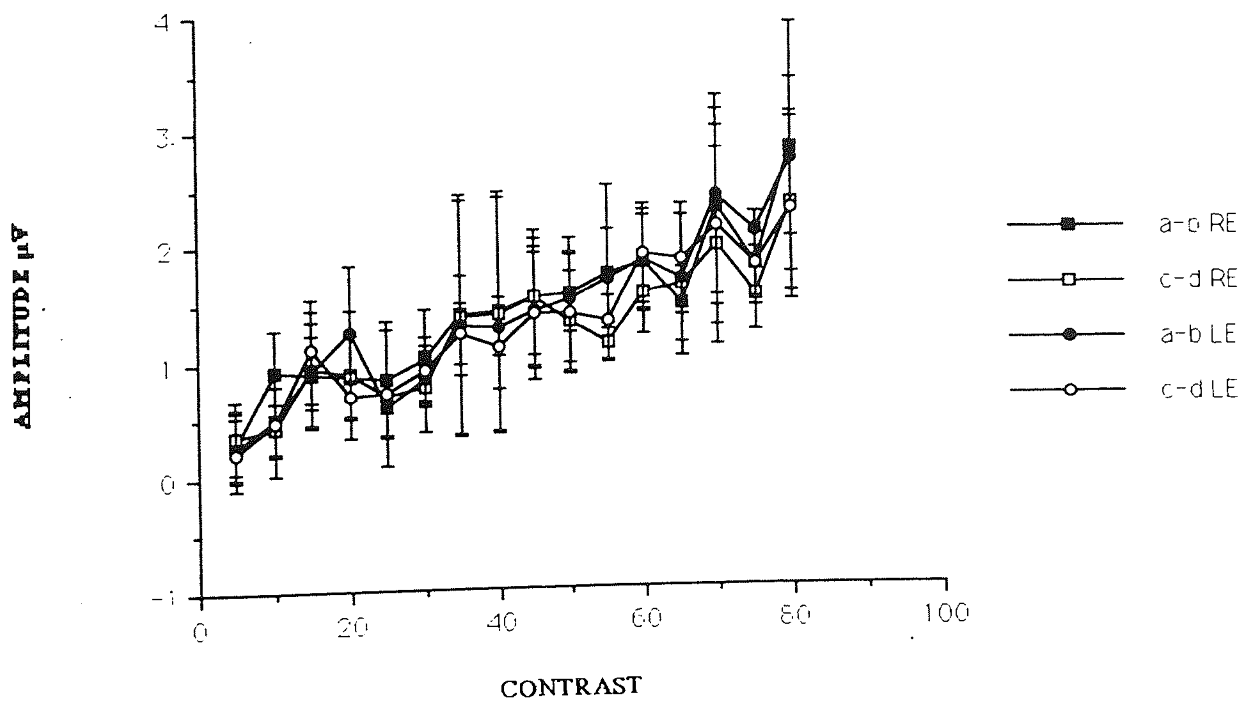


Figure 6.6.

GRAPH SHOWING CHANGE IN AMPLITUDE OF THE 8HZ ERG WITH CONTRAST



6.2. Experiments to design stimuli that preferentially stimulate the parvocellular pathway.

Introduction.

It has been established that the parvocellular pathway responds to chromatic or achromatic patterns of high spatial frequency and low temporal frequecny. This pathway is thought to demonstrate lower gain at low contrast levels and that the response amplitude increases as the contrast increases with no saturation. Thus by using a high spatial frequency stimulus that has low temporal characteristics, the amplitude of the VEP should continue to rise with increasing contrast even at high contrast levels. In order to demonstrate this it was necessary to develop a stimulus that changed very slowly over time. For this the VSG computer described above was used to produce a checkerboard pattern that was presented as a pattern onset offset stimulus. Additionally, rather than using instantaneous onset/offset, the pattern could be presented using an on and off cosine ramp modulation such that the checkerboard took a specified amount of time to reach maximum contrast where it remained for 200ms and then took the same specified amount of time to then disappear. This 'specified' amount of time for the pattern to appear and disappear was called the 'ramp' time. This type of pattern presentation could also be used for chromatic grating stimuli.

EXPERIMENT 1.

Effect of increasing the ramp time on the VEP.

Instrumentation.

Visual evoked potentials were recorded using the Pathfinder ll electrodiagnostic system. The bandpass of the stimulus was 0.5 to 70Hz. The VSG 2/1 grating generator was used to generate the stimului and to trigger the pathfinder using a spike pulse at the beginning of each modulation.

Silver-silver chloride electrodes were attached to the scalp using Blenderm tape and the interelectrode impedence was maintained at 5K-ohms or less. The electrode montage used was OZ referred to FZ, O1 referred to FZ and C3, and O2 referred to

FZ and C4, CZ acted as ground (in accordance to the methodology described in chapter 5). All recordings were taken in dim illumination.

Stimulus.

Two patterns were used, the first was a black and white checkerboard consisting of 6' checks at a contrast level of 85%; the second was an isoluminant red/green horizontal grating pattern of 4cpd. Objective isoluminance was used and was measured with a spot photometer. The subjective isoluminance of the stimulus was checked by counterphasing the stimulus at 16Hz and using red or green filters to achieve minimum flicker. Both stimuli were presented within a 2°34' X 3°26' field in order to isolate the foveal region in which the P cells are at a relatively higher concentration. The on and off cosine ramp modulation was used as described above, using ramp times of 0ms (transient VEP), 100ms, 200ms and 300ms and an interstimulus interval of 500ms.

Subjects.

6 healthy subjects volunteerd to take part in this study. 4 (SP, NE, RD and PH) were students at the university (aged between 21 and 24 years) and were relatively experienced in taking part in electrophysiological studies. One (MW) was a young volunteer aged 21years, the other (AD) was an old volunteer aged 78 years. All subjects had visual acuities of 6/5 or better and had no history of any ophthalmological disease. All had normal colour vision (checked using ishihara isochromatic plates).

Procedure.

On arrival the visual acuity of each subject was noted and they were optically corrected for the designated viewing distance. VEPs were measured monocularly. The subject was asked to fixate on a small spot in the centre of the CRT screen. 50 sweeps were averaged for each ramp time, and the recording was repeated. The black and white checkerboard was used for 6 of the subjects and the isoluminant grating pattern was used in 2 of the subjects. The procedure was repeated for a check of 3' in subject SP.

Results.

This experiment was conducted in order to decide on the ramp time that was slow enough not to evoke a response from the magnocellular pathway and fast enough to produce a repeatable, reliable response. The morphology of the waveform of the VEP to a checkerboard or grating presented with a raised cosine modulation appears with a major negativity whose latency changes with duration of the ramp. An example of a VEP using a 200ms ramp time is given in figure 6.7.

Tables A15 and A16 of appendix 1 give the latency of the major negative component (CII) as well as its amplitude from the preceeding positivity (CI-CII) for both black white and red green patterns. It is clear from the graphs presented in figure 6.8 that as the ramp time in increased the latency of CII increased and its amplitude decreases. Additionally, when using a ramp time of 300ms or above, a response could only be achieved in 50% of subjects presented with a black and white checkerboard. For this reason we decided that a 200ms ramp time was optimal and was used for further experimentation.

EXPERIMENT 2.

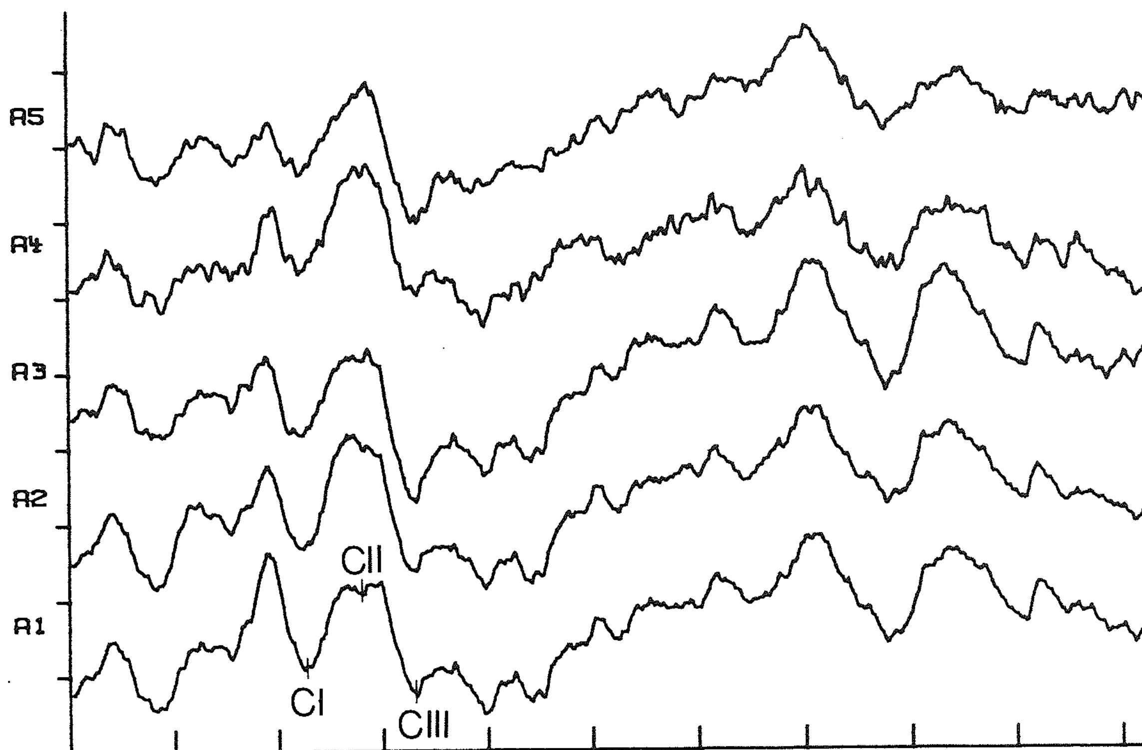
Effect of increasing contrast on the amplitude of the VEP when using an on and off cosine ramp of 200ms.

This experiment was undertaken to complement experiment 1 in section 6.1 illustrating how the amplitude of the VEP to a 6Hz counterphasing grating increases as the contrast increased up to a contrast level of around 30% after which the amplitude levels out. In the case of a high spatial frequency stimulus of low temporal frequency the amplitude of the VEP was expected to continue to rise.

Instrumentation.

This was the same as in experiment 1 above.

Figure 6.7. Example of a VEP to a 6' check modulated in time using a raised cosine ramp of 200ms (85% contrast).



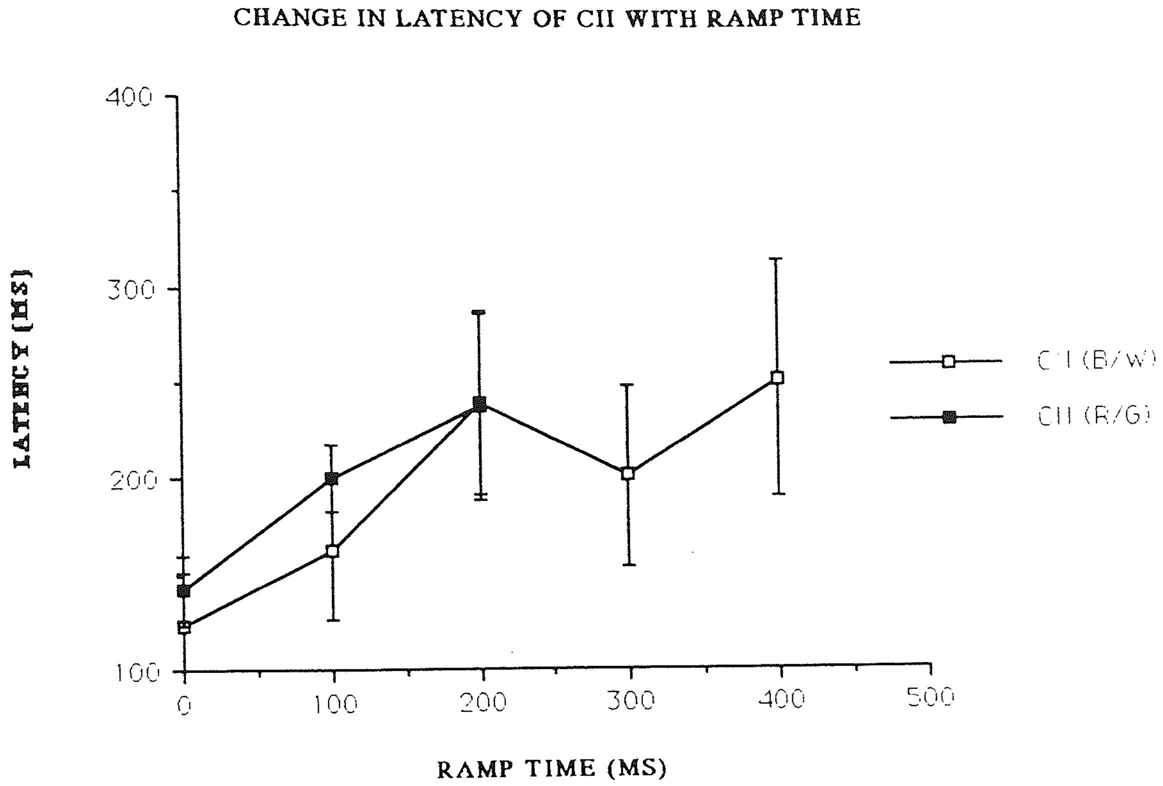
ms/div = 90.00

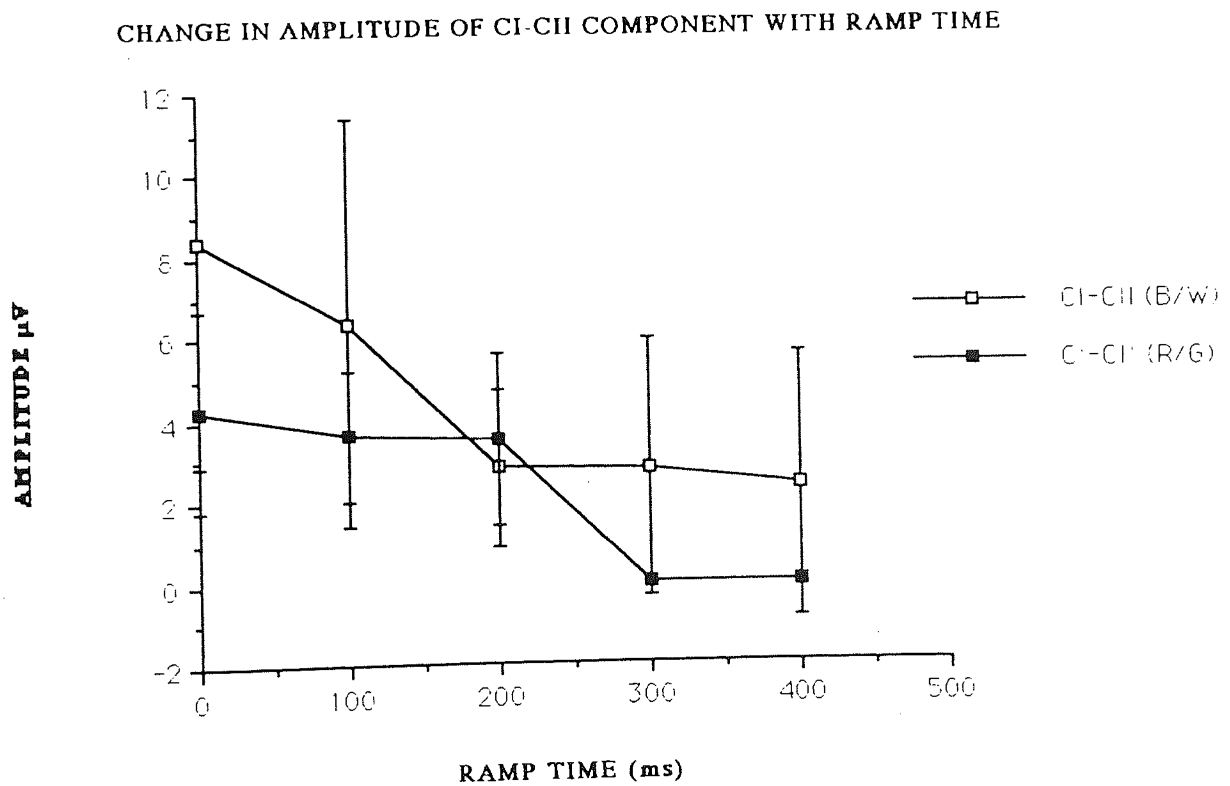
μv/div = 3.73

A1 (Oz-Fz)	
CI	167.80
CII	196.30
CIII	243.40

A2 (O1-Fz)	
CI	167.40
CII	196.20
CIII	241.20

Figure 6.8.





Stimulus.

A black and white checkerboard was generated using the VSG and displayed on the CRT. The spatial frequency of the checks were 6' and they were presented within a 2°34' X 3°26' field. An on and off cosine ramp modulation was used such that checkerboard took 200ms to reach maximum contrast where it remained for 200ms and then took a further 200ms to disappear. The interstimulus interval was 500ms. The contrast of the pattern was increased from 5% to 85% in 5% increments.

Subjects.

7 healthy subjects volunteerd to take part in this study. All were students at the Vision Sciences department and were relatively experienced in taking part in electrophysiological studies. They were all aged between 18 and 27 years and had corrected visual acuity of 6/5. They had no history of any ophthalmological disease.

Procedure.

On arrival the visual acuity of each subject was noted and they were optically corrected for the designated viewing distance. VEPs were measured monocularly. The subject was asked to fixate on a small spot in the centre of the CRT screen. 50 sweeps were averaged at each contrast level, and the recording was repeated. To prevent fatigue from effecting the results,the contrast levels were chosen randomly rather than increasing the contrast progressively from 5% upwards

Results.

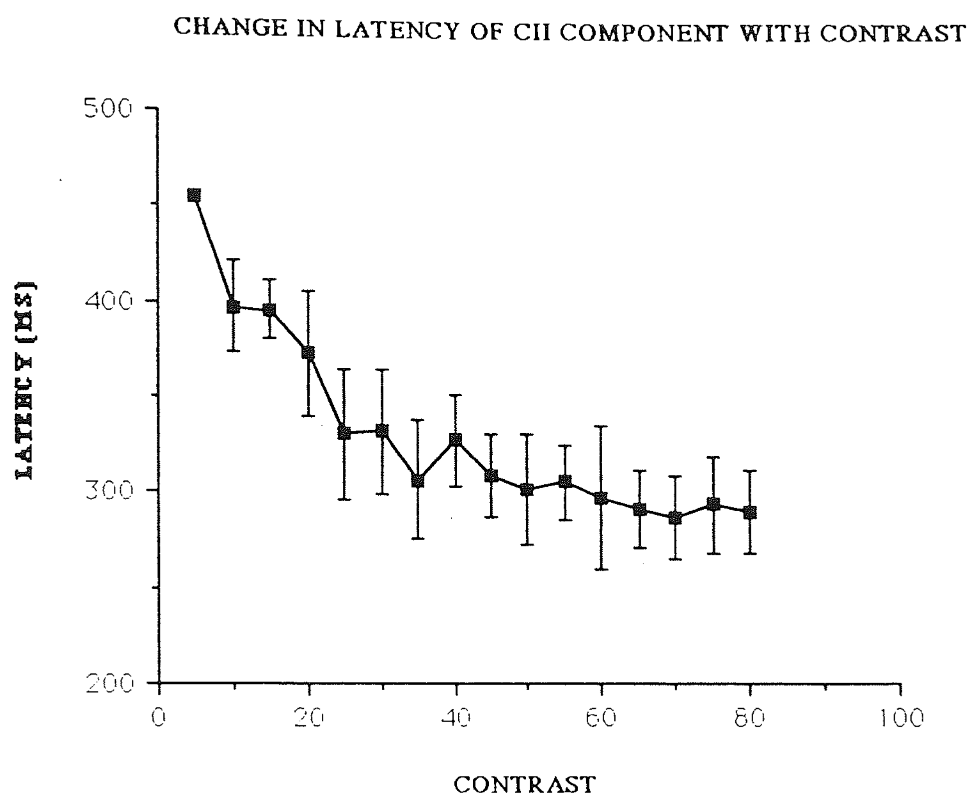
The latency of the major negative component (CII) was measured, and as the latency was the same in each channel, data is presented for the Oz-Fz channel only (table A17, appendix 1). The amplitude of the CII component was also measured from the preceeding positivity (CI-CII), data is presented for both the Oz-Fz and O1-C3 channels in tables A18 and A19 of appendix 1. Figure 6.9 shows the graphical representation of the above data. It can be seen that as the contrast of the checkerboard is decreased the latency of the CII component increases. Additonally it is clear that there is a gradual increase in amplitude of the response as the contrast is increased. This increase in amplitude continues without saturation and reaches higher values than those found for the magnocellular stimulus described above.

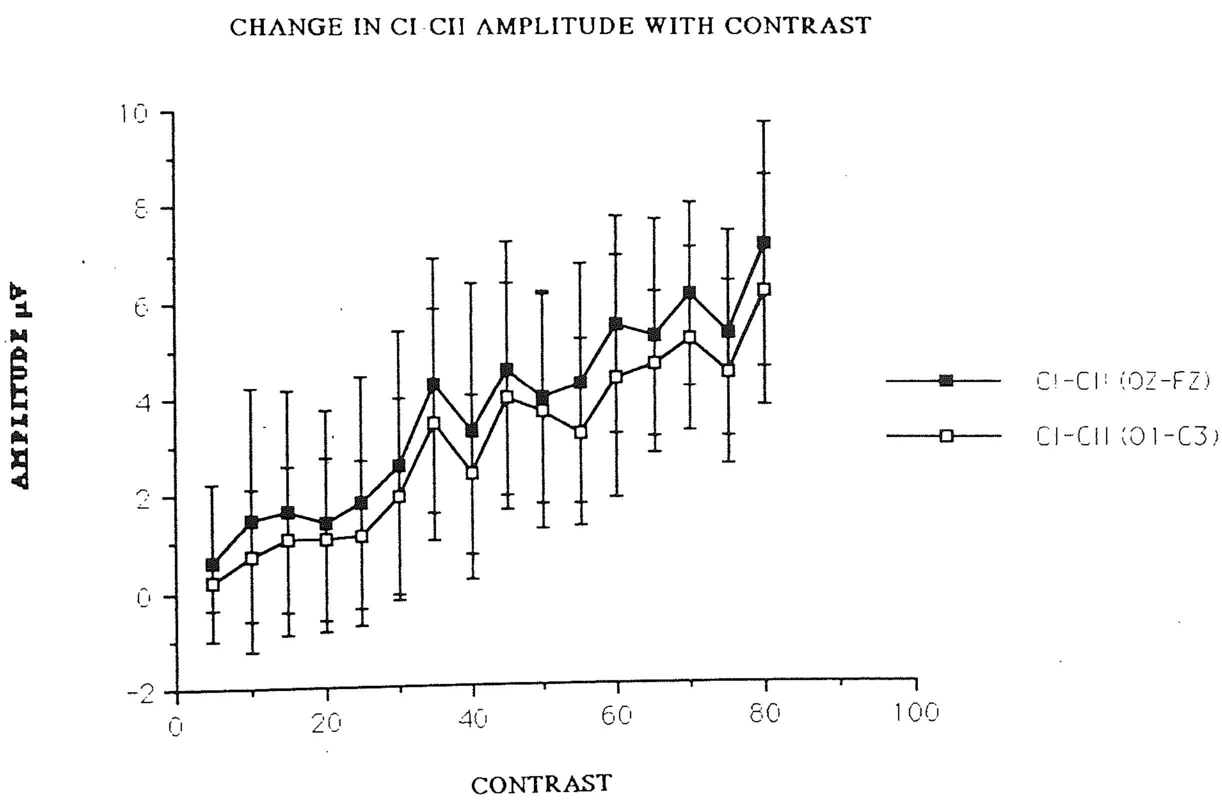
Notice also that the amplitudes for the Oz-Fz channel are consistently higher than those measured for the O1-C3 channel.

Discussion.

These data confirm that if a checkerboard or grating is presented with a raised cosine modulation of 200ms, the amplitude of the response will continue to rise as the contrast of the stimulus is increased. This therefore suggests that this type of stimulation is preferential to the parvocellular pathway. The consistently larger amplitude for the Oz-Fz channel may be due to the frontal negativity effecting the response and in this case adding to it. Alternatively it could be due to a more striatal source for the signal which would be maximal over Oz. The large interindividual differences in latency of the CII component is puzzling. It is possible that this is due to differing interindvidual contrast sensitivities such that the pattern of the stimulus becomes visible at different positions along the onset ramp. This is an important consideration as contrast sensitivity becomes more variable with age due to the influence of media changes and pupil size.

Figure 6.9.





General Discussion.

The above experiments were conducted in order to develop stimuli that would preferentially stimulate the magnocellular and parvocellular pathways. It was also important to consider that these stimuli were to be used to measure VEPs in very ill people, and hence had to be reasonably robust. For this reason, we were not seeking to 'isolate' the different pathways, only to find a method of preferential stimulation.

The above results suggest that to stimulate the magnocellular pathway, a checkerboard consisting of 73' black and white checks at a contrast of 30% and counterphasing at 6HZ would be acceptable as this fulfills the requirements of low spatial frequency, high temporal frequency and low contrast. To stimulate the parvocellular pathway two stimuli were developed. Both use an onset/offset presentation using a raised cosine modulation such that the pattern takes 200ms to reach maximum contrast, remains on for 200ms and takes a further 200ms to reach offset, thus avioding a response to movement . One was a 6' black and white checkerboard, using a contrast of 80%, providing a high spatial frequency, high contrast stimulus. The second was a 4cpd horizontal red/green isoluminant grating, which provides a chromatic stimulus. When using chromatic stimuli - the spatial frequency of the pattern can be lower because only the parvocellular pathway responds to colour.

The above stimuli were then used to evoke visual evoked potentials in patients with Parkinson's disease and Alzheimer's disease - the results of these experiments are discussed in the following chapters.

CHAPTER 7.

7. VISUAL EVOKED POTENTIALS IN PARKINSON'S DISEASE.

7.1. INTRODUCTION.

Visual evoked potentials have been measured in Parkinson's disease for a number of years, and a review of the literature was given is chapter 5. From this review it seems that, in general, the disease results in a delay of the P100 component of the pattern reversal VEP particularly when patterns of high spatial frequency are used. As the symptoms of Parkinson's disease are the result of a depletion of the neurotransmitter dopamine, the abnormal VEP may be due to a reduction in dopamine in the visual pathway. A review of the presence and function of dopamine in the visual pathway was given in chapter 4. It is known that dopamine is present in the retina particularly in association with the interplexiform cells, however information regarding its function remains speculative.

The problem with using only pattern reversal or flash stimuli to evoke visual evoked potentials is that they are not specific to a particular pathway, and thus do not provide an accurate tool for establishing which part of the visual pathway is being affected by the disease. It is therefore suggested that by using stimuli that preferentially activate the magnocelluar and parvocellular pathway one could learn which pathway is affected by Parkinson's disease and hence learn more about the function of dopamine in the visual pathway.

This study was therefore designed to measure the VEPs in a group of patients with Parkinson's disease to a series of stimuli that preferentially activate the magnocellular and parvocellular pathways and compare the results to a group of normal controls. The effect of medication was assessed by comparing the results between patients taking dopaminergic medication, those taking a combination of dopaminergic and anticholinergic medication and those not taking any medication at all.

7.2. METHOD.

Subjects.

26 patients with Parkinson's disease took part in the study - most of whom were volunteers who attended the neurophysiology department at Aston University. These patients were divided into 3 groups:

Group 1: 16 patients (6 male and 10 female) with a mean age of 64.19 years (± 7.31), all taking dopaminergic medication (DA) and having a mean visual acuity of 6/7.97 (±6/2.65).

Group 2: 7 patients (6 male and 1 female) with a mean age of 61.3 years (± 8.56), all taking a combination of dopaminergic (DA) and anticholinergic (ACH) medication, and having a mean visual acuity of 6/7.93 (± 6/2.24).

Group 3: 3 patients (1 male and 2 female) with a mean age of 69.33 years (± 4.04) and a mean visual acuity of 6/10.5 (± 6/6.54). One of these patients (MI) was previously from group 1 but repeated the procedure following 36 hours of drug abstention (with her doctor's consent). The half life of L-dopa is known to be between 0.77 and 1.06 hours and is excreted from the body within 24 hours. The remaining two patients were newly diagnosed patients at the Queen Elizabeth hospital and had not yet started any medication.

All patients were free from any ophthalmological disorder. Althought it was hoped that a higher number of patients could be seen who were not taking any medication, unfortunately one of the methods of diagnosing Parkinson's disease is by their improvement in symptoms following initiation of dopaminergic medication. For this reason most patients are taking dopaminergic medication even before their condition has been diagnosed.

33 controls took part in the study (21 males and 12 females). All were volunteers who regularly attended the Vision Sciences department at Aston University. They had a mean age of 63.27 years (± 11.82) and a mean visual acuity of 6/5.45 (± 6/1.62). All subjects were free from any neurological or ophthalmological disorder. Subject details are given in table A2.1. of appendix 2.

The investigations were approved by the University's and by the Hospital's Human Sciences Ethical Committee.

Stimuli.

From the studies described in the previous chapter, six stimulus parameters were used to generate visual evoked potentials.

(i) The first was a non-patterned D.C. flash of luminance 1363 cd/m^2. The rate of stimulation was one flash every second.It is thought that a luminance only stimulus containing no pattern information is likely to be transmitted by a tectal-association area pathway (see chapter 5). Since this pathway has a lack of spatial information it is probably magnocellular in origin.

(ii) The second stimulus was an achromatic checkerboard containing 60' checks. They were counterphased at 2Hz and had a contrast of 85%. This stimulus was presented within a 4°17' X 5°42' field. Due to its robustness this stimulus was used to demonstrate the procedure to the patient and to ensure that a VEP could be evoked - it probably stimulates both magno and parvocellular pathways.

(iii). The third stimulus was an achromatic checkerboard containing 10' checks. They were counterphased at 2Hz and had a contrast of 85%. This stimulus was also presented within a 4°17' X 5°42' field. Although the stimulus contained high spatial frequency components of high contrast - it is unlikely to provide much parvocellular system isolation and may well stimulate both systems. It was used in order to compared the results to those found by previous authors.

(iv) The fourth stimulus was an achromatic checkerboard of 73' checks. They were counterphased at 6Hz and had a contrast of 30%. The stimulus was presented within a 4°17' X 5°42' field. Due to its high temporal frequency, low spatial frequency and low contrast - this stimulus should stimulate the magnocellular pathway.

(v). The fifth stimulus was an achromatic checkerboard of 6' checks and 85% contrast. The checkerboard was presented using an on and off cosine ramp modulation such that the grating took 200ms to reach maximum contrast where it remained for 200ms and then took a further 200ms to disappear. The interstimulus interval was 500ms. In this case the field size was 2°34' X 3°26' to isolate the

foveal region in which the P cells are at a relatively higher concentration. Due to the low temporal frequency, small field and high spatial frequency this stimulus should provide some parovellular pathway isolation.

(vi) The sixth stimulus was a horizontal red/green square wave grating of 4cpd and 35% contrast. It was photometrically measured at isoluminance to provide a purely chromatic stimulus. The isoluminance was also subjectively checked by counterphasing the stimulus at 16Hz and using red or green filters to achieve minimum flicker. The grating was then presented using an on and off cosine ramp modulation such that the grating took 200ms to reach maximum contrast where it remained for 200ms and then took a further 200ms to disappear. The interstimulus interval was 500ms. The field size was again 2°34' X 3°26'. Due to the low temporal frequency, small field and chromaticity - this stimulus should stimulate the parvocellular pathway.

Instrumentation.

For the subjects attending Aston University the visual evoked potentials were recorded using the Nicolet Pathfinder II electrodiagnostic system. The bandpass of the system was 0.5 to 70Hz. For the two patients attending the Queen Elizabeth hospital it was necessary for us to use a portable setup that we could take to the hospital. We therefore used a Biologic traveller EP system. The bandpass of the system was 0.30 to 30 Hz

Flash stimulation was achieved using a Grass photostimulator fitted with a diffusor. The patterned stimuli were generated using a VSG 2/1 grating generator developed by Cambridge Research Systems and displayed on a CRT with 14 bit luminance resolution (E120 Flexscan 9080i 16 inch colour monitor) at a frame rate of 70Hz, with 624 pixels and 878 lines, using standard rastar technique. The gamma-corrected display was linear up to 90% contrast. The display screen had a mean luminance of 50 cd/m^2 and was 22.5cm vertical by 30cm horizontal. For the first four stimuli a square wave pulse was used to trigger the averager and for the last two stimuli a spike pulse was used at the beginning of each modulation.

Silver-silver chloride electrodes were attached to the scalp using Blenderm tape and the interelectrode impedence was maintained at 5K-ohms or less. The electrode montage used for subjects attending Aston University was OZ referred to FZ, O1 referred to FZ and C3, and O2 referred to FZ and C4, CZ acted as ground (in

accordance to the methodology described in chapter 5). The Traveller system was restricted to four channels, so the electrode montage used for the two patients at the Queen Elizabeth hospital was O1 referred to Fz and C3, and O2 referred to Fz and C4. All recordings were taken in dim illumination.

Procedure.

On arrival all participants were questioned with regard to ocular health and medical history. The patients with Parkinson's disease were particularly asked about dosage and frequency of dopaminergic and/or anticholinergic medication and the time of last dose. Unfortunately, as most of the patients were volunteers from the Parkinson's disease society we did not have access to their medical records and were therefore unable to note their Hoehn and Yahr rating. We therefore asked the patients the length of time they had been suffering from the disease and we objectively assessed their physical condition at the time the VEP was measured. Details of disease duration and medication is given in table A2.2 of appendix 2. All controls and patients were optically corrected for the designated viewing distance, and the visual acuity noted.Colour vision was checked using Ishihara pseudoisochromatic plates. Ocular health was checked by ophthalmoscopy examination. Flash VEPs were measured binocularly and monocularly while pattern VEPs were measured monocularly. For the flash stimulus the subjects were asked to fixate a small spot in the centre of the strobe, to aid concentration the subjects were asked to count the number of times the strobe flashed. For the pattern VEPs the subject was asked to fixate on a small spot in the centre of the CRT screen. 50 sweeps were averaged, and the recording was repeated. The order of presentation was varied to counteract any effects of order.

7.3. RESULTS.

In order to assess the compatibility between the Traveller and and Pathfinder electrodiagnostic systems VEPs were measured on two young controls (RD and VT) using both types of instrumentation. If the bandpass of each of the systems is set at the values used for the patients shown above (0.5 - 70Hz for the Pathfinder and 0.3 - 30Hz for the Traveller), then the latency of the measured components were consistently 4ms earlier for the Pathfinder. However, when the bandpass of the Pathfinder is changed to 0.3 - 30Hz, then the latencies become identical. There was no appreciable difference in amplitude between the conditions. These results are comparable to those found by Skuse and Burke (1990). In order to be able to

compare the results obtained at the Queen Elizabeth hospital on the the Traveller system to those obtained at Aston University using the Pathfinder, the latencies should be adjusted by reducing the value by 4ms.

(i). *Flash VEP.*

The latency of the P1 and P2 components were measured and the amplitude of the N2-P2 component. The individual results are given in tables A2.3-A2.6 of appendix 2 and the group mean results are given in table 7.1. These data include the 4ms adjustment for the two patients seen at the Queen Elizabeth hospital. Due to the unquestionable similarity between the five channels only the results from the O1-Fz channel are given. Students t test was used to perform the statistical analysis. It can be seen that the P1 latency is remarkably similar between the four groups and shows no statistically significant difference. The P2 latency is increased in all patient groups but is only significant for the patient group taking dopaminergic and anticholinergic medication (significance level $p < 0.037$). There was no significant difference in amplitude. Duration of illness made no difference to the latency or amplitude of any component.

Table 7.1. Mean results for binocular flash VEPs (O1-Fz channel).

	CONTROLS	PDpx + DA.	PD + DA + ACH	PD NO MED
P1 LATENCY	72.64 ms ± 6.10	68.80 ms ± 11.05	68.14 ms ± 12.01 ms	63.53 ms ± 8.14
P2 LATENCY	129.70 ms ± 11.98	132.38 ms ± 21.29	141.43 ms ± 17.59	133.33 ms ± 3.05
N2-P2 AMP	15.32 µv ± 8.05	17.71 µv ± 9.09	17.36 µv ± 5.96	23.00 µv ± 9.45

(ii). VEP to 60' check counterphasing at 2Hz and at 85% contrast.

The latency of the P100 and the amplitude of the N75-P100 component was measured. The individual results are given in tables A2.7-A2.10 of appendix 2, and the group mean results are given in table 7.2. Again the results are presented for the O1-Fz channel and the data for the two patients seen at the Queen Elizabeth hospital

include the 4ms adjustment in the latency values. It can be seen that the latency of the P100 component is delayed in the patients not taking medication but this delay did not reach statistical significance. There was no significant difference in amplitude of the N75-P100 component although the Parkinsonian patients tended to have a larger amplitude. Duration of illness made no difference to the latency or amplitude of any component.

Table 7.2. Mean results for monocular pattern reversal VEP to a 60' check counterphasing at 2Hz and 85% contrast (O1-Fz channel).

	CONTROL	PD + DA	PD + DA + ACH	PD NO MED
P100 LAT.	114.36 ms ± 12.43	117.50 ms ± 11.26	117.00 ms ±7.55	126.13 ms ±14.78
N75-P100 AMP	6.41 μv ± 3.03	7.74 μv ± 3.61	8.36μv ±4.45	8.85 μv ±4.61

(iii). *VEP to a 10' check counterphasing at 2Hz and at a contrast of 85%.*

The latency of the P100 and the amplitude of the N75-P100 component were measured. The individual results for the O1-Fz channel are presented in tables A2.11-A2.14 of appendix 2 and the group mean and standard deviations are given in table 7.3. Again a 4ms adjustment has been made to the latencies for the two patients seen at the Queen Elizabeth hospital. Although the latency of the P100 component is delayed in all patients with Parkinson's disease compared to normals - particularly those not taking medication - the delay did not reach statistical significance. The amplitude to the N75-P100 component was larger in Parkinsonian patients compared to normals but did not reach statistical significance. Duration of disease made no difference to the latency or amplitude for any patient group.

Table 7.3. Mean results for monocular pattern reversal VEP to a 10' check counterphasing at 2Hz and 85% contrast (O1-Fz channel).

	CONTROLS	PD + DA	PD + DA + ACH	PD NO MED
P100 LAT	121.00 ms ± 12.76	127.60 ms ± 12.35	128.33 ms ± 10.84	130.75 ms ± 14.10
N75-P100 AMP	6.31 μv ± 3.26	7.34 μv ± 2.50	7.84 μv ± 4.12	9.37 μv ± 5.54

(iv). *Steady state VEP to a 73' check counterphased at 6Hz and at a contrast of 30%.*

The VEP evoked by this stimulus again appeared as a sinusoidal waveform with 6 peaks occuring within the 500ms time window. The results were annalysed by measuring the amplitude of the first component (N1-P1) in μv; in addition the % power of the second harmonic was calculated from the power spectra obtained from the fast fourier transform of the wave. The individual results for the O1-Fz channel following right eye stimulation are given in table A2.15 of appendix 2. The group mean results are given in table 7.4.

Table 7.4. Mean results for monocular pattern reversal VEPs to a 73' check counterphasing at 6Hz and at 30% contrast (O1-Fz).

	CONTROLS	PD + DA	PD + DA + ACH	PD NO MED
N1-P1 AMP	3.09 μv ± 1.44	3.39 μv ± 1.78	3.44 μv ± 1.61	3.16 μv ± 0.04
% POWER	32.90 % ± 15.17	27.85 % ± 16.13	24.25 % ± 16.77	38.50 % ± 16.80

A students t test reveals no significant difference in amplitude or % power between groups. However, from the table it seems that both controls and parkinsonian patients not taking medication have a slightly higher % power compared to the two groups taking dopaminergic medication. This becomes more apparent if one consideres patient MI, the 11.7Hz frequency had a power of 46.7% while she was taking her medication, this increased to 53.9% following 36 hours of drug absention.

As the 11.7 Hz frequency falls within the realms of alpha brain activity, it was necessary to establish whether the above results were responses evoked by the stimulus, or merely reflected background brain activity. To do this the VSG computer was disconnected from the averager, but the stimulus was allowed to continue. A total of 8 seconds (in 4 second intervals) of EEG were measured on 14 patients while they continued to view the stimulus. An example of a print out of the spectral parameter output from one patient is given at the end of appendix 2. Brain activity at 11.7Hz was not found to exist in the EEG. This confirms that the VEPs above are the result of the 6Hz stimulus driving the visual pathway.

(vi). Pattern onset/offset VEP to a 6' achromatic check of 85% contrast presented using a 200ms ramp.

The latency of the major negative component was measured (CII) and its amplitude for the preceding positivity (CI-CII). The individual results are presented in table A2.16 of appendix 2 and the group mean results are given in table 7.5. These data are for the O1-Fz channel and include a 4ms adjustment in the latency for those patients seen at the Queen Elizabeth hospital. It can be seen that the CII component was only delayed in Parkinsonian patients who were not taking any medication - however this delay did not reach statistical significance. As indicated in chapter 6, the CII component showed a large interindividual difference in latency thus producing a large standard deviation. There was no statistical difference in amplitude of the CI-CII component between groups.

Table 7.5. Mean results for monocular pattern onset VEP to 6' achromatic check of 85% contrast, using a 200ms raised cosine ramp (O1-Fz channel).

	CONTROLS	PD + DA	PD + DA + ACH	PD NO MED
CII LATENCY	255.05 ms ± 36.43	252.66 ms ± 38.47	251.55 ms ± 38.95	306.98 ms ± 83.98
CI-CII AMP	4.87 μv ± 1.95	5.14 μv ± 3.27	3.85 μv ± 0.84	5.53 μv ± 1.97

(vi). *Pattern onset/offset VEP to a 4cpd red/green isochromatic horizontal square wave grating presented using a 200ms ramp.*

The latency of the major negative component was measured (CII) and its amplitude from the preceding positivity (CI-CII). The individual results are given in table A2.17 and the group mean results are given in table 7.6. Again these data are for the O1-Fz channel and include the 4ms adjustment in latency for the two patients seen at the Queen Elizabeth hospital. It can be seen that the Parkinsonian patients not taking medication have a delayed CII component but due to the large standard deviations - this difference did not reach statistical significance. There was no statistical difference in amplitude.

Table 7.6. Mean results for monocular pattern onset VEP to a 4cpd red/green isoluminant horizontal square wave grating, using a 200ms raised cosine ramp (O1-Fz channel).

	CONTROLS	PD + DA	PD + DA + ACH	PD NO MED
CII LATENCY	291.01 ms ± 33.81	282.61 ms ± 47.04	297.36 ms ± 26.95	315.65 ms ± 69.38
CI-CII AMP	5.02 μv ± 2.33	4.93 μv ±1.37	3.64μv ± 0.25	3.95μv ± 1.80

7.4 DISCUSSION.

These data suggest that Parkinson's disease itself does not have any detrimental effect on the flash visual evoked potential unless the patient is taking anticholinergic medication. It would therefore seem that dopamine has little involvement in the generation of the VEP to a flash stimulation, while acetylcholine seems to be involved in the generation of the P2 component.

The pattern stimulus designed to activate the magnocellular pathway failed to show any significant difference between groups. The slight reduction in % power in those patients taking dopaminergic medication may be the result of side-effects of the drugs. These can cause abnormal involuntary movements and agitation. These side-effects may create an increased amount of muscle activity can which contaminate the VEP.

Parkinson's disease resulted in an increase in latency of the P100 component of the pattern reversal VEP to a 60' and 10' check but only in patients not taking medication. However, only 3 patients fulfilled this condition, one of whom (EG) had a visual acuity of only 6/18 which would obviously result in a delay to the pattern reversal VEP (Wright, 1983) as indicated by P100 latencies of 140.53ms for a 60' check and 146.39ms for a 10' check. Additionally, subject MI had VEPs measured both when taking medication and following 36 hours of drug abstention. When the 60' check was used the P100 latency was 113.00ms when the patient was taking dopaminergic medication and 111.00ms following drug abstention. For the 10' check these latencies were 116.00ms and 119.00ms respectively. Thus it would seem that lack of dopamine has no significant effect on the pattern reversal VEP which is in contradiction to results found by other authors (see chapter 5).

Similar findings are presented for the two stimuli using a raised cosine ramp modulation of 200ms. The group mean results suggest that Parkinsonian patients who were not taking medication had a delayed CII component both when using a 6' check and when using a 4cpd isoluminant red/green horizontal square wave grating. However, this is largely due to patient EG who had a visual acuity of 6/18. The CII latency for subject MI was later when taking medication compared to the drug free condition.

These data indicate that Parkinson's disease has very little effect on the VEP unless the patient is taking anticholinergic medication. This is the case even if the stimuli

are designed to preferentially stimulate the magnocellular and parvocellular pathways. These results do not seem surprising when we consider what is known about dopamine in the visual pathway. As described in chapter 4 - dopamine is present in the retina where it acts as a neuromodulator. There is very little evidence of dopamine being present in any other part of the visual pathway, although it may have a role to play in visual attentional processes in the inferotemporal regions of the brain. Within the retina dopamine acts on the interplexiform cells and hence the horizontal cell activity and receptive field size. Dopamine concentration is effected by the level of dark adaption such that an increased amount of dopamine increases the receptive field size of the bipolar cells, which is known to occur during periods of darkness. An increased receptive field size results in improved light detection but reduced visual acuity. A reduction in dopamine should therefore result in reduced light sensitivity during dark adaption rather than reduced visual acuitiy. In view of this one would suspect that the ERG is more likely to be effected by Parkinson's disease - this is investigated in the next chapter.

CHAPTER 8.

8. ELECTRORETINOGRAMS IN PARKINSON'S DISEASE.

8.1. INTRODUCTION.

Due to the known presence of dopamine as a neuromodulator in the retina (chapter 4), one would expect a reduction in dopamine, as found in Parkinson's disease, to effect the electroretinogram as this represents retinal fuction. This hypothesis has been investigated by a number of authors and a review of their findings is given in section 5.3.1.2. of chapter 5. Although there is a large variation in results, it would seem that the b wave of the luminance ERG or the P50 of the pattern ERG, particularly to patterned stimuli of high spatial frequency is effected by a dopamine depletion.

The previous chapter illustrated how little Parkinson's disease effected the VEP. This chapter presents a study investigating the effect of the disease on the luminance and pattern ERG in an attempt to establish whether the delayed flash P2 component of the VEP found in patients taking anticholinergic medication could be reflected in the ERG, as this would give some indication as to the reason for the delay.

8.2 METHOD.

Subjects.

12 patients with Parkinson' disease took part in the study - all attended the neurophysiology unit at Aston University. These were divided into two groups.

Group 1. 6 patients (3 male and 3 female) with a mean age of 68.67 years (± 5.13), all taking dopaminergic medication (DA) and having a mean visual acuity of 6/8.75 (± 6/2.58).

Group 2. 6 patients (5 male and 1 female) with a mean age of 61.50 years (± 9.35), all taking a combination of dopaminergic (DA) and anticholinergic (ACH) medication and having a mean visual acuity of 6/8.25 (± 6/2.27).

14 controls took part in the study (9 male and 5 female). All were voulunteers who regularly attended the Vision Sciences department at Aston University. They had a mean age of 72.43 years (± 8.64) and a mean visual acuity of 6/6.4 (± 6/2.19). All patients and controls were free from any neurological or ophthalmological disorder. Subject details are included in tables 2.1 and 2.2 of appendix 1.

Stimuli.

Five stimulus parameters were used to generate electroretinograms.

(i). Photopic ERGs were generated using a non patterned flash of luminance 1925 cd/m^2. Ganzfeldt stimulation was achieved using a pair of goggles to scatter the light. The rate of stimulation was one flash every second.

(ii) Scotopic ERGs were generated following 10 minuits of dark adaption. A single flash of light was used of luminance 1925 cd/m^2. Again Ganzfeldt conditions were achieved using goggles.

(iii) The third stimulus was an achromatic checkerboard containing 48' checks. They were counterphased at 2Hz and had a contrast of 85%. This stimulus was presented within a 19°5' X 24°46' field.

(iv) The fourth stimulus was an achromatic checkerboard containing 26' checks. They were counterphased at 2 Hz and had a contrast of 85%. This stimulus was also presented within a 19°5' X 24°46' field.

(v) The fifth stimulus was an achromatic checkerboard containing 2°22' checks. They were counterphased at 6Hz and had a contrast of 30%. This stimulus was also presented within a 19°5' X 24°46' field.

We also made some attempts at evoking an ERG response using the 200ms raised cosine ramp described in the previous two chapters but were unable to produce a response in any subject and thus will not be considered further in this chapter.

Instrumentation.

Electroretinograms were also recorded using the Nicolet Pathfinder II electrodiagnostic system. The bandpass of the system was 0.5Hz to 500Hz for the

photopic and scotopic ERGs and 0.5 to 70Hz for the pattern ERGs. The flash and patterned stimuli were generated using the same systems as of the VEP study above. A square wave pulse was used to trigger the pathfinder.

DTL electrodes were used as the acitve electrodes and were referred to silver-silver choride electrodes at the outer canthus. An electrode placed on the forehead acted as ground. The methodology for electrode attachment is as described in section 5.2.1.2 (Thompson and Drasdo, 1987). All recordings were taken in dim illumination.

Procedure.

On arrival all participants were questioned with regard to ocular health and medical history. The patients with Parkinson's disease were particularly asked about dosage and frequency of dopaminergic and/or anticholinergic medication and the time of last dose. Unfortunately, as most of the patients were volunteers from the Parkinson's disease society we did not have access to their medical records and were therefore unable to note their Hoehn and Yahr rating. We therefore asked the patients the length of time they had been suffering from the disease and we objectively assessed their physical condition at the time the VEP was measured. All controls and patients were optically corrected for the designated viewing distance, and the visual acuity noted. Ocular health was checked using ophthalmoscopy. All ERGs were measured binocularly.

For the photopic ERGs the subjects were asked to keep their eyes directed in the straight ahead position and to keep blinking to a minimum. They were specifically askied not to blink each time the flash appeard. 150 sweeps were averaged and the recording was repeated. For the scotopic ERG the subject was kept in the dark for 10 minuites. Immediatedly prior to stimulation with a single flash of light, the subjects were asked to look straight ahead keeping their eyes as still as possible. They were aslo asked not to blink when the flash was switched on. Additionally the artefact rejection system was switched off so that a response would be averaged even if the subject blinked. If the ERG was spoiled with a blink reflex then a second ERG was attempted following a further 5 minuites of dark adaption.

For the patterned stimuli the subjects were asked to fixate on a small spot in the centre of the CRT screen, and asked to keep blinking to a minimum. 150 sweeps were averaged and the recording was repeated.

In all recordings, if the subjects had a high blink rate that produced many artefacts then they were asked not to blink at all for a period of 10 seconds while the recording was taken, the averager was then paused while the subject was allowed to blink. To prevent fatigue from effecting the results the order of presentation was varied between subjects.

8.3. RESULTS.

(i). *Photopic ERG.*

The latency of the a and b wave were measured and the amplitude of the a-b component. The individual results are given in table A3.1 of appendix 3 and the group mean results are given in table 8.1. Due to the similarity of the two eyes the data represents the responses from the right eye. A students t test was used to perform the statistical annalysis. It can be seen that the a wave latency is remarkably similar between groups and shows no significant difference. The b wave latency is later for the controls compared to the Parkinsonian patients. This difference is greatest for the patients taking anticholinergic medication but is only partially significant ($p < 0.066$). These patients taking anticholinergic medication also demonstrate the largest a-b wave amplitude but this does not reach statistical significance.

(ii). *Scotopic ERG.*

a and b wave latencies were measured in addition to the a-b wave amplitude. The individual results for the right eye are presented in table A3.2 of appendix 3 and the group mean results are shown in table 8.2. It can be seen that responses could not be achieved in 2 of the control subjects due to constant interference from the blink reflex, the group mean data therefore do not include these subjects. The latency of the a wave was slightly later at 27.533 ms in Parkinsonian patients taking dopaminergic medication only, compared to controls (24.967ms), but was only partially significant ($p < 0.053$). There was no significant difference in b wave latency or in a-b wave amplitude between groups.

Table 8.1. Mean results for photopic ERGs (right eye).

	CONTROLS	PD + DA	PD + DA + ACH
a WAVE LAT	17.63 ms	19.98 ms	16.67 ms
	± 2.64	± 3.91	± 2.93
b WAVE LAT	34.14 ms	31.53 ms	29.07 ms
	± 5.87	± 3.17	± 3.52
a-b AMP	51.70 ms	55.17 ms	82.32 ms
	± 38.14	± 33.78	± 21.74

Table 8.2. Mean results for scotopic ERG (right eye).

	CONTROLS	PD + DA	PD + DA + ACH
a WAVE LAT	24.97 ms	27.53 ms	24.40 ms
	± 2.12	± 3.06	±3.16
b WAVE LAT	50.77 ms	51.00 ms	52.47 ms
	± 8.39	± 4.42	±5.47
a-b AMP	229.45 μv	260.15 μv	272.65 μv
	± 88.07	± 78.14	± 83.16

(iii). *PERG to a 48' check counterphasing at 2Hz at a 85% contrast.*

The latency of the N35 and P50 components were measured and the peak to peak amplitude of the N35-P50 component. The individual results for the right eye are shown in table A3.3 of appendix 3 and the group mean results in table 8.3. There was no significant difference in N35 latency between groups. The P50 latency was slightly earlier and the N35-P50 amplitude greater for the Parkinsonian patients taking anticholinergic mediation. These results did not quite reach statistical significance ($p < 0.091$ for the P50 latency and $p < 0.073$ for the N35-P50 amplitude). There was no significant difference for the Parkinsonian patients taking dopaminergic medication only.

Table 8.3. Mean results for PERG to a 48' check of 85% contrast, counterphasing at 2Hz (right eye).

	CONTROLS	PD + DA	PD + DA + ACH
N35 LAT	34.31 ms ± 5.13	35.13 ms ± 5.41	32.07 ms ± 4.04
P50 LAT	56.63 ms ± 5.44	56.80 ms ± 3.30	53.78 ms ± 2.30
N35-P50 AMP	2.45 μv ± 0.98	2.71 μv ± 0.96	3.38 μv ± 1.05

(iv). *PERG to a 26' check counterphasing at 2Hz at 85% contrast.*

The latency of the N35 and P50 components and the peak to peak amplitude of the N35-P50 component were measured. The individual results for the right eye are presented in table A3.4 of appendix 3 and the group mean results are shown in table 8.4. There was no significant difference between groups for any component. However the N35 and P50 latencies were earliest in the Parkinsonian group taking anticholinergic medication. The greatest difference between groups occurred between the two Parkinsonian groups for the N35 latency, which was 38.400ms for the group taking dopaminergic medication and 32.733ms for the group taking a combination of dopaminergic and anticholinergic medication ($p < 0.065$).

(v). *PERG to a 2°22' check counterphasing at 6Hz and at 30% contrast.*

The ERG to this stimulus presented as a steady state ERG that resembled a sinusoid although it was rather arhythmical. As mentioned in chapter 6 it was not possible to assess the % power of the second harmonic in the waveform due to this poor rhythm, although it was obvious that 6 peaks were present in the 500ms time window used. We therefore measured the peak to peak amplitudes of the first (a-b) and second (c-d) components of the wave. The individual results for the right eye as displayed in table A3.5 of appendix 3. It can be seen that for one subject from each group we did not attempt to measure this ERG due to patient fatigue and discomfort due to the DTL fibre. In addition there is quite a high degree of failure rate where it was not possible to ellicit a response to this stimulus, 3 controls

showed no response and 3 Parkinsonian patients taking anticholinergic medication showed no response.The group mean results in table 8.5 are those from all subjects where a response could be achieved, and excludes those who failed to produce a response. There was no significant difference in amplitude between groups for either component.

Table 8.4.Mean results for PERG to a 26' check of 85% contrast counterphasing at 2Hz (right eye).

	CONTROLS	PD + DA	PD + DA + ACH
N35 LAT	36.14 ms ± 7.48	38.40 ms ± 5.04	32.73 ms ± 4.42
P50 LAT	58.40 ms ± 5.34	57.67 ms ± 4.29	55.73 ms ± 8.87
N35-P50 AMP	2.12 µv ± 1.01	2.22 µv ± 0.71	2.45 µv ± 0.44

Table 8.5. Mean results for PERG to a 2°22' check of 30% contrast counterphasing at 6Hz (right eye).

	CONTROLS	PD + DA	PD + DA + ACH
a-b AMP	1.28 µv ± 0.83	1.67 µv ± 0.52	1.17 µv ± 0.24
c-d AMP	1.29 µv ± 0.78	1.47 µv ± 0.59	2.24 µv ± 0.38

8.4. DISCUSSION.

These data indicate that Parkinson's disease does not have a great effect the ERG. However all of the patients seen were taking medication, so that the increased dopamine resulting from the drug intake probably effected these results. It is interesting to note that, although none of the results reached statistical significance, the photopic b wave, and the pattern reversal P50 component were all slightly

earlier and of higher amplitude in those patients taking a combination of anticholinergic and dopaminergic medication.

CHAPTER 9.

9. VISUAL EVOKED POTENTIALS IN ALZHEIMER'S DISEASE.

9.1. INTRODUCTION.

Visual evoked potentials have been measured in Alzheimer's disease for a number of years, and a review of the literature is given in chapter 5. From this review it seems that, in general, the disease results in a delay of the flash P2 component, the pattern reversal VEP remaining normal. There have been a number of studies at this department which confirm this statement. The following experiment was designed to accompany that of chapter 7 on Parkinson's disease, to establish whether the VEP abnormalities found in Alzheimer's disease can be isolated to a cholinergic deficit involving the magnocellular pathway. It is known that acetylcholine is present in the visual pathway - a review is given in chapter 6, and it also known that acetylcholine is a neurotransmitter found to be grossly reduced in the brain of patients with Alzheimer's disease. This disease can therefore be used to investigate the function of acetylcholine in the visual pathway.

This study was therefore designed to measure the VEP in a group of patients with Alzheimer's disease to the same series of stimuli as those used in chapter 7 that preferentially activate the magnocellular and parvocellular pathways and compare the results to a group of normal controls.

9.2. METHOD.

Subjects.

17 patients with Alzheimer's disease took part in the study (12 male and 5 female) They had an average age of 65.94 years (± 7.29) and a mean acuity of 6/10.74 (± 6/9.59). Two of the patients (JB and JT) had unreliable visual acuities of 6/36 because although they were able to see the test chart they had difficulty in recognising the numbers or symbols. When the mean acuity is calculated excluding these two patients it becomes 6/7.37 (±6/1.36).

Three patients (DH, MC and MS) were seen at Aston University, having been referred from the Woodbourne clinic in Edgebaston. The remaining patients were

volunteers who were under assessement, and were therefore seen at the Queen Elizabeth hospital. Diagnosis was performed by the consultants involved using standard mental tests. All patients were free from any ophthalmological disorder.

33 controls took part in the study (21 males and 12 females). All were volunteers who regularly attended the Vision Sciences department at Aston University and were the same group as those who took part in the Parkinson's disease study. They had a mean age of 63.27 years (± 11.82) and a mean visual acuity of 6/5.45 (± 6/1.62). All subjects were free from any neurological or ophthalmological disorder. Subject details are given in table A4.1.of appendix 4 (the asterix idicates the patients with unreliable subjective responses).

The investigations were approved by the University's and by the Hospital's Human Sciences Ethical Committee.

Stimuli.

From the studies described in the previous chapters, six stimulus parameters were used to generate visual evoked potentials.

(i) The first was a non-patterned D.C. flash of luminance 1363 cd/m^2. The rate of stimulation was one flash every second. It is thought that a luminance only stimulus containing no pattern information is likely to be transmitted by a tectal-association area pathway (see Chapter 5). Since this pathway has a lack of spatial information it is probably magnocellular in origin.

(ii) The second stimulus was an achromatic checkerboard containing 60' checks. They were counterphased at 2Hz and had a contrast of 85%. This stimulus was presented within a 4°17' X 5°42' field. Due to its robustness this stimulus was used to demonstrate the procedure to the patient and to ensure that a VEP could be evoked - it stimulates both magno and parvocellular pathways.

(iii). The third stimulus was an achromatic checkerboard containing 10' checks. They were counterphased at 2Hz and had a contrast of 85%. This stimulus was also presented within a 4°17' X 5°42' field. Although the stimulus contained high spatial frequency components of high contrast - it is unlikely to provide much parvocellular system isolation and may well stimulate both systems. It was used in order to compared the results to those found by previous authors.

(iv) The fourth stimulus was an achromatic checkerboard of 73' checks. They were counterphased at 6Hz and had a contrast of 30%. The stimulus was presented within a 4°17' X 5°42' field. Due to its high temporal frequency, low spatial frequency and low contrast - this stimulus should preferentially stimulate the magnocellular pathway.

(v). The fifth stimulus was an achromatic checkerboard of 6' checks and 85% contrast. The checkerboard was presented using an on and off cosine ramp modulation such that the grating took 200ms to reach maximum contrast where it remained for 200ms and then took a further 200ms to disappear. The interstimulus interval was 500ms. In this case the field size was 2°34' X 3°26' to isolate the foveal region in which the P cells are at a relatively higher concentration. Due to the low temporal frequency, small field and high spatial frequency this stimulus should provide some parovellular pathway isolation.

(vi) The sixth stimulus was a horizontal red/green square wave grating of 4cpd and 35% contrast. It was photometrically measured at isoluminance to provide a purely chromatic stimulus. The isoluminance was also subjectively checked by counterphasing the stimulus at 16Hz and using red or green filters to achieve minimum flicker. The grating was then presented using an on and off cosine ramp modulation such that the grating took 200ms to reach maximum contrast where it remained for 200ms and then took a further 200ms to disappear. The interstimulus interval was 500ms. The field size was again 2°34' X 3°26'. Due to the low temporal frequency, small field and chromaticity - this stimulus should stimulate the parvocellular pathway.

Instrumentation.

For the subjects attending Aston University the visual evoked potentials were recorded using the Nicolet Pathfinder II electrodiagnostic system. The bandpass of the system was 0.5 to 70Hz. For the patients attending the Queen Elizabeth hospital it was necessary for us to use a portable setup that we could take to the hospital. We therefore used a Biologic Traveller EP system. The bandpass of the system was 0.30 to 30 Hz.

Flash stimulation was achieved using a Grass photostimulator. The patterned stimuli were generated using a VSG 2/1 grating generator developed by Cambridge

Research Systems and displayed on a CRT with 14 bit luminance resolution (E120 Flexscan 9080i 16 inch colour monitor) at a frame rate of 70Hz, with 624 pixels and 878 lines, using standard rastar technique. The gamma-corrected display was linear up to 90% contrast. The display screen had a mean luminance of 50 cd/m^2 and was 22.5cm vertical by 30cm horizontal. For the first four stimuli a square wave pulse was used to trigger the pathfinder and for the last two stimuli a spike pulse was used at the beginning of each modulation.

Silver-silver chloride electrodes were attached to the scalp using Blenderm tape and the interelectrode impedence was maintained at 5K-ohms or less. The electrode montage used for subjects attending Aston University was OZ referred to FZ, O1 referred to FZ and C3, and O2 referred to FZ and C4, CZ acted as ground (in accordance to the methodology described in chapter 5). The traveller system was restricted to four channels, so that the electrode montage used for the two patients at the Queen Elizabeth hospital was O1 referred to Fz and C3, and O2 referred to Fz and C4. All recordings were taken in dim illumination.

Procedure.

On arrival all participants or their partners were questioned with regard to ocular health and medical history. Alzheimer' disease patients were also questioned with regard to the duration of illnes and general history. Details of disease duration can be found in table A4.1 of appendix 4. All controls and patients were optically corrected for the designated viewing distance, and the visual acuity noted.Colour vision was checked using Ishihara pseudoisochromatic plates, although in some Alzheimer's disease patients this was unreliable. Ocular health was checked by ophthalmoscopy examination. Flash VEPs were measured binocularly and monocularly while pattern VEPs were measured monocularly. For the flash stimulus the subjects were asked to fixate a small spot in the centre of the strobe, to aid concentration the subjects were asked to count the number of times the strobe flashed. For the patterned stimuli the subject was asked to fixate on a small spot in the centre of the CRT screen. 50 sweeps were averaged, and the recording was repeated. The order of presentation was varied to counteract any effects of order.

9.3. RESULTS.

In order to assess the compatibility between the Traveller and and Pathfinder electrodiagnostic systems VEPs were measured on two young controls (RD and

VT) using both types of instrumentation. If the bandpass of each of the systems is set at the values used for the patients shown above (0.5 - 70Hz for the Pathfinder and 0.3 - 30Hz for the Traveller), then the latency of the measured components were consistently 4ms earlier for the Pathfinder. However, when the bandpass of the Pathfinder is changed to 0.3 - 30Hz, then the latencies become identical. There was no appreciable difference in amplitude between the conditions (Skuse and Burke, 1990). In order to be able to compare the results obtained at the Queen Elizabeth hospital on the the Traveller system to those obtained at Aston University using the Pathfinder, the latencies should be adjusted by reducing the value by 4ms.

(i). *Flash VEP.*

The latency of the P1 and P2 components were measured and the amplitude of the N2-P2 component. The individual results for the binocular VEP are given in tables A2.3 and A4.2 of appendix 2 and appendix 4, and the group mean results are given in table 9.1. These data include the 4ms adjustment for the patients seen at the Queen Elizabeth hospital. Due to the unquestionable similarity between the five channels, only the results from the O1-Fz channel are given. Students t test was used to perform the statistical analysis. It can be seen that the P1 latency is remarkably similar between the two groups and shows no statistically significant difference. The P2 latency, however is markedly delayed in the Alzheimer's patients compared to controls - this difference was found to be significant ($p < 0.01$). There was no significant difference in amplitude. Duration of illness made no difference to the latency or amplitude of any component.

Table 9.1. Mean results for binocular flash VEP (O1-Fz channel).

	CONTROLS	AD PATIENTS
P1 LATENCY	72.64ms ± 6.10	74.12ms ± 11.80
P2 LATENCY	129.70ms ±11.99	156.14ms ±36.65
N2-P2 AMP	15.32ms ± 8.05	13.03ms ± 7.62

(ii). VEP to 60' check counterphasing at 2Hz and at 85% contrast.

The latency of the P100 and the amplitude of the N75-P100 component was measured. The individual results for right eye stimulation are given in tables A2.7 and A4.3 of appendix 2 and appendix 4, and the group mean results are given in table 9.2. Again the results are presented for the O1-Fz channel and the data for the patients seen at the Queen Elizabeth hospital include the 4ms adjustment in the latency values. It can be seen that the latency of the P100 component is delayed in the Alzheimer's patients, although it did not quite reach statistical significance ($p < 0.088$). There was no significant difference in amplitude of the N75-P100 component. Duration of illness made no difference to the latency or amplitude of any component.

Table 9.2.Mean results for monocular pattern reversal VEP to a 60' check counterphasing at 2Hz and 85% contrast (O1-Fz channel).

	CONTROLS	AD PATIENTS
P100 LATENCY	114.36ms ± 12.43	121.47ms ± 15.80
N75-P100 AMP	6.42ms ± 3.03	5.26ms ± 2.89

(iii). *VEP to a 10' check counterphasing at 2Hz and at a contrast of 85%.*

The latency of the P100 and the amplitude of the N75-P100 component were measured. The individual results for the O1-Fz channel following right eye stimulation are presented in tables A2.11 and A4.4 of appendix 2 and appendix 4, and the group mean and standard deviations are given in table 9.3. Again a 4ms adjustment has been made to the latencies for the patients seen at the Queen Elizabeth hospital. The latency of the P100 component is delayed in patients with Alzheimer's disease compared to normals - this delay was found to be statistical significance ($p < 0.015$). There was no significant difference in amplitude between the two groups. Duration of disease made no difference to the latency or amplitude of any component.

Table 9.3. Mean results for monocular pattern reversal VEP to a 10' check counterphasing at 2Hz and at 85% contrast (O1-Fz channel).

	CONTROLS	AD PATIENTS
P100 LATENCY	121.00ms ± 12.76	130.18ms ± 8.36
N75-P100	6.31ms ± 3.26	6.99ms ± 3.63

(iv). *Steady state VEP to a 73' check counterphased at 6Hz, (30% contrast).*

Again the visual evoked potential presented as a sinusoidal waveform with six peaks appearing within the 500ms time window used. The amplitude of the first (N1-P1) component was measured. The % power of the second harmonic was calculated from the power spectra obtained from the fourier transform of the wave. The individual results for the O1-Fz channel following right eye stimulation are given in table A2.15 and A4.5 of appendix 2 and 4. The group mean results are given in table 9.4.

From the table it can be seen that the amplitude of the N1-P1 component is slightly smaller in the Alzheimer's disease group, although a students t test reveals that this difference is not significant. The % power of the second harmonic in the power spectra of the VEP is also lower in the Alzheimer's disease patients - this difference approached significance ($p < 0.02$).

Table 9.4. Mean results for monocular pattern reversal VEPs to a 73' check counterphasing at 6Hz and at 30% contrast (O1-Fz).

	CONTROLS	AD PATIENTS
N1-P1 AMP	3.09μv ± 1.44	2.68μv ± 1.29
% POWER	32.90% ± 15.17	20.26% ± 15.88

(vi). *Pattern onset/offset VEP to a 6' achromatic check of 85% contrast presented using a 200ms ramp.*

The latency of the major negative component was measured (CII) and its amplitude for the preceding positivity (CI-CII). The individual results are presented in table A2.16 of appendix 2 and A4.6 of appendix 4, and the group mean results are given in table 9.5. These data are for the O1-Fz channel and include a 4ms adjustment in the latency for those patients seen at the Queen Elizabeth hospital. It can be seen that the CII component was only slightly delayed in Alzheimer's patients and this delay did not reach statistical significance. As indicated in chapter 6, the CII component showed a large interindividual difference in latency thus producing a large standard deviation, in addition there were a few controls and patients in which a response could not be achieved. There was no statistical difference in amplitude of the CI-CII component between groups.

Table 9.5. Mean results for monocular pattern onset VEP to a 6' achromatic check of 85% contrast using a 200ms raised cosine ramp (O1-Fz channel).

	CONTROLS	AD PATIENTS
CII LATENCY	255.05ms ±36.43	261.82ms ±64.93
CI-CII AMP	4.87µv ± 1.95	4.26µv ± 2.19

(vi). *Pattern onset/offset VEP to a 4cpd red/green isochromatic horizontal square wave grating presented using a 200ms ramp.*

The latency of the major negative component was measured (CII) and its amplitude from the preceding positivity (CI-CII). The individual results are given in tables A2.17 of appendix 2 and A4.7 of appendix 4, and the group mean results are given in table 9.6. Again these data are for the O1-Fz channel and include the 4ms adjustment in latency for the patients seen at the Queen Elizabeth hospital. It can be seen that the patients with Alzheimer's disease have a slightly delayed CII component but due to the large standard deviations - this difference did not reach statistical significance. There was no statistical difference in amplitude.

Table 9.6. Mean results for monocular pattern onset VEP to a 4cpd red/green isoluminant horizontal square wave grating using a 200ms raised cosine ramp (O1-Fz channel).

	CONTROLS	AD PATIENTS
CII LATENCY	291.01MS ± 33.81	299.92MS ± 45.09
CI-CII AMP	5.02μv ±2.33	4.65μv ± 3.07

9.4. DISCUSSION.

These data suggest that Alzheimer's disease has a significant effect on the visual evoked potential. The most significant difference is to the latency of the P2 component of the flash VEP. This latency was 129.70 ms in controls compared to 156.14ms in Alzheimer's disease patients.

Delays were also found for the P100 component of the pattern reversal VEP to both 60' and 10' checks in patients with Alzheimer's disease - although this difference was only significant for the 10' check. The CII component of the VEPs to both stimuli presented with a raised cosine ramp of 200ms were also slightly delayed - but not significantly. One could speculate that these differences were due to the reduction in mean visual acuity compared to the control group. However patient JB, who had an unreliable visual acuity of 6/36 produced pattern reversal VEPs with P100 latencies of 115.23ms for the 60' check and 126.95 ms for the 10' check - which are rather better than one would expect. The other patient JT who had an unreliable visual acuity of 6/36 was only able to participate in the flash VEP and the pattern reversal VEP to 60' check. The latter produced a P100 latency of 119.14 ms.

The VEP to the 73' check counterphasing at 6Hz also resulted in a slight reduction in the % power of the second harmonic frequency in Alzheimer's patients.

An observation of particular importance was the poor attention span of the Alzheimer's patients. It was often necessary to remind the patient to look at the centre of the screen. There were also frequent interruptions from the patients who became confused. It is impossible to guarantee that the patients were concentrating on the stimulus for the duration of the test. If the patient does not maintain fixation then there is likely to be a delay to the resulting pattern VEP. Accurate fixation is not as crucial when viewing the strobe during recording of the flash VEP. One would therefore expect that in non-cooperative patients the flash VEP to be less delayed than the pattern VEP. The results however show the contrary.

The large delay to the flash P2 component is therefore likely to be the result of Alzheimer's disease interferring with the transmission of the stimulus rather than due to the lack of attention on the part of the patient. This is in agreement with previous authors. We suggest that this delay is due to the reduction in the neurotransmitter acetylcholine. Further evidence for this is provided by those Parkinsonian patients in chapter 7 takining anticholinergic medication who also present with a delayed flash P2 component.

Acetylcholine is present in the retina and is involved in retino- cortical transmission along the tectal association area pathway rather than geniculo-cortical transmission. As explained in chapter 5, it is believed that luminance information is transmitted along this tectal-association area route. Although the transmission of this non-patterned stimulus is likely to be governed by the magnocellular cells of the retina, there is likely to be further division of this pathway into a luminance only pathway and a pathway involving structure, the luminance pathway being transmitted along the tectal-association area route and the pathway involving structure along the geniculo-cortical route. The data above suggests that Alzheimer's disease and anticholinergic medication (as taken by some Parkinson's disease patients) has little effect on the structured stimulus that was designed to activate the magnocellular pathway, but is detrimental to the luminance magnocellular pathway. This is further evidence that acetylcholine is involved in the transmission of luminance only information along a tectal-association area pathway.

CHAPTER 10.

10. EFFECT OF TOPICAL HYOSCINE HYDROBROMIDE ON THE VISUAL EVOKED POTENTIAL, ELECTRORETINOGRAM AND CONTRAST SENSITIVITY.

10.1. INTRODUCTION.

The previous chapters have shown than patients with Alzheimer's disease and those with Parkinson's disease who are taking anticholinergic medication, all have a delayed flash P2 component of the VEP. The effect on the pattern VEP is more unremarkable, the slight delays seen in Alzheimer's disease being likely to be due to lack of patient concentration. The administration of systemic hyoscine hydrobromide to normal subjects has also been shown to result in a delayed flash P2 component (chapter 5). More recently a study by Panchal (1994 unpublished PhD thesis, Aston University), showed that in 11 young healthy male volunteers there was a small but consistent delay to the flash P2 component of the VEP 1-4 hours following drug administration, the N2 latency and N2-P2 amplitude remaining normal. Pattern reversal responses showed no change in amplitude or latency of the P100 component.

The abnormal flash VEP found in Alzheimer's disease may be due to one of the following:

i. Alzheimer's disease and/or systemic anticholinergic drugs could have a mainly central action resulting in a cholinergic deficit affecting the tectal-association area pathway. Acetylcholine is thought to be a neurotransmitter present in the superior colliculus, but is not thought to be directly involved in the transmission of visual information in the LGN. Additionally, the P2 component of the flash VEP is thought to be generated in the association areas of the visual cortex (Spekreijse *et al*, 1977; Spehlmann *et al*, 1977; Regan and Spekreijse, 1986; Wright *et al*, 1987; Harding, 1991; Celesia *et al*, 1991).

ii. Alternatively, the VEP delays could be due to a more peripheral cholinergic deficit. ACh is present in the retina associated with displaced amacrine cells, although its function is uncertain. It is not thought to play a significant role in visual processing but is involved in determining the rate of spontaneous activity in the ganglion cells (Puro, 1985). In addition, Hinton *et al* (1986)and Saddun *et al*

(1990), in anatomical studies of the optic nerve and retina of AD patients, have shown depletion of the larger retinal ganglion cells and optic nerve fibres suggestive of a magnocellular deficit. These findings may be the result of either a retrograde degeneration, or due to the direct affect of AD or systemic hyoscine hydrobromide (in normals) on these structures.

iii. Furthermore, neurofibrillary tangles and senile plaques are found to be more numerous in the association areas of Alzheimer's patients compared to primary visual cortex. As already pointed out, the flash P2 component is generated in the association areas. However, as reversible neurofibrillary tangles and senile plaques are unlikely to be found in the association areas of young subjects following hyoscine hydrobromide administration, this hypothesis can be rejected as being the cause of the flash P2 component delay seen in AD.

In 1988 Morrison and Reilly conducted a contrast sensitivity study on 5 subjects before and following topical instillation of 3 drops of 0.025% hyoscine hydrobromide. Contrast sensitivity was measured to 2, 3, 5, and 10 cpd CRT gratings both stationary and phase reversed at 5.5 Hz, and to a stationary grating of 20cpd. The ascending method was used in which the subject gradually increased the contrast of the screen from a uniform field until the grating was just seen. In addition the contrast sensitivity to stationary laser interference fringes of 10 and 20 cpd was also measured. They found that the contrast sensitivity to a phase reversed 3 cpd grating pattern, was significantly reduced (by 40%) 79 minutes following drug instillation and by 25% at 49 minutes with marginal significance. Additionally they found significant reduction in contrast sensitivity to 2 and 5 cpd stationary and phase reversed gratings, at 60-150 mins following drug instillation.The gratings of high spatial frequency remained unaffected. This study would suggest that topical hyoscine effects cholinergic neurotransmission within the retina resulting in a deficit to those neurons responsible for the transmission of low spatial frequency information.

This study by Morrison and Reilly gives support to the second hypothesis described above suggesting that a peripheral abnormality is the cause of the delayed P2 component of the flash VEP found in AD patients. However, the finding in chapter 8 that anticholinergic medication in PD patients had no effect on the ERG suggests that the first hypothesis is true. In order to investigate this further, we measured the VEP and ERG following topical hyoscine hydrobromide instillation in young volunteers.

10.2.EXPERIMENT 1.

THE MEASUREMENT OF VEPS FOLLOWING THE ADMINISTRATION OF TOPICAL HYOSCINE HYDROBROMIDE.

10.2.1. METHOD.

Subjects.

5 subjects were selected from student volunteers. Contact lenses were avoided and subjects were excluded if they had a history of ocular pathology, migraine or epilepsy, or if they were taking any significant medication. Subjects were selected with grade A of the standardised iris pigmentation classification system (Seddon *et al*, 1990), as the effectiveness of the hyoscine drops is greatly reduced in highly pigmented eyes. This restriction leads to more rapid and standardised responses to the low concentration of the drug, with more rapid recovery.

Stimuli.

From the studies described in the previous chapters, four stimulus parameters were used to generate visual evoked potentials.

(i) The first was a non-patterned D.C. flash of luminance 1363 cd/m^2 generated using a Grass photostimulator. The rate of stimulation was one flash every second. It is thought that a luminance only stimulus containing no pattern information is likely to be transmitted by a tectal-association area pathway (see Chapter 5). Since this pathway has a lack of spatial information it is probably magnocellular in origin.

(ii) The second stimulus was an achromatic checkerboard containing 60' checks. They were counterphased at 1Hz and had a contrast of 85%. This stimulus was presented within a 4°17' X 5°42' field. Due to its robustness this stimulus was used to demonstrate the procedure to the patient and to ensure that a VEP could be evoked - it stimulates both magno and parvocellular pathways.

(iii) The third stimulus was an achromatic checkerboard of 2° checks. They were counterphased at 6Hz and had a contrast of 30%. The stimulus was presented

within a 4°17' X 5°42' field. Due to its high temporal frequency, low spatial frequency and low contrast - this stimulus should stimulate the magnocellular pathway.

(iv) The fourth stimulus was a horizontal red/green square wave grating of 4cpd and 35% contrast. It was photometrically measured at isoluminance to provide a purely chromatic stimulus. The isoluminance was also subjectively checked by counterphasing the stimulus at 16Hz and using red or green filters to achieve minimum flicker. The grating was then presented using an on and off cosine ramp modulation such that the grating took 300ms to reach maximum contrast where it remained for 200ms and then took a further 300ms to disappear. The interstimulus interval was 500ms. The field size was again 2°34' X 3°26'. Due to the low temporal frequency, small field and chromaticity - this stimulus should stimulate the parvocellular pathway.

Instrumentation.

The visual evoked potentials were recorded using the Nicolet Pathfinder II electrodiagnostic system. The bandpass of the system was 0.5 to 70Hz.
Flash stimulation was achieved using a Grass photostimulator strobe with diffuser. The patterned stimuli were generated using a VSG 2/1 grating generator developed by Cambridge Research Systems and displayed on a CRT with 14 bit luminance resolution (E120 Flexscan 9080i 16 inch colour monitor) at a frame rate of 70Hz, with 624 pixels and 878 lines, using standard rastar technique. The gamma-corrected display was linear up to 90% contrast. The display screen had a mean luminance of 50 cd/m^2 and was 22.5cm vertical by 30cm horizontal. For the first three stimuli a square wave pulse was used to trigger the Pathfinder and for the last two stimuli a spike pulse was used at the beginning of each modulation.

Silver-silver chloride electrodes were attached to the scalp using Blenderm tape and the interelectrode impedence was maintained at 5K-ohms or less. The electrode montage used for subjects attending Aston University was OZ referred to FZ, O1 referred to FZ and C3, and O2 referred to FZ and C4, CZ acted as ground (in accordance to the methodology described in chapter 5). All recordings were taken in dim illumination.

Procedure.

Precise refractive correction was determined and maintained for all visual tasks. This is important as the topical instillation of hyoscine hydrobromide results in mydriasis and cycloplegia as a result of the drug antagonising the muscarinic action of acetylcholine on post-synaptic parasympathetic nerves, consequently affecting the ciliary and sphincter pupillae muscles. The colour vision of all male volunteers was checked using ishihara pseudoisochromatic plates. The filtration angle was checked using Van Heriks method and only grades 3 or 4 (20-45°) were accepted. Since there is a very remote possibility of an uncontrolled rise in intraocular pressure (IOP) following the use of mydriatic drops, the pressure was measured at the beginning of the experiment using the Pulsair non-contact tonometer, subjects with more than 20mm Hg were excluded. IOP was continuously monitored throughout the experiment. Pupil diameter and amplitude of accommodation were recorded and used to monitor drug activity. The VA was recorded and an acuity of 6/6 or better in both eyes was required for inclusion. Fixed artificial pupils of 4mm diameter were adjusted before both eyes in an optometric trial frame, and the subjects were then trained to maintain exact central fixation. Flash and pattern VEPs were measured. For the flash stimulus the subjects were asked to fixate a small spot in the centre of the strobe, to aid concentration the subjects were asked to count the number of times the strobe flashed. For the pattern VEPs the subject was asked to fixate on a small spot in the centre of the CRT screen. 50 sweeps were averaged, and the recording was repeated. Each test was completed monocularly and all VEPs were repeated. Following the initial control measurement, one drop of 0.4% Benoxinate hydrochloride was instilled in each eye. This was done to increase the absorption of the hyoscine hydrobromide across the cornea. One minute later a 20μl drop of 0.125% hyoscine hydrobromide was instilled in the left eye using a micropipette, whilst occluding the puncta to prevent any systemic absorption of the drug through the nasal mucosa.

Amplitude of accommodation, refractive error, pupil diameter and IOP were again measured. VEPs to the four stimuli were then repeated. This routine was continued until 4 post-drug runs had been completed. Each run took approximately one hour, and the stimuli were presented in the same order for each run, so that each stimulus was presented at equal time intervals.

10.2.2. RESULTS.

It was found that the pupil diameter reached its maximum value of 8mm, and the amplitude of accommodation deteriorated to below 2D 20 mins following administration of hyoscine hydrobromide. Recovery of accommodation occurred 24 hours after instillation and recovery of the pupil diameter to 4mm occurred 48 hours after instillation of the drug.

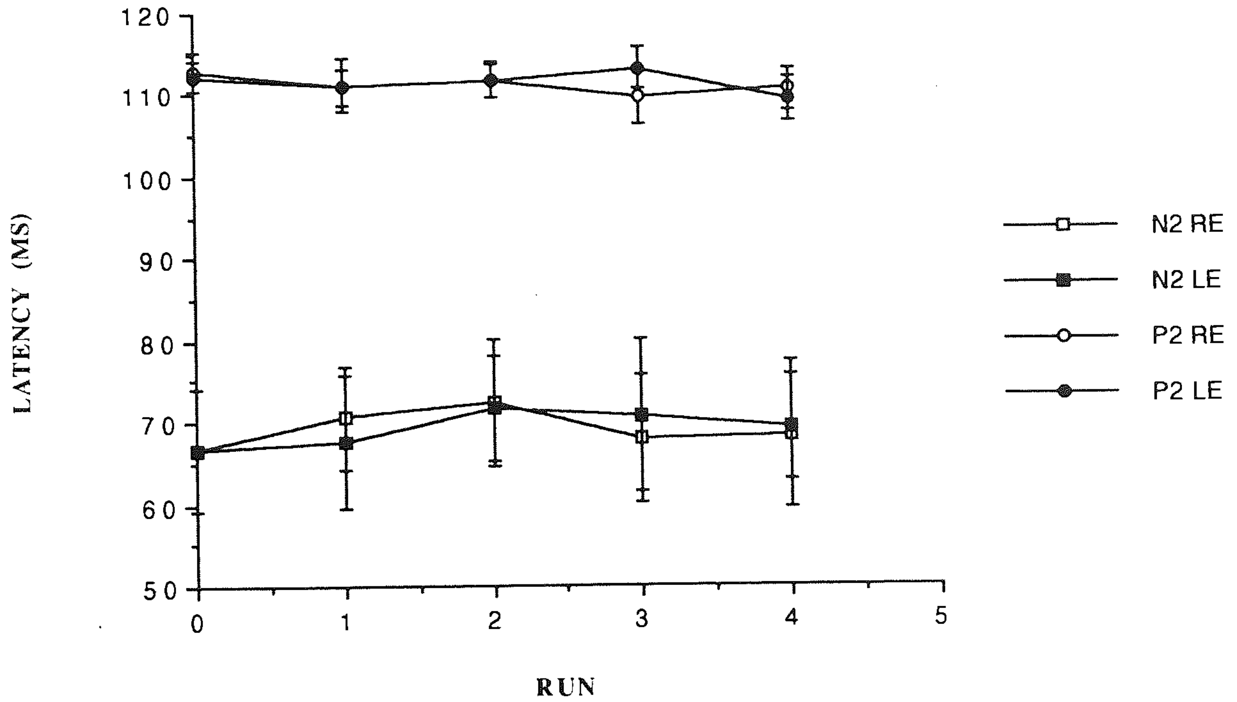
(i). Flash VEP

The latency of the N2 and the P2 component was measured, and the amplitude of the N2-P2 component. The data for the individual subjects for right (RE) and left eye (LE) and the interocular differences (value for RE - value for LE) are given in tables A5.1-A5.3 of appendix 5. Due to the unmistakable similarity between channels the data for the O1-Fz channel only are shown. The group mean results and standard deviations are shown in table 10.1.

The group mean latencies and amplitudes for each run were compared to the pre-drug condition. In addition the values for the right eye were compared to those of the left eye. A students t test showed that there was no significant difference between pre-drug control measurements and the four runs in which the drug was present. The t test was also used to show that there was no significant difference between right and left eyes (the left eye having received the hyoscine) at any time interval. This is shown graphically in figure 10.1. The error bars represent the standard error of the mean.

Figure 10.1

MEAN FLASH VEP N2 AND P2 LATENCY, BEFORE (RUN 0) AND FOLLOWING THE TOPICAL ADMINSTRATION OF HYOSCINE HYDROBROMIDE



MEAN AMPLITUDE OF THE FLASH N2-P2 COMPONENT BEFORE (RUN 0) AND FOLOWING THE TOPICAL ADMINISTRATION OF HYOSCINE HYDROBROMIDE

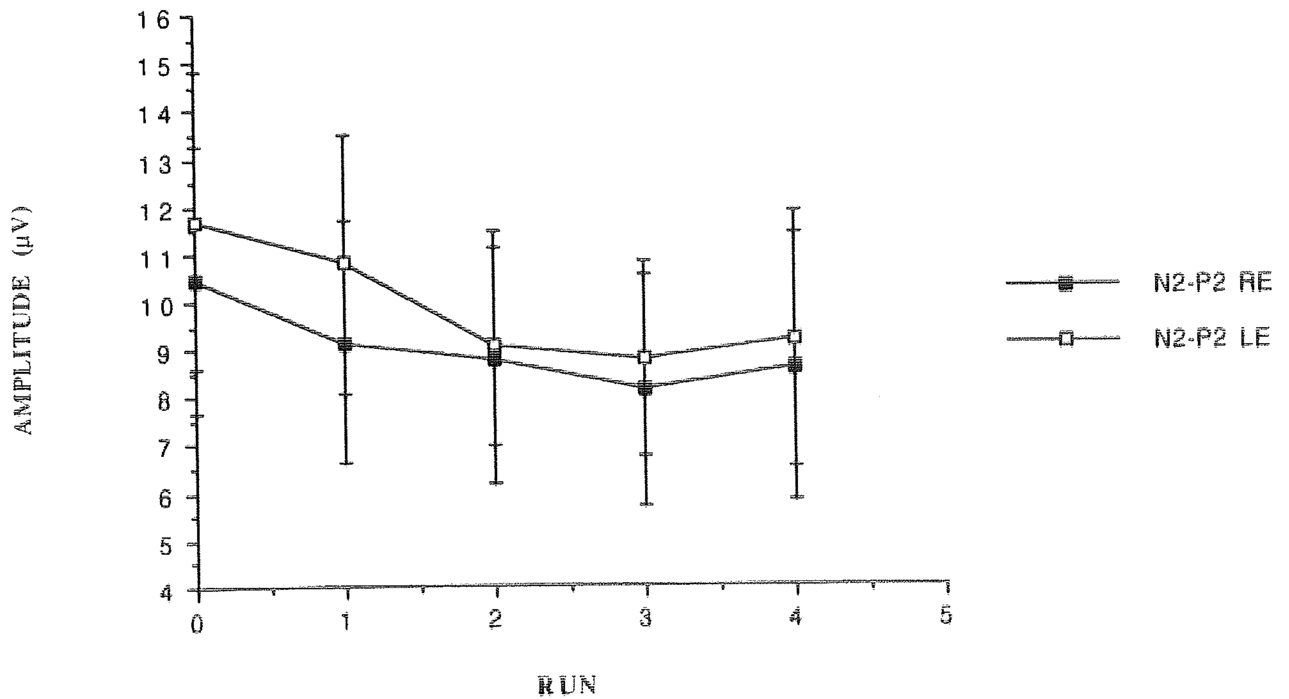


Table 10.1.

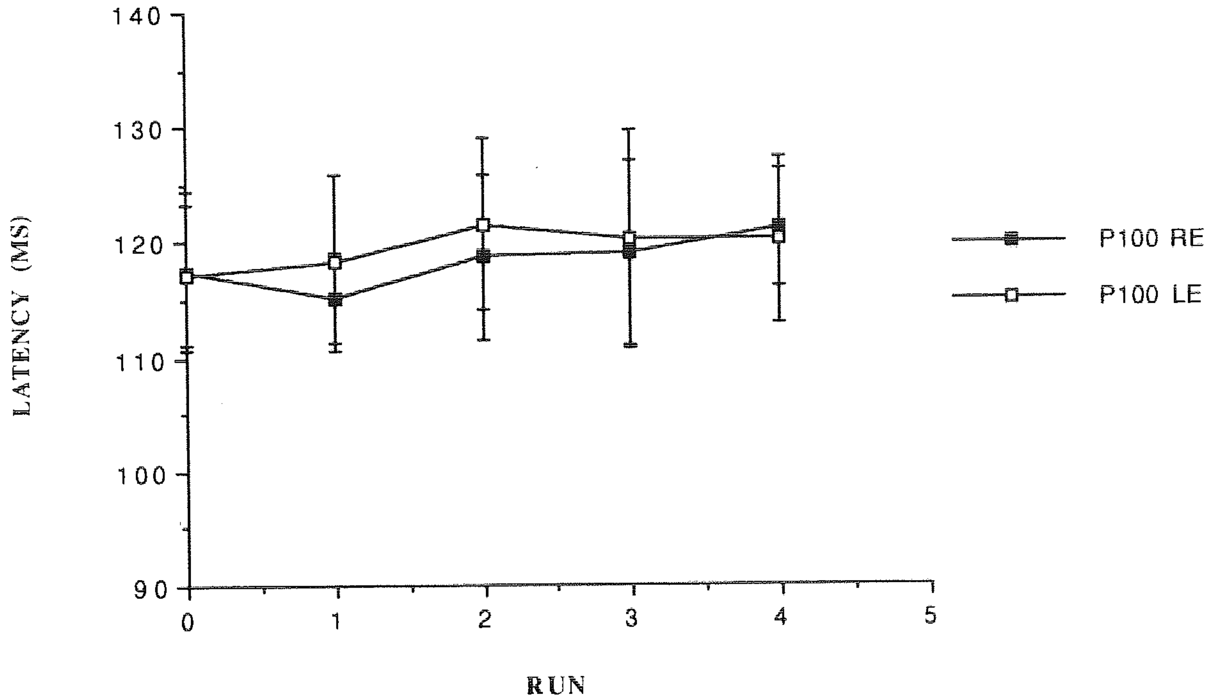
	N2 (MS)		P2 (MS)		N2-P2 (µV)	
	RE	LE	RE	LE	RE	LE
CONT	66.67 ±18.01	66.67 ± 15.45	112.83 ± 5.38	112.33 ± 4.50	10.47 ± 6.84	11.70 ± 7.62
RUN 1	70.67 ± 15.45	67.67 ±19.82	111.33 ± 7.53	111.00 ± 5.76	9.15 ± 6.25	10.81 ±6.64
RUN 2	72.33 ± 19.53	71.83 ± 15.68	112.00 ± 5.29	111.83 ± 5.27	8.79 ± 6.51	9.05 ± 5.10
RUN 3	68.17 ± 19.15	70.83 ± 22.71	109.83 ± 8.50	113.33 ± 5.96	8.11 ± 5.96	8.75 ±5.00
RUN 4	68.50 ± 22.21	69.33 ± 15.88	110.67 ± 6.41	109.50 ± 6.54	8.60 ± 6.89	9.18 ± 6.56

(ii). Pattern reversal VEP to a 60' check counterphasing at 1 HZ and at 85% contrast.

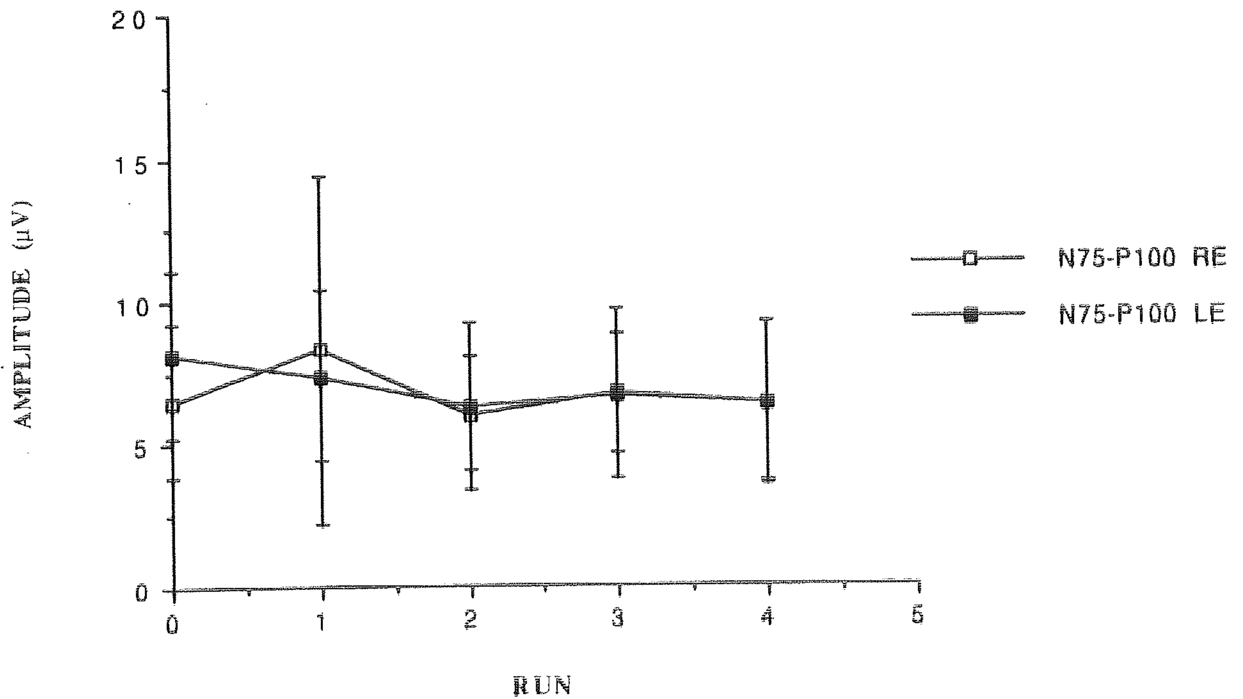
The latency of the P100 and the amplitude of the N75-P100 components were again measured. The data for each individual for channel O1-Fz are given in tables 5.4 to 5.5. of appendix 5. The group mean results and standard deviations are given in table 10.2 and are shown graphically in figure 10.2. The error bars of the graph represent the standard errors of the mean. The graph of the P100 latency indicates that the left eye latency was rather later than the right eye - however this did not reach statistical significance. There was no significant difference in amplitude between the two eyes for any time interval.

Figure 10.2

MEAN P100 LATENCY OF PATTERN REVERSAL VEP, BEFORE (RUN 0) AND FOLLOWING THE TOPICAL ADMINISTRATION OF HYOSCINE HYDROBROMIDE



MEAN AMPLITUDE OF N75-P100 COMPONENT OF PATTERN REVERSAL VEP, BEFORE (RUN 0) AND FOLLOWING THE TOPICAL ADMINISTRATION OF HYOSCINE HYDROBROMIDE



(iii). Pattern reversal VEP to a 2° check counterphasing at 6 Hz and at 30% contrast.

The steady state VEP to this stimulus presented as a sinusoidal waveform which was annalysed by obtaining a power spectrum of the fast fourier transform of the wave. The % power of the second harmonic was then compared between left and right eyes and between pre drug control and drugged runs.

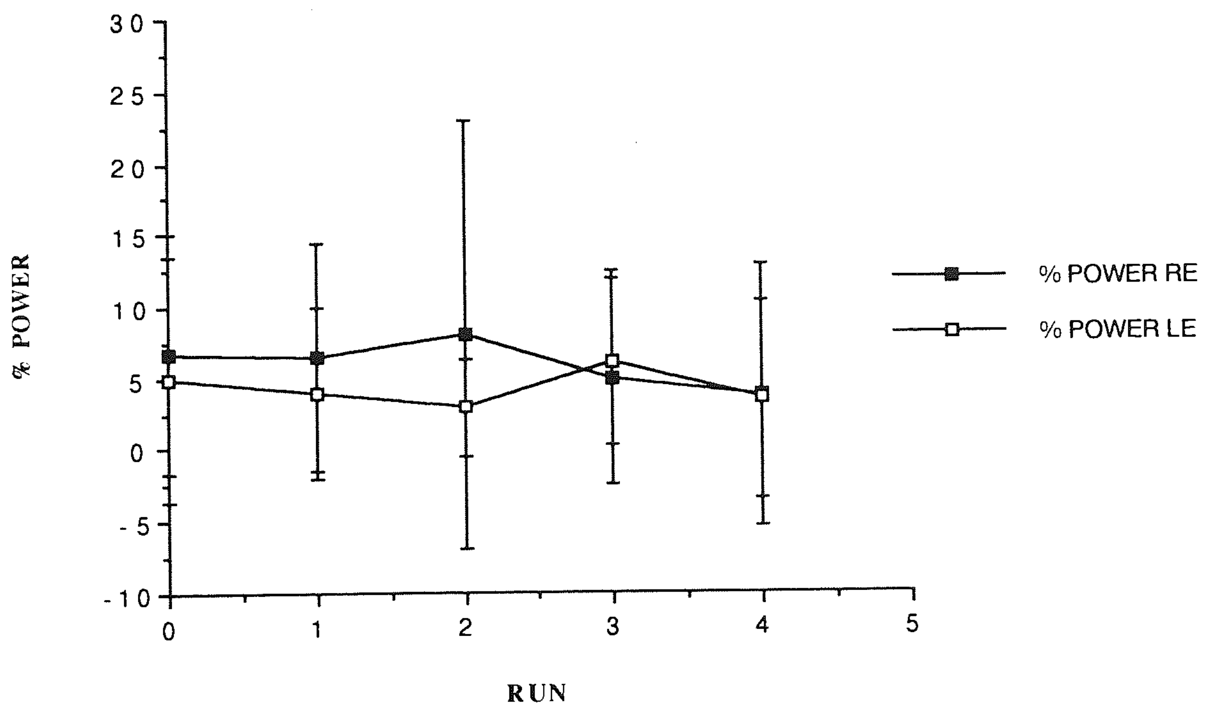
Table 10.2.

	P100 (ms)		N75-P100 (μV)	
	RE	LE	RE	LE
CONT	117.50 ± 6.92	117.17 ± 6.05	6.54 ± 2.67	8.16 ± 2.91
RUN 1	115.33 ± 3.88	118.33 ± 7.71	8.34 ± 6.07	7.41 ± 2.98
RUN 2	118.83 ± 7.11	121.67 ± 7.47	6.03 ± 2.00	6.29 ± 2.90
RUN 3	119.17 ± 8.06	120.33 ± 9.40	6.77 ± 2.08	6.74 ± 2.95
RUN 4	121.33 ± 5.13	120.33 ± 7.17	6.44 ± 2.77	6.42 ± 2.85

The % power for each individual for each run is given in table 5.6 of appendix 5. It can be seen from this table that subjects AD, PF and JG gave very poor results. The group mean results are given in table 10.3, and are illustrated graphically in figure 10.3. Although the graph reveals a lower % power for the left eye, due to the large standard errors, these did not reach statistical significance.

Figure 10.3

% POWER OF SECOND HARMONIC OF STEADY STATE VEP, BEFORE (RUN 0) AND FOLLOWING THE TOPICAL ADMINISTRATION OF HYOSCINE HYDROBROMIDE



(iv). VEP to a 4cpd horizontal red/green grating presented with a 300 ms onset/offset ramp.

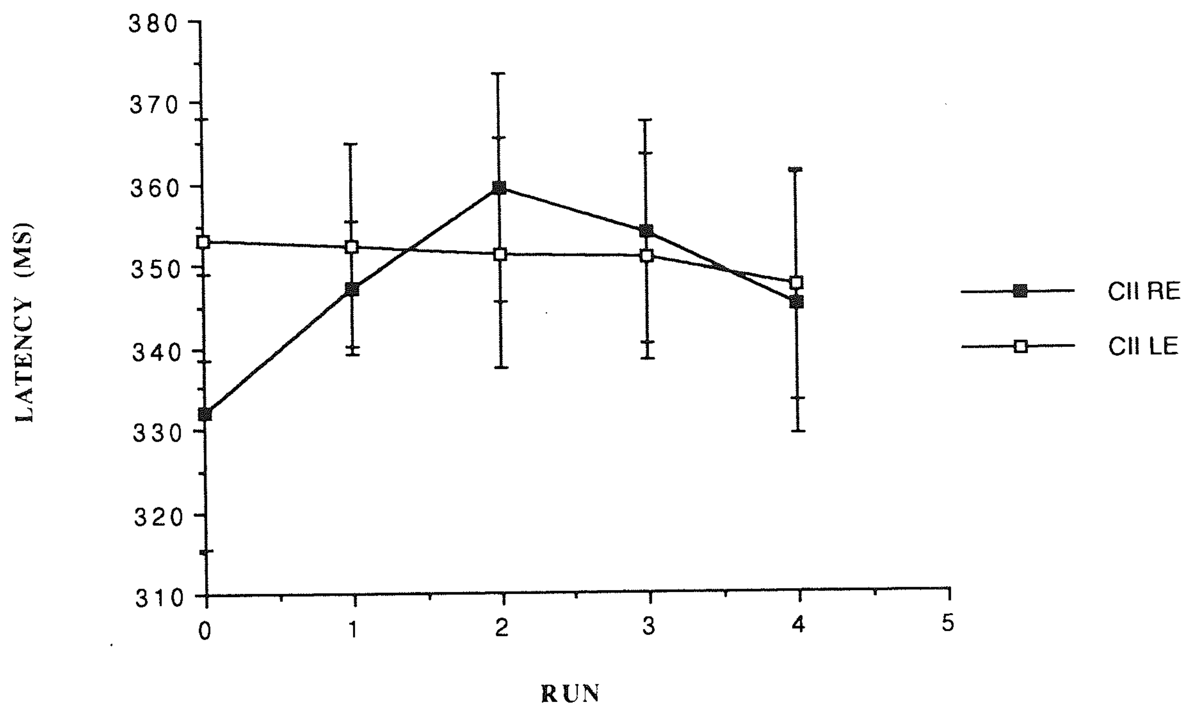
The latency of the major negative component (CII) and its amplitude from the preceding positivity (CI-CII) were measured. The results for each individual are shown in tables 5.7 - 5.8 of appendix 5. From these it can be seen that no response could be achieved from subject JG to this stimulus. The group mean results and standard deviations are given in table 10.4 and are illustrated graphically in figure 10.4 (the error bars representing the standard error of the mean). As we have repeatedly shown with this type of stimulus there is a large variation in latency of the CII component between subjects resulting in a high standard error. It was therefore not surprising to find that there was no significant difference between the right and left eyes or between pre-drug and drugged conditions.

Table 10.3.

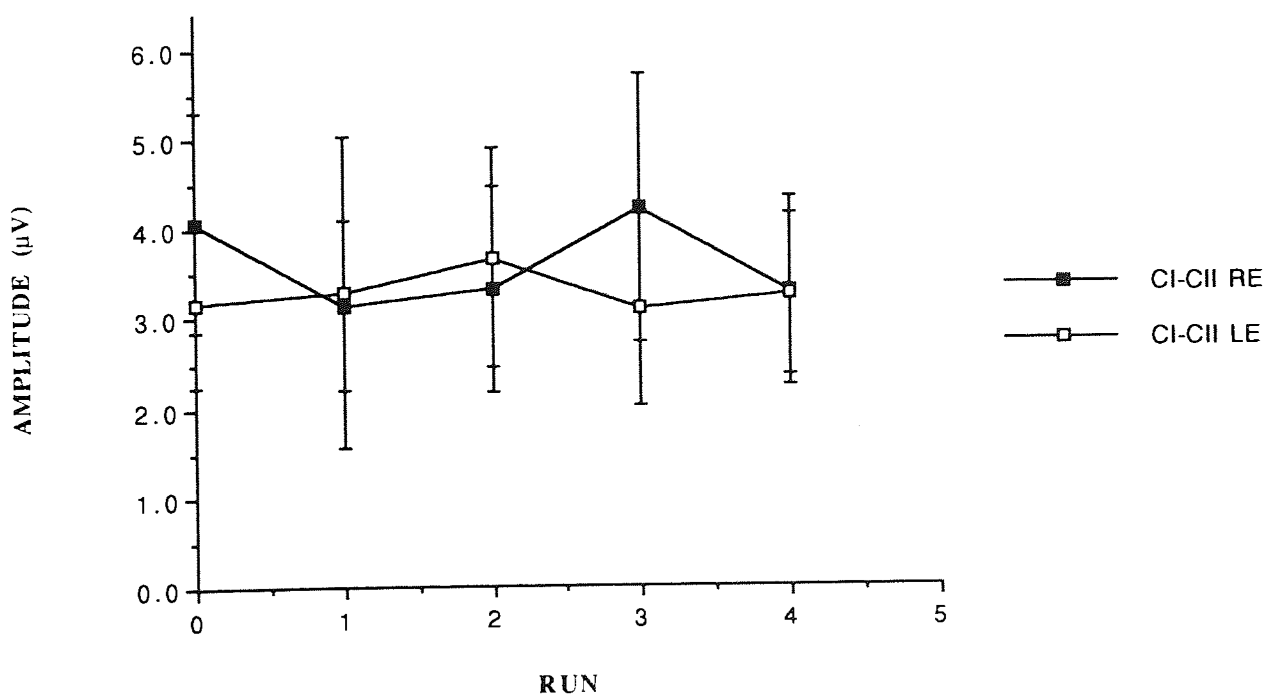
	% POWER	
	RE	LE
CONT	6.77 ± 8.34	4.95 ± 8.45
RUN 1	6.47 ± 8.01	3.98 ± 5.98
RUN 2	8.00 ± 14.94	2.95 ± 3.41
RUN 3	5.02 ± 7.53	6.20 ± 5.83
RUN 4	3.73 ± 9.15	3.57 ± 6.89

Figure 10.4

MEAN CII LATENCY, BEFORE (RUN 0) AND FOLLOWING THE TOPICAL ADMINISTRATION OF HYOSCINE HYDROBROMIDE



MEAN CI-CII AMPLITUDE, BEFORE (RUN 0) AND FOLLOWING THE TOPICAL ADMINISTRATION OF HYOSCINE HYDROBROMIDE



10.2.3. DISCUSSION.

From these results it can be seen that topical hyoscine hydrobromide has very little effect on the VEP no matter what form of stimulation is used. There are three possible conclusions one could draw from this:

1. One could speculate that a peripherally acting anticholinergic drug has no effect on the VEP. This would then suggest that the P2 delays of the flash VEP found in Alzheimer's disease and in normal controls taking systemic anticholinergics are due to the central affect of the drug.

Table 10.4.

	CII (ms)		C1-CII (μV)	
	RE	LE	RE	LE
CONT	332.20	353.32	4.08	3.17
	± 37.53	± 32.91	± 2.72	± 2.07
RUN 1	347.40	352.55	3.15	3.29
	± 18.24	± 24.79	± 2.10	± 3.49
RUN 2	359.64	351.56	3.22	3.68
	± 30.89	± 31.40	± 2.55	± 2.77
RUN 3	352.08	351.16	4.23	3.12
	± 30.50	± 28.11	± 3.34	± 2.45
RUN 4	345.32	347.60	3.29	3.26
	± 35.77	± 31.50	± 2.36	± 1.98

2. The second possibility is that topical administration of the drug has an effect on the retina that is not reflected in the VEP. In order to discount this possibility it is necessary to repeat the experiment but using electroretinograms, this is described in the next experiment.

3. The third, and particularly important possibility is that the drug does not pass into the posterior chamber to reach the retina. It is impossible to establish this without conducting an experiment involving direct analysis of the retinal tissue.

However the fact that Morrison and Reilly found that the topical administration of the drug affects contrast sensitivity, suggests that hyoscine does reach the retina.

10.3.EXPERIMENT 2.

THE MEASUREMENT OF THE ELECTRORETINOGRAM FOLLOWING THE TOPICAL ADMINISTRATION OF HYOSCINE HYDROBROMIDE.

10.3.1. METHOD.

Subjects.

4 subjects were selected from student volunteers. Contact lenses were avoided and subjects were excluded if they had a history of ocular pathology, migraine or epilepsy, or if they were taking any significant medication. Subjects were selected with grade A of the standardised iris pigmentation classification system (Seddon *et al*, 1990), as the effectiveness of the hyoscine drops is greatly reduced in highly pigmented eyes. This restriction leads to more rapid and standardised responses to the low concentration of the drug, with more rapid recovery.

Stimuli.

Five stimulus parameter were used to generate electroretinograms.

(i). Photopic ERGs were generated using a non patterned flash of luminance 1925 cd/m^2. Ganzfeldt stimulation was achieved using a pair of goggles to scatter the light. The rate of stimulation was one flash every second.

(ii) Scotopic ERGs were generated following 10 minutes of dark adaption. A single flash of light was used of luminance 1925 cd/m^2. Again Ganzfeldt conditions were achieved using goggles.

(iii) The third stimulus was an achromatic checkerboard containing 48' checks. They were counterphased at 2Hz and had a contrast of 85%. This stimulus was presented within a 19°5' X 24°46' field.

(iv) The fourth stimulus was an achromatic checkerboard containing 26' checks. They were counterphased at 2 Hz and had a contrast of 85%. This stimulus was also presented within a 19°5' X 24°46' field.

(v) The fifth stimulus was an achromatic checkerboard containing 2°22' checks. They were counterphased at 6Hz and had a contrast of 30%. This stimulus was also presented within a 19°5' X 24°46' field.

Instrumentation.

Electroretinograms were also recorded using the Nicolet Pathfinder II electrodiagnostic system. The bandpass of the system was 0.5Hz to 500Hz for the photopic and scotopic ERGs and 0.5 to 70Hz for the pattern ERGs. The flash and patterned stimuli were generated using the same systems as of the VEP study above. A square wave pulse was used to trigger the Pathfinder.

DTL electrodes were used as the active electrodes and were referred to silver-silver chloride electrodes at the outer canthus. An electrode placed on the forehead acted as ground. The methodology for electrode attachment was as section 5.2.1.2 (Thompson and Drasdo, 1987). All recordings were taken in dim illumination.

Procedure.

Precise refractive correction was determined and maintained for all visual tasks. The colour vision of all male volunteers was checked using ishihara pseudoisochromatic plates. The filtration angle was checked using Van Heriks method and only grades 3 or 4 (20-45°) were accepted. Since there is a very remote possibility of an uncontrolled rise in intraocular pressure (IOP) following the use of mydriatic drops, the pressure was measured at the beginning of the experiment using the Pulsair non-contact tonometer, subjects with more than 20mm Hg were excluded. IOP was continuously monitored throughout the experiment. Pupil diameter and amplitude of accommodation were recorded and used to monitor drug activity. The VA was recorded and an acuity of 6/6 or better in both eyes was required for inclusion.

For the photopic ERGs the subjects were asked to keep their eyes directed in the straight ahead position and to keep blinking to a minimum. They were specifically asked not to blink each time the flash appeared. 150 sweeps were averaged and the recording was repeated. For the scotopic ERG the subject was kept in the dark for

10 minutes. Immediately prior to stimulation with a single flash of light, the subjects was asked to look straight ahead keeping their eyes as still as possible. They were also asked not to blink when the flash was switched on. Additionally the artefact rejection system was switched off so that a response would be averaged even if the subject blinked. If the ERG was spoiled with a blink reflex then a second ERG was attempted following a further 5 minutes of dark adaption.

For the patterned stimuli the subjects were asked to fixate on a small spot in the centre of the CRT screen, and asked to keep blinking to a minimum. 150 sweeps were averaged and the recording was repeated.

In all recordings, if the subjects had a high blink rate that produced many artefacts then they were asked not to blink at all for a period of 10 seconds while the recording was taken, the averager was then paused while the subject was allowed to blink.

Following the initial control measurement, one drop of 0.4% Benoxinate hydrochloride was instilled in each eye. This was done to increase the absorption of the hyoscine hydrobromide across the cornea. One minute later a 20μl drop of 0.125% hyoscine hydrobromide was instilled in the left eye using a micropipette, whilst occluding the puncta to prevent any systemic absorption of the drug through the nasal mucosa. As mentioned, hyoscine hydrobromide results in marked dilation of the pupil. However, for ERG measurement an artificial pupil results in reduced retinal illumination and hence the waveform is affected by the partial dark adaption. To account for this it was decided to use a drug in the right, control eye, that dilated the pupil but which was not an anticholinergic. Phenylephrine is a sympathomimetic drug which fulfils this criteria as it acts directly on the alpha receptors of the effector fibres of the dilator pupillae and the smooth muscle of the (mucosal) blood vessels, thus causing mydriasis and blanching of the conjunctiva respectively. However it is shorter acting than hyoscine and so it was necessary to use 2 drops separated by 5 mins of a 10% concentration of the drug (minim).

Amplitude of accommodation, refractive error, pupil diameter and IOP were again measured. It was found that the amplitude of accommodation reached its minimum value of less than 2D in the left eye, and 7.50 D in the right eye 30 mins after drug administration. The pupil diameters measured 7.5mm (±0.91) in the right eye and 7.8mm (±0.85) in the left eye 30 mins after drug administration. ERGs to the five stimuli were then repeated. This routine was continued until 4 post-drug runs had

been completed, except subject AW who found the DTL fibres irritating and had to discontinue the study after only two post-drug runs. Each run took approximately one hour, and the stimuli were presented in the same order for each run, so that each stimulus was presented at equal time intervals.

10.3.2. RESULTS.

(i). Pattern reversal ERG to a 48' check counterphasing at 2Hz and at 85% contrast.

The latency of the N35 and P50 components were measured, in addition to the N35-P50 amplitude. The results from both eyes of each individual are given in tables 5.9 - 5.11 of appendix 5. The group mean results are presented in table 10.5, and are illustrated graphically in figures 10.5 - 10.7, the error bars represent the standard error of the mean.

Table 10.5

	N35 (MS)		P50 (MS)		N35-P50 (µV)	
	RE	LE	RE	LE	RE	LE
CONT	29.20	29.35	52.00	51.90	4.78	4.30
	±2.55	± 3.39	± 1.82	± 1.51	± 1.00	± 0.98
RUN 1	25.00	26.90	45.70	46.80	4.79	3.95
	± 1.68	±1.36	± 1.77	± 2.67	± 1.41	±0.77
RUN 2	26.00	27.60	46.60	46.20	4.49	4.22
	± 1.18	± 0.57	± 1.77	± 2.56	± 0.82	± 0.55
RUN 3	25.60	26.40	44.53	44.40	4.57	4.03
	± 1.06	± 0.80	± 0.83	± 0.40	± 1.47	±1.14
RUN 4	25.07	25.47	45.33	45.07	4.94	3.95
	± 2.05	± 3.03	± 0.23	± 0.23	± 2.47	± 2.31

Figure 10.5

PERG 48' CHECK COUNTERPHASING AT 2HZ (N35 LATENCY), BEFORE (RUN 0) AND FOLLOWING THE TOPICAL ADMINISTRATION OF HYOSCINE HYDROBROMIDE

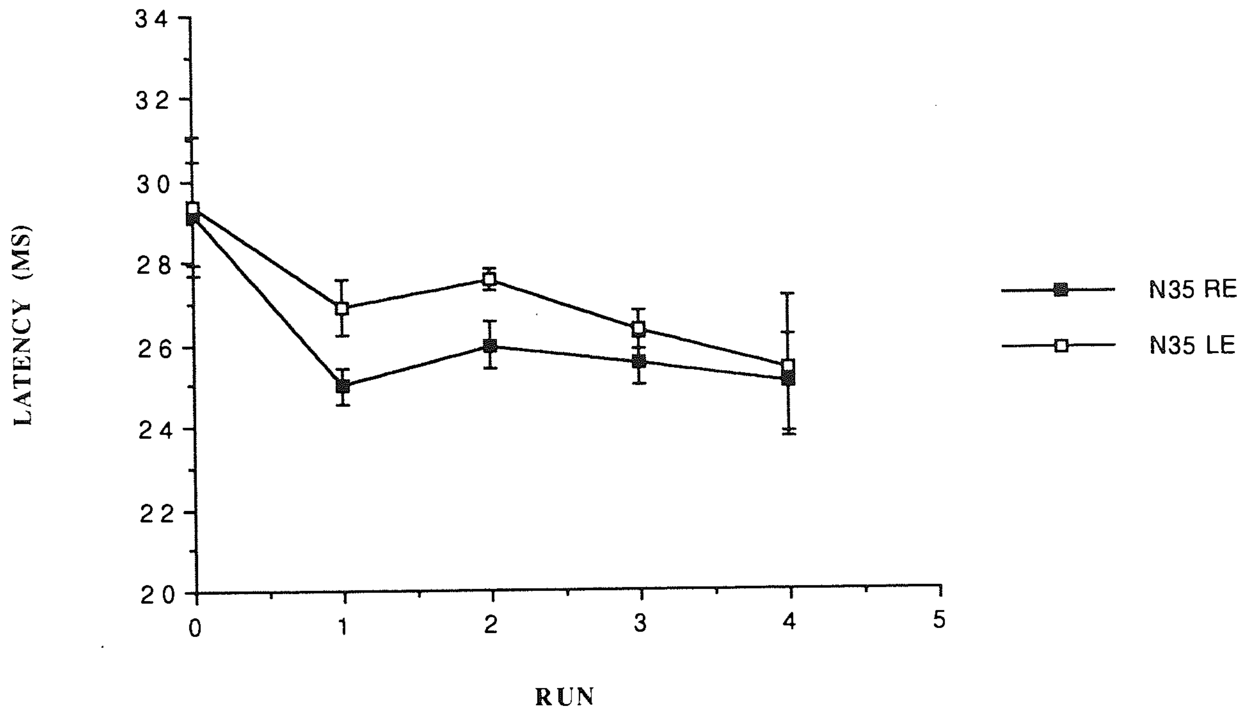


Figure 10.6

PERG 48' CHECK COUNTERPHASING AT 2HZ (P50 LATENCY), BEFORE (RUN 0) AND FOLLOWING THE TOPICAL ADMINISTRATION OF HYOSCINE HYDROBROMIDE

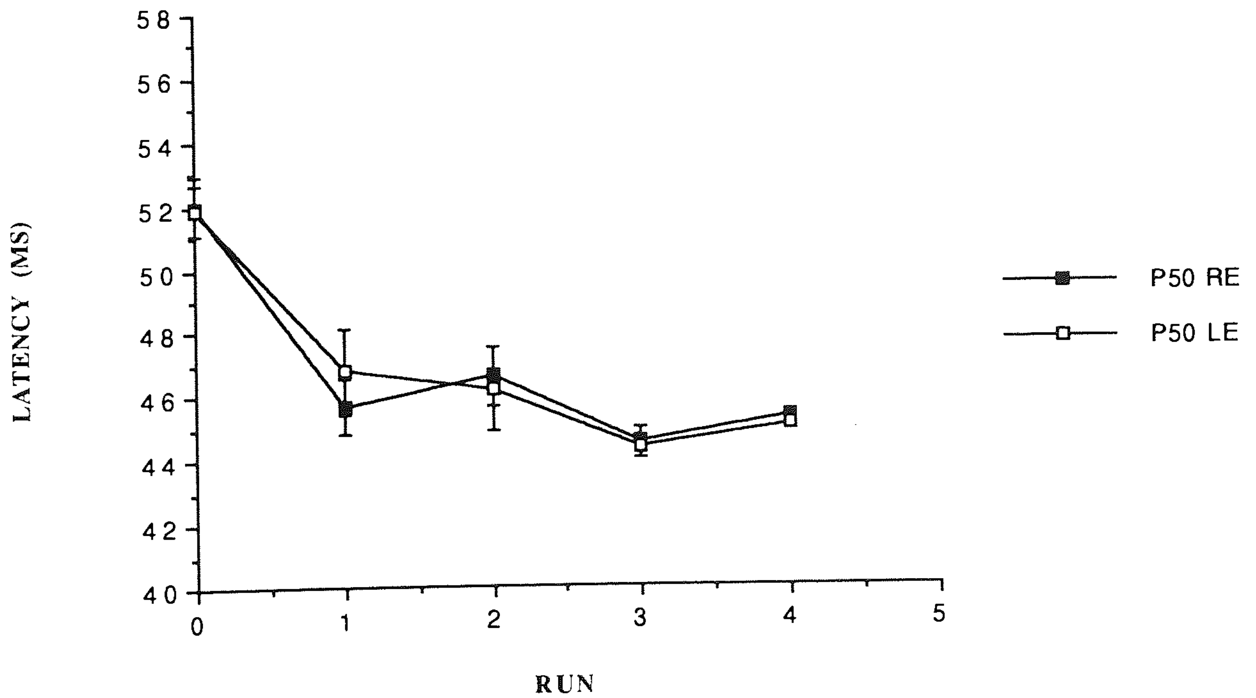
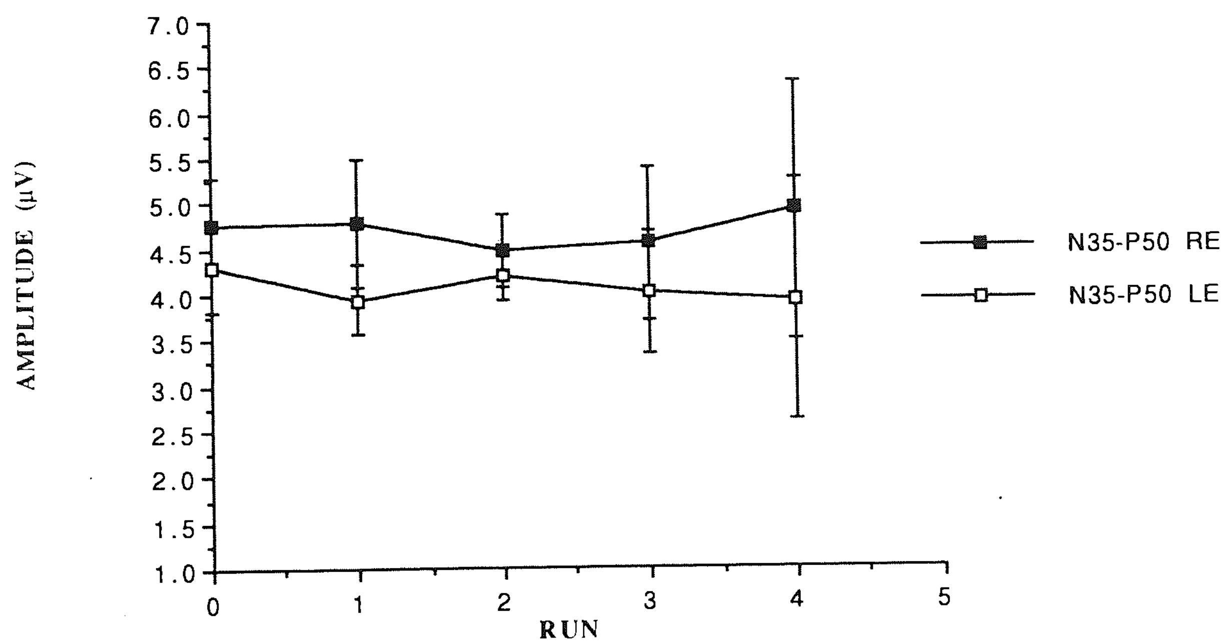


Figure 10.7



These data show a slight increase in latency of the N35 component in the left eye following drug administration, and a slight reduction in the N35-P50 amplitude. However a students t test found that there was no statistical significance between the two eyes for any component. The consistent reduction in amplitude from the left eye is largely due to subject RD who demonstrated a reduced amplitude ERG to all stimuli in the left eye both before and after drug administration and is thought to be the result of a poorly inserted DTL fibre, (this subject has previously shown ERGs of equal amplitude in the two eyes). An interesting point to note is the reduction in latency in both eyes following administration of the drugs, which can only be due to the effect of the increased pupil size.

(ii) Pattern reversal ERG to a 26' check counterphasing at 2Hz and at 85% contrast.

The latency of the N35 and P50 components were measured, in addition to the N35-P50 amplitude. The results from both eyes of each individual are given in tables 5.12 - 5.14 of appendix 5. The group mean results are presented in table 10.6, and are illustrated graphically in figures 10.8 - 10.10, the error bars represent the standard error of the mean.

Table 10.6

	N35 (MS)		P50 (MS)		N35-P50 (μV)	
	RE	LE	RE	LE	RE	LE
CONT	28.60 ±6.07	29.30 ± 3.42	55.40 ± 2.41	54.20 ± 2.39	3.63 ± 0.55	4.03 ± 0.68
RUN 1	26.30 ± 0.89	27.00 ±1.74	46.70 ± 1.44	48.50 ± 3.84	3.16 ± 1.54	2.96 ±0.38
RUN 2	25.70 ± 0.76	27.90 ± 3.98	47.30 ± 3.60	46.70 ± 2.36	3.33 ± 0.68	3.15 ± 0.64
RUN 3	25.33 ± 1.29	27.20 ± 0.70	46.40 ± 1.06	45.47 ± 1.22	3.77 ± 0.80	3.37 ±0.62
RUN 4	25.60 ± 1.44	26.00 ± 0.70	47.33 ± 0.23	45.20 ± 1.44	4.00 ± 2.21	2.92 ± 1.77

Figure 10.8

PERG 26' CHECK COUNTERPHASING AT 2HZ (N35 LATENCY), BEFORE (RUN 0) AND FOLLOWING TOPICAL ADMINISTRATION OF HYOSCINE HYDROBROMIDE

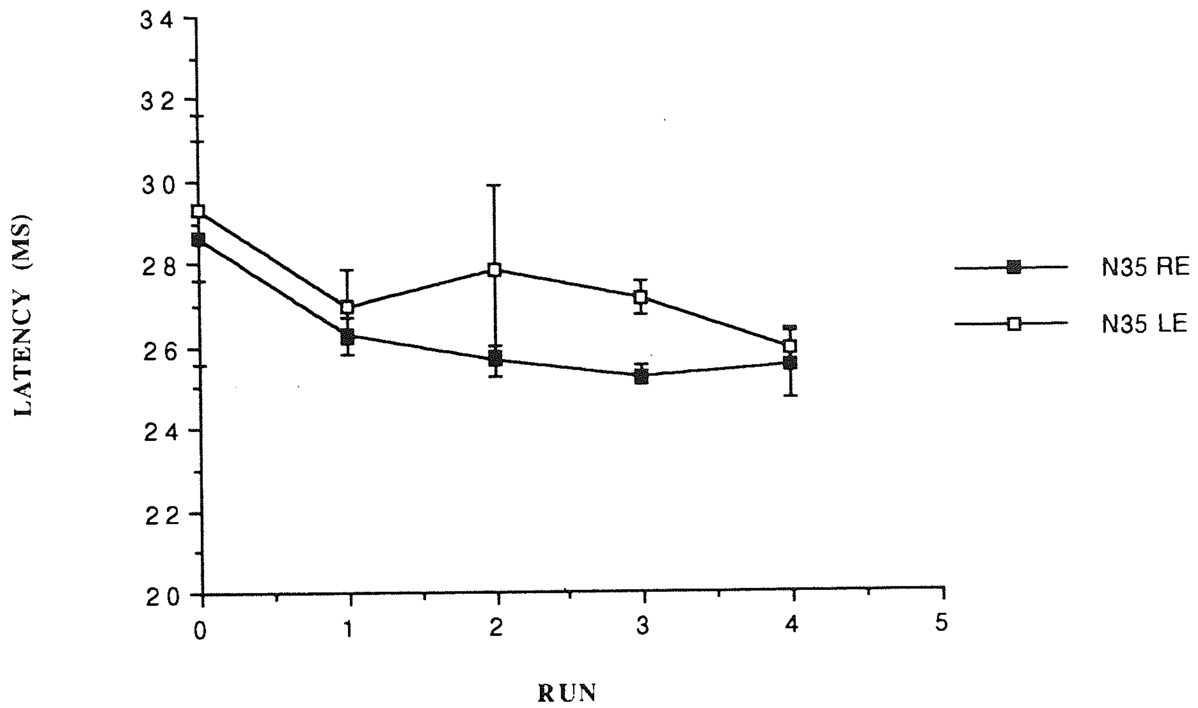


Figure 10.9

PERG 26' CHECK COUNTERPHASING AT 2HZ (P50 LATENCY), BEFORE AND FOLLOWING TOPICAL ADMINISTRATION OF HYOSCINE HYDROBROMIDE

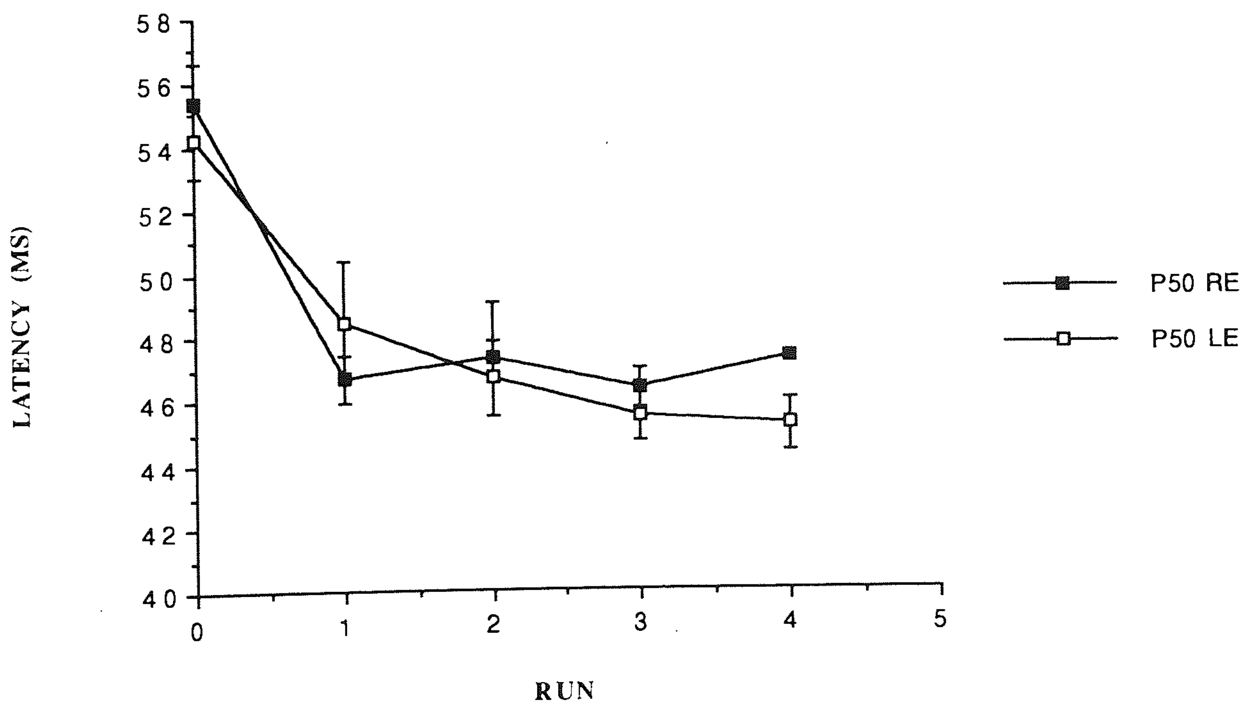
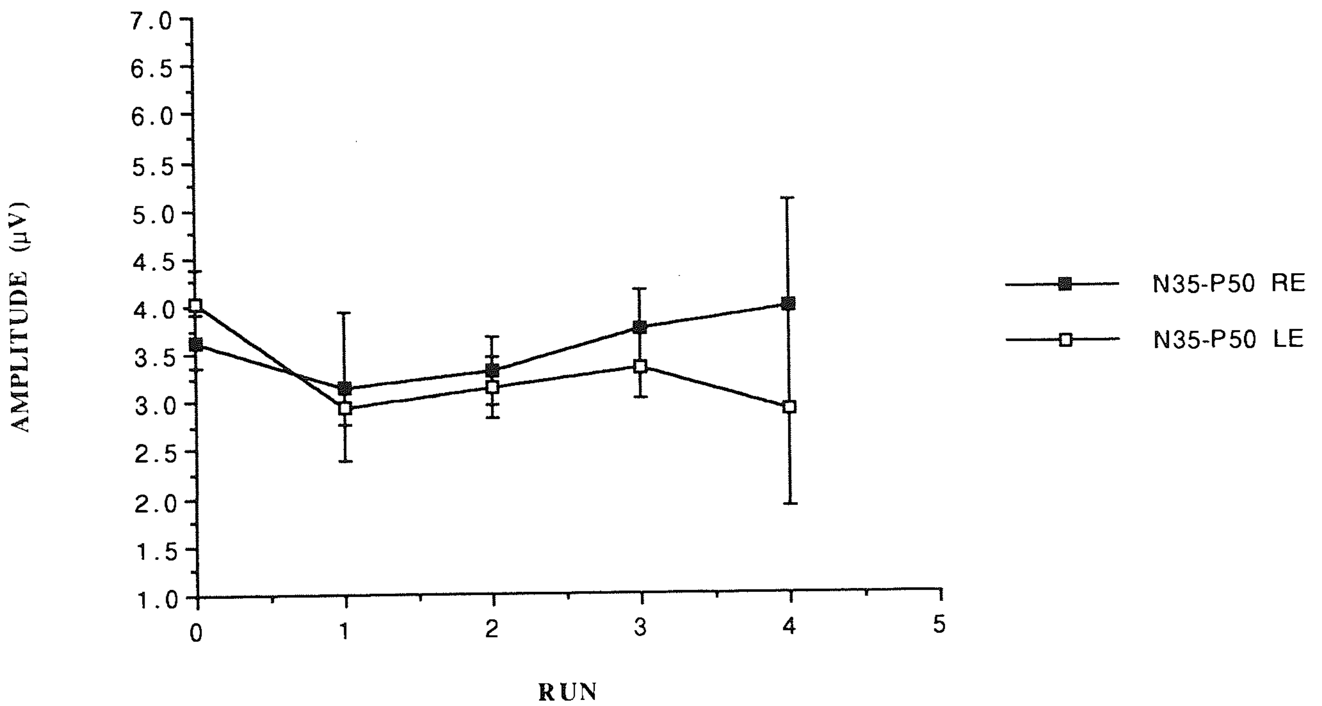


Figure 10.10



Once again the latency of the N35 component appeared to be slightly later in the left eye following administration of hyoscine hydrobromide compared to the right eye. However a t test reveals that this difference did not reach statistical significance. There was no statistical difference between any other of the components measured. The reduction in latency of the N35 and P50 components in both eyes following drug administration was again noticeable.

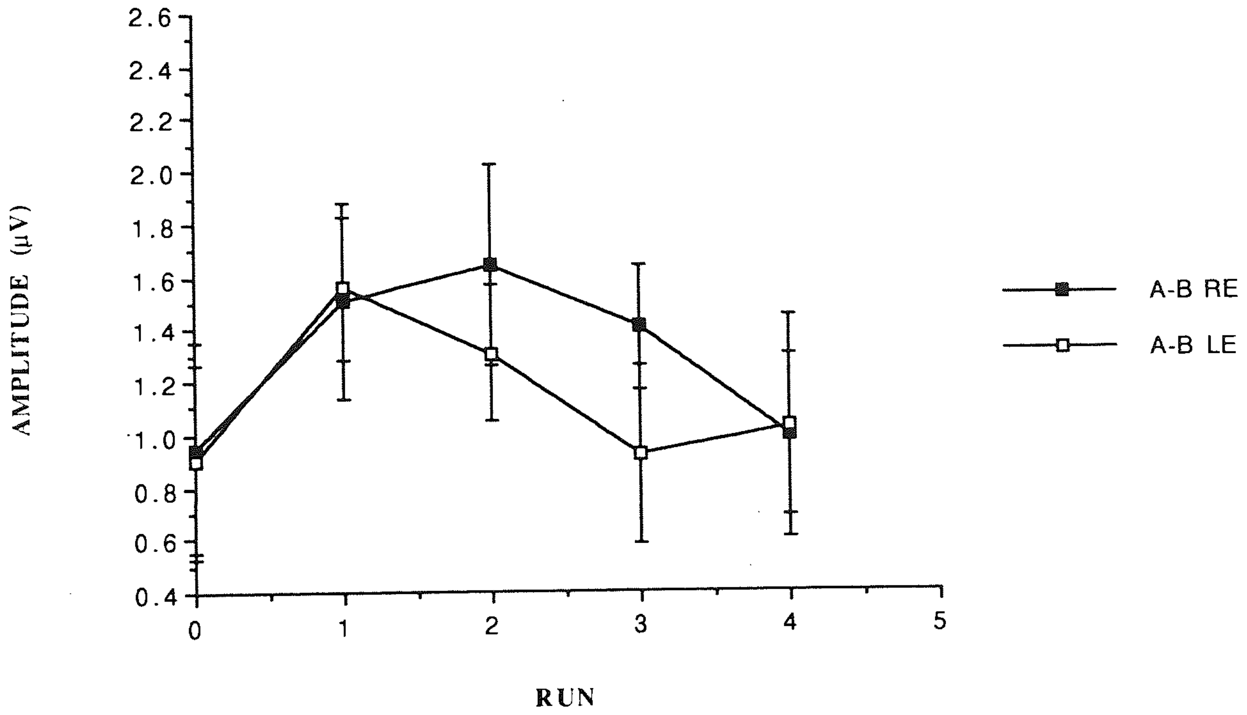
(iii) Pattern reversal ERG to a 2°22' check counterphasing at 6Hz and at 30% contrast.

This stimulus presented as a steady state ERG that resembled a sinusoid, although it was rather arhythmical. As mentioned previously we were unable to assess the % power of the second harmonic in the waveform due to this arhythmic morphology, even though it was obvious that 6 peaks were present within the 500ms time window. Therefore the peak to peak amplitude of the first component (a-b) was measured. The results from both eyes of each individual are given in tables 5.15 of appendix 5. The group mean results are presented in table 10.7, and are illustrated graphically in figure 10.11, the error bars represent the standard error of the mean.

Table 10.7

	a-b (μV)	
	RE	LE
CONT	0.95 ±0.79	0.90 ± 0.74
RUN 1	1.51 ± 0.74	1.56 ±0.53
RUN 2	1.65 ± 0.75	1.31 ± 0.52
RUN 3	1.41 ± 0.41	0.92 ± 0.58
RUN 4	1.00 ± 0.53	1.03 ± 0.74

Figure 10.11



The graph shows that any change in amplitude falls within 1μV. A t test, not surprisingly, confirmed no statistical difference between the left and right eye at any time interval.

(iv) Photopic ERG.

The latency of the a and b wave components were measured, in addition to the a-b amplitude. The results from both eyes of each individual are given in tables 5.16 - 5.18 of appendix 5. The group mean results are presented in table 10.8, and are illustrated graphically in figures 10.12 - 10.14, the error bars represent the standard error of the mean.

Table 10.8

	a (MS)		b (MS)		a-b (μV)	
	RE	LE	RE	LE	RE	LE
CONT	14.55 ±0.64	14.95 ± 0.68	29.45 ± 3.92	29.40 ± 2.39	88.22 ± 48.32	83.21 ± 53.55
RUN 1	13.90 ± 0.38	14.30 ± 0.20	26.80 ± 1.35	26.70 ± 1.28	152.93 ± 26.02	117.90 ± 23.18
RUN 2	14.13 ± 0.70	13.53 ± 1.35	26.70 ± 1.00	27.00 ± 1.33	126.07 ± 41.71	113.96 ± 29.89
RUN 3	13.87 ± 0.23	14.00 ± 0.00	27.60 ± 0.40	27.60 ± 1.83	161.06 ± 47.08	128.86 ± 48.38
RUN 4	14.00 ± 0.80	14.00 ± 0.40	27.60 ± 1.44	27.73 ± 1.62	141.61 ± 55.19	122.90 ± 49.65

It can be seen from the graphs that there is very little difference in latency of the a or b waves between the two eyes - they were not found to be statistically different using the t test. The reduction in latency of the b wave in both eyes following drug administration is still present. The amplitude of the a-b component is reduced in the left eye in all post drug runs - although the difference is not statistically different.

Figure 10.12

PHOTOPIC ERG a WAVE LATENCY, BEFORE (RUN 0) AND FOLLOWING TOPICAL ADMINISTRATION OF HYOSCINE HYDROBROMIDE

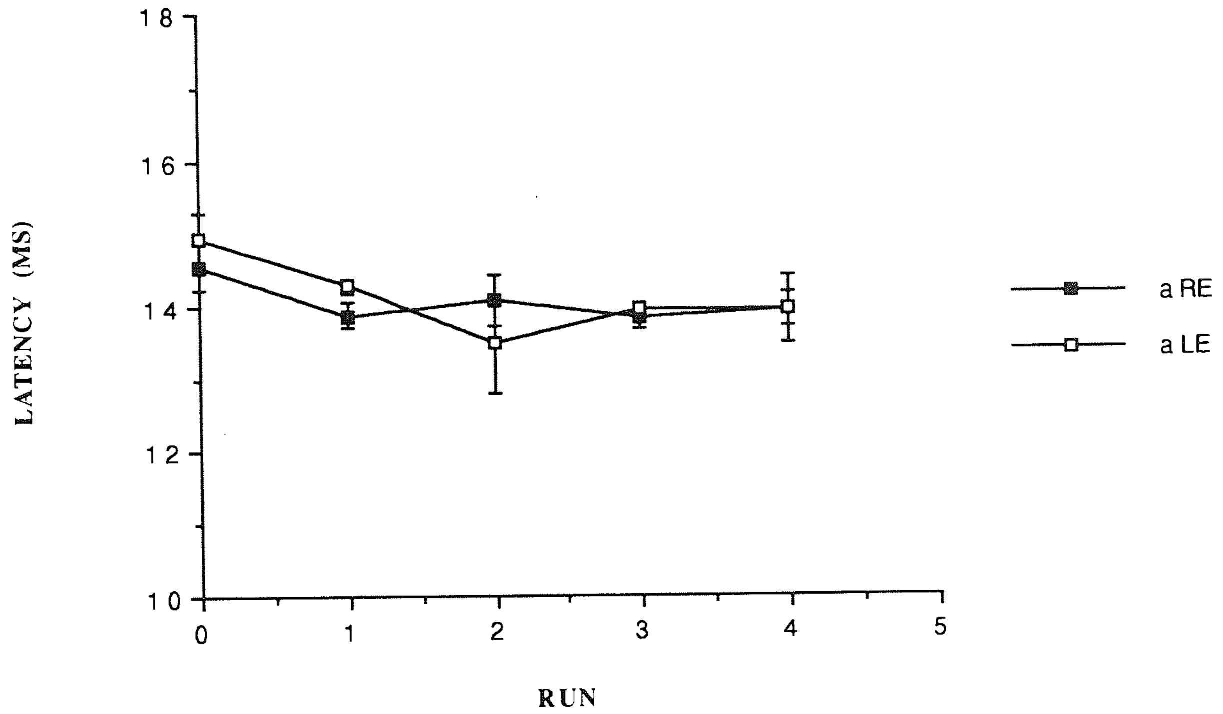


Figure 10.13

PHOTOPIC ERG b WAVE LATENCY, BEFORE (RUN 0) AND FOLLOWING TOPICAL ADMINISTRATION OF HYOSCINE HYDROBROMIDE

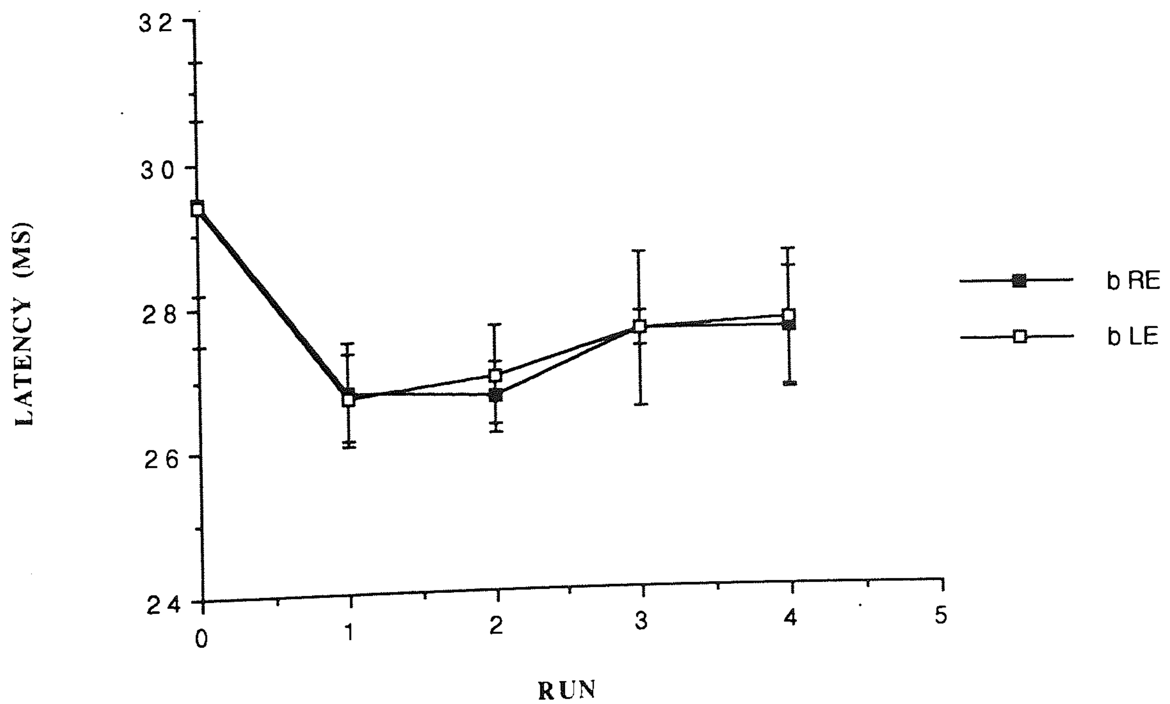
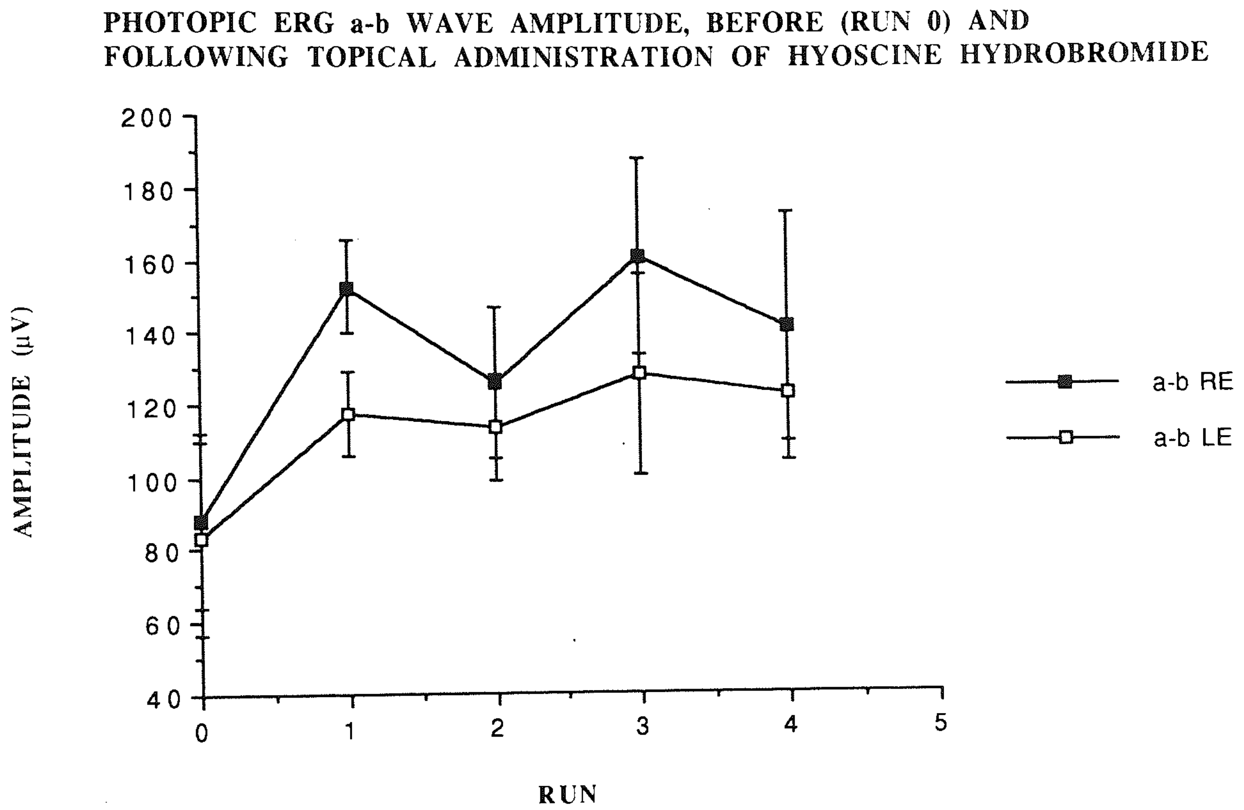


Figure 10.14



(v). Scotopic ERG.

The latency of the a and b wave components were measured, in addition to the a-b amplitude. The results from both eyes of each individual are given in tables 5.19 - 5.21 of appendix 5. The group mean results are presented in table 10.9, and are illustrated graphically in figures 10.15 - 10.17, the error bars represent the standard error of the mean.

Table 10.9

	a (MS)		b (MS)		a-b (μV)	
	RE	LE	RE	LE	RE	LE
CONT	21.40 ± 0.69	22.00 ± 1.13	45.90 ± 6.84	45.10 ± 5.70	260.15 ± 48.92	225.87 ± 100.62
RUN 1	21.30 ± 0.60	22.00 ± 1.31	40.52 ± 2.52	42.50 ± 6.12	344.23 ± 35.94	252.53 ± 107.23
RUN 2	22.00 ± 1.39	22.00 ± 1.08	41.60 ± 2.08	41.00 ± 1.16	293.55 ± 50.34	271.87 ± 73.58
RUN 3	21.33 ± 0.46	21.47 ± 0.61	46.40 ± 5.92	42.80 ± 2.43	374.99 ± 73.01	286.73 ± 129.94
RUN 4	21.47 ± 0.46	21.73 ± 0.23	42.93 ± 5.83	39.73 ± 0.46	324.99 ± 68.25	271.55 ± 106.07

Again there was no statistical difference in latency of the a or b wave between the right and left eye at any time interval. There appears to be marked reduction of the a-b wave amplitude for the left eye that was present even before drug administration - this is largely due to subject RD (see table 5.21 of appendix 5). However due to the large standard deviation this difference did not reach statistical difference. If one considers the other subjects, it can be seen that in other, but not all post drug situations the amplitude of a-b component is slightly reduced in the left compared to right eye. It is possible that this could be to the continued pupil reactions of the right eye resulting in an increased pupil size during dark adaption. Although if this were the only reason one would have expected the amplitude of the photopic ERG to be reduced in the right eye compared to the left - which does not seem to be the case.

Figure 10.15

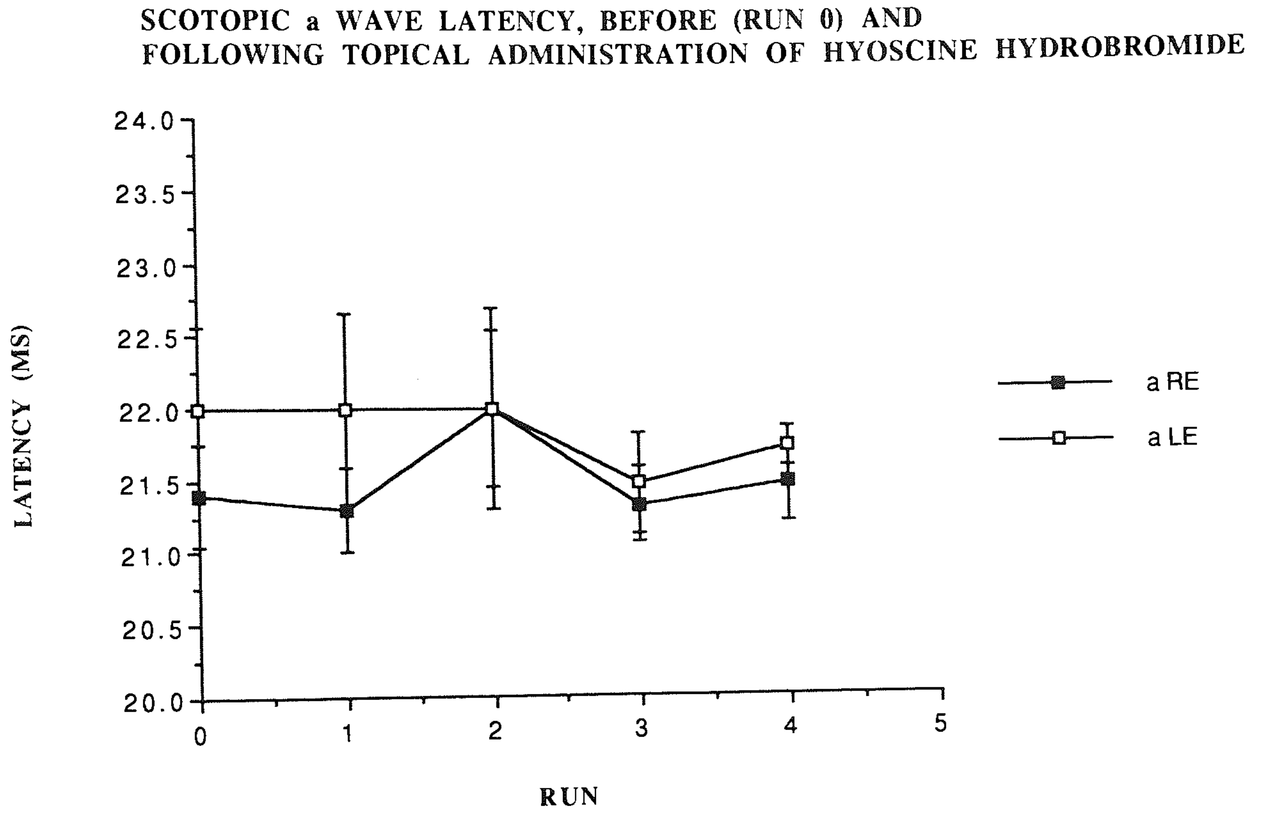


Figure 10.16

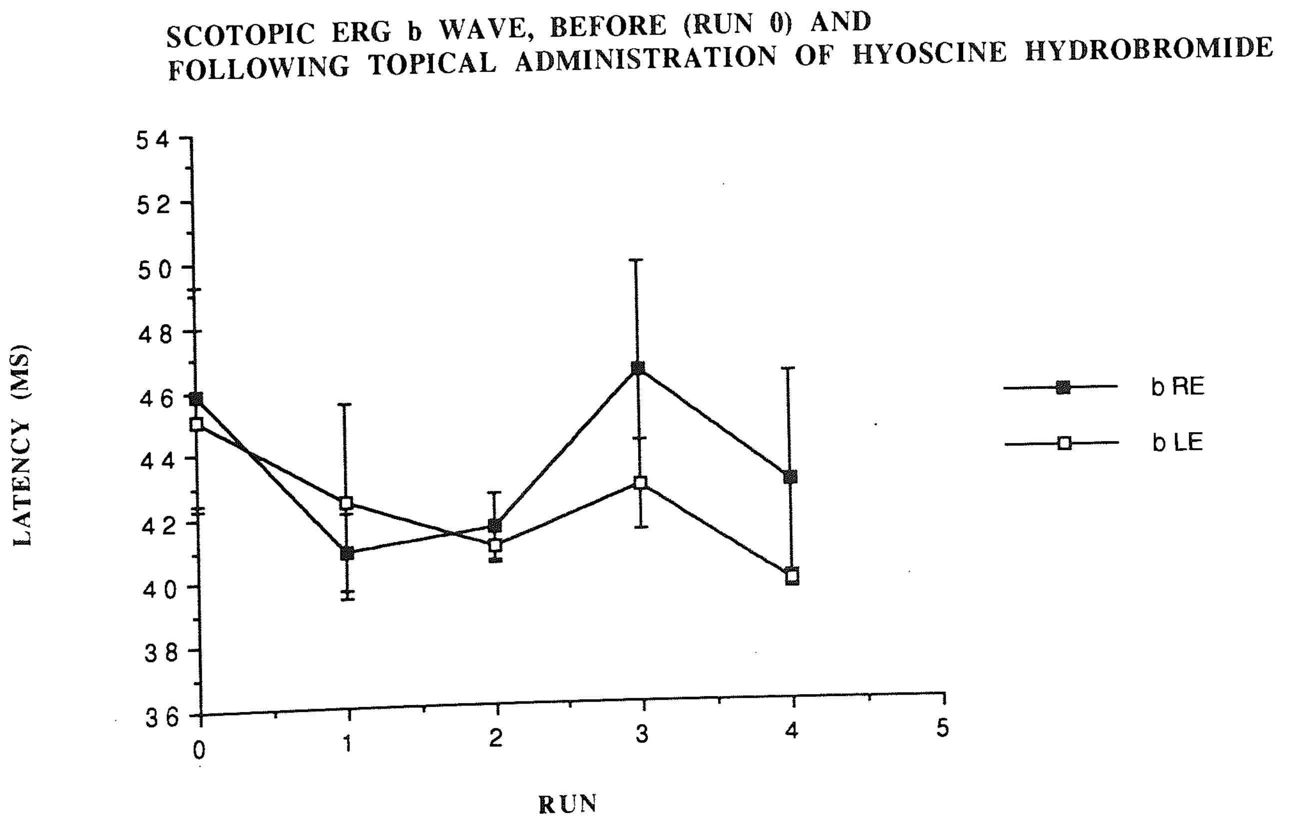
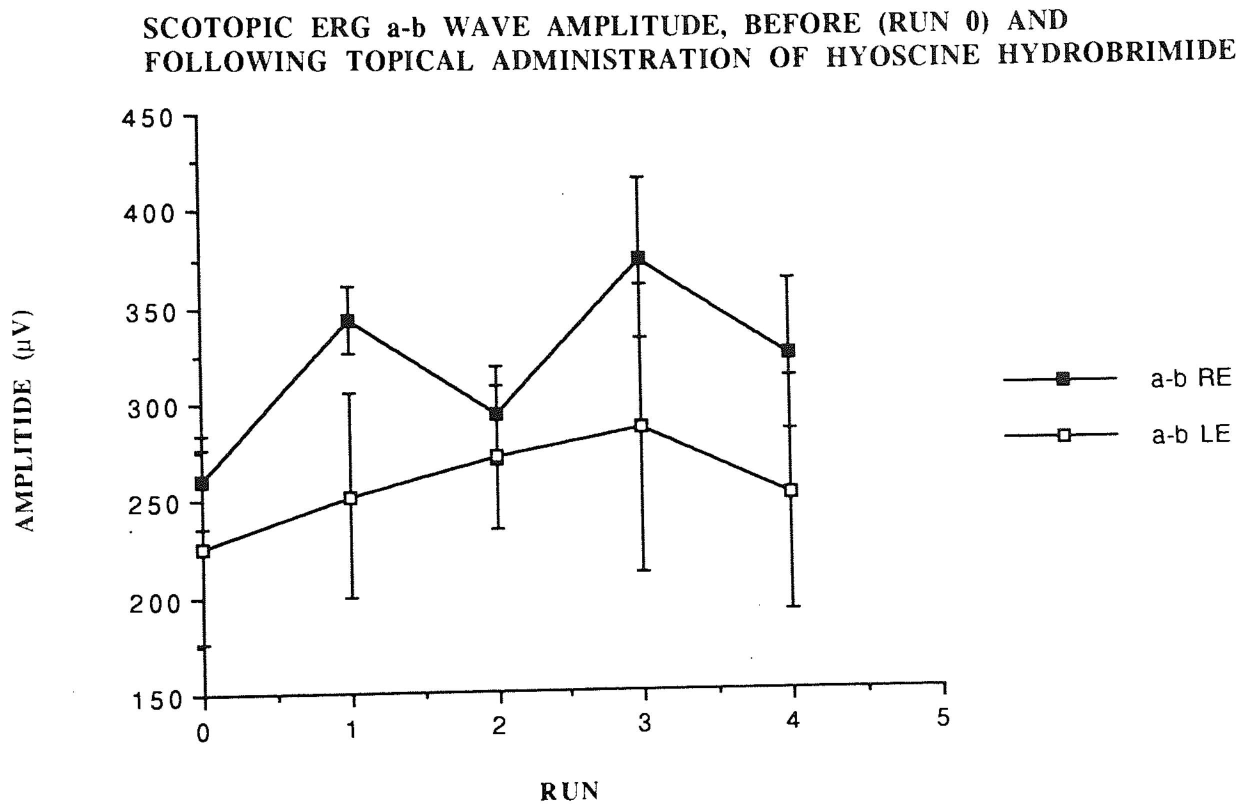


Figure 10.17



10.3.3. DISCUSSION.

These results demonstrate that the administration of topical hyoscine hydrobromide has little or no effect on the latency of the ERG compared to the administration of phenylephrine - no matter what type of stimulus is used. Thus the reduction in latency observed is more likely to be due to the increased pupil diameter. However, although not statistically significantly different, hyoscine hydrobromide administration seemed to reduce the amplitude of the photopic and scotopic ERG. Subject RD was the major contributor to this difference, and further experimentation with an increased number of subjects is necessary before this can be confirmed.

Thus we still cannot be assured that hyoscine hydrobromide reaches the retina following topical instillation. It was therefore decided to repeat the experiments performed by Morrison and Reilly, with the addition of a more critical measure of contrast sensitivity.

10.4. EXPERIMENT 3.

THE MEASUREMENT OF CONTRAST SENSITIVITY IN SUBJECTS FOLLOWING TOPICAL ADMINISTRATION OF HYOSCINE HYDROBROMIDE.

10.4.1. METHOD.

Subjects.

3 subjects were selected from student volunteers. Contact lenses were avoided and subjects were excluded if they had a history of ocular pathology, migraine or epilepsy, or if they were taking any significant medication. Subjects were selected with grade A of the standardised iris pigmentation classification system (Seddon *et al*, 1990), as the effectiveness of the hyoscine drops is greatly reduced in highly pigmented eyes. This restriction leads to more rapid and standardised responses to the low concentration of the drug, with more rapid recovery.

Stimuli.

Stimulus parameters were chosen such that they were comparable to those used by Morrison and Reilly in which a significant reduction in contrast sensitivity was observed. In addition 2 further stimulus parameters were used which provided improved magnocellular stimulation.

(i) 5.0 cpd horizontal grating counterphasing at 5.5 Hz presented within a 12°41' X 16°42' field. This stimulus was used because it was comparable to one used by Morrison and Reilly that resulted in a reduced contrast sensitivity following topical administration of hyoscine hydrobromide.

(ii). 5.0 cpd stationary horizontal grating presented within a 12°41' X 16°42' field. This stimulus was used to act as a control as it provides no magnocellular pathway isolation.

(iii). 0.1 cpd horizontal grating drifting at 10Hz presented within a 6°25' X 8°32' field. This low spatial frequency stimulus, drifting at a high temporal frequency provides improved magnocellular stimulation.

(iv) 1.0 cpd horizontal grating drifting at 10Hz presented within a 6°25' X 8°32' field. This stimulus, like (iii), provides improved magnocellular stimulation. In addition its spatial frequency is comparable to that used by Morrison and Reilly.

Each stimulus is presented within a temporal envelope consisting of a 100ms rise and fall time, the grating remaining at maximum contrast for 800ms.

Instrumentation.

The grating patterns were generated on the VSG 2/1 grating generator described above (10.2.1).

Procedure.

Two criteria were used to measure contrast sensitivity (CS), detection and direction discrimination. For the criteria of detection the stimulus (using stimuli i and ii) was presented on one of two sequential trials (chosen randomly) separated in time by 500ms. The non stimulus trial was a blank field of the same mean luminance as the

stimulus trial. For the criteria of direction discrimination the stimulus (using stimuli iii and iv) was presented on each trial and the observer was required to detect direction of motion, randomly chosen to be up or down. For each criteria each trial was accompanied by an audible tone.

Contrast threshold detection with a staircase procedure was used, converging on the 79% threshold, preceded by a manual adjustment of contrast to near threshold. Each step of the staircase was 1db and the last 6 reversals were averaged to estimate the mean. Each datum is the mean of 3 staircase runs.

Precise refractive correction was determined and maintained for all visual tasks The colour vision of subject SA was checked using ishihara pseudoisochromatic plates. The filtration angle was checked using Van Heriks method and only grades 3 or 4 (20-45°) were accepted. Since there is a very remote possibility of an uncontrolled rise in intraocular pressure (IOP) following the use of mydriatic drops, the pressure was measured at the beginning of the experiment using the Pulsair non-contact tonometer, subjects with more than 20mm Hg were excluded. IOP was continuously monitored throughout the experiment. Pupil diameter and amplitude of accommodation were recorded and used to monitor drug activity. The VA was recorded and an acuity of 6/6 or better in both eyes was required for inclusion. Fixed artificial pupils of 4mm diameter were adjusted before the right eye in an optometric trial frame while the left eye was occluded, and the subjects were then trained to maintain exact central fixation. Contrast sensitivity to the four stimuli were then measured monocularly.

Following this initial control measurement, one drop of 0.4% Benoxinate hydrochloride was instilled in each eye. This was done to increase the absorption of the hyoscine hydrobromide across the cornea. One minute later 2, 20μl drops of 0.125% hyoscine hydrobromide were instilled in the right eye separated by 5 mins, using a micropipette, whilst occluding the puncta to prevent any systemic absorption of the drug through the nasal mucosa. The concentration of hyoscine hydrobromide used was stronger than that used by Morrison and Reilly.

Amplitude of accommodation, refractive error, pupil diameter and IOP were again measured. Contrast sensitivity to the four stimuli were then repeated. This routine was continued until 2 post-drug runs had been completed. Each run took approximately 30 minutes, and the stimuli were presented in the same order for each run, so that each stimulus was presented at equal time intervals.

10.4.2. RESULTS.

Grating detection.

(i) Contrast sensitivity to a 5.0 cpd grating counterphasing at 5.5Hz.

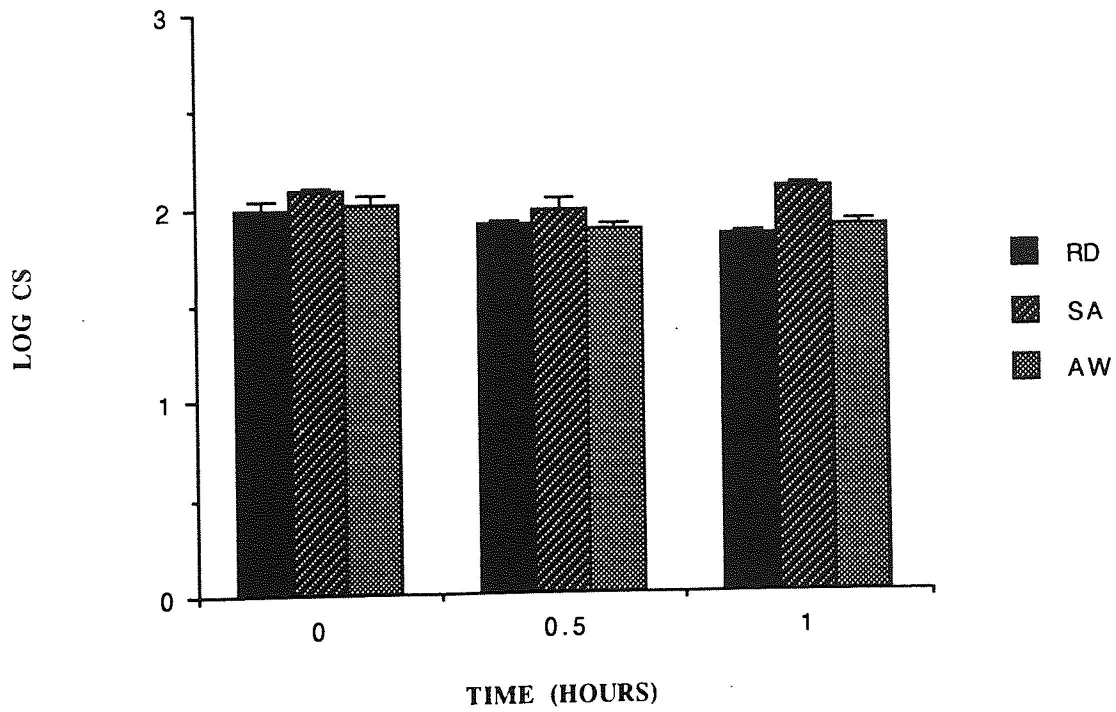
The results for each individual are given in table 10.10. This table shows the mean contrast sensitivity (CS) (which is the inverse of the % contrast threshold), and the standard deviation. The log contrast sensitivity is also shown (log CS).The log contrast sensitivity is used for all statistical analysis, as CS does not form a normal distribution.

Table 10.10.

SUBJECT	CONTROL		RUN 1		RUN 2	
	CS	LOG	CS	LOG	CS	LOG
RD	100.15 ± 15.51	1.997 ± 0.067	83.77 ± 6.55	1.922 ± 0.033	72.74 ± 4.92	1.861 ± 0.030
SA	125.23 ± 7.40	2.097 ± 0.025	100.84 ± 20. 88	1.997 ± 0.092	127.77 ± 9.99	2.106 ± 0.034
AW	106.94 ± 18.53	2.025 ± 0.072	79.34 ± 10.07	1.897 ± 0.054	81.46 ± 10.92	1.908 ± 0.059

These results are presented graphically in figure 10.18, the error bars represent the standard error of the mean. A students t test was used to compare the contrast sensitivity measured during the two post-drug runs to the control measurement for each individual. Although the graph indicates a small reduction in contrast sensitivity following drug administration in subjects RD and AW, the change did not reach statistical significance. No statistically significant difference was found for any subject.

Figure 10.18



(ii) Contrast sensitivity to a stationary 5.0 cpd grating.

The results for each individual are given in table 10.11. This table shows the mean contrast sensitivity (CS), and the standard deviation. The log contrast sensitivity is also shown (log CS).

Table 10.11.

SUBJECT	CONTROL		RUN 1		RUN 2	
	CS	LOG	CS	LOG	CS	LOG
RD	139.44	2.142	136.45	2.133	170.67	2.230
	± 18.73	± 0.060	± 14.35	± 0.047	± 17.93	± 0.046
SA	203.22	2.308	157.15	2.194	164.49	2.214
	± 9.87	± 0.021	± 18.13	± 0.049	± 20.89	± 0.054
AW	154.81	2.189	105.39	2.014	92.26	1.962
	± 12.15	± 0.035	± 25.70	± 0.109	± 11.02	± 0.055

These results are presented graphically in figure 10.19, the error bars represent the standard error of the mean. A students t test was used to compare the contrast sensitivity measured during the two post-drug runs to the control measurement for each individual. Although the graph indicates a small reduction in contrast sensitivity following drug administration in subject AW, the change did not reach statistical significance. No statistically significant difference was found for any subject.

Grating direction discrimination.

(iii) Contrast sensitivity to a 0.1 cpd grating drifting at 10Hz.

The results for each individual are given in table 10.12. This table shows the mean contrast sensitivity (CS) and the standard deviation. The log contrast sensitivity is also shown (log CS).

Figure 10.19

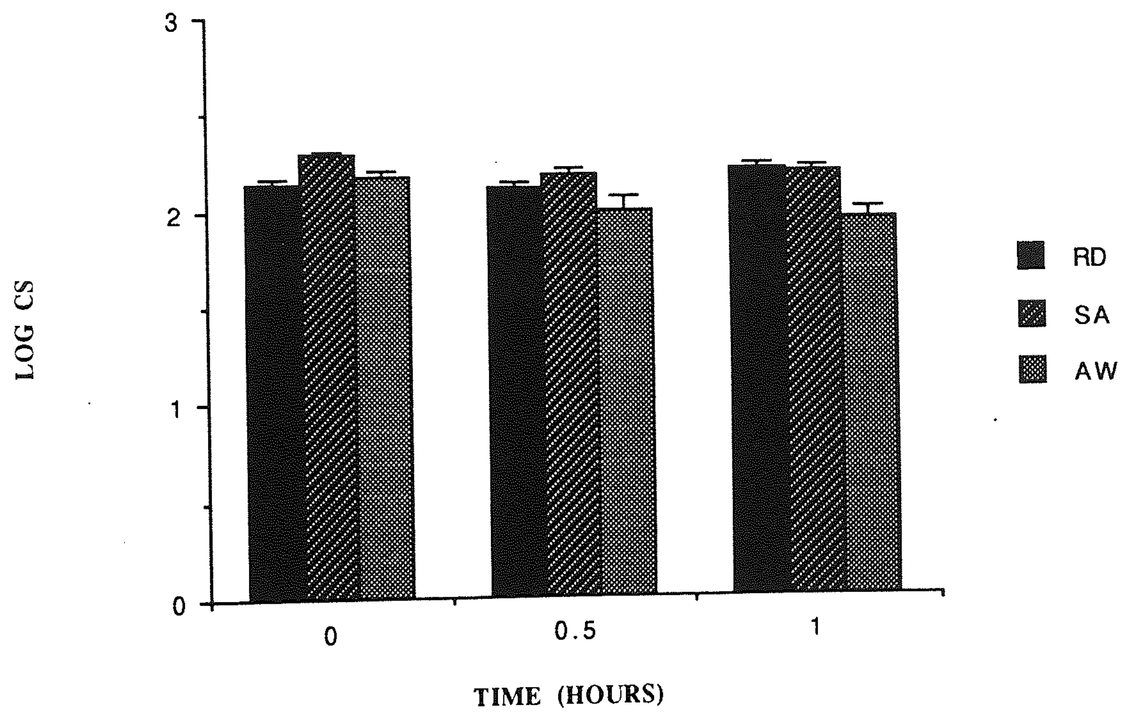


Table 10.12.

SUBJECT	CONTROL		RUN 1		RUN 2	
	CS	LOG	CS	LOG	CS	LOG
RD	160.58	2.206	134.44	2.128	149.98	2.175
	± 4.68	± 0.013	± 9.57	± 0.031	± 12.82	± 0.037
SA	231.80	2.363	246.90	2.392	300.34	2.475
	± 31.11	± 0.057	± 18.94	± 0.034	± 40.25	± 0.058
AW	136.93	2.136	129.23	2.106	143.24	2.155
	± 8.49	± 0.026	± 22.95	± 0.077	± 8.47	± 0.025

These results are presented graphically in figure 10.20, the error bars represent the standard error of the mean. A students t test was used to compare the contrast sensitivity measured during the two post-drug runs to the control measurement for each individual. Although the graph indicates a small increase in contrast sensitivity following drug administration in subject SA, the change did not reach statistical significance. No statistically significant difference was found for any subject.

(iv) Contrast sensitivity to a 1.0 cpd grating drifting at 10Hz.

The results for each individual are given in table 10.13. This table shows the mean contrast sensitivity (CS) and the standard deviation. The log contrast sensitivity is also shown (log CS).

These results are presented graphically in figure 10.21, the error bars represent the standard error of the mean. A students t test was used to compare the contrast sensitivity measured during the two post-drug runs to the control measurement for each individual. No statistically significant difference in contrast sensitivity was found for any subject.

Figure 10.20

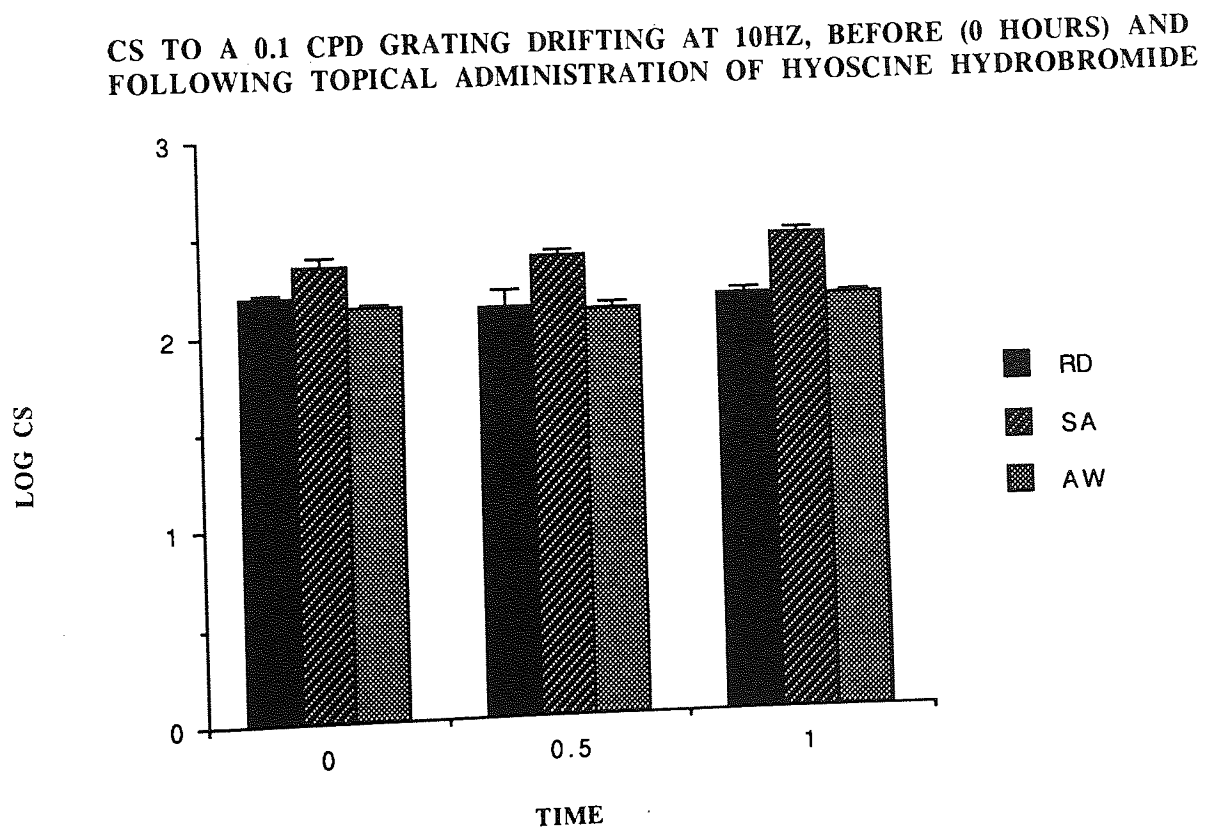


Table 10.13.

SUBJECT	CONTROL CS	CONTROL LOG	RUN 1 CS	RUN 1 LOG	RUN 2 CS	RUN 2 LOG
RD	271.87	2.433	252.85	2.403	264.16	2.419
	± 23.23	± 0.036	± 5.57	± 0.009	± 34.86	± 0.055
SA	441.03	2.645	373.50	2.572	403.58	2.606
	± 12.69	± 0.013	± 8.33	± 0.009	± 22.59	± 0.024
AW	242.12	2.383	264.43	2.417	242.00	2.383
	± 16.52	± 0.030	± 46.99	± 0.083	± 13.93	± 0.025

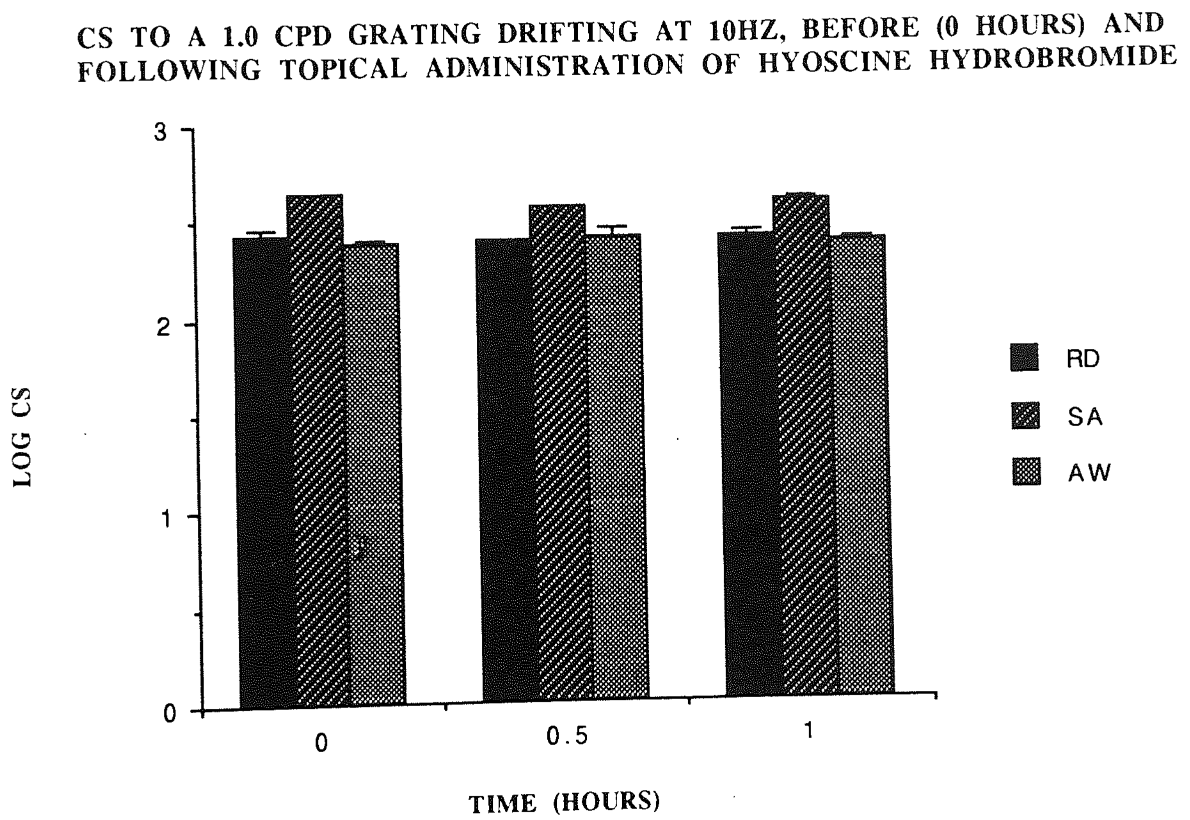
10.4.3. DISCUSSION.

From these results it can be seen that we were unable to replicate the results found by Morrison and Reilly. Topical administration of hyoscine hydrobromide had no effect on contrast sensitivity in either movement discrimination tasks or contrast detection tasks. The effects noted by the above authors may have been caused by the increased pupil size as there is no indication that they used an artificial pupil to compensate for the mydriasis produced by the drug.

GENERAL DISCUSSION.

The above experiments reveal that the topical administration of hyoscine hydrobromide has no effect on the latency or amplitude of the VEP, has no effect on the latency of the ERG but may result in a small reduction in amplitude of the photopic and scotopic ERG, and has no effect on contrast sensitivity (which contradicts the findings of Morrison and Reilly, 1987). This suggests that either the drug is unable to pass beyond the iris to reach the retina, or that it has no significant effect on retinal function.

Figure 10.21



If one considers the profound effect that systemic hyoscine hydrobromide has on the P2 component of the flash VEP, and yet it has no effect on the ERG (as illustrated in chapter 8) it seems reasonable to assume that the above findings are more likely to be due to topical hyoscine hydrobromide having no significant effect on retinal function. Further evidence to support this, is the fact that contrast sensitivity measurements on patients with Alzheimer's disease have not been found to be significantly different from age matched normal controls (Schlotterer *et al*, 1983; Wright, 1985; Wright and Richardson, 1986; Wright *et al*, 1984, 1986). If the delayed P2 component of the flash VEP were due to depleted retinal acetylcholine, it would mean that this neurotransmitter was of particular significance in the transmission of visual information through the retina. If this were the case, one would expect contrast sensitivity to be likewise affected.

These data therefore support the first hypothesis described in the introduction, suggesting that the VEP delay found in AD and in PD patients taking anticholinergic medication and in young normals following systemic administration of hyoscine hydrobromide is due to a cholinergic deficit in the tectal-association area pathway.

CHAPTER 11.

11. GENERAL DISCUSSION, CONCLUSIONS, AND FUTURE WORK.

11.1. General Discussion and Conclusions.

This project was undertaken in order to use electrophysiology to discover more about the visual pathway, with particular reference to the neurotransmitters acetylcholine and dopamine. To do this, stimuli were designed to preferentially activate magnocellular and parvocellular portions of the visual pathway; and Alzheimer's disease and Parkinson's disease were used to show the effect of a diminution of acetylcholine and dopamine respectively on visual function.

Parallel pathways within the primate visual system are known to exist. From the extensive literature (reviewed in chapter 4), it is has been stated that approximately 80% of retinal ganglion cells are parvocellular and approximately 10% are magnocellular (Wurtz and Albano, 1980; Stone, 1983; Kaplan *et al*, 1991; Garey *et al*, 1992). It is also known that 20% of post chiasmal fibres leave the main bulk of fibres and continue as the brachium towards the superior colliculus (SC) (Cogan, 1972; Harrington, 1990). The remainder continue to the LGN.

A review of the physiology of the superior colliculus is given in section 4.2.3. of chapter 4 and indicates that the cells of this structure respond to the sudden movement of a stimulus, the sudden appearance of a stimulus within the field or a stimulus suddenly flashed on; and is unresponsive to stimulus detail or colour (Humphrey, 1968; Cyander and Berman, 1971; Schiller and Malpelli, 1977). In addition, anatomical projections from the retina to the SC are mainly from W and Y type cells. These properties of SC cells are characteristic of a magnocellular system. Thus one could hypothesize that as only 10% of ganglion cells are magnocellular and that approximately 20% of post chiasmal fibres pass to the SC which has mainly magnocellular characteristics, that the majority of magnocellular cells are projected by a tectal-association area pathway and only a small proportion of magnocellular cells are projected along the geniculo-cortical route. The parvocellular cells, however, are projected solely along the geniculo-cortical pathway. As shall be discussed, the experimentation described in this thesis provides more evidence to support this hypothesis.

Acetylcholine (ACh) and dopamine (DA) are both neurotransmitters known to be present in the visual pathway. DA is present in the retina where it is associated with interplexiform cells and influences the receptive field sizes of bipolar cells via horizontal cell action. In conditions of low illumination, dopamine is released from interplexiform cells which depresses horizontal cell activity thus reducing surround inhibition, increasing the receptive field size to detect light. Acetylcholine is also present in the retina but is associated with displaced amacrine cells. These cells are involved in the modification and organisation of ganglion cells. Retinal ACh is not thought to have a significant role in the aspect of visual processing but rather it is involved in the rate of spontaneous activity (Puro, 1985). The SC is also thought to receive cholinergic projections (Shute and Lewis, 1967; DeLima and Singer, 1986; Fitzpatrick and Raczowski, 1991), although evidence remains sparce, particularly regarding human SC. This thesis provides further evidence that the tectal-association area pathway has a major cholinergic influence.

It was first of all necessary to design stimuli that would preferentially stimulate magnocellular and parvocellular pathways, while at the same time be robust enough to be used in a clinical environment. Chapter 6 describes how information derived from the extensive literature was used to develop such stimuli. In essence, a stimulus that was constructed from a low spatial frequency (73') achromatic checkerboard of low contrast (30%) and counterphasing at a high temporal frequency should preferentially stimulate the magnocellular pathway; while the stimuli that were constructed from a high spatial frequency (6') achromatic checkerboard of high contrast (85%) or 4cpd horizontal isoluminant red/green grating, and were presented using a pattern onset/offset cosine ramp modulation such that they took 200ms to come on, where they remained on for 500ms and took a further 200ms to go off, should preferentially stimulate the parvocellular pathway. In addition to these stimuli, flash (magnocellular) and pattern reversal stimulation using 60' and 10' checks were also used.

The VEP study on patients with Alzheimer's disease described in chapter 9, showed that the disease resulted in a marked delay of the flash P2 component, confirming other reports (Visser *et al*, 1976; Harding, 1988, 1990; Harding *et al*, 1981, 1984, 1985; Wright *et al*, 1984, 1985, 1986). However, their response to a 72' check counterphasing at 6Hz (a stimulus that also activates magnocellular cells) was not significantly different from normal controls. Similar results were also found in those Parkinsonian patients who were taking anticholinergic medication. AD patients also showed a slight delay to all other stimuli but only the VEP to a 10'

check showed a significant delay of the P100 component. It was thought that this delay was due to the poor concentration ability of some patients as they found it very difficult to maintain their fixation for any length of time.

As mentioned in chapter 10, administration of systemic hyoscine hydrobromide to young normals also resulted in a delayed flash P2 component. However, it was shown in this chapter, that topical administration of this drug did not have the same detrimental effect on the flash VEP; nor did it have any effect on the ERG or on contrast sensitivity (this latter study contradicting the results found by Morrison and Reilly, 1989). In addition chapter 8 shows that anticholinergic medication in PD patients had no effect on their ERG. These data suggest that the delays described above in AD patients and in patients and normals taking anticholinergic drugs are due to a central cholinergic deficit rather than peripheral effects as suggested by Hinton *et al* (1986) and Saddun *et al* (1990).

Evidence has been provided in section 5.1.2.1. of chapter 5 to suggest that the P2 component of the flash VEP is generated in the association areas of the visual cortex. In addition this component has been shown to be preserved in some cortically blind patients suggesting that it must be transmitted along an extrageniculate pathway terminating in the association areas i.e. the tectal-association area pathway. The fact that flash P2 component was affected by an ACh deficit, but that the other magnocellular stimulus was not, supports the hypothesis that the magnocellular pathway can be divided into two portions. The major magnocellular pathway responds to unstructured stimuli, luminance changes and movement and is transmitted along the cholinergic tectal-association area pathway, the minor magnocellular pathway responds to structured stimuli and is transmitted along the non-cholinergic geniculo-cortical pathway.

Visual evoked potential measured in PD patients who were either taking dopaminergic medication only, or who were not taking medication at all showed a flash response that was not significantly different from controls. PD patients taking dopaminergic medication also had normal pattern reversal VEPs to 60' and 10' achromatic checks, and their responses to all other stimuli were not significantly different from controls. Unfortunately only 3 patients were seen who were not taking medication. One of these patients (EG) had a visual acuity of only 6/18 due to early cataracts. This patient presented with a significant delay to the pattern

evoked VEPs as expected from her visual acuity. However the other patient (MI) was seen both in conditions of drug administration and following drug abstention, and her VEPs were the same for both conditions.

These results contradict those of Bodis-Wollner, (1978, 1979, 1984, 1985, 1990) who found that the P100 component of the pattern reversal VEP to a vertical 14' grating was delayed in PD patients and returned to normal following l-dopa administration. However, if one considers the function of DA in the retina, the results found by Bodis-Wollner seem unusual. DA has a general regulatory function, effecting receptive field size and its action influenced by background lighting conditions A DA deficit should result in a decrease in receptive field size such that in photopic conditions visual acuity should not be affected. However, in scotopic conditions where a large receptive field is required to be an effective photodetector, a dopamine deficit should compromise this photodetection. Therefore the VEP to high spatial frequency stimuli should be unaffected by PD in photopic conditions. However, one would suspect that the ERG, particularly the scotopic ERG may be affected.

Chapter 8 presents an ERG study on PD patients. Unfortunately, as explained above, we were unable to see any patients who were not taking dopaminergic medication as an improvement in symptoms following treatment is a form of diagnosis hence most PD patients are prescribed dopaminergic medication very early in the course of their illness. The ERGs in the PD patients seen were not significantly different from controls. This is obviously an area for future work.

11.2. Future Work.

To further investigate the hypothesis that the magnocellular pathway can be divided into two separate portions, a tectal-association area pathway and a geniculo-cortical pathway, the following 3 experiments could be used:

1. As previously mentioned, the SC is involved in the detection of movement. A drifting pattern such as a horizontal grating drifting vertically up the screen of a monitor could be used to evoke VEPs in AD patients or normal subjects taking an anticholinergic drug such as hyoscine hydrobromide. In addition, the stimulus should be presented using an an on and off cosine modulation with a slow ramp time to prevent the resulting VEP from being affected by the sudden appearance of the pattern. One would expect an ACh depletion of have a detrimental effect on VEP

to this type of stimulus. Such a stimulus has already been generated on the VSG grating generator described in this thesis.

2. The SC also responds to circular patches of light between 30' and 1.3° in diameter. A low contrast achromatic circular stimulus of low spatial frequency could also be used to generate VEP in AD patients or in normal subjects taking anticholinergic drugs. The advantage of such a stimulus is that it contains no distinct edges or corners which provide powerful stimuli for the parvocellular pathway.

3. The flash stimulus used to generate the flash VEP is the ultimate low spatial frequency stimulus. It would be interesting to determine the critical spatial frequency at which the VEP switches from being a geniculo-cortical response to being a tectal-association area response. To do this one could use the VSG to generate a low contrast checkerboard pattern counterphasing at 6Hz as before but the spatial frequency could be varied. VEPs could then be measured in AD patients or normals taking anticholinergic drugs to gradually increasing spatial frequencies until a delay in the P2 component is detected. At this point the stimulus has switched to the cholinergic tectal-association area pathway.

The magnocellular superior-colliculus-association area pathway has been largely neglected in the literature. The possibility of two magnocellular pathways is the unique outcome of this thesis and deserves further investigation.

REFERENCES.

Adachi-Usami, E., Hosoda, L., To
temporal frequency characteristics determined by pattern visually evoked cortical potentials. Documenta Ophthalmologica 69: 139-144.

Agid, Y., Javoy-Agid, F. & Ruberg, M. (1987). Biochemistry of neurotransmitters in Parkinson's disease. In: C.D. Marsden & S. Fahn (eds): Movement Disorders 2, Butterworths, pp 166-230.

Aguglia, U., Gambarelli, D., Farnarier, G., Quattrone, A. (1991). Different susceptibilities of the geniculate and extrageniculate visual pathways to human Creutzfeldt-Jacob disease (a combined neurophysiological - neuropathological study). Electroencephalography and Clinical Neurophysiology 78: 413-423.

Åhlin, A., Nyback, H., Junthe, T., Ohman, G., Nordgrem, I. (1991). THA in Alzheimer's disease: Clinical, biochemical and pharmacokinetic findings. In: K. Iqbal, D.R.C. Mc Lachlan, B. Winbald, H.M. Wisniewski (eds). Alzheimer's disease: Basic Mechansims, Diagnosis and Therapeutic Stratergies. John Willey and Sons publishers, pp 621-625.

Åkesson, H.O. (1969). A population study of senile and arteriosclerotic psychoses. Human Heredity 19: 546-566.

Albenese, A., Altavista, M.C., Gozzo, S., Rossi, P., Colosimo, C., Bentivoglio, A.R., Perretta, G., Elia, M., Monaco, V., Macchi, G. (1990). Chronic Administration of MPTP to Marmosets. In M.B. Streifler, A.D. Korczyn, E. Melamed, M.B.H. Youdim (eds). Advances in Neurology Vol 53: Parkinson's disease: Anatomy , Pathology and Therapy. Raven Press, New York,. pp 239-244.

Alhainen, K., Riekkinen, P.Sr., Helkala, E.-L., Partanen, J., Laulcimaa, V., Reinikainen, K., Soininen, H., Airaksinen, M. (1991). The effect of THA on cognitive function and spectral power EEG in Alzheimer's disease: Preliminary results of an open study. In: K. Iqbal, D.R.C. Mc Lachlan, B. Winbald, H.M. Wisniewski (eds). Alzheimer's disease: Basic Mechansims, Diagnosis and Therapeutic Stratergies. John Willey and Sons publishers, pp 611-619.

Alvord, E.D., Forno, L., Kusske, J.A., Kaufmann, R.J., Rhodes, J.S. & Goetowski, C.R. (1974). The pathology of parkinsonism. A comparison of degeneration in cerebral cortex and brainstem. Advances in Neurology 5: 175-193.

Amaducci, L.A., Fratiglioni, L., Rocca, W.A., Fischer, C., Levrea, P., Pedone, D., Bracco, L., Lippi, A., Gandolfo, C., Bino, G., Prencipe, M., Bonatti, M.L., Girotti, F., Carella, F., Tavolato, B., Ferla, S., Lenzi, G.L., Carolei, A., Gambi, A., Grigoletto, F., Schoenberg, B.S. (1986). Risk factors for clinically diagnosed Alzheimer's disease: A case-control study of an Italian population. Neurology 36: 922-931.

Aoki, C. & Kabak, S. (1992). Cholinergic terminals in the cat visual cortex: Ultrastructural basis for interaction with glutamate-immunoreactive neurons and other cells. Visual Neuroscience, 8: 177-191.

Aquilonius, S.M. & Hartvig, P. (1986). A Swedish county with unexpecdedly high utilization of anti-parkinsonian drugs. Acta Neurologica Scandinavica 74: 379-382.

Arai, H., Schmodt, M.L., Lee, V.M-Y, Hurtig, H.I., Greenberg, B.D., Adler, C.H., Trojanowski, M.D. (1992). Epitope analysis of senile plaque components in the hippocampus of patients with Parkinson's disease. Neurology **42**: 1315-1322.

Armstrong, R.A., Meyers, D., Smith, C.U.M. (1988). Further studies on the patterns of senile plaques in senile dementia of the Alzheimer type (SDAT) with a hypothesis on the colonization of the cortex. Neuroscience Research Communications **4**(1): 17-24.

Armstrong, R.A., Meyers, D., Smith, C.U.M. (1990). The relationship between the spatial pattern of senile plaques and neurofibrillary tangles in Alzheimer's disease. Neuroscience Research Communication **7**(2): 105-111.

Armstrong, R.A., Nocklin, D., Sumi, S.M., Alvord, E.C. (1990). Neuropathological changes in the visual cortex in Alzheimer's disease. Neuroscience Research Communications **6**(3): 163-171.

Ariel, M. & Daw, N.W. (1982). Pharmacological analysis of directionally sensitive rabbit retinal ganglion cells. Journal of Physiology **324**: 161-185.

Babel, J., Stangos, N., Korol, S., Spiritus, M. (1977). Ocular electrophysiology. A clinical and experimental study of ERG, EOG and VER. George Thieme Publishers, Stuttgart. pp. 1-172.

Baggio, C., Scarpino, O., Magi, M., Cenacchi, T., Bolcioni, G., Angeleri, F. (1991). New techniques for the visualization of EEG fourier analysis: Comparison of power, coherence, and phase pattern between elderly normals and SDAT patients. In: K. Iqbal, D.R.C. Mc Lachlan, B. Winbald, H.M. Wisniewski (eds). Alzheimer's disease: Basic Mechansims, Diagnosis and Therapeutic Stratergies. John Willey and Sons publishers, pp 69-72.

Bajalan, A.A.A., Wright, C.E., Van der Vliet, V.J. (1986). Changes in the human visual evoked potential caused by anticholinergic agent hyoscine hydrobromide: comparison with results in Alzheimer's disease. Journal of Neurology, Neurosurgery and Psychiatry **49**: 175-182.

Baldessarini, R.J. and Tarsy, D. (1980). Dopamine and the pathophysiology of dyskinesias induced by antipsychotic drugs. Annual Review of Neuroscience **3**:23-41.

Ban, T.A. (1989). Introduction to the diagnosis and treatment of old age dementias. In: E. Ban & H.E. Lehman (eds). Diagnosis and Treatment of Old Age Dementias. Modern Problems of Pharmacopsychiatry Vol 23, Karger, Switzerland, pp 1-9.

Bancher, C., Lassmann, H., Budka, H., Jellinger, K., Grundke-Iqubal, I., Iqubal, K., Wiche, G., Seitelberger, F. & Wisniewski, H.M. (1989). Antigenic profile of Lewy bodies: Immunocytochemical evidence for protein phosphorylation and ubiquitation. Journal of Neuropathology and Experimental Neurology **48**(1): 81-93.

Barbeau, A. & Pourcher, E. (1982): New data on the genetics of genetics of Parkinson's disease. Canadian Journal of Neurological Sciences **9**: 53-60.

Barbeau, A., Roy, M & Boyer, L. (1984). Genetic studies in Parkinson's disease. Advances in Neurology **40**: 333-339.

Barbeau, A., Roy, M. & Langston, W. (1985). Neurological consequence of industrial exposure to 1-methyl-4-phenyl 1236 tetrahydropyridine (letter). Lancet **1**: 747.

Barrett, G., Blumhardt, L., Halliday, A.M., Halliday, E., Kriss, A. (1976). A paradox in the lateralisation of the visual evoked response. Nature **261**: 253-255.

Basse, E.W. (1983). Electroencephalography. In: B. Reisberg (ed). Alzheimer's disease: The free press, Macmillan Inc, New York, Collier Macmillan, London, pp. 231-236.

Bassi, C.J. & Lehmkuhle, S. (1990). Clinical implications of parallel visual pathways. Journal of the American Optometric Association, **61**: 98-110.

Bennett, D.A. & Evans, D.A. (1992). Alzheimer's disease. In: R. Bone (ed). Disease-a-month Vol XXXVIII No 1. Mosby Year Book, pp. 1-65.

Benson, D.F. (1982). The use of positron emission scanning techniques in the diagnosis of Alzheimer's disease. In: S. Corkin et al (eds). Alzheimer's disease: A report of Progress Aging Vol 19. Raven Press, New York, pp 79-82.

Benson, D.F. (1987). Clinical diagnosis of Alzheimer's disease. In: G.G. Genner, & R.J. Wurtman (eds). Advancing Frontiers in Alzheimer's disease Research, pp. 235-248.

Berg, L., Hughes, C.P., Coben, L.A., Danziger, W.L., Martin, R.L., Knesevich, J. (1982). Mild senile dementia of the Alzheimer type: research diagnostic criteria, recruitment, and description of a study population. Journal of Neurology, Neurosurgery, and Psychiatry **45**: 962-968.

Berg, L., Danziger, W.L., Storandt, M., Coben, LA., Gado, M,. Hughes, C.P. Knesevich, J.W., Botwinick, J. (1984). Predictive features in mild senile dementia of the Alzheimer type. Neurology **34**: 563-569.

Berger, B.D. and Stein, L. (1969). An analysis of the learning deficits produced by scopolamine. Psychopharmacology **14**: 271-283.

Bergmann, K., Kay, D.W.K., Forster, E.M., McKenchie, A.A., Roth, M. (1973). A follow-up study of randomly selected community residents to assess the effects of chronic brain syndrome and cerebrovascular disease. In: R. De la Fuente, M.N. Weisman (eds). Psychiatry 2: Proceedings of the V World Congress of Psychiatry, Mexico 1971. Amsterdam Excepts Medica; International Congress Series No 274, pp 856-865.

Bernheimer, H., Birkmayer, W., Hornykiewicz, O., Jellinger, K. & Seitelberger, F. (1973). Brain dopamine and the syndromes of Parkinson and Huntington. Journal of Neurological Sciences **20**: 415-455.

Berninger, T.A. (1986). The pattern electroretinogram and its contamination. Clinical Vision Science **1**: 185-190.

Berninger, T. & Arden, G. (1991). The pattern electroretinogram. In J.R. Hackenliveley & G.B. Arden (eds): Principles and Practice of Clinical Electrophysiology of Vision. Mosby-Year Book, Inc. pp. 291-300.

Berninger, T.A., Arden, G.B., Hogg, C.R., Frumkes, T. (1989). Separable evoked retinal and cortical potentials from each major visual pathway: preliminary results. British Journal of Ophthalmology **73**(7): 502-511.

Bharucha, N.E., Bharucha, E.P., Bharucha, A.E. et al. (1988). Prevalence of Parkinson's disease in the Parsi community of Bombay, India. Archives of Neurology **45**: 1321-1323.

Bharucha, N.E., Stokes, L., Schoenberg, B.S. et al. (1986). A case-control study of twin pairs discordant for Parkinson's disease: A search for an environmental risk factor. Neurology **36**: 284-288.

Bhaskar, P.A., Vanchilingam,E., Bhaskar, E.A., Devaprabhu, A., Ganesan, R.A. (1986). Effect of L-dopa on visual evoked potentials in patients with Parkinson's disease. Neurology **36**: 1119-1121.

Biggins, C.A., Boyd, J.L., Harrop, F.M., Madeley, P., Mindham, R.H.S., Randall, J.I., Spokes, E.G.S. (1992). A controlled, longitudinal study of dementia in Parkinson's disease. Journal fo Neurology, Neurosurgery and Psychiatry **55**: 566-571.

Bigl, V. & Schober, W. (1977). Cholinergic transmission in subcortical and cortical visual centres of rats: no evidence for the involvement of primary optic system. Experimental Brain Research **27**: 211-219.

Birkmayer, G.J.D. & Birkmayer, W. (1989) Stimulation of endogenous L-dopa biosynthesis a new principle for the therapy of Parkinson's disease. Acta Neurologica Scandinavica **126**: 163-187.

Birkmayer, W. & Birkmayer, G.J.D. (1989) Strategy and tactic of modern Parkinson therapy. Acta Neurologica Scandinavica **126**: 63-66.

Bjorklund, A., Gage, F.H., (1988). Grafts of fetal cholinergic neurons in rat models of aging and dementia. In: R.D. Terry (ed). Aging and the Brain. Raven Press, New York, pp 243-257.

Bobak, P., Bodis-Wollner,I., Marx, M.S. (1988). Cortical contrast gsin control in human spatial vision. Journal of Physiology **405**: 421-437.

Bobak, P., Bodis-Wollner, I., Harnois, C., Thornton, J. (1984). VEPs in humans reveal high and low spatial contrast mechanisms. Investigative Ophthalmology and Visual Science **25**: 980-983.

Bodis-Wollner, I. (1985). Pattern evoked potentials in Parkinson's disease are stimulus dependent. Neurology **35**: 1676.

Bodis-Wollner, I. (1988). Altered spatio-temporal contrast vision in Parkinson's disease and MPTP treated monkeys: The role of dopamine. In: Bodis-Wollner & Piccolino (eds): Neurology and Neurobiology Volume 43; Dopaminergic Mechanisms in Vision, Alan R Liss Inc., pp 193-203.

Bodis-Wollner, I. (1990). The visual system in Parkinson's disease. In B. Cohen & I. Bodis-Wollner (eds): Vision and the Brain. Raven Press Ltd., New York. pp 297-316.

Bodis-Wollner, I. & Hendley, C.D. (1979). On the separability of two mechanisms involved in the detection of grating patterns in humans. Journal of Physiology, **291**: 251-263.

Bodis-Wollner, I. & Onofrj, M. (1986). The visual system in Parkinson's disease. In: M.D. Yahr & K.J. Bergmann (eds): Advances in Neurology, **45**: 323-327.

Bodis-Wollner, I. & Yahr, M.D. (1978). Measurements of visual evoked potentials in Parkinson's disease. Brain **101**: 661-671.

Bodis-Wollner, I., Brannan, J.R., Ghilardi, M.F., Mylin, L.H. (1990). The importance of physiology to visual evoked potentials. In J.T. Desmedt (ed): Visual Evoked Potentials. Elsevier Science publishers B.V. pp. 1-24.

Bodis-Wollner, I., Mitra, S., Bobak, P., Guillory, S. (1984). Low frequency distortion in spatio-temporal threshold surface in Parkinson's disease. Investigative Ophthalmology and Visual Science supplement **25**: 313

Bodis-Wollner, I., Marx, M., Mitra, S., Bobak, P., Mylin, L. & Yahr, M. (1987). Visual dysfunction in Parkinson's disease: Loss in spatio-temporal contrast sensitivity. Brain, **110**: 1675-1698.

Bodis-Wollner, I., Mitra, S., Bobak, P. & Guillory, S. (1984). Low frequency distortion in spatio-temporal threshold surface in Parkinson's disease. Investigative Ophthalmology and Visual Science suppl. 25:313.

Boller, F. (1985). Parkinson's disease and Alzheimer's disease - are they associated? In: J.T. Hutton & A.D. Kenny (eds): Senile Dementia of the Alzheimer Type. Neurology and Neurobiology **18**: 119-130.

Boller, F., Mizutani, I., Roessmann, U. & Gambetti, P. (1979) Parkinson's disease, dementia and Alzheimer's disease: Clinicopathological correlations. Annals of Neurology **7**: 329-335

Bowen, D.M., Davison, A.N. (1985). Importance of acetylcholine and tangle-bearing cortical neurons in Alzheimer's disease. Proceedings of the 5th Meeting. Eur. Soc. Neurc. **17**: 275-278.

Boycott, B.B. (1988). Horizontal cells of mammalian retinae. Neuroscience Research supplement 8: 97-111.

Boycott, B.B. & Wassle, H. (1974). The morphological types of ganglion cells of the domestic cat's retina. Journal of Physiology, **240**: 397-419.

Brandt, J., Mellits, E.D,m Rovner, B., Gordon, B., Selness, O.A., Folstein, M.F. (1989). Relation of age of onset and duration of illness to cognitive functioning in Alzheimer's disease. Neuropsychiatry, Neuropsychology and Behavoural Neurology **2**(2): 93-101.

Breakefield, X.O., Orloff, G., Castiglione, C., Coussens, L., Axelrod, F.B., Ullrich, A. (1984). The gene for beta-nerve growth factor is not defective in familial dysautonomia. Proceedings of the National Academy of Sciences of the USA **81**: 4213-4216.

Brecha, N. (1983). Retinal neurotransmitter: Histochemical and biochemical studies. In: P.C. Emson (ed): Chemical neuroanatomy. Raven Press, New York, pp 85-129.

Brindley, G.S. (1970). Physiology of the retina and visual pathway, Edward Arnold Publishers.

Brodmann, K. (1905). Beitraage zur histologischen lokalisation der grosshinrinde. Dritte mittelung: Dierinderfelder der mederen affen. Journal of Psychology and Neurology **4**: 177-226.

Brody, J.A., Hirano, A. & Scott, R.M. (1971). Recent neuopathologic observations in amylotrophic lateral sclerosis and parkinsonism - dementia complex of Guam. Neuology **21**: 528-535.

Brown, P. (1992). Rescuing minds from disease and decay. New Scientist suppl **1**: 1-8.

Brucke, T., Wenger, S., Asenbaum, S., Fertl, E., Pfafflmeyer, N., Muller, C., Podreka, I. & Angelberger, P. (1993). Dopamine D2 Receptor imaging and measurement with SPECT. Advances in Neurology **60**: 494-500.

Budinger, T.F. (1987). New technologies for noninvasive imaging in aging and dementia. In: G.G. Glenner & R.J. Wurtman (eds). Advancing frontiers in Alzheimer's disease research, pp 175-199.

Bulens, C., Meerwaldt, J.D., Van der Wildt, G.J. & Keemink, C.J. (1986). Contrast sensitivity in Parkinson's disease. Neurology, **36**: 1121-1125

Bulens, C., Meerwaldt, J.D., Van der Wildt, G.J. & Keemink, C.J. (1989). Visual contrast sensitivity in drug-induced Parkinsonism. Journal of Neurology, Neurosurgery and Psychiatry, **52**: 341-345.

Bunney, B.S. & Aghajanian, G.K. (1976) Dopaminergic influence in the basal ganglia: Evidence for striatonigral feedback regulation. In: M.D, Yahr (es): The Basal Ganglia, Raven Press, Ltd., pp 249-267.

Burn, D.J., Mark, M.H., Playford, E.D., Maraganore, D.M., Zimmerman, T.R., Duvoisin, R.C. Harding, A.E., Marsden, C.D. & Brooks, D.J. (1992). Parkinson's disease in twins studies with 18F-dopa and positron emission tomography. Neurology **42**: 1894-1900.

Burns, R.S., Allen, G.S. & Tulipan, N.B. (1990). Adrenal medullary tissue transplantation in Parkinson's disease: A review. Advances in Neurology **53**: 571-576.

Busse, E.W. (1983). Electroencephalography. In: B. Reisberg (ed). Alzheimer's disease: The free press, Macmillan Inc, New York, Collier Macmillan, London, pp. 231-236.

Cajal, S.R. (1893). La retine des vertebres. La Cellule **9**: 17-257 (Translation by D. Maguire and R.W. Rodieck. In: The vertebrate Retina. Freeman, San Francisco, 1973).

Cajal, S.R. (1911). Histologie du systeme nerveux de l'homme et des vertebres vol II. Maloine, Paris (Reimpress Instituto Cajal, CSIC 1955, Madrid).

Carpenter, M.B. (1976). Anatomical organization of the corpus striatum and related nuclei. In M.D. Yahr (ed): The Basal Ganglia. Raven Press, Ltd., pp 1-36.

Calne, D.B. (1989). Is Parkinson's disease one disease? Journal of Neurology, Neurosurgery, Psychiatry (suppl 4): 18-21.

Calne, D.B., Duvoisin, R.C. & Mc Geer, E. (1984). Speculations on the etiology of Parkinson's disease. Advances in Neurology **40**: 353-360.

Calne, D.B. & Eldad, M. (1986). Chairmen for session on Movement Disorders ll. Neurology **36** (suppl): 215-218.

Calne, D.B. & Langston, T.W. (1983). Aetiology of Parkinson's disease. Lancet 2: 1457-1459.

Calne, D.B. & Snow, B.J. (1993). PET imaging in parkinsonism. Advances in Neurology **60**: 484-487.

Calzetti, S., Franchi, A., Taratufolo, G., Groppi, E. (1990). Simultaneous VEP and PERG investigations in early Parkinson's Disease. Journal of Neurology, Neurosurgery and Psychiatry **53**: 114-117.

Carlsson, A. (1976). Some aspects of dopamine in the basal ganglia. In: M.D., Yahr (ed): The Basal Gangila. Raven Press, Ltd., New York, pp. 181-189.

Carlsson, A. (1980). Changes in neurotransmitter systems in the aging brain and in Alzheimer's disease. In: B. Reisberg (ed). Alzheimer's disease: The free press, Macmillan Inc, New York, Collier Macmillan, London, pp. 100-106.

Carpenter, M.B. (1976). Anatomical organization of the corpus striatum and related nuclei. In: M.D. Yahr (ed): The Basal Ganglia. Raven Press, Ltd., New York, pp. 1-36.

Casagrande, V.A. & Norton, T.T. (1991). Lateral geniculate nucleus: a review of its physiology and function: A.G. Leventhal (ed): The neural basis of visual function. General ed: J.R. Cronly-Dillon: Vision and visual dysfunction, **4**: 41-84.

Celesia, G.G. & Daly, R.F. (1977). Effect of ageing on visual evoked responses. Archives of Neurology **34**: 403-407.

Celesia, G.G., Bushnell, D., Toleikis, S.C. & Brigell, M.G. (1991). Cortical blindness and residual vision: is the "second" visual system in humans capable of more than rudimentary visual perception. Neurology, **41**: 862-869.

Celesia, G.G., Cone, S., Kaufman, D. (1986). Effects of age and sex on pattern electroretinogram and visual evoked potentials. Electroencephalography and Clinical Neurophysiology **64**: 24.

Celesia, G.G., Villa, A.E.P., Brigell, M., Rubboli, G., Bolcini, G., Fiori, M.G. (1993). An electrophysiological study of visual processing in Alzheimer's disease. Electroencephalography and Clinical Neurophysiology **87**: 97-104.

Chalupa, L.M. (1991). Visual function of the pulvinar. In: A.G. Leventhal (ed): The neural basis of visual function. General ed: J.R. Cronly-Dillon: Vision and Visual dysfunction, **4**: 140-160.

Chatellier, G., Lacomblez, L. (1990). Tacrine (tetrahydroaminoacridine; THA) and lecithin in senile dementia of the Alzheimer type: a multicentre trial. British Medical Journal **300**: 495-499.

Chiueh, C.C., Firnau, G., Burns, R.S., Nahmias, C., Chirakal, R., Kopin, I.J., Garnett, E.S. (1986). Determination and visualization of damage to striatal dopaminergic terminals in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine -induced parkinsonism by [18F]-Labeled 6-Fluro-L-DOPA and positron emission tomography. In M.D. Yahr and K.J. Bergmann (cds). Advances in Neurology Vol **45**. Raven Press. New York. pp: 167-169.

Chouza, C., Aljanti, R., Scaramelli, A., De Medina, O., Caamono, J.L., Buzo, R., Fernandez, A. & Romero, S. (1989). Combination of selegiline and controlled release levodopa in the treatment of fluctuations of clinical disability in parkinsonian patients. Acta Neurologica Scandinavica **80** (126): 127-137.

Chui, H.C., Teng, E.L., Henderson, V.W., Mog, A.C. (1985). Clinical subtypes of dementia of the alzheimer type. Neurology, **35**: 1544-1550.

Cleland, B.G. & Enroth-Cugell, C. (1968). Quantitative aspects of sensitivity and summation in the cat retina. Journal of Physiology, **198**: 17-38.

Cleland, B.G. & Levick, W.R. (1974). Brisk and sluggish concentrically organised ganglion cells in the cat's retina. Journal of Physiology, **240**: 421-456.

Cleland, B.G., Dubin, M.W. & Levick, W.R. (1971). Sustained and transient neurones in the cat's retina and lateral geniculate nucleus. Journal of Physiology, **217**: 473-496.

Cleland, B.G., Levick, W.R. & Wassle, H. (1975). Physiological identification of a morphological class of ganglion cell. Journal of Physiology, **248**: 151-171.

Clement, R.A., Flanagan, J.G., Harding, G.F.A. (1984). Source derivation of the visual evoked response to pattern reversal stimulation. Electroencephalography and Clinical Neurophysiology **62**: 74-76.

Clough, C.G., Bergmann, K.J. & Yahr, M.D. (1984). Cholinergic and dopaminergic mechanisms in Parkinson's disease after long term L-dopa administration. Advances in Neurology **40**: 131-140

Coben, L.A., Danziger, W.L., Hughes, C.P. (1983). Visual evoked potentials in mild senile dementia of Alzheimer type. Electroencephalography and Clinical Neurophysiology **55**: 121-130.

Coben, L.A., Chi, D., Snyder, A.Z., Storandt, M. (1990). Replication of a study of frequency analysis of the resting awake EEG in mild probable Alzheimer's disease. Electroencephalography and Clinical Neurophysiology **75**: 148-154.

Coburn, K.L., Ashford, J.W., Moreno, M.A. (1991). Visual evoked potentials in dementia: Selective delay of flash P2 and probable Alzheimer's disease. Journal of Neuropsychiatry **3** (4): 431-435.

Cogan, D.G. (1972). Neurology of the visual system. Fifth edition. Charles C. Thomas publishers, Springfield, Illinois.

Cohen, G. (1988). Oxygen radicals and Parkinson's disease. In: B. Halliwell (ed): Oxygen Radicals and Tissue Injury. FASEB: 130-135.

Cohen, J., & Dowling, J.E. (1983). The role of the retinal interplexiform cell: Effects of 6-hydroxydopamine on the spatial properties of carp horizontal cells. Brain Research, **264**: 307-310.

Coleman, R.J., Quinn, N.P., Traub, M. & Marsden, C.D. (1990). Nasogastric and intravenous infusions of (+)-4-propyl-9-hydroxynaphthoxazine (PHNO) in Parkinson's disease. Journal of Neurology, Neurosurgery and Psychiatry **53**: 102-105.

Connolly, M. & Van Essen, D. (1984). The representation of the visual field in parvicellular and magnocellular layers of the lateral geniculate nucleus of Macaque monkey. The Journal of Comparative Neurology, **226**: 544-564.

Cooper, I.S. (1969). Involuntary movement disorders. Hoeper, New York.

Copeland, J.R.M., Kelleher, M.J., Kellet, J.M. et al. (1976). A semistructured clinical interview for the assessment of diagnosis and mental state in the elderly. The Geriatric Mental State Schedule I. Development and reliability. Psychol. Med. **6**: 439-449

Corkin, S. (1981). Acetylcholine, aging and Alzheimer's disease: Implications for treatment. Trends in Neuroscience **4**: 287-290.

Cosi, V., Vitelli, E., Gozzoli, A., Corona, M., Ceroni, M., Callieco, R. (1982). Visual evpked potentials in ageing of the brain. In J. Courjon, F. Mauguiere, M. Revol (eds): Clinical Applications of Evoked Potentials in Neurology. New York, Raven Press. pp. 109-115.

Coupland, S.G. (1991). Electrodes for clinical electrophysiological testing. In J.R. Hackenliveley & G.B. Arden (eds): Principles and Practice of Clinical Electrophysiology of Vision. Mosby-Year Book, Inc. pp. 177-182.

Crapper, D.R. (1976). Functional consequences of neurofibrillary degeneration. In: R.D. Terry & S. Gershon (eds). Neurobiology of Aging. Raven Press, New York, pp 405-432.

Crapper, D.R., Dalton, A.J., Skopitz, M., Eng, P., Scott, J.W., Hachinski, V.C. (1975). Alzheimer's degeneration and histopathologic findings. Archives of Neurology **32**: 618-623.

Crapper, McLachlan, D.R., Kruck, T.P., Lukiw, W.J., Krishnan, S.S. (1991). Would decreased aluminium injection reduce the incidence of Alzheimer's disease? Canadian Medical Association Journal **145**(7): 793-804.

Crook, T. (1985). Clinical drug trials in Alzheimer's disease. Annals New York Academy of Science **444**: 428-436.

Crow, T.J. and Grove-White, I.G. (1973). An analysis of the learning deficit following hyoscine administration in man. British Journal of Pharmacology **49**: 322-327.

Csanda, E. & Tarczy, M. (1993). Protective effect of selegiline in the early and late phases of Parkinson's disease. Advances in Neurology **60**: 672-676.

Cummings, J.L. & Benson, D.F. (1983). Mental status examination. In: Dementia: A clinical approach. Butterworths, USA, pp. 15-34.

Cummings, J.L. & Benson, D.F. (1983). Cortical dementias: Alzhemer and Pick disease. In: Dementia: A clinical approach. Butterworths, USA, pp. 35-56.

Curcio, C. & Allen, K.A. (1990). Topography of ganglion cells in human retina. The Journal of Comparative Neurology, **300**: 5-25.

Cyander, M. & Berman, N. (1972). Receptive-field organisation of monkey superior colliculus. Journal of Neurophysiology, **35**: 187-201.

Danesi, M.A., Huxley, P., Murray, N.M.F. Flash and pattern VEP in dementia. Electroencephalography and Clinical Neurophysiology **61**: S196 (abs).

Davis, S.M. & Niemeyer, G. (1986). Dopamine influences the light peak in the perfused mammalian eye. Investigative Ophthalmology and Vision Science, **27**: 330-335.

Davison, A.N. (1986). New concepts in the pathophysiology of Alzheimer's disease. In: M. Briley, A. Kato, M. Weber (eds). New Concepts in Alzheimer's disease. Pierre Fabre monograph series vol 1, pp 1-16.

Davson, H. (1990). Physiology of the eye; 5th edition. Macmillan Press.

Dawson, W.W., Trick, G.L., Litzkow, C.A. (1979). Improved electrode for electroretinography. Investigative Ophthalmology and Visual Science **18** (9): 988-991.

Dawson, W.W., Trick, G.L. Maida, T.M. (1982). Evaluation of the DTL corneal electrode. In G. Niemeyer and Ch. Huber (eds): Documenta Ophthalmologica Proceedings series **3**: 81-88.

De Leon, M.J. & George, A.E. (1983). Computed Tomography studies of Alzheimer's disease. In: B. Reisberg (ed). Alzheimer's disease: The free press, Macmillan Inc, New York, Collier Macmillan, London, pp. 258-266.

De Leon, M.J., George, A.E., Kluger, A., Franssen, E., Ferris, S.H., Wolf, A.P. (1989). PET-deoxyglucose, CT, and neuropathology of age related white matter pathology in normals and Alzheimer's patients. Psychiatry Research **29**: 359-360.

De Lima, A.D. & Singer, W. (1987). The brainstem projection to the lateral geniculate nucleus in the cat: Identification of cholinergic and monoaminergic elements. The Journal of Comparative Neurology, **259**: 92-121.

De Monasterio, F.M. & Gouras, P. (1975). Functional properties of ganglion cells of the rhesus monkey retina. Journal of Physiology, **251**: 167-195.

Derrington, A.M & Lennie, P. (1984). Spatial and temporal contrast sensitivities of neurons in lateral geniculate nucleus of macaque. Journal of Physiology, **357**: 219-240.

Derrington, A.M., Krauskopf, J. & Lennie, P. (1984). Chromatic mechanisms in lateral geniculate of macaque. Journal of Physiology, **357**: 241-265.

Desimone, R., Schein, S.J., Moran, J., & Ungerleider, L.G. (1985). Contour, colour and shape analysis beyond the striate cortex. Vision Research, **25** (3): 441-452.

Dinner, D.S., Luders, H., Hanson, M., Lesger, R.P., Klem, G. (1985). Pattern evoked potentials (PEPs) in Parkinson's disease. Neurology **35**: 610-613.

Domenici, L., Trimarchi, C., Piccolino, M., Fiorentini, A. & Maffei, L. (1985). Dopaminergic drugs improve human visual conrast sensitivity. Human Neurobiology, **4**: 195-197.

Dow, B.M. (1991). Colour vision. In: A.G. Leventhal (ed): The neural basis of visual function. General ed: J.R. Cronly-Dillon: Vision and Visual dysfunction, **4**: 316-338.

Dowling, J.E. (1986). Dopamine: A retinal neuromodulator. Trends in Neuroscience: 236-240.

Dowling, J.E. (1990). Functional and pharmacological organisation of the retina: dopamine, interplexiform cells, and neuromodulation. In: B. Cohen & I. Bodis-Wollner (eds): Vision and the brain. Raven Press, Ltd, New York, pp 1-18.

Drachman, D.A. (1977). Memory and cognitive function in man: does the choliergic system have a specific role? Neurology **27**: 783-790.

Drachman, D.A. (1983). The pharmacological basis for cholinergic investigation of Alzheimer's disease. In: B. Reisberg (ed). Alzheimer's disease: The free press, Macmillan Inc, New York, Collier Macmillan, London, pp. 340-345.

Drachman, D.A., Leavitt, J., Chicago, M.A. (1974). Human memory and the cholinergic system. Archives of Neurology **30**: 113-121.

Drachman, D.A., Lippa, C.F. (1991). The etiology of Alzheimer's disease: The pathogenesis of Dementia. Annals New York Academy of Sciences: 176-186.

Drasdo, N. (1977). The neural representation of visual space. Nature **166** (5602): 554-556.

Drasdo, N. (1980). Cortical potentials evoked by pattern presentation in the foveal region. In C. Barber (ed) Evoked Potentials. MTP Press Ltd. pp. 167-174.

Drasdo, N. (1983). Electrophysiology of the human visual system. Ophthalmic and Physiological Optics **3** (3): 321-329.

Drasdo, N. (1991). Evoked potentials. In: A. Valberg & B.B. Lee (eds): From Pigments to Perception. Plenum press, New York, London. pp 223-226.

Drasdo, N. & Thompson, D.A. (1989). Distortion of spatial selectivity by pattern onset stimulation. Documenta Ophthalmologica **72**: 1-8.

Drasdo, N., Thompson, D.A. (1992). An optical stimulator for studying the topography of electrical and magnetic visual evoked responses. Documenta Ophthalmologica **81**: 219-225.

Drasdo, N., Thompson, D.A., Arden, G.B. (1990). A comparison of pattern ERG amplitudes and nuclear layer thickness in different zones of the retina. Clinical Vision Science 5 (4): 415-420.

Drasdo, N., Thompson, D.A., Thompson, C.M., Edwards, L. (1987). Complementary components and local variation of the pattern electroretinogram. Investigative Ophthalmology and Visual Science **28**: 158-162.

Duffy, F.H., Albert, M.S., McAnulty, G. (1984). Brain electrical activity in patients with presenile and senile dementia of the Alzheimer type. Annals Neurology **16**: 439-448.

Dulaney, E., Stern, M., Hurtig, H. et al. (1990). The epidemiology of Parkinson's disease: A case-control study of young-onset versus old-onset patients. Movement Disorders **5** (suppl 1): 12.

Dustman, R.E., Schenkenberg, T., Lewis, E.G., Beck, E.C. (1977). The cerebral evoked potential: Life-span changes and twin studies. In J.E. Desmedt (ed) Visual Evoked Potentials in Man: New Developments. Clarendon Press, Oxford. pp. 363-377.

Duvoisin, R.C. (1986). Genetics of Parkinson's disease. Advances in Neurology **45**: 307-312

Duvoisin, R.C., Eldridge, R., Williams, A., Nutt, J. & Calne, D. (1981). Twin study of Parkinson's disease. Neurology **31**: 77-80.

Duyckaerts, C., Gaspar, P., Costa, C., Bonnet, A.-M., Hauw, J.-J. (1993). Dementia in Parkinson's disease: Morphometric data. In: H. Narabyashi, T. Nagatsu, N. Yanagisawa and Y. Mizuno (eds). Advances in Neurology **60**, Raven Press Ltd., New York, pp. 447-455.

Dykes, R.W. (1990). Acetylcholine and neuronal plasticity in somatosensory cortex. In: M. Steriade & D. Biesold (eds): Brain cholinergic systems. Oxford Science Publications, pp 294-313.

Dymecki, J. & Freed, W.J. (1990). Effects of transplantation of cross-species substantia nigra into the lateral ventricle of rats with experimentally induced hemiparkinsonism. Advances in Neurology **53**: 551-558.

Edwards, L., Drasdo, N. (1988). Topography of visual evoked potentials (VEPs) elicited by pattern and luminance stimulation in the foveal area. Electroencephalography and Clinical Neurophysiology Scientific 69: 40 (abs).

Ehinger, B. (1983). Functional role of dopamine in the retina. In: N. Osborne & G. Chader (eds): Progress in Retinal Research, Volume 2, Pergamon Press, pp. 213-232.

Ehinger, B. (1983). Connexions between retinal neurons with identified neurotransmitters. Vision Research, **23** (11): 1281-1291.

Ehle, A.L., Stewart, M., Lellelid, N.E., Leventhal, N.A. (1982). Normal checkerboard pattern reversal evoked potentials in parkinsonism. Electroencephalography and Clinical Neurophysiology **54**: 336-338.

Eidelberg, D. (1992). Positron Emission Tomography studies in parkinsonism. Neurologic Clinics **10** (2): 421-433.

Eldridge, R. & Ince, S.E. (1984). The low concordance rate for Parkinson's disease in twins. Neurology **34**: 1354-1356.

Elizan, T.S., Yahr, M.D., Moros, D.A., Mendoza, M.R., Pang, S. & Bodian, C.A. (1990). L-Deprenyl, a MAO-B inhibitor, as an adjunct to conventional L-Dopa therapy in Parkinson's disease: Experience in 200 patients. Advances in Neurology **53**: 431-436.

Ellis, C.J.K. & Ikeda, H. (1988). Evidence for retinal dopamine deficiency in Parkinson's disease. In: Dopaminergic Mechanisms in Vision. Alan R Liss, Inc. pp. 239-251.

Ellis, C.J.K., Allen, T.G.J., Marsden, C.D., Ikeda, H. (1987). Electroretinographic abnormalities in idiopathic Parkinson's disease and the effects of levodopa administration. Clinical Vision Science **1** (4): 347-355.

Engedal, K., Oftedal, S.I., Lilleaas, F., Laake, P. (1989). Electroencephalography, visual evoked potentials, and cerebral CAT-scan as diagnostic tools in senile dementia of Alzheimer type. Aging **1**: 139-145.

Enroth-Cugell, C. & Robson, J.G. (1966). The contrast sensitivity of retinal ganglion cells of the cat. Journal of Physiology **187**: 517-552.

Estable-Puig, R.F., Estable-Puig, J.F., Van Murthy, M.R., Radouco-Thomas, S., Chawla, S., Radouco-Thomas, M., Radouco-Thomas, C. (1986). On the pathogenesis and therapy of dementia of the Alzheimer ype: some neurophathological, biochemical, genetic and pharmacotherapeutic considerations. Progress in Neuro-Psychopharmacology and Biological Psychiatry **10**: 355-390.

Fahn, S. (1989) Adverse effects of levodopa in Parkinson's disease. In: D.B. Calne (ed): Drugs for the Treatment of Parkinson's Disease. Handbook of Experimental Pharmacology **88**: 385-431.

Fahn, D. & Marsden, C.D. (1987). The treatment of dystonia. In:C.D. Marsden & S. Fahn (eds). Movement Disorders 2, Butterworths, pp 359-382.

Farrer, L.A., Meyer, S.R.H., Cupples, L.A., StGeorge-Htslop, P.H., Bird, T.D., Rossor, M.N., Mullan, M.J., Polinski, R., Nee, L., Heston, L., Van Breeckhoven, C., Martin, J-J., Crapper-McLachlan, D., Growden, J.H. (1990). Transmission and age-at-onset patterns in familial Alzheimer's disease. Neurology **40**:395-403.

Fazzini, A., Fleming, J. & Fahn, S. (1990). Cerebrospinal fluid antibodies to coronovirus in patients with Parkinson's disease. Neurology **40** (suppl 1): 169.

Fenton, G.W. (1986). Electrophysiology of Alzheimer's disease. British Medical Bulletin **42** (1): 29-33.

Ferris, S.H. (1983). Neuropeptides in the treatment of Alzheimer's disease. In: B. Reisberg (ed). Alzheimer's disease: The free press, Macmillan Inc, New York, Collier Macmillan, London, pp. 369-373.

Ferris, S.H., De Leon, M.J. (1983). The PET scan in the study of Alzheimer's disease. In: B. Reisberg (ed). Alzheimer's disease: The free press, Macmillan Inc, New York, Collier Macmillan, London, pp. 286-291.

Ferry, G. (1985). Dementia research sheds new light on old brains. New Scientist (Aug): 33-35.

Ferry, G. (1988). Alzheimer's disease: A new age. New Scientist: 44-47.

Ferry, G. (1987). New light on Parkinson's disease. New Scientist: 56-58.

Fiandaca, M.S., Kordower, J.H., Hansen, J.T., *et al.* (1988). Adrenal medullary autografts into the basal ganglia of Cebus monkey: injury-induced regeneration. Experimental Neurology **102**: 76-91.

Fibiger, H.C. (1991). Cholinergic mechanisms in learning, memory and dementia: a review of recent evidence. Trends in Neurosciences **14** (6): 220-223.

Field, P.A. (1983). Psychometric differentiation of the dementias: An overview. In: B. Reisberg (ed). Alzheimer's disease: The free press, Macmillan Inc, New York, Collier Macmillan, London, pp. 201-210.

Filley, C.M., Davis, K.A., Schmitz, S.P., Stears, J.C., Heaton, R.K., Kelly, J., Culig, K.M., Scherzinger, A.L. (1989). Neuropsychological performance and magnetic resonance imaging in Alzheimer's disease and normal aging. Neruophsychiatry, Neuropsychology, and Behavoural Neurology 2 (2): 81-91.

Fischer, P., Berner, P. (1991). Clinical and epidemiological aspects of dementia in the elderly. Journal of Neurology Transmission (suppl) 3 3: 39-48.

Fischer, A., Brandeis, R., Karton, I., Pittel, Z., Dachir, S., Sapir, M., Grunfeld, Y., Levy, A., Heldman, E. (1990). AF102B: Rational, treatment strategy for Alzheimer's disease: Recent advances. In: R.J. Wurtman et al (eds). Advances in Neurology 5 1, Alzheimer's Disease. Raven Press, New York, 257-259.

Fischman. H.K. (1983). Chromosomal factors. In: B. Reisberg (ed). Alzheimer's disease: The free press, Macmillan Inc, New York, Collier Macmillan, London, pp. 161-165.

Fishman, L.J. & Karwoski, C. (1991). In J.R. Hackenliveley & G.B. Arden (eds): Principles and Practice of Clinical Electrophysiology of Vision. Mosby-Year Book, Inc. pp. 112-114.

Fitzpatrick, D. & Raczhowski, D. (1991). The localization of neurotransmitters in the geniculostriate pathway. In: B. Dreher & S.R. Robinson (eds): Neuroanatomy of the visual pathways and their development. General ed: J.R. Cronly-Dillon: Vision and visual dysfunction, 3: 278-301.

Flanagan, J.G. & Harding, G.F.A. (1986). Source derivation of the visually evoked potential. Documenta Ophlalmologica 6 2: 97-105.

Fornadi, F. & Ulm, G. (1990). Early combination with deprenyl: a retrospective analysis. Advances in Neurology 5 3: 437-440.

Forno, L.S. (1986). Lewy body in Parkinson's disease. Advances in Neurology 4 5: 35-43

Forno, L.S. (1991). Neuropathologic features of Parkinson's, Huntington's and Alzheimer's disease. Annals of New York Accademy of Sciences: 5-16.

Fox, C.A. & Rafols, J.A. (1976). The striatal efferents in the globus pallidus and in the substantia nigra. In: M.D., Yahr (ed): The Basal Ganglia. Raven Press, Ltd., New York, pp. 37-55.

Frankel, J.P., Lees, A.J., Kempster, P.A. & Stern, G.M. (1990). Subcutaneous apomorphine in the treatment of Parkinson's disease. Journal of Neurology, Neurosurgery and Psychiatry 5 3: 96-101.

Fratiglioni, L., Grut, M., Forell, Y., Grafstrom, M., Holmen, K., Eriksson, K., Sandman, P., Johnson, P., Forsell, L., Viitanen, M., Winbald, B. (1991). Prevalence of dementia in advanced age: Preliminary results from the Kungshalmen project. In: K. Iqbal, D.R.C. McLachlan, B. Winbald, H.M. Wisniewski (eds). Alzheimer's disease: Basic Mechanisms, Diagnosis and Therapeutic Strategies. John Wiley and Sons Ltd, pp 357-362.

Frederick, J., Rayborn, M., Laties, A., Lam, D. & Hollyfield, J. (1982). Dopaminergic neurons in the human retina. The Journal of Comparative Neurology, 2 1 0: 65-79.

Freed, C.R., Breeze, R.E., Rosenberg, N.L. & Schneck, S.A. (1993). Embryonic dopamine cell implants as a treatment for the second phase of Parkinson's disease: Replacing failed nerve terminals. Advances in Neurology **60**: 721-728.

Friedland, R.P. & Luxenberg, J. (1988). Neuroimaging and dementia. In: W.H. Theodore (ed). Clinical Neuroimaging; Frontiers of Clinical Neuroscience Vol 4. Alan R. Liss, Inc., New York, pp. 139-163.

Frlich, L., Eilles, C., Ihl, R., Maurer, K., Lanczik, M. (1989). Stage-dependent reductions of regional cerebral blood flow measured by HMPAO-SPECT in dementia of Alzheimer type. Psychiatry Research **29**: 347-350.

Fukuda, Y. (1971). Receptive field properties of cat optic nerve fibres with special reference to conduction velocity. Vision Research, **11**: 209-226.

Fukuda, Y. & Stone, J. (1974). Retinal distribution and central projections of Y-, X- and W-cells of the cat's retina. Journal of Neurophysiology, **37**: 749-772.

Fuld, P.A. (1983). Psychometric differentiation of the dementias: an overview.In: B. Reisberg (ed). Alzheimer's disease: The free press, Macmillan Inc, New York, Collier Macmillan, London, pp. 201-210.

Gamzu, E.R., Thal, L.J., Davis, K.L. (1990). Therapeutic trials using taurine and other cholinesterase inhibitors. In: R.J. Wurtman et al (eds). Advances in Neurology **51**, Raven Press, New York, pp 241-245.

Garcia de Yebenes, J., Gervas, J.J., Inglesias, J., Menaj et al. (1982). Biochemical finding in a case of parkinsonism secondary to brain tumor. Annals of Neurology **11**: 313-316.

Garey, L.J., Dreher, B. & Robinson, S.R. (1991). The organisation of the visual thalamus. In: B. Dreher & S.R. Robinson (eds): Neuroanatomy of the visual pathways and their development. General ed: J.R. Cronly-Dillon: Vision and visual dysfunction, **3**: 176-234.

Gawel, M.J., Das, P., Vincent, S., Rose, F. (1981). Visual and auditory evoked responses in patients with Parkinson's disease. Journal of Neurology, Neurosurgery and Psychiatry **44**: 227-232.

Gawel, M., Riopelle, R., Libman, I. & Bouchard, S. (1986). Bromocriptine in the treatment of Parkinson's disease: a double blind study against L-dopa/Carbidopa. Advances in Neurology **45**: 535-538.

Gemmell, H.G., Sharp, P.F., Smith, F.W., Benson, J.A.O., Ebmeier, K.P., Davidson, J., Evans, N.T.S., Roeda, D., Newton, R., Mallard, J.R. (1989). Cerebral blood flow measured by SPECT as a diagnostic tool in the study of dementia. Psychiatry Research **29**: 327-329.

Geraghty, J.J., Jankovic, J., Zetusky, W.J. (1985). Association between essential tremor and Parkinson'd disease. Annals of Neurology **17**: 329-333.

Gerstendbrand, F. & Werner, W.H. (1990). The classification of Parkinson's disease. Advances in Neurology **53**:

Gherardi, R., Roudes, B., Fleury, J., Probst, C et al. (1985). Parkinsonian syndrome and central nervous system lymphoma involving the substantia nigra. Acta Neuropathologica **65**: 338-343.

Ghilardi, M.F., Bodis-Wollner, I., Onofrj, M.C., Marx, M.S., Glover, A.A. (1988). Spatial frequency-dependent abnormalities of the pattern electroretinogram and visual evoked potentials in a parkinsonian monkey model. Brain **111**: 131-149.

Ghilardi, M.F., Marx, M.S., Glover, A., Bodis-Wollner, I., Onofji, M. (1985). Primary and cognitive evoked potentials are differentially affected by dopaminergic deficiency in the monkey. In: Multimodal Applications of Evoked Potentials, Chapter 58, pp.413-419.

Gibb, W.R.G. & Lees, A.J. (1987). The progression of idiopathic Parkinson's disease is not explained by age-related changes: Clinical and pathological comparisons with post encephalitic parkinsonian syndrome. Acta Neuropathology (Berl) **73**: 195-201.

Gibb, W.R.G., Fearnley, J.M. & Lees, A. J. (1990). The anatomy and pigmentation of the human substantia nigra in relation to selective neuronal vulnerability. Advances in Neurology **53**:31-34

Gibb, W.R.G., Narabayashi, H., Yokochi, M., Iizuka, R. & Lees, A.J. (1991). New pathologic observations in jeuvenile onset parkinsonism with dystonia. Neurology **41**: 820-822.

Gibson, P.H. (1978). Light and electron microscopic observations on the relationship between Hirano bodies, neuron and glial perikarya in the human hippocampus. Acta Neuropathology (Berl) **42**: 165-171.

Gilbert, C.D., Ts'o, D.Y. & Wiesel, T.N. (1991). Lateral interactions in visual cortex. In: Valberg & Lee (eds): From Pigments to Perception, Plenum Press, pp 239-247.

Gilchrist, J. (1988). The psychology of vision. In: K. Edwards & R. Llewellyn, (eds): Optometry. Butterworths, pp 25-43.

Gilles, C., De Buyl, O., Genevrois, C., Salma, M., Mendlewicz, J. (1989). Specificity of visual evoked potentials alterations in Alzheimer's disease: comparison with normal aging, depression and scopolamine administration in young healthy volumteers. Acta Neurol. Belg. **89**: 226-227.

Gimenez-Roldan, S., Mateo, D., Escalona-Zapata, J. (1986). Familial Alzheimer's disease presenting as levodopa-responsive Parkinsonism. In: M.D. Yahr and K.J. Bergmann (eds). Advances in Neurology **45**, Raven Press, Ltd., New York, pp. 431-436.

Glacobini E., Becker, R. (1991). New cholinesterase inhibitors for treatment of Alzheimer's disease. In: K. Iqbal, D.R.C. Mc Lachlan, B. Winbald, H.M. Wisniewski (eds). Alzheimer's disease: Basic Mechansims, Diagnosis and Therapeutic Stratergies. John Willey and Sons publishers, pp 627-631..

Glowinski, J. (1990). Recent findings on dopaminergic transmission of the basal ganglia. Advances in Neurology **53**: 67-73.

Godwin-Austin, R.B. & Lowe, J. (1987). The two types of Parkinson's disease. In: Rose, F.C. (ed): Parkinson's disease: Clinical and Experimental Advances, Libbey, London.

Goetz, C.G. & Diederich, N.J. (1992). Dopaminergic agonists in the treatment of Parkinson's disease. Neurologic Clinics **10** (2): 527-540.

Golbe, L.I., Cody, R.A. & Duvoisin, R.C. (1986). Smoking and Parkinson's disease: Search for a dose response relationship. Archives of Neurology **43**: 774-778.

Golbe, L.I., Miller, D.C. & Duvoisin, R.C. (1990). Autosomal dominant Lewy-body Parkinson's disease. Advances in Neurology **53**: 287-292.

Gonce, M. & Delwaide, P.J (1984). Clinical neurophysiological assessment of Parkinson's disease. Advances in Neurology **40**: 365-373.

Gottlob, I., Wundsch, L., Pflug, R. (1985). Possible role of amacrine cells in the generation of the mammalian ERG b-wave. Documenta Ophthalmologica **61**: 55-63.

Gottlob, I., Schneider, E., Heider, W., Skrandies, W. (1987). Alteration of visual evoked potentials and electroretinograms in Parkinson's disease. Electroencephalography and Clinical Neurophysiology **66**: 349-357.

Gouras, P. (1969). Antidromic responses of orthodromically identified ganglion cells in monkey retina. Journal of Physiology, **204**: 407-419.(cited)

Grasse, K.L. & Cynader, M. (1991). The accessory optic system in frontal-eyed animals. In: A.G. Leventhal (ed): The neural basis of visual function. General ed: J.R. Cronly-Dillon: Vision and visual dysfunction, **4**: 111-139.

Graybiel, A.M. (1972). Some extrageniculate visual pathways in the cat. Investigative Ophthalmology, **11**: 322-332.

Graybiel, A.M., Hirsch, E.C. & Agid, Y. (1990). The nigrostriatal system in Parkinson's disease. Advances in Neurology **53**: 17-30.

Greenfield, J.G. & Bosanquet, F.D. (1953). The brain-stem lesions in parkinsonism. Journal of Neurology, Neurosurgery and Psychiatry **16**: 213-226.

Griff, E.R. (1991). Electroretinographic components arising in the distal retina. In J.R. Hackenliveley & G.B. Arden (eds): Principles and Practice of Clinical Electrophysiology of Vision. Mosby-Year Book, Inc. pp. 91-98.

Griffin, A.E. & Burke, W. (1974). The distribution and nerve fibre groups in the optic tracts and LGN of Macaca irus. Proceedings of the Austrian Physiololgy and Pharmacology Society **5**: 74 P

Growdon, J.H. & Corkin, S. (1986). Cognitive impairments in Parkinson's disease. In: M.D. Yahr and K.J. Bergmann (eds). Advances in Neurology **45**, Raven Press, Ltd., New York, pp. 383-392.

Growdon, J.H., Wurtman, R.J. (1988). The future of cholinergic precursor treatment in Alzheimer's disease. In: R. Karzman (ed). Biological Aspects of Alzheimer's Disease; Banbury report 15, Cold Spring Harbor Laboratory, pp 451-459.

Guillery, R.W. (1969). The organisation of the synaptic interconnections in the laminae of the dorsal lateral geniculate nucleus of the cat. Z. Zellforsch, **96**: 1-38

Gurtland, B., Kurianski, J., Sharpe, L., Simon, R., Stiller, P., Birkett, P. (1977). The comprehensive assessment and referral evaluation (CARE). Rationale,

development, and reliability. International Journal of Aging and Human Development **8** (1): 9042.

Hadjiconstantinou, H., Qu, Z., Mariani, A. & Neff, N.H. (1988) MPTP Neurotoxicity and retinal dopaminergic neurons. In: Bodis-Wollner & Piccolino (eds): Neurology and Neurobiology Volume 43; Dopaminergic Mechanisms in Vision, Alan R Liss Inc.: pp 193-203

Hagnell, O., Lanke, J., Rorsman, B., Ojesjo, L. (1981). Does the incidence of age psychosis decrease? A prospective, longitudinal study of a complete population investigated during the 25 year period1947-1972: The Lundby study. Neuropsychobiology **74**: 201-211.

Hagnell, O., Lanke, J., Rorsman, B., Ohman, R., Ojesjo, L. (1983). Current trends in the incidence of senile and multi-infarct dementia. A prospective study of a total population followed over 25 years: The Lundy study. Archives Psychiatry Neurological Science **233**: 423-438.

Hakim, A.M. & Mathieson, G. (1979). Dementia in Parkinson's disease: A neuropathologic study. Neurology **29**: 1209-1214.

Hallanger, A.E., Levey, A.I., Lee, H.J., Rye, D.B. & Wainer, B.H. (1987). The origins of cholinerigic and other subcortical afferents to the thalamus in the rat. Journal of Comparative Neurology, **262**: 105-124.

Halliday, A.M., Barrett, G., Carroll, W.M., Kriss, A. (1982). Problems in defining the normal limits of the visual evoked potential. In J. Courjon, F. Mauguiere, J. Revol (eds): Clinical Applications of Evoked Potentials in Neurology **32**: 1-9; Raven Press, New York.

Halliwell, B. (1989). Oxidants and the central nervous system: some fundamental questions. Acta Neurologica Scandinavica **126** (80): 23-33.

Hardie, R.J. (1989). Problems and unanswered questions concerning levodopa treatment in Parkinson's diesease. Acta Neurologica Scandinavica **126**: 77-82.

Hardie, R.J., Lees, A.J. & Stern, G.M. (1984). On-off fluctuations in Parkinson's disease. Brain **107**: 487-506.

Harding, G.F.A. (1974). The visual evoked response. In M.J., Roper-Hall *et al* (eds): Advances in Ophthalmology **28**: 2-28.

Harding, G.F.A. (1982). The flash visual evoked visual response and its use in ocular conditions. Journal of Electrophysiology Technology **8**: 63-78.

Harding, G.F.A. (1988). Neurophysiology of vision and its clinical application. In. K. Edwards and R. Llewellyn (eds): Optomrtry. Butterworths, pp. 44-60.

Harding, G.F.A. (1990). The visual evoked potential in neuro-ophthalmic disorders. In J.T. Desmedt (ed): Visual Evoked Potentials. Elsevier Science Publishers B.V. pp. 147-167.

Harding, G.F.A. (1991). Visual evoked cortical potentials: Basic recording. In J.R. Hackenliveley & G.B. Arden (eds): Principles and Practice of Clinical Electrophysiology of Vision. Mosby-Year Book, Inc. pp. 399-407.

Harding, G.F.A. (1991). Origin of visiual evoked cortical potentials components. In J.R. Hackenliveley & G.B. Arden (eds): Principles and Practice of Clinical Electrophysiology of Vision. Mosby-Year Book, Inc. pp. 132-144.

Harding, G.F.A. (1991). Technical issues in visual evoked cortical potential recording. In J.R. Hackenliveley & G.B. Arden (eds): Principles and Practice of Clinical Electrophysiology of Vision. Mosby-Year Book, Inc. pp. 435-441.

Harding, G.F.A. & Wright, C.E. (1986). Visual evoked potentials in acute optic neuritis. In R.F. Hess & G.T. Plant (eds): Optic Neuritis. Cambridge University Press. pp 230-254.

Harding, G.F.A., Smith, G.S., Smith, P.E. (1980). The effect of various stimulus parameters on the lateralisation of the visual evoked potential. In C. Barber (ed) Evoked Potentials. Lancaster, MTP Press. pp. 213-218.

Harding, G.F.A., Wright, C.E., Orwin, A. (1985). Primary presenile dementia: The use of the visual evoked potential as a diagnostic indicator. British Journal of Psychiatry **147**: 533-540.

Harding, G.F.A., Doggett, C.E., Orwin, A., Smith, E.J. (1981). Visual evoked potentials in pre-senile dementia. Documenta Ophthalmologica Proceedings Series **27**: 193-201.

Harding, G.F.A., Wright, C.E., Orwin, A., Smith, E.J. (1984). The visual evoked potential in Alzheimer's disease. In R.H. Nodar, C. Barber (eds): Evoked Potentials ll. The Second International Evoked Potentials Symposium. Butterworths. pp. 473-479.

Harrington, D.O., Drake, M.V. (1990). The Visual Fields. Sixth Edition: Text and atlas of clinical perimetry. C.V. Mosby company, USA.

Hartline, H.K. (1938). The response of single optic nerve fibres of the vertebrate eye to illumination of the retina. American Journal of Physiology, **121**: 400-415. (cited)

Hassler, R. (1938). Zur Pathologie der paralyse agitans und des postenzephalitischen Parkinsonism. Journal fur Psychologie und Neurologie **48**: 387-476.

Heinonen, E.H. & Rinne, U.K. (1989). Selegiline in the treatment of Parkinson's disease. Acta Neurologica Scandinavica **80** (126): 103-111.

Heiss, W.D., Pawlik, G., Herholz, K., Szelies, B., Wenhard, K. (1989). Positron emission tomography as an imaging tool in psychiatric disorders. Psychiatry Research **29**: 351-352.

Henderson, A.S. (1986). The epidemiology of Alzheimer's disease. British Medical Bulletin **42**(1): 3-10.

Henderson, B., Good, P.A., Hitchcock, E.R., Clough, C.G., Hughes, R.C., Kenny, B.G. (1992). Visual evoked cortical responses and electroretinogram following implantation of human fetal mesencephalon to the right caudate nucleus in Parkinson's disease. Journal of the Neurological Sciences **107**: 183-190.

Henry, G.H. (1991). Afferent inputs, receptive field properties and morphological cell types in different laminae of the striate cortex. In: A.G. Leventhal (ed): The neural basis of visual function. General ed: J.R. Cronly-Dillon: Vision and Visual dysfunction, **4**: 223-245.

Hinton, D.R., Sadun, A.A., Blanks, J.C. & Miller, C.A. (1986). Optic nerve degeneration in Alzheimer's disease. New England Journal of Medicine **315** (8): 485-487.

Hirano, A. (1981). A guide to neuropathology. Igaku-Shoin. Tokyo, New York.

Hirano, A., Malamud, N. & Kurland, L.T. (1961). Parkinsonism - dementia complex, an endemic disease on the island of Guam. 11 pathological features. Brain **84**: 662-679.

Hirsch E.C., Graybiel, A.M. & Agid, Y. (1989). Selective vulnerability of pigmented dopamine neurons in Parkinson's Disease. Acta Neurologica Scandinavica **80** (126): 19-22

Hitchcock, E.R., Clough, C., Hughes, R. & Kenny, B. (1988). Embryos and Parkinson's disease. The Lancet (letter) , pp 1274.

Ho, S.C., Woo, J. & Lee, C.M. (1989). Epidemiologic study of Parkinson's disease in Hong Kong. Neurology **39**: 1314-1318.

Hoehn, M.M (1992). The natural history of Parkinson's disease in the pre - levodopa and post - levodopa eras. Neurologic Clinics **10** (2): 331-339.

Hoehn, M.M. & Yahr, N. (1967). Parkinsonism: Onset, progression and mortality. Neurology **17** (5): 427 - 442.

Hofman, A., Schulte,W., Tanja, T.A., Van Duijn, C.M., Haaxma, R., Lameris, A.J., Otten, U.M., Saan, R.J. (1989). History of dementia and Parkinson's disease in first degree relatives of patients with Alzheimer's disease. Neurology **39**: 1589-1592.

Hollander, E., Mohs, R.C., Davis, K.L. (1986). Cholinergic approaches to the treatment of Alzheimer's disease. British Medical Bulletin **42**(1): 97-100.

Hollister, L.E. (1985). Survey of treatment attempts in senile dementia of the Alzheimer type. In: C.G. Gottfries (ed). Normal Aging, Alzheimer's Disease and Senile Dementia. L'Universite de Brixelles, Belgium, pp 299-306.

Hopelman, M.D. and Corn, T.H. (1988). Cholinergic blockade as amodel for cholinergic depletion. Brain **111**: 1079-1110.

Hornykiewicz, O. (1976). Neurohumoral interactions and basal ganglia function and dysfunction. In: M.D. Yahr (ed): The Basal Ganglia, Raven Press, Ltd., pp 269-280.

Hornykiewicz, O. (1989). The neurochemical basis of the pharmacology of Parkinson's disease. In: D.B., Calne (ed): Drugs for the Treatment of Parkinson's Disease. Handbook of Experimental Pharmacology **88**:185-204.

Hornykiewicz, O.& Kish, S.J. (1986). Biochemical pathophysiology of Parkinson's disease. Advances in Neurology **45**: 19-34

Houser, C.R., Crawford, G.D., Barber, R.P., Salvaterra, P.M. & Vaughn, J.E. (1983). Organization and morphological characteristics of cholinergic neurons: An immunocytochemical study with monoclonal antibody to choline acetyltransferase. Brain Research, **266**: 97-119.

Hubel, D.H. & Wiesel, T.N. (1968). Receptive fields and functional architecture of monkey striate cortex. Journal of Physiology, **195**:215-

Hubel, D.H. & Wiesel, T.N. (1977). The Ferrier lecture: Functional architecture of macaque monkey visual cortex. Proceedings of the Royal Society of London B. **198**: 1-59.

Hughes, A.J., Ben-Shlomo, Y., Daniel, S.E. & Lees, A.J. (1992). What features improve the accuracy of clinical diagnosis in Parkinson's disease: A clinicopathologic study. Neurology **42**: 1142-1146.

Hughes, C.P., Berg. L., Danziger, W.L., Coben, L.A., Martin, R.L. (1982). A new clinical scale for the staging of dementia. British Journal of Psychiatry, **140**: 566-572.

Hughes, J.T. (1989). Aluminium encephalopathy and Alzheimer's disease. The Lancet (March) lett: 490-491.

Huisman, U.W., Posthuma, J., Visser, S.L., Jonker, C., De Rijke, W. (1987). The influence of attention on visual evoked potentials in normal adults and dementias. Clinical Neurology and Neurosurgery **89** (3): 151-155.

Hull, B.M. & Drasdo, N. (1990). The influence of age on the pattern reversal electroretinogram. Ophthalmic and Physiological Optics **10**: 49-53.

Hull, B.M & Thompson, D.A. (1988). A review of the clinical applications of the pattern electroretinogram. Ophthalmic and Physiological Optics **9**: 143-152.

Humphrey, N.K. (1968). Responses to visual stimuli of units in the superior colliculus of rats and monkeys. Experimental Neurology, **20**: 312-340.

Huppert, F.A. & Tym, E. (1986). Clinical and neuropsychological assessment of dementia. British Medical Bulletin **42** (1): 1-18

Ikeda, H. & Robbins, J. (1988). Development of neurochemical separation of ON and OFF channels at retinal ganglion cells. Documanta Ophthalmologica, **69**: 175-186.

Ineichen, B. (1987). Measuring the rising tide: How many dementia cases will there be by 2001. British Journal of Psychiatry **150**: 193-200.

Ingling Jr, C.R. & Grigsby, S.G. (1990). Perceptual correlates of magnocellular and parvocellular channels: seeing form and depth in afterimages. Vision Research, **30** (6): 823-828.

Ingvar, D.H. (1983).Cerebral blood flow and cerebral metabolism in Alzheimer's disease. In: B. Reisberg (ed). Alzheimer's disease: The free press, Macmillan Inc, New York, Collier Macmillan, London, pp. 278-285.

Iqbal, K. (1991). Prevalence and neurobiology of Alzheimer's disease: Some highlights. In: K. Iqbal, D.R.C. McLachlan, B. Winbald, H.M. Wisniewski (eds). Alzheimer's disease: Basic Mechanisms, Diagnosis and Therapeutic Strategies. John Wiley and Sons Ltd, pp 1-5.

Irvin, G.E., Norton, T.T., Sesma, M.A. & Casagrande, V.A. (1986). W-like response properties of interlaminar zone cells in the lateral geniculate nucleus of a primate (Galago crassicaudatus). Brain Research, **362**: 254-270.

Ishii, Y. & Nakamura, Y. (1981). Distribution and ultrastructure of Alzheimer's neurofibrillary tangles in postencephalitic parkinsonism of Economo type. Acta Neuropathologica **55**: 59-62.

Iudice, A., Virgilli, P., Muratorio, A. (1980). The electroretinogram in Parkinson's disease. Research Communication in Psychology, Psychiatry and Behavior 5 (3): 283-289.

Iuvone, P.M. (1986). Neurotransmitters and neuromodulators in the retina: Regulation, interactions, and cellular effects. In: R. Adler & D. Faber (eds): The retinal: A model for cell biology studies. Part ll, Academic Press, Inc., (London), Ltd., pp 2-72.

Jacoby, R.J. & Levy, R. (1980). Computed Tomography in the elderly 2. Senile Dementia: diagnosis and functional impairment. British Journal of Psychiatry **136**: 256-269.

Jaffe, M.J., Bruno, G., Campbell, G., Lavine, R.A., Karson, C.N., Weinberger, D.R. (1987). Ganzfeld electroretinographic findings in parkinsonism: Untreated patients and the effect of levodopa intravenous infusion. Journal of Neurology, Neurosurgery and Psychiatry **50**: 847-852.

Jankovic, J. (1987). The neurology of tics. In C.D. Marsden and S. Fahn (eds). Movement Disorders II; Butterworths. pp: 383-405.

Jankovic, J. (1987). Pathophysiology and clinical assessment of motor symptoms in Parkinson's disease. In: W.C. Koller (ed): Handbook of Parkinson's disease; Marcel Dekker Inc, New York: 99-126.

Jankovic, J. & Orman, J. (1986). Parallel double-blind study of pergolide in Parkinson's disease. Advances in Neurology **45**: 551-554.

Jansen, E.N.H. & Meerwaldt, J.D. (1986). Long-term treatment with high-dosage bromocriptine in advanced Parkinson's disease. Advances in Neurology **45**: 539-545.

Jeffreys, D.A. (1980). The nature of pattern VEPs. In C. Barber (ed): Evoked Potentials. MTP Press Ltd. pp. 149-159.

Jeffreys, D.A. & Axford, J.G. (1972). Source locations of pattern specific components of human visual evoked potentials. l. Components of striate cortical origin. Experimental Brain Research 16: 1-21.

Jeffreys, D.A. & Axford, J.G. (1972). Source locations of pattern specific components of human visual evoked potentials. ll. Components of extrastriate cortical origin. Experimental Brain Research 16: 22-40.

Jeffreys, D. (1977). The physiological significance of pattern visual evoked potentials. In J.E. Desmedt (ed): Visual Evoked Potentials in Man: New Developments. Clarendon Press, Oxford. pp. 134-167.

Jellinger, K. (1974). Pathomorphologie des Parkinson - syndromes. Aktuelle Neurologie **1**: 83-98.

Jellinger, K. (1986). Pathology of parkinsonism: In S.Fahn, C.D. Marsden, R. Duvoisin (eds): Recent Developments in Parkinsonism, Raven Press, Ltd., pp 33-66.

Jeillinger, K. (1987). The pathology of parkinsonism. In: C.D. Marsden & S. Fahn (eds): Movement Disorders 2, Butterworths, pp 124-165.

Jellinger, K. (1990). New developments in the pathology of Parkinson's disease. Advances in Neurology **53**: 1-16.

Jellinger, K.A. (1991). Pathology of Parkinson's disease: Changes other than the nigrostriatal pathway. Molecular and Chemical Neuropathology **14** (3): 153-197.

Jellinger, J. (1989). Pathology of Parkinson's syndrome. In D.B., Calne (ed): Drugs for the Treatment of Parkinson's Disease. Handbook of Experimental Pharmacology **88**: 47-112.

Jellinger, K. & Riederer, P. (1984). Dementia in Parkinson's disease and (pre)senile dementia of Alzheimer type: Morphological aspects and changes in the intracerebral MAO activity. Advances in Neurology **40**: 199-210.

Johnson, W.G., Hodge, S.E. & Duvoisin, R. (1990). Twin studies and the genetics of Parkinson's disease - a reappraisal. Movement Disorders **5** (3): 187-194.

Jorm. A.F. & Henderson, A.S. (1985). Possible Improvement to the diagnostic criteria for dementia in DSM-lll. British Journal of Psychiatry **147**: 394-399.

Jorm, A.F., Korten, A.E., Henderson, A.S. (1987). The prevalence of dementia: A quantitative integration of the literature. Acta. Psychiatrica Scandinavica **76**: 465-479.

Joya-Pardo C.J., Londono, J.L., Pardo, C.A. (1991). Risk factors in clinically diagnosed Alzheimer;s disease: A case-control study in Columbia (South America) In: K. Iqbal, D.R.C. McLachlan, B. Winbald, H.M. Wisniewski (eds): Alzheimer's disease: Basic Mechanisms, Diagnosis and Therapeutic Strategies. John Wiley and Sons Ltd, pp 363-368.

Kaas, J.H. & Krubitzer, L.A. (1991). The organisation of the extrastriate visual cortex. In: B. Dreher & S.R. Robinson (eds): Neuroanatomy of the visual pathways and their development. General ed: J.R. Cronly-Dillon: Vision and visual dysfunction, **3**: 302-323.

Kaplan, E. (1991). The receptive field structure of retinal ganglion cells in cat and monkey. In: A.G. Leventhal (ed): The neural basis of visual function. General ed: J.R. Cronly-Dillon: Vision and Visual dysfunction, **4**: 10-40.

Kaplan, E. & Shapley, R.M. (1982). X and Y cells in the lateral geniculate nucleus of macaque monkeys. Journal of Physiology, **330**: 125-143.

Kaplan, E. & Shapley, R.M. (1986). The primate retina contains two types of ganglion cells with high and low contrast sensitivity. Proceedings of the National Academy of Sciences (USA), **83**: 2755-2757.

Kaplan, E., Lee, B.B. & Shapley, R.M. (1991). New views of primate retinal function. In: N. Osborne & J. Cohaden (eds): Progress in Retinal Research, **9**: 273-336.

Karten, H., Keyser, K. & Brecha, N. (1990). Biochemical and morphological heterogenity of retinal ganglion cells. In: B. Cohen & I. Bodis-Wollner (eds): Vision and the Brain, pp 19-33.

Karwoski, C. & Kawasaki, K. (1991). The pattern electroretinogram. In J.R. Hackenliveley & G.B. Arden (eds): Principles and Practice of Clinical Electrophysiology of Vision. Mosby-Year Book, Inc. pp. 291-300.

Katz, B. & Rimmer, S. (1989). Ophthalmic manifestations of Alzheimer's disease. Survey of Ophthalmology **34**(1): 31-43.

Katz, B., Rimmer,S., Iragui, V., Katzman, R. (1989). Abnormal pattern electroretinogram in Alzheimer's disease:evidence for retinal ganglion cell degeneration. Annals Neurology **26**: 221-225.

Katzman, R. (1986). Alzheimer's disease. The New England Journal of Medicine **314**(15): 964-971.

Katzman, R., Lasker, B., Bernstein, N. (1988). Advances in the diagnosis of dementia: Acuracy of diagnosis and consequences of misdiagnosis of disorders causing dementia. In: R.D. Terry (ed). Aging and the Brain. Raven press, New York, pp. 17-62.

Kessler, I.I. (1972). Epidemiologic studies of Parkinson's disease ll: A hospital based survey. American Journal of Epidemiology **95**: 308-318.

Kessler, I.I. (1972). Epidemiologic studies of Parkinson's disease lll: A community based survey. American Journal of Epidemiology **96**: 242-254.

Khachaturian, Z.S. (1980). Diagnosis of Alzheimer's disease. Archives of Neurology **42**: 1097-1105.

Kisby, G.E., Ellison, M. & Spencer, P.S. (1992). Content of the neurotoxins cycasin (methylazoxymethanol B-D-glucoside) and BMAA (B-N-methylamino-L-alanine) in cycad flour prepared by Guam Chamorros. Neuology **42**: 1336-1340.

Kiyosawa, M., Bosley, T.M., Chawluk, J., Jamieson, D., Schatz, N.J., Savino, P.J., Sergott, R.C., Reivich, N.J. & Alavi, A. (1989). Alzheimer's disease with prominent visual symptoms. Ophthalmology, **96** (7): 1077-1085.

Klaue, R. (1940). Parkinsonsche krankheit (paralysis agitans) und postenzephalitischer parkinsonismus. Versuch einer klinish - anatomischen differentialdiagnose. Archiv fur Psychiatrie und Nervenkrankheiten, **111**: 251-321.

Klawans, H.L., Lupton, M. & Simon, L. (1976). Calcification of the basal ganglia as a cause of levodopa resistant parkinsonism. Neurology **26**: 221-225.

Knoll, J., Ecsery, Z., Kelmen, K., Nievel, J., Knoll, B. (1965). Phenylisopropylmethylpropinylamine (E-250), a new psychic energizer. Archives of International Pharmacodynamics **155**: 154-164.

Kokmen, E., Beard, C.M. (1991). Epidemiologic studies of dementia in Rochester, Minnesota. In: K. Iqbal, D.R.C. McLachlan, B. Winbald, H.M. Wisniewski (eds). Alzheimer's disease: Basic Mechanisms, Diagnosis and Therapeutic Strategies. John Wiley and Sons Ltd, pp 343-351.

Koller, W.C. (1992). How accurately can Parkinson's disease be diagnosed. Neurology **42** (suppl 1): 6-16.

Koller, W.C. (1992). Controlled-release carbidopa-levodopa: old drug - new drug. Neurology **42** (suppl 1): 4-5.

Koller, W. C., Vetere-Overfield, B., Gray, C., et al. (1990). Environmental risk factors in Parkinson's disease. Neurology **40**: 1218-1221.

Koller, W.C., Waxman, M. & Morantz, R. (1990). Adrenal neural transplants in Parkinson's disease. Advances in Neurology **53**: 559-566.

Kondo, K. (1984): Epidemiological clues for the etiology of Parkinson's disease. Advances in Neurology **40**: 345-351.

Kopin, I.J. (1986) Toxins and Parkinson's disease: MPTP Parkinsonism in humans and animals. In M.D. Yahr and K.J. Bergmann (eds). Advances in Neurology Vol **45**. Raven Press. New York. pp: 137-144.

Kopin, I.J., Bankiewicz, K.S., Plunkett, R.J., Jacobowitz, D.M. & Oldfield, E.H. (1993). Tissue implants in treatment of Parkinsonian syndromes in animals and implications for use of tissue implants in humans. Advances in Neurology **60**: 707-714.

Korczyn, A.D., Inzelberg, R., Treves, T., Neufeld, M., Reider, I., Rabey, P.M. (1986). In: M.D. Yahr and K.J. Bergmann (eds): Advances in Neurology **45**, Raven Press, Ltd., New York, pp. 399-403.

Kordower, J.H., Cochran, E., Penn, R.D., *et al.* (1991). Putative chromaffin cell survival and enhanced host-derived TH-fiber innervation following a functional adrenal medulla autograft for Parkinson's disease. Annals Neurology **29**: 405-412.

Kordower, J.H., Fiandaca, M.S., Notter, M.F.D. *et al.* (1990). NGF-like trophic support from peripheral nerve for grafted rhesus adrenal chromaffin cells. Journal of Neurosurgery **73**: 418-428.

Korth, M. & Horn, F. (1992). Color contrast mechanisms in the human pattern ERG. Clinical Vision Science **7** (4): 293-304.

Kosaka, K., Yoshimura, M., Ikeda, K. & Budka, H. (1984). Diffuse type of Lewy body disease. Clinical Neuropathology **3**: 185-192.

Kramer, S.G. (1971). Dopamine: A retinal neurotransmitter. (1) Retinal uptake, storage, and light-stimulated release of H3-Dopamine in vivo. Investigative Ophthalmology **10** (6): 438-451.

Kuffler, S.W. (1953). Discharge patterns and functional organisation of mammalian retina. Journal of Neurophysiology, **16**: 37-68.

Kulikowski, J.J. & Tolhurst, D.J. (1972). Psychophysical evidence for sustained and transient detectors in human vision. Journal of Physiology **232**: 149-162.

Kupersmith, M.J., Shakin, E., Siegel, I., Lieberman, A. (1982). Visual system abnormalities in patients with Parkinson's disease. Archives of Neurology **39**: 284-286.

Kulikowski, J.J. (1991). On the nature of visual evoked potentials, unit responses and psychophysics. In A. Valberg & B.B. Less (eds): From Pigments to Perception, Plenum Press, New York & London. pp. 197-209.

Lampe, T.H., Norris, J., Risse, S.C, Owen-Williams, E., Keenan, T. (1991). Therapeutic potential of thyrotropin-releasing hormone and lecithin co-administration in Alzheimer's disease In: K. Iqbal, D.R.C. McLachlan, B. Winbald, H.M. Wisniewski (eds): Alzheimer's disease: Basic Mechanisms, Diagnosis and Therapeutic Strategies. John Wiley and Sons Ltd, pp 643-648.

Lang, A.E. & Blair, R.D.G. (1989). Anticholinergic drugs and amantadine in the treatment of Parkinson's disease. In: D.B. Calne (ed): Drugs for the Treatment of Parkinson's Disease. Handbook of Experimental Pharmacology **88**: 307-323.

Langson, J.W. (1987). MPTP: The promise of a new neurotoxin. In C.D. Marsden and S. Fahn (eds): Movement Disorders II; Butterworths. pp: 73-90.

Lapchack, P.A., Araujo, D.M., Quirion, R. (1989). Muscarinic and nicotinic receptors in Alzheimer's disease: Rationale for cholinergic drug treatment. In: E.M. Meyer, J.W. Simpkins, J. Yamomoto (eds): Novel Approaches to the Treatment of Alzheimer's Disease. Advances in Behavioural Biology **36**: 53-61.

Lee,B.B., Pokorny, J., Smith, V.C., Martin, P.R. & Valberg, A. (1990). Luminance and chromatic modulation sensitivity of macaque ganglion cells in human observers. Journal of the Optical Society of America **7** (12): 2223-2236.

Leestma, J.E. & Andrews, J.M. (1969). The fine structure of the Marinesco body. Archives of Pathology **88**: 413-436.

Lehmann, H.E. (1989). Diagnosis of the dementias. In: E. Ban, H.E. Lehmann (eds). Diagnosis and Treatment of old age dementias. Modern Problems of Pharmacopsychiatry, Basel, Karger Vol 23, pp 10-20.

Lehmann, D., Meles, H.P., Mir, Z. (1977). Average muli-channel EEG potential fields evoked from upper and lower hemi-retina. Electroencephalography and Clinical Neurophysiology **43**: 725-731.

Lennie, P. (1980). Parallel visual pathways: A review. Vision Research, **20**: 561-594.

Le Vay, S. & Nelson, S.B. (1991). Columnar organization of the visual cortex. In: A.G. Leventhal (ed): The neural basis of visual function. General ed: J.R. Cronly-Dillon: Vision and Visual dysfunction **4**: 266-315.

Leventhal, A.G., Rodieck, R.W. & Dreher, B. (1981). Retinal ganglion cell classes in cat and old world monkeys: Morphological and central projections. Science **213**: 1139-1142.

Leventhal, A.G., Rodieck, R.W. & Dreher, B. (1985). Central projections of cat retinal ganglion cells. Journal of Comparative Neurology **237**: 216-226.

Levin, B.E., Llabre, M.M., Ansley, J., Weiner, W.J. & Sanchez-Ramos, J. (1990). Do Parkinsonians exhibit visuospatial deficits. In: M.B. Streifer, A.D. Korczyn, E. Melamed & M.B.H. Youdim (eds): Advances in Neurology Vol **53**; Parkinson's disease: Anatomy, Pathology, and Therapy: 311-315.

Levin. B.E., Llabre, M.M., Reisman, S., Weiner, W.J., Sanchez-Ramos, J., Singer, C. & Brown, M.C. (1991). Visuospatial impairment in Parkinson's disease. Neurology 41: 365-369.

Levin, B.E., Tomer, R., Rey, G.J. (1992). Cognitive impairments in Parkinson's disease. Neurology Clinics 10(2): 471-485

Lewis, D.A., Campbell, M.J., Terry, R.D. & Morrison, J.H. (1987). Laminar and regional distribution of neurofibrillary tangles and neuritic plaques in Alzheimer's disease: A quantitative study of visual and auditory cortices. Journal of Neuroscience, 7: 1799-1808.

Le Witt, P.A. (1989). The pharmacology of levodopa in treatment of Parkinson's disease: An update. In: D.B. Calne (ed): Drugs for The Treatment of Parkinson's Disease. Handbook of Experimental Pharmacology 88: 325-384.

Le Witt, P.A. (1992). Treatment strategies for extension of levodopa effect. Neurology Clinics 10 (2): 511-526.

Lewy, F.H. (1912). Paralysis agitans I. Pathologiesche anatomie. In M. Lewandowsky (ed): Handbuch der Neurologie, Springer, Berlin. pp: 920-933.

Li, G., Shen, Y.C., Li, Y.T., Chen, C.H., Zhau, Y.W., Silverman, J.M. (1992). A case-control study of Alzheimer's disease in China. Neurology 42: 1481-1488.

Li, S.C., Schoenberg, B.S., Wang, C.C. et al. (1985). A prevalence survey of Parkinson's disease and other movement disorders in the People's Republic of China. Archives of Neurology 42: 655-657.

Lieberman, A. (1992). An integrated approach to patient management in Parkinson's disease. Neurologic Clinics 10 (2): 553-565.

Lieberman., A., Ransohoff, J., Berczeller, P., Brous, P., Eng., K., Goldstein, M., Kaufman, P., Koslow, M., Chin, L. (1989). Adrenal medullary transplants as a treatment for advanced Parkinson's disease. Acta Neurologica Scandinavica 126: 189-196.

Lindvall, B. & Bjorkland, A. (1989). Transplantation strategies in the treatment of Parkinson's disease: experimental basis and clinical trials. Acta Neurologica Scandinavica 80 (126): 197-210.

Lindvall, B. & Olsson, J.E. (1986). Treatment of early morning akinesia with low-dose bromocriptine. Advances in Neurology 45: 543-546.

Lindvall, O., Rehncrona, S., Brundin, P., Gustavii, B., et al. (1989). Human fetal dopamine neurons grafted into the striatum in two patients with severe Parkinson's disease. Archives of Neurology, 46:615-631.

Lindvall, O., Brundin, P., Winder, H., Rehncrona, S., Gustavii, B., Frackowiak, R., Leenders, K., Sawle, G., Rothwell, J., Marsden, C. & Bjorklund, A. (1990). Grafts of fetal dopamine neurons survive and improve motor function in Parkinson's disease. Science 247:574-577.

Livingstone, M.S. & Hubel, D.H. (1988). Do the relative mapping densities of the magno- and parvocellular systems vary with eccentricity. The Journal of Neuroscience, 8 (11): 4334-4339.

Lu, C. & Fender, D.H. (1972). The interaction of colour and luminance in stereoscopic vision. Investigative Ophthalmology, **11**: 482-489.

Luquin, M.R., Obeso, J.A., Martinez-Lange, J.M & Tresguerres, J. (1986). Parenteral administration of lisuride in Parkinson's disease. Advances in Neurology **45**: 561-568

Lynch, J.J., Silveira, L.C.L., Perry, V.H. & Merigan, W.H. (1992). Visual effects of damage to P ganglion cells in macaques. Visual Neuroscience **8**: 575-583.

Madrazo, I., Drucker-Colin, R., Diaz, V., *et al.* (1987). Open microsurgical autograft of adrenal medulla to the right caudate nucleus in two patients with intractable Parkinson's disease. New England Journal of Medicine **316**: 831-834.

Maffei, L. & Fiorentini, A. (1981). Electroretinograhic responses to alternating grating before and after section of the optic nerve. Science **211**: 953-955.

Maffei, L. & Fiorentini, A. (1990). Pattern visual evoked potentials and electroretinograms in man and animals. In J.T. Desmedt (ed): Visual Evoked Potentials. Elsevier Science publishers B.V. pp. 25-33.

Maffei, L., Fiorentini, A., Bisti, S., Hollander, H. (1985). Pattern ERG in the monkey after sections of the optic nerve. Experimental Brain Research **59**: 423-425.

Mann, D.M.A. (1985). The neuropathology of Alzheimer's disease: A review with pathogenetic, aetiological and therapeutic considerations. Mechanisms of Aging and Development **31**: 213-255.

Mann, D.M.A., Tucker, C.M., Yates, P.O. (1987). The topographic distribution of senile plaques and neurofibrillary tangles in the brains of non-demented persons of different ages. Neuropathology and Applied Neurobiology **13**: 123-139.

Maraganore, D.M., Harding, A.E. & Marsden, C.D. (1991). A clinical and genetic study of familial Parkinson's disease. Movement Disorders **6** (3); 205-211.

Mariani, A. (1989). Synaptic organization of classical neurotransmitter phenotypes in the primate retina. Neuroscience Research, suppl. 10: 101-116.

Marrocco, R.T. (1976). Sustained and transient cells in monkey lateral geniculate nucleus; conduction velocities and response properties. Journal of Neurophysiology, **39**: 340-353.

Marsden, C.D. (1987). Parkinson's disease in twins. Journal of Neurology, Neurosurgery and Psychiatry **50**: 105-106.

Marsden, F.D. & Fahn, S. (1987). Problems in Parkinson's disease and other akinetic-rigid syndromes. In: C.D. Marsden & S. Fahn (eds): Movement Disorders 2, Butterworths, pp 65-72.

Martin, W.R.W. & Calne, D.B. (1987). Imaging techniques and movement disorders. In: C.D. Marsden & S. Calne (eds): Movement Disorders 2: pp4-16.

Martin, W.R.W., Stoessl,.A.J., Adam, M.J., Ammann, W., Bergstrom, M., Harrop, R., Laihinen, A., Rogers, J.G., Ruth, T.J., Sayre, C.I., Pate, B.D., Calne, D.B. (1986). Possitron emmission tomography in Parkinson's disease: Glucose and DOPA metabolism. Advances in Neurology **45**:95-98.

Marttila, R.J. & Rinne, U.K. (1976). Arteriosclerosis, heredity, and some previous infections in the etiology of Parkinson's disease. A case-control study. Clinical Neurology and Neurosurgery 76: 46-56.

Marttila, R.J. & Rinne, U.K. (1989). Epidemiological approaches to the etiology of Parkinson's disease. Acta Neurologica Scandinavica 80 (126): 13-18.

Marttila, R.J., Kaprio, J., Koskenvuo, M.D. & Rinne, U.K. (1988). Parkinson's disease in a nationwide twin cohort. Neurology 38: 1217-1219.

Martyn, C.N., Candy, J. (1991). Aluminium in the causation of Alzheimer's disease: Population based studies in England and Wales. In: K. Iqbal, D.R.C. McLachlan, B. Winbald, H.M. Wisniewski (eds): Alzheimer's disease: Basic Mechanisms, Diagnosis and Therapeutic Strategies. John Wiley and Sons Ltd, pp 383-386.

Marx, M., Bodis-Wollner, I., Bobak, P., Harnois, C., Mylin, L., Yahr, M. (1986). Temporal frequency-dependent VEP changes in Parkinson's disease. Vision Research 26 (1): 185-193.

Masland, R.H. & Tauchi, M. (1986). The cholinergic amacrine cell. Trends in Neuroscience: 218-223.

Mattock, C., Marmot, M. & Stern, G. (1988). Could Parkinson's disease follow intrauterine influenza? A speculative hypothesis. Journal of Neurology, Neurosurgery and Psychiatry 51: 738-756.

Matsuyama, H. (1983). Incidence of neurofibrillary change, senile plaques and granulovacuolar degeneration in aged individuals. In: B. Reisberg (ed). Alzheimer's disease: The free press, Macmillan Inc, New York, Collier Macmillan, London, pp. 149-154.

Matsuyama, H. (1983). Genetic factors in dementia of the Alzheimer type. In: B. Reisberg (ed). Alzheimer's disease: The free press, Macmillan Inc, New York, Collier Macmillan, London, pp. 155-160.

Mayeux, R. (1990). Therapeutic strategies in Alzheimer's disease. Neurology 40:175-180.

Mayeux, R., Stern, Y., Spanton, S. (1985). Heterpgeneity in dementia of the alzheimer type: evidence of subgroups. Neurology 35: 453-461.

Mc Cormick, D. (1989). Cholinergic and noradrenergic modulation of thalamocortical processing. Trends in Neuroscience 12 (6): 215-221

Mc Geer, E.G. & Mc Geer, P.L. (1989). Biochemical neuroanatomy of the basal ganglia. In: D.B., Calne (ed): Drugs for the Treatment of Parkinson's Disease. Handbook of Experimental Pharmacology 88:113-148.

Mc Khann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., Stadlan, E.M. (1984). Clinical diagnosis of Alzheimer's disease.: Report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 34: 939-944.

Meier-Ruge, W. (1983). New prospects in neuropharmacology of senile dementia. In: J. Cervos-Navarro & H.-I. Sarkander (eds). Brain Aging: Neuropathology and Neuropharmacology. Aging 21, Raven Press, pp 391-400.

Mendez, M.F., Mendez, M.A., Martin, R., Smyth, K.A. & Whitehouse, P.J. (1990). Complex visual disturbances in Alzheimer's disease. Neurology **40**: 439-443.

Merigan, W. (1989). Chromatic and achromatic vision of macaques: Role of the P pathway. The Journal of Neuroscience **9** (3): 776-783.

Merigan, W. (1991). P and M pathway specialization in the macaque. In: A. Valberg & B.B. Lee (eds) : From Pigments to Perception, pp 117-125.

Merigan, W.H. & Eskin, T.A. (1986). Spatio-temporal vision of macaques with severe loss of P Beta retinal ganglion cells. Vision Research **26** (11): 1751-1761.

Merigan, W.H. & Maunsell, J.H.R. (1990). Macaque vision after magnocellular lateral geniculate lesions. Visual Neuroscience **5**: 347-352.

Meyer, J.S. (1983). Cerebral blood flow: Use in differential diagnosis of Alzheimer's disease. In: B. Reisberg (ed). Alzheimer's disease: The free press, Macmillan Inc, New York, Collier Macmillan, London, pp. 267-277.

Michel, P., Commenges, D., Dartigues, J.F., Gagnon, M., Barberger-Gateau, P., Letenneru, L. et al. (1991). Study of the relationship between aluminium concentration in drinking water and risk of Alzheimer's disease. In: K. Iqbal, D.R.C. McLachlan, B. Winbald, H.M. Wisniewski (eds). Alzheimer's disease: Basic Mechanisms, Diagnosis and Therapeutic Strategies. John Wiley and Sons Ltd, pp 387-391.

Mindham, R.H.S., Biggins, C.A., Boyd, J.L., Harrop, F.M., Madeley, P., Randall, J.I., Spokes, E,G.S. (1993). A controlled study of dementia in Parkinson's disease over 54 months. In: H. Narabayashi, T. Nagatsu, N. Yanagisawa & Y. Mizuno (eds). Advances in Neurology **60**, Raven Press Ltd., New York, pp. 470-474.

Mongel, C., Dowling, J.E. (1987). The interplexiform horizontal cell system of the fish retina: Effect of dopamine, light stimulation and time in the dark. Proceedings of the Royal Society of London B. **231**: 91-121.

Montgomery, E.B. Jr. (1992). Pharmacokinetics and pharmacodynamics of lavodopa. Neurology **42** (suppl 1): 17-22.

Moore, R.Y. & Bloom, E.E. (1979). Distribution of putative neurotransmitters in the neocortex. Neuroscience **4**: 1-30.

Morgante, L., Rocca, N.A., Di Rosa, A.E., De Domenico, P., Grigoletto, F., Meneghini, F., Reggio, A., Savettieri, G., Castiglione, M.G., Patti, F. & Di Perri, R. (1992). Prevalence of Parkinson's disease and other types of parkinsnism. Neurology **42**: 1901-1907.

Morris, J.C., Draizner, M., Fulling, K., Grant, E.A., Golding, J. (1989). Clinical and pathological aspects of Parkinsonism in Alzheimer's disease. Archives of Neurology **46**: 651-657.

Morrison, J.D. & Reilly, J. (1989). The effects of 0.025% hyoscine hydrobromide eyedrops on visual function in man. Ophthalmic and Physiological Optics, **9**: 41-45.

Mortimer, J.A. (1983). Alzheimer's disease and senile dementia: Prevalence and Incidence. In: B. Reisberg (ed). Alzheimer's disease: The free press, Macmillan Inc, New York, Collier Macmillan, London, pp. 141-147.

Mortimer, J.A., Schuman, L.M., French, L.R. (1981). Epidemiology of dementing illness. In: J.A. Mortimer, L.M. Sohyman (eds). The Epidemiology of Dementia. New York, Oxford University Press, pp 3-23. (cited).

Mouradin, M.M., Heuser, I.J., Boronti, F. & Chase, T. (1990). Modification of central dopaminergic mechanisms by continuous levodopa therapy for advanced Parkisnon's disease. Annals of Neurology **27** (1); 18-23.

Murray, I.J. & Parry, N.R.A. (1989). Generating VEPs specific to parvo and magno pathways in humans. In J. Kulikowski (es): Seeing in Contour and Colour. pp 471-477.

Murray, I.J., Parry, N.R.A., Carden, D., Kulikowski, J.J. (1987). Human visual evoked potentials to chromatic and achromatic gratings. Clinical Vision Science **1** (3): 231-244.

Mutch, W.J. (1988). The epidemiology of Parkinson's disease. In: Chemistry of Surgery: Which holds the key? A symposium held at the Royal College of Physicians, London. Parkinson's Disease Society.

Myllyla, V.V., Sotaaniemi, K.A., Tunominen, J. & Heinonen, E.H. (1989). Selegiline as primary treatment in early phase Parkinosn's disease - an interim report. Acta Neurologica Scandinavica **80** (126): 177-182.

Nandy, K. (1983). Immunologic factors. In: B. Reisberg (ed). Alzheimer's disease: The free press, Macmillan Inc, New York, Collier Macmillan, London, pp. 135-138.

Nelson, J. (1988). Amblyopia: the cortical basis of binocularity and vision loss in strabismus. In: K. Edwards & R. Llewellyn, (eds): Optometry. Butterworths, pp 189-216.

Nelson, J.I. & Seiple, W.H. (1991). Human VEP contrast modulation sensitivty: separation of magno- and parvocellular components. Electroencephalography and Clinical Neurophysiology **84**: 1-12.

Newman, E.A. & Fishman, L.J. (1991). The b-wave. In J.R. Hackenliveley & G.B. Arden (eds): Principles and Practice of Clinical Electrophysiology of Vision. Mosby-Year Book, Inc. pp. 101-111.

Nguyen-Legros, J. (1988). Functional neuroarchitecture of the retina: Hypothesis on the dysfunction of retinal dopaminergic circuitry in Parkinson's disease. Surg. Radiol. Anat. **10**: 137-144.

Nightingale, S., Mitchell, K.W., Howe, J.W. (1986). Visual evoked cortical potentials and pattern electroretinograms in Parkinson's disease and control subjects. Journal of Neurology, Neurosurgery and Psychiatry **49**: 1280-1287.

Nishiyama, K., Mizuno, T., Sakuta, M. & Kurisaki, H. (1993). Chronic dementia in Parkinson's disease treated by anticholinergic agents: Neuropsychological and Neuroradiological Examination. Advances in Neurology **60**: 479-482.

Norton, T.T., Casagrande, V.A., Irvin, G.E., Sesma, M.A. and Petry, H.M. (1988). Contrast sensitivity functions of W-, X- and Y-like relay cells in lateral geniculate nucleus of bush baby (Galago crassicaudatus). Journal of Neurophysiology, **59**: 1639-1656.

O'Brien, C., Ho Sung, J., Mc Geachie, R.E., Lee, M.C. (1990). Striatonigral degeneration: Clinical MRI, and pathologic correlation. Neurology **40**: 710-711.

Obrist, W.D. (1980). Electroencephalography inm aging and dementia. In: Amaducci, et al (eds). Aging Vol 13. Raven Press, pp 227-236.

Odom, J.V. (1991). Amplifiers and specical purpose data aquisition systems.In J.R. Hackenliveley & G.B. Arden (eds): Principles and Practice of Clinical Electrophysiology of Vision. Mosby-Year Book, Inc. pp. 183-192.

Oertel, W.H., Schwarz, J., Tatsch, K., Arnold, G., Gasser, T. & Kirsch, C-M. (1993). IBZM - SPECT as predictor for dopamimetic responsiveness of patients with de novo parkinsonian syndrome. Advances in Neuology **60**: 519-524.

Ogawa, H., Tominaga, S., Kubo, N. et al. (1984). Shinshin-Igaku (Psychosom Med) **24**: 467-477.

Ogden, T.E. & Miller, R.F. (1966). Studies of the optic nerve of the rhesus monkey: Nerve fiber spectrum and physiological properties. Vision Research, **6**: 485-506.

Olanow, C.W. (1992). Magnetic Resonance Imaging in parkinsonism. Neurologic Clinics **10** (2): 405-420.

Olanow, C.W. (1993). MAO-B Inhibitors in Parkinson's disease. Advances in Neurology **60**: 666-672.

Olanow, C.W. & Alberts, M.J. (1986). Double-blind controlled study of pergolide mesylate as an adjunct to sinemet in the treatment of Parkinson's disease. Advances in Neurology **45**: 555-560.

Olsson, J.E. and the European Multicentric Trial Group. (1990). Bromocriptine and levodopa in early combination in Parkinson's disease: First results of the Collaborative European Multicentric Trial.

Onofrj, M., Ghilardi, M.F., Basciani, M., Gambi, D. (1986). Visual evoked potentials in Parkinsonism and dopamine blockade reveal a stimulus-dependent dopamine function in humans. Journal of Neurology, Neurosurgery, and Psychiatry **49**: 1150-1159.

Orban, G.A. (1991). Quantitative electrophysiology of visual cortical neurnes.In: A.G. Leventhal (ed): The neural basis of visual function. General ed: J.R. Cronly-Dillon: Vision and Visual dysfunction, **4**: 173-222.

Ordy, J.M., Brizzee, K.R. (1979). Sensory coding: Sensation, perception, information processing, and sensory-motor integration from maturity to old age: In: Ordy & Brizzee (eds). Sensory Systems and Communication in the Elderly. Aging Vol 10. Raven Press, New York, pp 1-11.

Orwin, A., Wright, C.E., Harding, G.F.A., Rowan, E.B., Rolfe, E.B. (1986). Serial visual evoked potential recordings in Alzheimer's disease. British Medical Journal **293**: 9-10.

Osborne, N.N & Ghazi, H. (1988). Does Noradrenaline behave as a neurotransmitter of hormone in the mammalian retina? Neuroscience Research suppl. 8: 197-210.

Ossenblok, P. & Spekreijse, H. (1991). The extrastriate generators of the EP to checkerboard onset. A source localization approach. Electroencephalography and Clinical Neurophysiology **80** (3): 181-193

Parnavelas, J.G. & Mc Donald, J.K. (1983). The cerebral cortex. In: P.C. Emson (ed): Chemical neuroanatomy, Raven Press, New York, pp 505-549.

Paulus, W.M., Homberg, V., Cunningham, K., Halliday, A.M (1986). Colour and brightness coding in the central nervous system: theoretical aspects and visual evoked potentials to homogenous red and green stimuli. Proceedings of the Royal Society London. series B. **227**: 53-66.

Pearl, D.P., Brody, A.R. (1980). Alzheimer's disease: X ray spectrometric evidence of aluminium accumulation in neurofibrillary tangle bearing neurons. Science **208**: 297-298.

Pearson, R.C.A., Esiri, M.M., Hiorns, R.W., Wilcock, G.K., Powell, T.P.S. (1985). Anatomical correlates of the distribution of the pathological changes in the neocortex in Alzheimer's disease. Proceedings of the National Acadamy of Science, USA **82**: 4531-4534.

Pepeu, G & Spignoli, G. (1990). Neurochemical actions of "nootropic drugs" In: R.J. Wurtman et al (eds): Advances in Neurology **51**, Alzheimer's Disease. Raven Press, New York, 247-252..

Perl, D.P., Steele, J.C., Loerzel, A., Kurland, L.T. (1991). Amylotrophic lateral sclerosis-Parkinsonism dementia complex of Guam as a model of Alzheimer's disease. In: K. Iqbal, D.R.C. McLachlan, B. Winbald, H.M. Wisniewski (eds): Alzheimer's disease: Basic Mechanisms, Diagnosis and Therapeutic Strategies. John Wiley and Sons Ltd, pp 375-381.

Perossini, M. & Fornaro, P. (1990). Electroretinographic effects induced in humans by psychopharmacologic agents. Documenta Ophthalmologica **75**: 1-6.

Perry, E.K., Perry, R.H. (1983). Acetylcholinesterase in Alzheimer's disease. In: B. Reisberg (ed). Alzheimer's disease: The free press, Macmillan Inc, New York, Collier Macmillan, London, pp. 93-99.

Peters, B.H., Levin, H.S. (1982). Chronic oral physostigmine and lecithin administration in memory desorders of aging. In: S.Corkin, et al (eds): Alzheimer's Disease: a report of progress. Aging **19**, Raven Press, New York, pp 421-426.

Peterson, C., Kress, V., Vallee, R. & Goldman, J.E. (1988). High molecular weight microtubule-associated proteins bind to actin lattices (Hirano bodies). Acta Neuropathology (Berl): 77.

Phillipson, O.T., Kilpatrick, I.C. & Jones, M.W. (1987). Dopaminergic innervation of the primary visual cortex in the rat, and some correlations with the human cortex. Brain Research Bulletin, **18**: 621-623.

Philpot, M.P., Amin, D., Levy, R. (1990). Visual evoked potentials in Alzheimer's disease: correlations with age and severity. Electroencephalography and Clinical Neurophysiology **77**: 323-329.

Pierelli, F., Peppe, A., Stanzione, P., Stefano, E., Rizzo, P.A., Bernardi, G., Moroculti, C. (1988). Electrophysiological (PERG, VEP) abnormalities in Parkinson Disease are reversed by L-dopa. In Dopaminergic Mechanisms in Vision. Alan R. Liss, Inc. pp. 253-265.

Pilas, B., Scana, T., Kalyanaraman, B. & Swartz, H.M. (1988). The effect of melanin on iron associated decomposition of hydrogen peroxide. Free Radical Biolology and Medicine **4**: 285-293.

Plunkett, R.J., Bankiewicz, K.S., Cummings, A.C. *et al.* (1990). Long-term evaluation of hemiparkinsonian monkeys after adrenal autografting or cavitation alone. Journal of Neurosurgery **73**: 918-926.

Poewe, W., Kleedorfer, B., Wagner, M., Bosch, S. & Schelosky, L. (1993). Continuous subcutaneous apomorphine infusions for fluctuating Parkinson's disease: Long-term follow-up in 18 patients. Advances in Neurology **60**: 656-660.

Pollak, P., Benabid, A.L., Gervason, C.L., Hoffmann, D., Seigneuret, E. & Perret, J. (1993). Long-term effects of chronic stimulation of the ventral intermediate thalamic nucleus in different types of tremor. Advances in Neurology **60**: 408-413.

Pollock, V.E., Schneider, L.S., Chui, H.C., Henderson, V., Zemansky, M., Sloane, R.B. (1989). Visual Evoked Potentials in Dementia: A Meta-Analysis and Empirical Study of Alzheimer's disease patients. Biol Psychiatry **25**: 1003-1013.

Polyak, S.L.(1957). The vertebrate visual system. University of Chicago Press.

Portin, R. & Rinne, U.K. (1986). Predictive factors for cognitive deterioration and dementia in Parkinson's disease. In: M.D. Yahr and K.J. Bergmann (eds). Advances in Neurology **45**, Raven Press Ltd., New York, pp. 413- 416

Potter, P.E., Morrison, R.S. (1991). Basic fibroblast growth factor protects septal-hippocampal cholinergic neurons against lesions induced by AF64A. In: K. Iqbal, D.R.C. McLachlan, B. Winbald, H.M. Wisniewski (eds). Alzheimer's disease: Basic Mechanisms, Diagnosis and Therapeutic Strategies. John Wiley and Sons Ltd, pp 639-642.

Price, D.L. (1986). New persectives on Alzheimer's disease. Annual review of Neuroscience **9**: 489-512.

Prusky, G., Shaw, C. & Cyander, M.S. (1987). Nicotinic receptors are located on lateral geniculate terminals in cat visual cortex. Brain Research, **412**: 131-138.

Przuntek, H.& Kuhn, W. (1990). The effect of R-(-)-deprenyl in de novo parkinsonian patients pretreated with levodopa and decarboxylase inhibitor correlated to depression and MHPS, HIAA and HVA levels of cerebrospinal fluid. Advances in Neurology **53**: 445-450.

Przuntek, H., Kuhn, W. & Kraus, P. (1989). The effect of R-(-)-deprenyl in de novo parkinsonian patients pretreated with levodopa and decarboxylase inhibitor correlated to depression and MHPG, HIAA and HVA levels in the cerebrospinal fluid. Acta Neurologica Scandinavica **80** (126): 153-156.

Puro, D.G. (1985). Cholinergic systems. In: W.W. Morgan (ed): Retinal transmitters and modulators: Models for the brain. Vol 1, CRC Press, Inc., Broca Raton, Florida, pp 64-91.

Purpura, D.P. (1976). Physiological organization of the basal ganglia. In: M.D., Yahr (ed). The Basal Ganglia. Raven Press, Ltd., New York, pp. 91-114.

Purpura, K., Kaplan, E. & Shapley, R.M. (1988). Background light and the contrast gain of primate P and M retinal ganglion cells. Proceedings of the National Academy of Science (USA), **85**: 4534-4537.

Quick reference to the diagnosis criteria from DSM-lll-R. (1987). American Psychiatric Association.

Quinn, N. (1990) The modern management of Parkinson's disease. Journal of Neurology, Neurosurgery and Psychiatry **53**: 93-95.

Rabey, J.M., Grynberg, E. & Graff, E. (1990). Cholinergic muscarinic binding of blood lymphocytes in patients with Parkinson's disease. Advances in Neurology **53**: 129-134

Rabey, J.M., Treves, T., Streifler, M. & Korczyn, A.D. (1986). Comparison of efficacy of lisuride hydrogen meleate with increased doses of levodopa in parkinsonian patients. Advances in Neurology **45**: 568-572.

Rail, D., Scholtz, C. & Swash, M. (1981). Post-encephalitic parkinsonism: Current experience. Journal of Neurology, Neurosurgery and Psychiatry **44**: 670-676.

Rajput, A.M., Offord, K.P., Beard, M.C. & Kurland, L.T. (1984). Epidemiology of Parkinson's disease. Incidence, classification and mortality. Annals Neurology **16**: 278-287.

Ray, P.G., Meador, K.J., Loring, D.W., Murro, A.M., Buccafusco, J.J., Yang, X-H., Zamrini, E.Y., Thompson, W.O., Thompson, E.E. (1991). Effects of scopolamine on visual evoked potentials in aging and dementia. Electroencephalography and Clinical Neurophysiology **80**: 347-351.

Redburn, D.A. (1988). Neurotransmitter systems in the outer plexiform layer of mammalian retina. Neuroscience Research, suppl. 8: 127-136.

Regan, D. (1988). Visual sensory loss in patients with Parkinson's disease. In Bodis-Wollner & Piccolino (eds): Neurology and Neurobiology Volume 43; Dopaminergic Mechanisms in Vision, Alan R Liss Inc.: pp 221-225.

Regan, D. & Spekreijse, H. (1986). Evoked potentials in vision research 1961-1986. Vision Research **26**: 1461-1480.

Reisberg. B. (1983) (i). An overview of current concepts of Alzheimer's disease, senile dementia, and age-associated cognitive decline. In: B. Reisberg (ed). Alzheimer's disease: The free press, Macmillan Inc, New York, Collier Macmillan, London, pp. 3-20.

Reisberg. B. (1983) (ii). Clinical Presentation, diagnosis and symptomatology of age-associated cognitive decline and Alzheimer's diseawse. In: B. Reisberg (ed). Alzheimer's disease: The free press, Macmillan Inc, New York, Collier Macmillan, London, pp. 173-187.

Report from the Medical Research Council Alzheimer's disease workshop, 1987.

Rhoades, R.W., Mooney, R.D. & Fiah, S.E. (1991). Retinotopic and visuotopic representation in the mammalian superior colliculus. In: B. Dreher & S.R. Robibson (eds): Neuroanatomy of the visual pathway and their development. Gereral ed: J.R. Cronly-Dillon: Vision and visual dysfunction, **3**: 150-175.

Richardson, E.P. Jr. (1965). Remarks on the pathology of Parkinson's disease. In: A.Barbeau, L.J. Doshay, E.A. Spiegel (eds): Parkinson's Disease: Trends in Research and Treatment, Grune and Stratton, New York, pp 63-68.

Ridley, R.M., Bowes, P.M., Baker, H.F., Crow, T.J. (1984). An involvement of acetylcholine in object discrimination, learning and memory in the marmoset. Neuropsychologica **22**: 253-264.

Riederer, P., Konradi, C. & Youdim, M.B.H. (1990). The role of MAO in dopaminergic transmission. Advances in Neurology **53**: 149-154.

Riederer, P. & Lange, K.W. (1992). Pathogenesis of Parkinson's disease. Current Opinion in Neurology and Neurosurgery **5** (5): 295-300.

Riederer, P., Lange, K.W. & Youdim, M.B.H. (1993). Recent advances in pharmacological therapy of Parkinson's disease. Advances in Neurology **60**: 626-636.

Riederer, P., Sofic, E., Rawch, W.D., Schmidt, B., Reynolds, G.P., Kellinger, K., Youdim, M.B.H. (1989). Transition metals, ferritin, glutathione and ascorbic acid in Parkinsonian brain. Journal of Neurochemistry **50**: 515-520.

Rinne, U.K. (1986). Dopamine agonists as primary treatment in Parkinson's disease. Advances in Neurology **45**: 519-524.

Rinne, U.K. (1989). Combination of a dopamine agonist, MAO-B inhibitor and levodopa - a new strategy in the treatment of early Parkinson's disease. Acta Neurologica Scandinavica **80** (126): 165-169.

Roberts, E. (1976). Some thoughts about the basal ganglia. In: M.D., Yahr (ed). The Basal Ganglia. Raven Press, Ltd., New York, pp. 191-203.

Roberts, E. (1982). Potential Therapies in Aging and Senile Dementia. Annals New York Academy of Science **396**: 165-178.

Robins, L.N., Helzer, J E., Croughan, J., Ratcliffe, K.S. (1981). National Institute of Mental Health Diagnostic Interview Schedule: its history, characteristics and validity. Archives of General Psychiatry **38**: 381-389.

Rodieck, R.W. (1965). Quantitative analysis of cat retinal ganglion cell response to visual stimuli. Vision Research **5**: 588-601.

Rodieck, R.W. (1979). Visual pathways. Annual Review Neuroscience, **2**: 193-225.

Rodieck, R.W., Binmoeller, K.F., Dineen, J. (1985). Parasol and midjet ganglion cells of the human retina. Journal of Comarative Neurology **233**: 115-132.

Rogan, E.N., Sullivan, T.M. (1991). Risk factors for Alzheimer's disease projected int the 21st century. In: K. Iqbal, D.R.C. McLachlan, B. Winbald, H.M. Wisniewski (eds). Alzheimer's disease: Basic Mechanisms, Diagnosis and Therapeutic Strategies. John Wiley and Sons Ltd, pp 369-372.

Rosati, G., Granieri, E., Pinna, L. et al. (1980). The risk of Parkinson disease in Mediterranean people. Neurology 30: 250-255.

Rosenberg, G.S., Greenwold, B., Davis, K.L. (1983). Pharmacologic treatment of Alzheimer's disease: An overview. In: B. Reisberg (ed). Alzheimer's disease: The free press, Macmillan Inc, New York, Collier Macmillan, London, pp. 329-339.

Roth, M. (1986). The association of clinical and neurological findings and its bearing on the classification and aetiology of Alzheimer's disease. British Mediacal Bulletin 42(1): 42-50.

Roth, M., Tym, E., Mountjoy, C.Q., Hippert, F.A., Hendrie, H., Verma, S., Goddard, R. (1986). CAMDEX: a standardized instrument for the diagnosis of mental disorder in the elderly with special reference to the early detection of dementia. British Journal of Psychiatry.

Rowe, M.H. (1991). Functional organisation of the retina. In: B. Dreher & S.R. Robinson (eds) Neuroanatomy of the visual pathways and their development. General editor: J.R. Cronly-Dillon: Vision and visual dysfunction, 3: 1-68.

Rubinstein, M.P. & Harding, G.F.A. (1981). The visually evoked subcortical potential: is it related to the electroretinogram? Investigative Ophthalmology and Visual Science 21(2): 335-344.

Ruessmann, K. & Beneicke, U. (1991). P2 latency of the flash visual evoked potential in dementia. International Journal of Neuroscience 56: 273-276.

Ruskell, G. (1988). Neurology of visual perception. In: K. Edwards & R. Llewellyn, (eds): Optometry. Butterworths, pp 3-24

Rutledge, J.N., Schallert, T. & Hall, S. (1993). Magnetic resonance imaging in parkinsonisms. Advances in Neurology 60: 529-534.

Sadun, A.A. & Bassi, C. (1990). The visual system in Alzheimer's disease. In: A. Cohen & I. Bodis-Wollner (eds): Vision and the Brain, pp 331-347.

Sagar, H. (1991). Parkinson's disease: Dac Donald Optima, London.

Sage, J.I & Mark, M.H. (1992). The rationale for continuous dopaminergic stimulation in patients with Parkinson's disease. Neuology 42 (suppl 1): 23-28.

Sandler, M. & Glover, V. (1989). Monoamine oxidase inhibitors in Parkinson's disease. In: D.B. Calne (ed): Drugs for the Treatment of Parkinson's Disease. Handbook of Experimental Pharmacology 88: 411-431.

Sannita, W.G., Fioretto, M., Maggi, L., Rosadini, G. (1988). Effects of scopolamine parenteral administration on the electroretinogram, visual evoked potentials, quantitative electroencephalogram of healthy volunteers. Documenta Opthalmologica 67: 379-388.

Sauer, H., Frodl, E.M., Kupsch, A., Bruggencate, G. & Oertel, W.H. (1992). Cryopreservation, survival and function of intrastriatal fetal mesencephalic grafts in a rat model of Parkinson's disease. Experimentel brain Research 90: 54-62.

Sawai, H., Fukuda, Y & Wakakuwa, K. (1985). Axonal projections of X-cells to the superior colliculus and to the nucleus of optic tract in cats. Brain Research, 341: 1-16.

Scatton, B., Javoy-Agid, F., Rouquier, L., Dubois, B. & Agid, Y. (1983). Reduction of cortical dopmine, noradrenaline, serotonin and their metabolites in Parkinson's disease. Brain Research **275**: 321-328.

Schapira, A.H.V., Cooper, J.M., Dexter, D., Clark, J.B., Jenner, P. & Marsden, C.D. (1990). Mitochondrial complex 1 deficiency in Parkinson's disease. Journal of Neurochemistry **54**: 823-827.

Schiller, P. (1990). The On and Off channels of the visual system. In: B. Cohen & I. Bodis-Wollner (eds): Vision and the brain. Raven Press, Ltd, New York, pp 35-41.

Schiller, P.H. (1991). The colour-opponent and broad-band channels of the primate visual system. In: A. Valberg & B.B. Lee (eds): From Pigments to Perception, pp 127-132.

Schiller, P.H. & Malpeli, J.G. (1977). Properties of tectal projections of monkey retinal ganglion cells. Journal of Neurophysiology, **40** (2): 428-445.

Schiller, P.H. & Malpeli, J.G. (1978). Functional specificity of lateral geniculate nucleus laminae of the rhesus monkey. Journal of Neurophysiology, **41**: 788-797.

Schiller, P.H., Logothesis, N.K. & Charles, E.R. (1990). Role of the colour-opponent and broad-band channels in vision. Visual Neuroscience, **5**: 321-346.

Schlotterer, G., Moscovitch, M. & Mc Lachlan, C. (1983). Visual processing deficits as assessed by spatial frequency contrast sensitivity and backward masking in normal ageing and Alzheimer's disease. Brain, **107**: 309-325.

Schneck, M.K. (1983). Nootropics. In: B. Reisberg (ed). Alzheimer's disease: The free press, Macmillan Inc, New York, Collier Macmillan, London, pp. 362-367..

Schochet, S.S., Wyatt, R. & Mc Cormick, W.F. (1970). Intracytoplasmic acidophilic granules in the substantia nigra. Archives of Neurology **22**: 550 - 555.

Schoenberg, B.S. (1986). Descriptive epidemiology of Parkinson's disease: Disease distribution and hypothesis formulation. Advances in Neurology **45**: 277-284.

Schoenberg, B.S. (1987). Epidemiology of movement disorders. In: C.D. Marsden & S. Fahn (eds): Movement Disorders 2, Butterworths, pp17-32.

Schoenberg, B.S., Anderson, D.W., Hoerer & A.F. (1985). Prevalence of Parkinson's disease in the biracial population of Copiah County Mississippi. Neurology **35**: 841-845.

Schoenberg, B.S., Osuntokun, B.O., Adeuja, A.O.G. et al. (1988). Comparison of the prevalence of Parkinson's disease in black populations in the rural US and in rural Nigeria: Door-to-door community studies. Neurology **38**: 645-646.

Schwartz, W.J. & Gainer, H. (1977). Suprachiasmatic nucleus: Use of 14-C-labelled deoxyglucose uptake as a functional marker. Science, **197**: 1089-1091.

Seddon, J.M., Samagian, C.R., Glynn, R.J., Sperduto, R.D., Gragoudas, E.S., & the eye disorders case-sontrol study group. (1990). Evaluation of an iris color classification system. Investigative Ophthalmology and Visual Science **31**(8): 1592-1598

Semchuk, K.M., Love, E.J. & Lee, R.G. (1991). Parkinson's disease and exposure to rural environmental factors - a population based control study. Canadian Journal of Neurological Sciences **18** (3): 279-286.

Semchuk, K.M., Love, E.J. & Lee, R.G. (1992). Parkinson's disease and exposure to agricultural work and pesticide chemicals. Neurology **42**:1328-1335.

Sereno, M.I. & Allman, J.M. (1991). Cortical visual areas in mammals. In: A.G. Leventhal: The neural basis of visual function. General ed: J.R. Cronly-Dillon: Vision and visual dysfunction, **4**: 160-172

Shapley, R. & Perry, V.H. (1986). Cat and monkey retinal ganglion cells and their visual functional roles. Trends in Neuroscience: 229-235.

Shapley, R., Reid, R.C.& Kaplan, E. (1991). Receptive field structure of P and M cells in the monkey. In: A. Valberg & B.B. Lee: From pigments to perception: Advances in understanding visual prcesses.pp 95-104.

Shaw, N.A. & Cant, B.R. (1980). Age dependent changes in the latency of the pattern visual evoked potential. Electroencephalography and Clinical Neurophysiology **48**: 237-241.

Shigematsu, Y. & Yamada, M. (1988). Effects of dopamine on spatial properties of horizontal cell responses in the carp retina. Neuroscience research Suppl. 8: 69-80.

Shoulson, I. (1989). Experimental therapeutics directed at the pathogensis of Parkinson's disease. In: D.B.Calne (ed). Drugs for the Treatment of Parkinson's Disease. Hanbook of Experimental Pharmacology **88**: 289-305.

Shults, C.W. (1992). Future perfect? presymptomatic diagnosis, neural transplantation and trophic factors. Neurologic Clinics **10** (2): 567-593.

Shute, C.C.D. & Lewis, P.R. (1967). The ascending cholinergic reticular system: Neocortical, olfactory and subcortical projections. Brain, **90**: 497-519.

Sillito, S. & Zeki, S. (1983). Cholinergic modulation of the functional organization of the cat visual cortex. Brain Research, **289**: 143-155.

Simms, N.R., Bowen, D.M. (1983). Changes in choline acetyltransferase and acetylcholine sysnthesis. In: B. Reisberg (ed). Alzheimer's disease: The free press, Macmillan Inc, New York, Collier Macmillan, London, pp. 88-106.

Sitarm, N., Weingartner, H., Kaye, W.H., Ebert, M.H., Epstein, R. (1983). Combination treatment of Alzheimer dementia. In: B. Reisberg (ed). Alzheimer's disease: The free press, Macmillan Inc, New York, Collier Macmillan, London, pp. 355-361.

Siversten, B., Dupont, E., Mikkelsen, B., Mogensen, P., Kasmussen, C., Boesen, F. & Heinonen, E. (1989). Selegiline and levodopa in early or moderately advanced Parkinon's disease: a double-blind controlled short- and long- term study. Acta Neurologica Scandinavica **80** (126): 147-152.

Skuse, N.F. & Burke, D. (1990). Power spectrum and optimal filtering for visual evoked potentials to pattern reversal. Electroencephalography and Clinical Neurophysiology **77**: 199-204.

Sladek, J.R. & Shoulson, I. (1988). Neuroal transplantation: a call for patience rather than patients. Science **240**: 1386-1388.

Sloan, E.P. & Fenton, G.W. (1992). Serial visual evoked potential recording in geriatric psychiatry. Electroencephalography and Clinical Neurophusiology **84**: 325-331.

Sloan, E.P., Fenton, G.W., Standage, K.P. (1992). Anticholinergic drug effects on quantitative electroencephalogram, visual evoked potential, and verbal memory. Biological Psychiatry. **31**: 600-606.

Smith, A.T., Early, F., Jones, G.H. (1990). Comparison of the effects of Alzheimer's disease, normal aging and scopolamine on human transient visual evoked potentials. Psychopharmacology **102**: 535-543.

Soininen, H., Partanen, J., Laulumaa, V., Paakkonen, A., Helkala, E.-L,. Riekkinen, P.J. (1991). Serial EEG in Alzheimer's disease: 3 year follow-up and clinical outcome. Electroencephalography and Clinical Neurophysiology **79**: 342-348.

Sokol, S. & Moskowitz, A. (1981). Effect of retinal blur on the peak latency of the pattern evoked potential. Vision Research **21**: 1279-1286.

Sollazzo, D. (1985). Influence of L-dopa / carbidopa on pattern reversal VEP: behavoural differences in primary and secondary parkinsonism. Electroencephalography and Clinical Neurophysiology **61**: 236-242.

Spehlmann, R. (1971). Acetylcholine and the synaptic transmission of non-specific impulses to the visual cortex. Brain, **94**: 139-150.

Spehlmann, R., Gross, R.A., Ho, S.U., Leestma, J.E. & Norcross, K.A. (1977). Visual evoked potentials and post mortem findings in a case of cortical blindness. Annals of Neurology, **2**: 531-534.

Spekreijse, H. (1991). Localixation of the electromagnetic sources of the pattern onset response in man. In: A. Valberg & B.B. Lee (eds): From Pigments to Perception. Plenum press, New York, London. pp 211-221.

Spekreijse, H., Estevez, O., Reits, D. (1977). Visual evoked potentials and the physiological analysis of visual proceses in man. In J.E. Desmedt (ed): Visual Evoked Potentials: New Developments. Oxford, England, Clarendon Press. pp 16-87.

Stacy, M. & Jankovic, J. (1992). Differential diagnosis of Parkinson's disease and the parkinsonism plus syndromes. Neurologic Clinics **10** (2): 341-359.

Stanzione, P., Tagliati, M., Porcu, P., Bernardi, G. (1991). Haloperidol delays pattern electroretinograms more than visual evoked potentials in normal humans: A pharmacological tool in Parkinson's disease pathophysiology. Clinical Vision Science **6** (2): 137-147.

Steel, J.C., Richardson, J.C., Olszewski, J. (1964). Progressive supranuclear palsy. Archives of Neurology **10**: 333-359.

Stein, B.E. & Meredith, M.A. (1991). Functional organisation of the superior colliculus. In: A.G. Leventhal: The neural basis of visual function. General ed: J.R. Cronly-Dillon: Vision and visual dysfunction, **4**: 85-110.

Stegg, G., Ingvarsson, P.E., Johnels, B., Valls, M., Thorselius, (1989). Objective measurement of motor disability in Parkinson's disease. Acta Neurologica Scandinavica **126**: 67-76.

Stern, G. & Lees, A. (1986). Long-term effects of Bromocriptine given to de novo patients with idiopathic Parkinson's disease. Advances in Neurology **45**: 525-528.

Stocchi, F., Bramante, L., Monge, A., Viselli, F., Baronti, F., Stefano, E. & Ruggieri, S. (1993). Apomorphine and lisuride infusion: A comparative Chronic Study. Advances in Neurology **60**: 653-656.

Stockard, J.J., Hughes, J.F., Sharbrough, F.W. (1979). Visually evoked potentials to electronic pattern reversal: Latency variations with gender, age and technical factors. American Journal of EEG. Technology **19**: 171-204.

Stone, J. (1983). Parallel processing in the visual system, Plenum Press, New York.

Stone, J. & Fukuda, Y. (1974). Properties of cat retinal ganglion cells: A comparison of W-cells with X- and Y-cells. Journal of Neurophysiology, **37**: 722-745.

Strasburger, H., Murray, I.J., Remky, A. (1993). Sustained and transient mechanisms in the steady-state visual evoked potential: onset presentation compared to pattern reversal. Clinical Vision Science **8** (3): 211-234.

Straumanis, J.J., Shagass, C., Schwartz, M. (1964). Visually evoked cerebral response changes associated with chronic brain syndromes and aging.

Struppler, A., Gurfinkel,V., Mathis, J. & Max, T. (1993). Motor performance in parkinsonism following stereotactic thalamotomy. Advances in Neurology **60**: 403-407.

Sunderland, T., Tariot, P.N., Newhouse, P.A. (1988). Differential responsivity of mood, behaviour, and cognition to cholinergic agents in elderly neuropsychiatric populations. Brain Research Reviews **13**: 371-389.

Sutcliffe, R.L.G., Prior, R., Mawby, B. & Mc Quillan, W.J. (1985). Parkinson's disease in the district of Northampton Health Authority, United Kingdom. Acta Neurologica Scandinavica **72**: 363-379.

Svenson, L.W. (1991). Regional disparities in the annual prevalence rates of Parkinson's disease in Canada. Neuroepidemiology **10**: 205-210.

Syed, A.B., Armstrong, R.A. & Smith, C.U.M. (1993). Ophthalmic and Physiologic Optics, **13**.

Tanner, C.M. (1992). Epidemiology of Parkinson's disease. Neurologic Clinics **10** (2): 317-329.

Tanner, C.M. (1992). Occupational and environmental causes of parkinsonism. Occupational Medicine **7** (3): 503-513.

Tanner, C.M., Chen, B., Wang, W. et al. (1987). Environmental factors in the etiology of Parkinson's disease. Canadian Journal of Neurological Sciences **14**: 419-423.

Tanner, C.M., Goetz, C.G., Glantz, R.H. & Klawans, H.L. (1986). Pergolide mesylate: four years experience in Parkinson's disease. Advances in Neurology **45**: 547-550.

Teravainen, H., Tsui, J., Calne, D.B. (1989). Evaluation of Parkinson's Disease. In D.B., Calne (Ed): Drugs for the Treatment of Parkinson's Disease. Handbook of Experimental Pharmacology **88**: 271-279.

Terry, R.D., Davies, P. (1980) Dementia of the Alzheimer type. Annual Review of Neuroscience **3**:77-95

Terry, R. & Katzman, R (1983). Senile dementia of the Alzheimer type: Defining a disease. In: R. Katzman & R. Terry (eds). Neurology of Aging. F.A. Davis, Philadelphia, pp 51-54.

Tetrud J.W. & Langston, J.W. (1989). MPTP-induced parkinsonism as a model for Parkinson's disease. Acta Neurologica Scandinavica **126**: 35-40.

Tetrud, J.W. & Langston, J.W. (1992) Protective and preventative therapeutic strategies: Monoamine oxidase inhibitors. Neurologic Clinics **10** (2): 541-552.

Teychenne, P.F. & Parker, S. (1989). Double-blind, crossover placebo controlled trial of selegiline in Parkinson's disease - an interim analysis. Acta Neurologica Scandinavica **80** (126): 119-125.

Thal, L.J., Masur, D.M., Blau, A.D., Fuld, P.A., Klauber, M.R. (1989). Chronic oral physostigmine without lecithin improves memory in Alzhiemer's disease. Journal of the American Geriatrics Society **37**: 42-48.

Thal, L.J., Masur, D.M., Fuld, P.A., Sharpless, N.S., Davis, P. (1983). Memory improvement with oral physostigmine and lecithin in Alzheimer's disease. In: R. Karzman (ed). Biological Aspects of Alzheimer's Disease; Banbury report 15, Cold Spring Harbor Laboratory, pp 461-476.

Thiessen, B., Rajput, A.H., Laverty, W. & Desai, H. (1990). Age, environments, and the number of substantia nigra neurons. Advances in Neurology **53**: 201-206.

Thompson, D.A. & Drasdo, N. (1987). An improved method for using the DTL fibre in electroretinography. Ophthalmic and Physiological Optics **7** (3): 315-319.

Thompson, D.A. & Drasdo, N. (1987). Computation of the luminance and pattern components of the bar pattern electroretinogram. Documenta Ophthalmologica 66: 233-244.

Thompson, D.A. & Drasdo, N. (1989). The influence of stimulus contrast on the latency and amplitude of the pattern ERG. Vision Research **29** (3): 309-313.

Thurma, B.D. (1928). The cytoarchitecture of the corpus geniculature laterale. Journal of Comparative Neurology, **46**: 173-200

Tolhurst, D.J. (1973). Separate channels for the analysis of the shape and movement of a moving visual stimulus. Jounal of Physiology, **231**: 385-402.

Tomlinson, B.E & Corsellis, J.A.N. (1984). Ageing and the dementias. In: J.H. Adams, J.A.N. Corsellis, L.W. Duchen (eds): Greenfields Neuropathology 4th edn, Arnold, London, pp 951-1025.

Tork, I. & Turner, S. (1981). Histochemical evidence for a catecholaminergic (presumably dopaminergic) projection from the ventral tegmentum to visual cortex in cat. Neuroscience letter, 24: 215-219/

Torok, B., Meyer, M., Wildberger, H. (1992). The influence of pattern size on amplitude, latency and waveform of retinal and cortical potentials elicited by checkerboard pattern reversal and stimulus onset-offset. Electroencephalography and Clinical Neurophysiology 84: 13-19.

Trick, L.R. (1987). Age-related alterations in retinal function. Documenta Ophthalmologica 65: 35-43.

Trick, G.L., Barris, M.C., Bickler-Bluth, M. (1989). Abnormal pattern electroretinograms in patients with senile dementia of the Alzheimer type. Annals of Neurology 26: 226-231.

Troscianko, Y. & Calvert, J. (1992). Impaired parallel visual mechanisms in Parkinson's disease: Implications for the role of dopamine in visual attention. Clinical Vision Science, 8 (3): 281-287.

Tyrell, P.J. & Rossor, M.N. (1989). Extrapyramidal signs in dementia of the Alzheimer type. Lancet ii: 920.

Updyke, B.V. (1983). A re-evaluation of the functional organisation and cytoarchitecture of the feline lateral posterior complex, with observations on adjoining cell groups. Journal of Comparative Neurology, 219: 143-181.

Uren, S.M., Stewart, P., Crosby, P.A. (1979). Subject cooperation and the visual evoked response. Investigative Ophthalmology and Visual Science 18 (6): 648-652.

Vaclav, F. & Balik, J. (1978). Possible indication of dopaminergic blockade in man by electroretinography. International Pharmacopsychiatry 13: 151-156.

Valverde, F. (1991). The organisation of the striate cortex. In: B. Dreher & S.R. Robinson (eds): Neuroanatomy of the visual pathways and their development. General ed: J.R. Cronly-Dillon: Vision and visual dysfunction, 3: 235-277.

Van der Drift, J.H.A. (1986). Low-dosage treatment in de novo patients with Parkinson's disease: A prospective study. Advances in Neurology 45: 529-534.

Van Der Voet, G.B., Mariani, E., De Wolff, F.A. (1991). Aluminium neurotoxicity. In: W. Graumann, J. Drukker (eds). Histo- and Cytochemistry as a Tool in Environmental Toxicology: Progress in Histo and Cytochemistry Vol 23, Fischer Verlag, Stuttgart, New York, pp 235-242.

Van Duijn, H., Beckmann, M.K.F., Stoof, J.C. (1985) VEP latency delay by a single dose of Haloperidol. Electroencephalography and Clinical Neurophysiology 61 (3): S172-S173.

Van Essen, D.C. (1979). Visual areas of the mammalioan cerebral cortex. Annual Review of Neuroscience, 2: 227-263.

Van Essen, D.C., Felleman, D.J., De Yoe, E.A., & Knierim, J.J. (1991). Probing the primate visual cortex: Pathways and perspectives. In: A. Valberg, & B.B. Lee (eds): From Pigmants to Perception, Plenum Press, pp 227-237.

Vieregge, P., Schiffke, K.A., Muller, B. & Ludin, H.P. (1992). Parkinson's disease in twins. Neurology **42**: 1453-1461.

Vieregge, P., Ziemens, G., Piosinski,A., Freudenberg, M., Kompf, D. (1991). Parkinsonian features in advanced Down's syndrome. Journal Neural. Transm (suppl) **33**: 119-124.

Visser, S.L. (1991). The electroencephalogram and evoked potentials in normal aging and dementia. Event-related Brain Research, EEG suppl. **42**: 289-303.

Visser, S.L., Van Tilberg, W., Hooijer, C., Jonker, C., De Rijke, W. (1985). Visual evoked potentials (VEPs) in senile dementia (Alzheimer type) and in non-organic behavioural disorders in the elderly; comparison with EEG parameters. Electroencephalography and Clinical Neurophysiology **60**: 115-121.

Visser, S.L., Stam, F.C., Tilberg, W., Velde, W., Blom, J., Rijke, W. (1976). Visual evoked responses in senile and presenile dementia. Electroencephalography and Clinical Neurophysiology **40**: 385-392.

Ward, C.D., Duvoisin, R.C., Ince, S.E., Nutt, J.D., Eldridge, R. & Calne, D.B. (1983). Parkinson's disease in 65 pairs of twins and in a set of quadruplets. Neurology **33**:815-824.

Ward, C.D., Duvoisin, R.C., Ince, S.E., Nutt, J.D., Eldridge, R., Calne, D.B. & Dambrosia, J. (1984). Parkinson's disease in twins. Advances in Neurology **40**: 341-344.

Watts, R.L., Bakay, R.A.E., Freeman, A., *et al.* (1992). Assessment of autologous adrenal-to-caudate grafting for parkinsonism in man. International Journal of Neurology

Watts, R.L., Bakay, R.A.E., Herring, C.J. *et al.* (1990). Preliminary report on adrenal medullary grafting and cografting with sural nerve in the treatment of hemiparkinson monkeys. Progress in Brain Research **82**: 581-591.

Werblin, F.S., Maguire, G., Lukasiewicz, P., & Eliasof, S. (1991). Detection of movement by neural interactions at the inner plexiform layer of the vertebrate retina. In: A.G. Leventhal (ed): The neural basis of visual function. General ed: J.R. Cronly-Dillon: Vision and Visual dysfunction, **4**: 1-9.

West, R. (1991). Parkinson's disease. From the Office of Health Economics No **103** BSC Print Ltd., London.

Whitehouse, P.J. (1986). Clinical and neurochemical consequences of neuronal loss in the nucleus basalis of Meynert in Parkinson's disease and Alzheimer's disease In: M.D. Yahr & K.J. Bergmann (eds). Advances in Neurology **45**, Raven Press Ltd., New York, pp. 393-397.

Wiesel, T.N/ & Hubel, D.H. (1966). Spatial and chromatic interactions in the lateral geniculate body of the Rhesus monkey. Journal of Neurophysiology, **29**: 1115-1156.

Willmer, E.N. (1982). Anatomy of the visual system. In: H.B. Barlow & J.D. Mollon, (eds): The Senses. Cambridge University Press, pp 35-45.

Winder, H., Tetrud, J., Rehncrona, S., Snow, B.J., Brundin, P., Bjorklund, A. Lindvall, O. & Langston, J.W. (1993). Fifteen months' follow-up on bilateral embryonic mesencephalic grafts in two cases of severe MPTP-Induced parkinsonism. Advances in Neurology **60**: 729-733.

Wisiniewski, H.M., Terry, R.D. (1976). Neuropathology of the aging brain. In: R. Terry & S. Gersham (eds). Neurobiology of Aging. Raven Press, New York, pp 265-280.

Wisniewski, K.E., Wisniewski, H.M. (1983). Age-associated changes and dementia in Down's syndrome. In: B. Reisberg (ed). Alzheimer's disease: The free press, Macmillan Inc, New York, Collier Macmillan, London, pp. 319-326.

Wolfson, L.I., Leeders, K.L., Brown, L.L., Jones, T. (1985). Alterations of regional cerebral blood flow and oxygen metabolism in Parkinson's disease. Neurology **35**: 1399-1405.

Wolters, E.Ch., Horstink, M.W.I.M., Roos, R.A.C., Jansen, E.N.H., and the Dutch Sinemet CR Study Group. (1993). Superior clinical efficacy of Sinemet CR 50/200 Versus Sinemet 25/100 in patients with fluctuating Parkinson's disease: An open and a double-blind, double-dummy, multicenter treatment evaluation. Advances in Neurology **60**: 648-653.

Wong, G.F., Gray, C.S., Hassanein, R.S. & Koller, W.C. (1991). Environmental risl factors in siblings with Parkinson's disease. Archives of Neurology **48**: 287-289.

Wood, C.C. (1982). Application of dipole localization methods to source identification of human evoked potentials. Annala of the New York Acadadmy of Sciences **388**: 139-155.

Wooten, R.C. (1987). Pharmacokinetics of levodopa. In: C.D. Marsden & S. Fahn (eds): Movement Disorders 2, Butterworths, pp 231-249.

Wright, C.E. (1983). PhD Thesis Proceedings.

Wright, C.E. (1985). The use of electrophysiology in the diagnosis of Alzheimer's disease. Alzheimer's disease Society News No 3.

Wright, C.E., Furlong, P.L. (1988). Visual Evoked Potentials in Elderly Patients with Primary or Multi-Infarct Dementia. Journal of Psychiatry **152**: 679-682.

Wright, G.M. & Richardson. (1986). Serial visual evoked potential recordings in Alzheimer's disease. British Medical Journal, **293**

Wright, C.E., Drasdo, N., Harding, G.F.A. (1987). Pathology of the optic nerve and visual association areas. Brain **110**: 107-120.

Wright, C.E., Harding, G.F.A. & Orwin, A. (1984). Presenile dementia - The use of flash and pattern VEP in diagnosis. Electroencephalography and Clinical Neurophysiology, **57**: 405-415.

Wright, C.E., Harding, G.F.A. & Orwin, A. (1986). The flash and pattern VEP as a diagnostic indicator of dementia. Documenta Ophthalmologica, **62**: 89-96.

Wright, C.E., Williams, D.E., Drasdo, N., Harding, G.F.A. (1985). The influence of age on the electroretinogram and visual evoked potential. Documenta Ophthalmologica **59**: 365-384.

Wurtman, R.J. (1985). Alzheimer's disease. Science America (Jan): 48-56.

Wurtz, R.H. & Albano, J.E. (1980). Visual motor function of the primate superior colliculus. Annual Review of Neuroscience, **3**: 189-226.

Yaar, I. (1980). The effect of levodopa treatment on the visual evoked potentials in parkinsonian patients. Electroencephalography and Clinical Neurophysiology **50**: 267-274.

Yahr, M.D., Flizan, T.S. & Moros, D. (1989). Selegiline in the treatment of Parkinson's disease - long term experience. Acta Neurologica Scandinavica **80** (126): 157-161.

Yen, S.H., Dickson, D.W., Peterson, C. & Goldman, J.E. (1986). Cytoskeletal abnormalities in neuropatholog. Progress in Neuropathology **6**: 63-90

Yesavage, J.A. (1983). Use of vasoactive medication in the treatment of senile dementia. In: B. Reisberg (ed). Alzheimer's disease: The free press, Macmillan Inc, New York, Collier Macmillan, London, pp. 374-380..

Youdim, M.B.H., Ben-Shachar, D. & Riederer, P. (1989). Is Parkinson's disease a progressive siderosis of substantia nigra resulting in iron and melanin induced neurodegeneration. Acta Neurologica Scandinavica **126** (80): 47-54.

Young, S. & Concar, D. (1992). These cells were made for learning. New Scientist suppl. **2**: 2-8.

Yuen, P. & Baxter, D.W. (1963). The morphology of Marinesco bodies (paranucleolar corpuscles) in the melanin-pigmented nuclei of the brain stem. Journal of Neurology, Neurosurgery and Psychiatry. **26**: 178-183.

Zekki, S. (1993). A Vision of the Brain. Blackwell scientific publications.

Ziering, A., Berger, L., Heineman, S.D., Lee, J. (1947). Piperidine derivatives Part III, 4-Ayrlpiperidines. Journal of Organic Chemistry **12**: 894-903.

APPENDIX 1.

KEY:

- : No response

† : Not done (due to lack of time, technical problems &/or patient fatigue)

Amplitude of the N_1-P_1 component of the steady state VEP to changes in contrast.

The results are in μV from channel 1 (O_z-F_z).

CONTRAST	5%	10%	15%	20%	25%	30%	35%	40%	45%	50%	55%	60%	65%	70%	75%	80%	85%
SUBJECT																	
A W	1.57	0.00	0.00	2.69	3.15	4.12	2.27	4.05	3.71	3.19	3.41	6.05	4.63	7.08	6.47	4.84	7.82
I M	0.87	2.00	0.00	1.42	2.86	0.09	2.27	1.74	3.13	3.36	1.53	2.94	3.10	0.79	1.03	2.79	1.37
N S	0.00	3.70	0.00	3.71	0.00	0.00	0.00	0.00	3.19	1.97	0.54	2.26	1.80	3.68	2.95	2.49	3.86
N B	1.93	0.62	0.15	1.19	1.05	0.78	1.13	0.61	0.68	0.00	1.97	1.23	2.29	0.52	1.59	0.73	1.96
T C	0.00	1.82	0.82	2.66	3.00	3.70	3.37	3.82	2.70	1.77	0.00	2.61	4.79	0.88	2.27	2.61	2.24
K L	0.00	2.37	5.64	7.21	7.86	7.89	5.91	7.11	5.13	5.74	4.36	8.32	7.42	7.48	7.90	9.41	10.16
R B	0.00	2.18	1.83	1.55	5.16	2.91	2.90	4.16	3.83	5.00	2.71	1.07	3.02	1.75	3.26	3.13	7.12
H C	0.00	0.00	2.44	0.88	1.69	2.90	2.73	4.78	1.24	0.91	2.65	1.75	2.12	1.94	2.24	1.84	3.31
Mean	0.55	1.59	1.36	2.65	3.10	2.80	2.57	3.28	2.95	2.74	2.15	3.28	3.65	3.02	3.46	3.48	4.73
S D	±0.81	±1.29	±1.97	±2.08	±2.47	±2.61	±1.72	±2.36	±1.43	±1.97	±1.45	±2.57	±1.88	±2.81	±2.43	±2.66	±3.22

TABLE A1

Amplitude of the N_2-P_2 component of the steady state VEP to changes in contrast.

The results are in μV from channel 1 (O_z-F_z).

CONTRAST	5%	10%	15%	20%	25%	30%	35%	40%	45%	50%	55%	60%	65%	70%	75%	80%	85%
SUBJECT																	
A W	2.55	0.00	0.00	2.58	3.45	4.72	3.90	6.00	2.92	5.94	4.19	3.01	3.16	4.63	5.28	2.16	7.50
I M	1.89	2.45	0.00	1.39	2.28	1.27	2.84	2.96	1.18	2.82	2.77	2.52	1.63	1.27	2.52	2.24	0.96
N S	0.00	2.30	0.00	3.59	0.00	0.00	0.00	0.00	2.67	0.72	0.70	2.93	5.04	0.88	2.32	3.85	2.13
N B	1.96	1.26	1.27	1.41	1.15	0.96	1.13	1.12	1.69	0.00	5.18	2.05	4.39	1.27	2.97	1.70	3.28
T C	0.00	1.57	3.30	2.52	2.48	3.43	2.65	1.62	2.39	2.73	0.00	1.98	2.54	6.07	5.78	3.00	6.16
K L	0.00	1.28	5.74	6.86	6.18	5.84	6.02	6.06	7.65	8.06	6.30	7.22	5.86	9.40	8.51	8.86	6.47.
R B	0.00	1.67	1.36	1.70	1.21	2.90	3.05	2.25	4.27	3.38	2.98	3.04	4.16	1.95	6.10	4.08	6.20
H C	0.00	0.00	1.99	2.18	2.49	2.08	1.83	2.92	3.93	3.89	3.91	2.85	3.84	5.40	2.67	4.65	4.79
Mean	0.80	1.32	1.71	2.78	2.41	2.65	2.68	2.87	3.34	3.44	3.25	3.20	3.83	3.94	4.52	3.82	4.69
S D	±1.12	±0.92	±2.00	±1.80	±1.86	±1.97	±1.82	±2.18	±2.03	±2.62	±2.13	±1.68	±1.36	±3.07	±2.24	±2.29	±2.33

TABLE A2

Amplitude of the N_1-P_1 component of the steady state VEP to changes in contrast.

The results are in μV from channel 4 (O_1-C_3).

CONTRAST	5%	10%	15%	20%	25%	30%	35%	40%	45%	50%	55%	60%	65%	70%	75%	80%	85%
SUBJECT																	
A W	0.00	0.00	0.00	0.50	1.50	2.10	0.50	2.50	2.10	1.50	0.90	4.25	2.00	3.50	4.75	2.82	4.50
I M	1.25	1.25	0.00	2.00	1.50	0.25	3.00	1.50	3.00	3.00	2.50	3.00	3.00	0.25	3.00	3.50	1.50
N S	0.00	4.00	3.00	0.75	2.00	2.75	2.00	0.50	4.00	1.75	0.75	3.75	3.25	6.00	4.00	3.00	3.50
N B	0.00	0.00	0.00	0.00	0.00	0.00	0.15	0.00	0.10	0.00	0.60	0.60	1.33	0.60	0.20	0.50	0.70
T C	0.00	0.00	0.20	1.50	2.50	3.25	3.00	2.30	0.10	1.70	1.00	1.00	3.25	0.70	1.00	0.75	2.00
K L	0.00	2.75	4.00	6.00	7.00	4.90	3.70	7.00	5.00	3.60	4.00	7.25	6.75	4.00	6.25	7.50	8.00
R B	0.00	1.75	1.25	2.75	4.20	2.50	2.75	3.50	4.25	3.00	2.50	2.50	3.25	1.75	3.75	3.00	3.00
H C	0.00	0.00	0.00	1.00	1.75	2.00	1.00	5.25	2.50	1.75	2.75	3.00	2.75	2.75	0.75	2.50	4.25
Mean	0.16	1.22	1.06	1.81	2.56	2.22	2.01	2.82	2.63	2.04	1.94	3.17	3.29	2.44	2.96	2.95	2.75
S D	±0.44	±1.53	±1.59	±1.90	±2.14	±1.58	±1.32	±2.37	±1.83	±1.13	±1.17	±2.07	±1.60	±2.00	±2.14	±2.14	±2.15

TABLE A3

Amplitude of the N_2-P_2 component of the steady state VEP to changes in contrast.

The results are in μV from channel 4 (O_1-C_3).

CONTRAST	5%	10%	15%	20%	25%	30%	35%	40%	45%	50%	55%	60%	65%	70%	75%	80%	85%
SUBJECT																	
A W	0.00	0.00	0.00	0.50	1.25	2.50	2.25	2.25	2.20	3.25	0.85	2.25	2.00	2.50	2.50	0.90	2.75
I M	0.75	1.25	0.00	2.00	2.00	0.50	1.50	2.75	1.25	2.00	3.00	1.00	1.75	1.50	2.50	2.00	1.50
N S	0.00	1.50	3.00	4.00	0.75	3.00	1.75	2.75	3.75	0.25	0.50	1.75	1.50	1.50	3.00	1.75	3.00
N B	0.00	0.00	0.00	0.00	0.00	0.00	1.30	0.00	0.20	0.00	3.50	2.43	3.15	1.50	0.75	0.10	1.70
T C	0.00	0.00	0.20	2.50	3.60	1.75	1.25	2.30	2.00	2.00	0.75	1.25	3.25	4.00	3.75	3.00	5.75
K L	0.00	1.00	4.00	6.00	5.90	4.60	4.80	4.00	6.50	5.50	5.50	7.00	4.75	5.50	6.00	7.00	6.00
R B	0.00	1.75	1.25	2.00	1.00	3.75	3.00	2.90	3.75	3.50	3.75	2.50	4.25	4.25	5.25	4.25	3.25
H C	0.00	0.00	0.00	1.00	4.00	1.75	2.75	3.25	3.75	3.55	3.00	3.75	5.50	5.75	3.50	3.00	6.75
Mean	0.09	0.69	1.06	2.25	2.31	2.23	2.33	2.53	2.93	2.47	2.61	2.74	3.27	3.21	3.41	3.43	3.84
S D	±0.27	±0.77	±1.59	±1.96	±2.00	±1.56	±1.19	±1.16	±1.94	±1.81	±1.76	±1.92	±1.47	±1.80	±1.65	±2.27	±2.04

TABLE A4

% Power of second harmonic component (12Hz) of steady state VEP for each subject.

The results are from channel 1 ($O_Z - F_Z$).

CONTRAST	5%	10%	15%	20%	25%	30%	35%	40%	45%	50%	55%	60%	65%	70%	75%	80%	85%
SUBJECT																	
A W	1.5%	2.4%	12.2%	3.4%	30.8%	20.4%	20.5%	19.7%	23.6%	19.4%	35.2%	20.2%	21.9%	20.7%	48.4%	15.4%	33.7%
I M	5.3%	9.0%	0.0%	22.5%	18.2%	13.2%	17.3%	20.8%	19.0%	10.4%	20.1%	13.4%	19.3%	10.4%	16.1%	15.7%	0.0%
N S	0.0%	9.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	14.3%	0.0%	12.9%	0.0%	0.0%
N B	0.0%	2.5%	2.4%	0.0%	0.0%	1.7%	15.3%	3.2%	1.9%	0.0%	26.0%	5.5%	7.6%	7.4%	4.6%	7.9%	26.7%
T C	0.0%	0.0%	0.0%	0.0%	5.7%	6.0%	0.0%	2.3%	0.0%	5.0%	0.0%	4.7%	8.3%	10.8%	0.0%	0.0%	8.6%
K L	3.7%	21.6%	30.4%	32.9%	35.7%	29.5%	16.7%	30.6%	26.2%	29.3%	27.3%	36.4%	35.7%	41.5%	32.7%	35.3%	34.0%
R B	0.0%	8.0%	7.7%	11.8%	3.3%	16.1%	14.7%	16.6%	30.0%	17.1%	11.0%	15.2%	17.2%	22.8%	22.8%	15.0%	39.8%
H C	0.0%	0.0%	0.0%	7.7%	3.2%	0.0%	6.5%	13.4%	0.0%	9.6%	5.6%	10.9%	32.6%	9.7%	8.1%	12.7%	26.4%
Mean	1.94%	6.56%	6.59%	9.79%	12.11%	10.86%	11.38%	13.33%	12.59%	11.35%	15.65%	13.29%	19.61%	15.41%	18.23%	12.75%	21.15%
S D	±2.36	±7.17	±10.63	±12.14	±14.31	±10.79	±8.07	±10.74	±13.31	±10.16	±13.40	±11.35	±10.28	±12.78	±16.04	±11.20	±15.95

TABLE A5

% Power of second harmonic component (12Hz) of steady state VEP for each subject.

The results are from channel 4 (O_1-C_3).

CONTRAST	5%	10%	15%	20%	25%	30%	35%	40%	45%	50%	55%	60%	65%	70%	75%	80%	85%
SUBJECT																	
A W	0.0%	0.0%	9.0%	7.4%	42.5%	46.0%	30.9%	30.2%	30.0%	26.1%	42.2%	34.4%	33.6%	32.8%	60.6%	28.2%	54.9%
I M	41.2%	14.5%	13.0%	28.9%	28.2%	20.6%	19.9%	20.2%	20.8%	26.7%	20.7%	15.1%	20.6%	16.9%	19.2%	23.6%	21.9%
N S	24.5%	17.5%	0.0%	12.9%	31.2%	0.0%	0.0%	0.0%	0.0%	26.1%	0.0%	12.9%	0.0%	21.0%	40.2%	34.5%	0.0%
N B	23.1%	0.0%	0.0%	0.0%	0.0%	4.0%	43.9%	0.0%	7.4%	0.0%	43.7%	14.0%	0.0%	0.0%	0.0%	0.0%	23.2%
T C	19.4%	22.4%	18.2%	23.8%	38.9%	32.4%	0.0%	20.9%	20.3%	29.9%	33.6%	30.4%	43.7%	23.4%	0.0%	12.5%	12.1%
K L	4.8%	49.1%	55.2%	50.9%	63.0%	57.8%	49.9%	54.8%	55.5%	54.2%	52.5%	62.3%	59.8%	65.4%	61.0%	61.6%	62.1%
R B	0.0%	43.4%	33.5%	25.4%	49.6%	46.9%	46.1%	31.4%	54.7%	37.4%	38.7%	33.1%	55.7%	49.4%	44.6%	46.7%	55.6%
H C	0.0%	30.7%	0.0%	36.6%	14.1%	0.0%	30.4%	36.5%	0.0%	41.6%	0.0%	36.3%	55.5%	40.7%	37.7%	36.9%	48.4%
Mean	14.13%	22.20%	16.11%	23.24%	33.44%	25.96%	27.64%	24.25%	23.59%	30.25%	28.93%	29.81%	33.61%	31.20%	32.91%	30.50%	34.78%
S D	±15.28	±18.18	±19.54	±16.38	±19.90	±23.16	±19.66	±18.41	±22.11	±15.66	±20.03	±16.40	±24.45	±20.48	±24.27	±19.25	±23.29

TABLE A6

Amplitude of the a-b component of the 6Hz steady state ERG to changes in contrast.

The results are in μV for the right eye.

CONTRAST	5%	10%	15%	20%	25%	30%	35%	40%	45%	50%	55%	60%	65%	70%	75%	80%
SUBJECT																
N E	0.00	0.00	1.46	1.00	1.42	2.11	1.78	1.77	1.97	1.56	1.83	2.30	2.01	2.04	2.87	4.07
G R	0.00	0.00	1.30	1.00	0.91	0.52	1.59	1.43	1.60	2.20	2.40	1.97	2.04	2.49	2.75	3.75
E W	0.78	3.12	0.50	2.08	2.25	1.99	2.81	2.22	2.92	2.33	+	2.37	+	3.48	+	4.05
C H	0.00	0.00	1.10	1.40	0.72	1.96	2.02	1.92	2.04	2.55	3.66	3.28	3.08	3.29	3.08	4.27
V T	0.00	0.55	1.00	0.80	1.62	1.05	1.78	2.17	2.37	1.72	2.25	2.15	3.10	2.94	3.30	3.04
K L	0.00	0.00	0.00	1.12	1.25	1.61	1.66	1.47	2.25	2.00	2.42	1.83	3.39	2.66	3.40	3.25
A D	0.00	0.00	0.00	1.38	1.05	1.49	0.88	1.45	1.48	2.19	1.13	2.11	2.27	3.07	3.25	3.26
J B	0.00	0.00	0.00	0.97	1.68	0.79	3.12	3.50	0.96	2.91	+	+	+	5.61	+	+
Mean	0.10	0.46	0.67	1.22	1.36	1.44	1.96	1.99	1.95	2.18	2.28	2.29	2.65	3.20	3.11	3.67
S D	±0.28	±1.09	±0.62	±0.40	±0.49	±0.59	±0.71	±0.69	±0.60	±0.43	±0.83	±0.47	±0.61	±1.08	±0.26	±0.49

TABLE A7

Amplitude of the c-d component of the 6Hz steady state ERG to changes in contrast.

The results are in μV for the right eye.

CONTRAST	5%	10%	15%	20%	25%	30%	35%	40%	45%	50%	55%	60%	65%	70%	75%	80%
SUBJECT																
N E	0.00	0.00	0.64	1.66	0.99	2.37	1.93	1.61	2.03	1.26	1.68	2.20	2.00	2.80	2.97	4.05
G R	0.00	0.00	0.00	0.00	1.32	1.20	1.31	2.31	1.76	1.73	2.45	1.51	2.86	3.37	3.05	4.57
E W	0.50	0.50	0.70	1.50	2.25	2.10	2.80	2.00	2.80	2.00	†	2.30	†	3.40	†	4.00
C H	0.00	0.00	1.31	1.25	1.28	2.22	2.07	1.92	2.30	3.05	2.75	2.92	2.85	3.78	2.33	5.38
V T	0.00	0.84	0.40	0.99	1.38	1.23	1.52	2.11	2.44	1.64	2.17	2.20	3.02	3.16	3.26	3.32
K L	0.00	0.00	0.00	1.24	1.21	1.24	1.64	1.14	1.77	2.31	1.50	2.27	2.88	3.53	3.40	1.50
A D	0.00	0.00	0.00	1.67	0.92	1.23	1.28	2.02	1.14	2.05	1.83	2.92	2.37	2.67	2.87	2.82
J B	0.00	0.00	0.00	0.49	2.74	1.29	2.39	1.71	3.07	1.98	†	†	†	4.27	†	†
Mean	0.06	0.17	0.38	1.10	1.51	1.61	1.87	1.85	2.16	2.00	2.06	2.25	2.66	3.37	2.98	3.66
S D	±0.18	±0.32	±0.48	±0.59	±0.64	±0.52	±0.54	±0.36	±0.62	±0.53	±0.48	±0.50	±0.39	±0.52	±0.37	±1.26

TABLE A8

Amplitude of the a-b component of the 6Hz steady state ERG to changes in contrast.

Results are in μV for the left eye.

CONTRAST	5%	10%	15%	20%	25%	30%	35%	40%	45%	50%	55%	60%	65%	70%	75%	80%
SUBJECT																
N E	0.00	0.00	1.63	2.13	1.56	2.17	2.62	2.50	2.49	2.72	2.15	2.40	2.85	3.62	4.04	3.68
G R	0.00	0.00	1.42	1.00	1.91	1.69	2.52	2.28	1.94	2.51	2.77	1.46	1.87	3.04	2.77	4.25
E W	1.58	1.01	0.64	1.28	1.12	0.79	1.81	2.04	1.43	2.54	†	3.56	†	2.78	†	3.54
C H	0.00	0.00	0.31	1.46	1.27	2.78	2.47	2.35	2.31	3.08	2.52	3.06	2.44	3.71	3.33	5.79
V T	0.00	1.51	0.90	1.70	1.53	2.10	2.15	2.69	2.40	2.67	2.51	2.63	2.97	4.08	3.89	4.98
K L	0.00	0.00	0.00	1.20	1.68	1.25	1.74	1.42	1.29	1.74	1.46	1.27	2.24	2.30	3.07	2.56
A D	0.00	0.00	0.00	1.20	1.20	1.60	1.05	2.15	2.06	2.21	1.80	2.32	2.85	2.90	3.80	3.43
J B	0.00	0.00	0.00	1.40	1.78	2.63	2.62	2.88	1.22	2.03	†	†	†	5.17	†	†
Mean	0.20	0.32	0.61	1.42	1.51	1.88	2.12	2.29	1.89	2.44	2.20	2.39	2.54	3.45	3.48	4.03
S D	±0.56	±0.60	±0.65	±0.35	±0.29	±0.68	±0.56	±0.45	±0.51	±0.43	±0.50	±0.82	±0.43	±0.90	±0.51	±1.07

TABLE A9

Amplitude of the c-d component of the 6Hz steady state ERG to changes in contrast.

Results are in μV for the left eye.

CONTRAST	5%	10%	15%	20%	25%	30%	35%	40%	45%	50%	55%	60%	65%	70%	75%	80%
SUBJECT																
N E	0.00	0.00	0.00	2.46	1.83	2.68	2.15	2.73	3.22	1.85	3.31	2.54	2.84	4.13	3.75	3.26
G R	0.00	0.00	0.00	0.00	2.03	1.53	2.24	2.26	1.78	2.43	3.03	2.23	2.68	2.39	2.82	4.38
E W	0.50	1.00	0.40	1.00	1.12	1.10	1.60	2.00	1.40	2.30	†	3.00	†	2.70	†	3.50
C H	0.00	0.00	0.94	1.69	1.51	2.74	1.58	2.88	2.06	2.32	2.25	2.92	2.52	3.73	2.66	4.49
V T	0.00	1.67	0.68	2.14	1.92	2.31	2.22	2.43	2.34	2.85	2.66	2.77	3.04	4.57	3.30	4.90
K L	0.00	0.00	0.00	0.89	0.99	1.46	1.70	1.10	1.14	1.67	1.68	1.95	2.15	2.51	3.00	2.50
A D	0.00	0.00	0.00	0.96	1.95	1.14	1.46	2.20	1.36	1.77	1.75	1.37	3.06	2.69	4.08	3.31
J B	0.00	0.00	0.00	2.23	0.74	1.16	1.82	2.39	3.00	2.38	†	†	†	4.90	†	†
Mean	0.06	0.33	0.25	1.42	1.51	1.77	1.85	2.25	2.04	2.20	2.45	2.40	2.72	3.45	3.27	3.76
S D	±0.18	±0.64	±0.38	±0.85	±0.50	±0.70	±0.31	±0.54	±0.77	±0.40	±0.67	±0.59	±0.35	±1.00	±0.55	±0.85

TABLE A10

Amplitude of the a-b component of the 8Hz steady state ERG to changes in contrast.

Results are in μV for the right eye.

CONTRAST	5%	10%	15%	20%	25%	30%	35%	40%	45%	50%	55%	60%	65%	70%	75%	80%
SUBJECT																
J A	0.50	1.19	0.82	1.04	0.58	0.56	0.64	0.96	1.34	1.33	2.78	2.08	1.83	2.70	2.16	4.46
L M	0.36	0.92	0.46	0.88	1.06	0.92	0.72	0.97	1.37	1.57	1.87	2.07	1.11	2.27	1.59	2.64
N E	0.11	0.47	0.58	0.41	0.65	0.70	1.07	0.79	1.07	1.26	1.23	1.18	1.66	1.48	1.44	1.72
E W	0.74	1.37	1.39	1.18	1.77	1.39	3.41	3.46	2.32	1.74	†	2.01	†	2.38	†	2.28
J B	0.00	0.97	1.52	1.29	0.57	1.67	1.67	2.04	†	2.20	†	2.25	†	3.70	†	3.88
G R	0.00	0.51	0.64	0.50	0.44	0.86	0.97	0.74	1.14	1.35	1.10	1.47	1.29	1.36	2.06	2.08
Mean	0.29	0.91	0.90	0.88	0.85	1.02	1.41	1.43	1.55	1.58	1.75	1.84	1.47	2.32	1.81	2.84
S D	±0.30	±0.36	±0.45	±0.36	±0.50	±0.43	±1.04	±1.05	±0.51	±0.35	±0.77	±0.42	±0.33	±0.86	±0.35	±1.09

TABLE A11

Amplitude of the c-d component of the 8Hz steady state ERG to changes in contrast.

Results are in μV for the right eye.

CONTRAST	5%	10%	15%	20%	25%	30%	35%	40%	45%	50%	55%	60%	65%	70%	75%	80%
SUBJECT																
J A	0.65	0.55	0.96	0.78	0.78	0.59	0.82	1.09	1.50	1.33	1.40	1.72	2.00	2.09	2.02	2.61
L M	0.71	0.34	0.71	1.29	0.39	0.80	0.18	0.90	1.30	1.03	1.02	1.46	1.65	1.45	1.30	1.96
N E	0.43	0.35	0.32	0.65	0.09	0.66	0.97	0.86	0.98	0.79	1.07	1.36	1.52	1.33	1.34	1.71
E W	0.40	0.60	1.50	1.80	1.77	1.30	3.20	3.50	2.30	1.60	†	1.70	†	2.30	†	2.30
J B	0.00	0.00	1.60	0.60	0.80	1.00	1.60	1.00	2.20	2.00	†	2.10	†	3.50	†	3.80
G R	0.00	0.65	0.55	0.24	0.29	0.23	1.42	1.07	0.93	1.25	1.07	1.06	1.40	1.23	1.58	1.75
Mean	0.36	0.42	0.94	0.89	0.69	0.76	1.37	1.40	1.54	1.33	1.14	1.57	1.64	1.98	1.56	2.36
S D	±0.31	±0.24	±0.52	±0.56	±0.60	±0.37	±1.03	±1.03	±0.59	±0.43	±0.17	±0.36	±0.26	±0.86	±0.33	±0.79

TABLE A12

Amplitude of the a-b component of the 8Hz steady state ERG to changes in contrast.

Results are in μV for the left eye.

CONTRAST	5%	10%	15%	20%	25%	30%	35%	40%	45%	50%	55%	60%	65%	70%	75%	80%
SUBJECT																
J A	0.46	0.00	1.30	1.56	0.37	0.54	1.23	1.44	0.66	1.16	2.33	1.63	2.38	2.64	2.06	2.94
L M	0.00	0.79	0.74	1.15	0.84	0.98	1.29	1.42	1.27	0.90	1.47	1.52	1.35	1.66	2.29	2.28
N E	0.63	0.79	0.63	1.00	0.94	1.03	1.12	0.86	1.42	1.65	1.54	1.98	1.51	1.56	1.92	2.05
E W	0.53	0.39	0.93	0.94	0.71	1.14	1.69	1.55	1.85	2.12	+	2.41	+	3.29	+	3.08
J B	0.00	0.50	1.29	2.26	0.34	0.78	1.88	1.27	2.10	2.20	+	2.30	+	3.57	+	3.89
G R	0.00	0.51	0.59	0.63	0.42	0.65	0.66	1.17	1.19	1.11	1.41	1.30	1.52	1.78	2.18	2.27
Mean	0.27	0.50	0.91	1.26	0.60	0.85	1.31	1.29	1.42	1.52	1.69	1.86	1.69	2.42	2.11	2.75
S D	±0.30	±0.29	±0.32	±0.58	±0.26	±0.23	±0.43	±0.25	±0.51	±0.55	±0.43	±0.45	±0.67	±0.88	±0.16	±0.69

TABLE A13

Amplitude of the c-d component of the 8Hz steady state ERG to changes in contrast.

Results are in μV for the left eye.

CONTRAST	5%	10%	15%	20%	25%	30%	35%	40%	45%	50%	55%	60%	65%	70%	75%	80%
SUBJECT																
J A	0.63	0.00	0.86	0.34	0.64	0.78	1.23	0.85	1.02	1.54	1.46	2.15	2.09	1.54	2.05	2.22
L M	0.00	0.87	0.86	0.86	0.81	0.64	1.36	1.39	0.98	1.10	1.19	1.94	2.10	1.37	2.01	1.55
N E	0.60	0.90	0.79	0.79	0.72	0.98	0.92	1.28	0.98	0.87	1.56	1.45	2.00	1.81	1.73	1.90
E W	0.00	0.20	0.90	0.90	0.70	1.40	1.50	1.50	1.80	2.00	†	2.40	†	3.00	†	3.00
J B	0.00	0.00	2.00	0.80	0.50	1.00	1.50	1.00	2.40	2.00	†	2.20	†	3.47	†	3.50
G P	0.00	0.94	1.20	0.58	0.97	0.72	0.91	0.60	1.24	0.90	1.06	1.34	1.30	1.68	1.44	1.60
Mean	0.21	0.49	1.10	0.71	0.72	0.92	1.24	1.10	1.40	1.40	1.32	1.91	1.87	2.15	1.81	2.30
S D	±0.32	±0.46	±0.46	±0.21	±0.16	±0.28	±0.27	±0.35	±0.58	±0.52	±0.23	±0.43	±0.38	±0.87	±0.28	±0.79

TABLE A14

Latency in milliseconds of C11 component of the VEP to a 6′ black and white checkerboard with increasing ramp time.

RAMP TIME	0	100	200	300	400 (ms)
SUBJECT					
SP1	104.04	142.80	160.46	177.00	288.00
A D	154.00	204.40	243.00	-	-
M M	156.00	200.00	260.00	-	-
P H	134.00	-	289.00	-	-
N E	96.68	133.30	-	170.90	180.18
R D	98.00	132.00	244.00	256.00	288.00
Mean	123.79	162.50	239.29	201.30	252.06
S D	±27.73	±36.51	±47.83	±47.48	±62.45
SP2 3′ Chk	(137.70)	(187.72)	(237.14)	(270.80)	(322.40) (ms)

Latency in milliseconds of C11 component of the VEP to a 4 CPD red/green isoluminant horizontal grating with increasing ramp time.

RAMP TIME	0	100	200	300	400 (ms)
SUBJECT					
A D	155.00	212.80	300.60	-	-
P H	129.00	187.60	252.00	-	-
Mean	142.00	200.20	238.25	-	-
S D	±18.38	±17.82	±49.29	-	-

TABLE A15

Amplitude in μV of C1-C11 component of the VEP to a 6′ black and white checkerboard with increasing ramp time.

RAMP TIME	0	100	200	300	400 (ms)
SUBJECT					
SP1	16.61	12.05	5.62	6.86	8.17
A D	2.50	2.00	2.00	0.00	0.00
M M	8.00	5.00	4.20	0.00	0.00
P H	2.00	0.00	2.00	0.00	0.00
N E	10.75	11.76	0.00	5.71	3.99
R D	10.60	7.50	3.00	4.00	2.00
Mean	8.41	6.39	2.80	2.76	2.36
S D	±5.54	±4.98	±1.95	±3.16	±3.26
SP2 3′ Chk	(10.37)	(7.54)	(12.62)	(12.09)	(8.85)

Amplitude in μV of C1-C11 component of the VEP to a 4 CPD red/green isoluminant horizontal grating with increasing ramp time.

RAMP TIME	0	100	200	300	400 (ms)
SUBJECT					
A D	2.50	2.50	2.00	-	-
P H	6.00	4.75	5.00	-	-
Mean	4.25	3.63	3.50	-	-
S D	±2.47	±1.59	±2.12	-	-

TABLE A16

Latency of major negative component of VEP to a 6′ check using a 200ms raised cosine ramp with changing contrast.

The results are in milliseconds for the O_z-F_z channel.

CONTRAST	5%	10%	15%	20%	25%	30%	35%	40%	45%	50%	55%	60%	65%	70%	75%	80%
SUBJECT																
K L	-	-	-	-	-	-	331.20	327.60	325.80	329.40	313.20	311.40	307.80	309.60	302.40	309.60
J A	455.00	414.00	397.00	396.00	352.80	342.00	349.20	306.00	324.00	325.00	309.60	327.60	309.60	293.40	286.20	293.40
T F	-	-	-	-	-	284.40	266.40	315.00	313.20	271.80	297.00	239.40	280.00	255.60	270.00	300.00
N E	-	-	-	-	-	-	277.20	-	270.00	261.00	289.80	262.80	259.20	257.40	268.20	252.00
R S	-	-	-	-	-	-	-	-	-	-	-	334.80	315.00	302.40	343.80	-
P M	-	-	410.40	-	291.60	345.60	313.20	†	300.60	309.60	286.20	†	284.40	288.00	291.60	†
J A1	-	379.80	367.20	349.20	347.40	356.40	304.20	361.80	325.80	315.00	340.00	311.40	288.00	306.00	297.00	295.20
Mean	455.00	396.90	395.70	372.60	330.60	332.10	306.90	327.60	309.90	302.10	306.00	297.90	292.00	287.50	294.17	290.04
S D		±24.18	±15.34	±33.09	±33.88	±32.38	±31.46	±24.46	±21.88	±28.76	±19.45	±38.11	±19.92	±22.40	±25.39	±22.08

TABLE A17

Amplitude of major negative component of VEP to a 6′ check using a 200ms raised cosine ramp with changing contrast.

The results are in μV for the O_z-F_z channel.

CONTRAST	5%	10%	15%	20%	25%	30%	35%	40%	45%	50%	55%	60%	65%	70%	75%	80%
SUBJECT																
K L	0.00	0.00	0.00	0.00	0.00	0.00	7.50	3.50	7.80	6.50	7.80	9.50	5.00	9.00	8.60	10.50
J A	4.31	6.89	6.84	4.93	6.60	7.45	7.02	8.31	5.05	6.31	6.65	6.82	7.71	7.62	7.66	8.38
T F	0.00	0.00	0.00	0.00	0.00	3.90	5.30	4.25	3.75	5.00	4.00	4.00	1.50	7.50	5.00	7.50
N E	0.00	0.00	0.00	0.00	0.00	0.00	4.30	0.00	3.80	8.00	3.00	5.25	7.45	3.80	3.70	6.00
R S	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	4.00	7.75	4.90	3.25	†
P M	0.00	0.00	2.00	†	2.80	3.00	2.00	†	4.40	3.60	3.80	†	4.00	4.30	3.20	†
J Al	0.00	3.65	2.70	3.80	3.80	3.80	3.75	3.65	7.50	3.65	4.75	3.65	3.60	6.00	6.00	3.65
Mean	0.62	1.51	1.65	1.46	1.87	2.59	4.27	3.29	4.61	4.01	4.29	5.54	5.29	6.16	5.34	7.21
S D	±1.63	±2.74	±2.55	±2.28	±2.61	±2.80	±2.67	±3.10	±2.63	±2.23	±2.53	±2.27	±2.43	±1.94	±2.17	±2.57

TABLE A18

Amplitude of major negative component of VEP to a 6′ check using a 200ms raised cosine ramp with changing contrast.

The results are in μV for the 0_1-C_3 channel.

CONTRAST	5%	10%	15%	20%	25%	30%	35%	40%	45%	50%	55%	60%	65%	70%	75%	80%
SUBJECT																
K L	0.00	0.00	0.00	0.00	0.00	0.00	7.50	3.00	7.50	5.80	6.67	9.50	5.00	9.00	8.60	9.20
J A	1.46	3.50	3.75	3.54	3.54	5.21	5.42	5.00	3.33	4.17	3.75	3.75	5.00	5.00	5.00	7.50
T F	0.00	0.00	0.00	0.00	0.00	3.13	2.08	2.92	2.92	3.54	3.33	3.54	2.50	6.46	3.75	6.67
N E	0.00	0.00	0.00	0.00	0.00	0.00	3.75	1.67	5.42	7.50	2.50	3.96	5.83	4.17	4.17	5.00
R S	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.92	7.08	4.17	2.92	┼
P M	0.00	0.00	2.50	┼	1.67	2.29	2.92	┼	5.21	2.50	3.54	┼	4.00	4.00	3.13	┼
J A1	0.00	1.67	1.25	3.00	2.92	3.13	2.50	1.88	3.75	2.50	3.13	2.92	3.54	3.75	4.17	2.92
Mean	0.21	0.74	1.07	1.09	1.16	1.97	3.45	2.41	4.02	3.72	3.27	4.43	4.71	5.22	4.53	6.24
S D	±0.55	±1.37	±1.52	±1.70	±1.55	±2.04	±2.43	±1.67	±2.36	±2.44	±1.97	±2.52	±1.52	±1.90	±1.92	±2.40

TABLE A19

APPENDIX 2.

KEY:

- : No response

| : Not done (due to lack of time, technical problems &/or patient fatigue)

Subject Details

CONTROLS

SUB.	AGE	VA	SEX
EB	58	6/5	F
EB1	78	6/5	M
WB	78	6/4	M
BB	51	6/4	M
EB2	53	6/5	F
TB	67	6/5	M
PB	68	6/6	M
AD	77	6/6	M
JD	71	6/5	M
HD	68	6/4	M
CD	60	6/5	M
EE	70	6/5	M
LF	61	6/6	M
MG	48	6/5	F
PH	55	6/5	F
LJ	47	6/5	F
AL	78	6/9	F
TM	73	6/6	M
AM	82	6/9	M
KN	49	6/5	M
NOR	78	6/5	M
EN	77	6/6	F
MP	74	6/5	F
CR	50	6/5	F
PR	51	6/5	F
MR	56	6/5	F
CS	72	6/12	M
CS1	72	6/5	F
AS	73	6/5	M
MS	66	6/5	F
PW	51	6/5	M
MW	46	6/5	M
SW	68	6/5	M
WP	76	6/7.5	M

PD + Doperminergic Medication

SUB.	AGE	VA	SEX
AW	45	6/6	M
RN	52	6/9	M
MS	68	6/12	F
SR	62	6/7.5	M
RB	65	6/7.5	M
MV	69	6/12	F
BO	68	6/12	F
FA	76	6/7.5	M
IH	65	6/7.5	M
MI	65	6/6	F
AJ	67	6/12	F
JD	61	6/5	F
AC	63	6/6	F
IN	71	6/5	F
MT	62	6/5	F
PN	68	6/7.5	F
JP*	74	6/12	F

PD + Doperminergic & Anticholinergic Medication

SUB.	AGE	VA	SEX
JP	48	6/12	F
LE	53	6/6	M
DB	73	6/6	M
GR	67	6/7.5	M
KB	66	6/9	M
RH	62	6/9	M
JD	60	6/6	M

PD taking no Medication

SUB.	AGE	VA	SEX
MI	65	6/6	F
FD	73	6/7.5	M
EG	70	6/18	F

Table A2.1

Subject Medication Details (* :Anticholinergics).

SUBJECT	Disease Duration (Yrs.)	Medication
A W	15	Selegiline, (Rheumox), Celance, Dantrium, (Co-dydramiol), Madopar.
R N	11	Selegiline, Madopar.
M S	8	Sinemet.
S R	7	Selegiline, (Eldepryl), Sinemet, (Securun).
R B	10	Sinemet, Selegiline, (Atenolol), (Aspirin).
M U	1½	Selegiline, (Zantac).
B O	9	Sinemet, Selegiline, Bromocriptine, (Imipramine).
F A	4	Selegiline, Sinemet, (Aspirin), (Digoxin), (Frumil), (Lactulose).
I H	12	Selegiline, Amantadine, Madopar, (Diazapan).
M I	8	Selegiline, Madopar.
A J	9	Selegiline, Sinemet (controlled release), Sinemet L.S.
J D	15	Selegiline, Madopar, Bromocriptine, (Imipramine).
A C	5	Sinemet plus Madopar, Selegiline.
I N	12	Selegiline, Sinemet-plus, Sinemet (controlled release)
M T	11	Selegiline, Sinemet.
P N	8	Celance, Sinemet.
J P	6	Selegiline, Sinemet-plus, Sinemet, Bromocriptine, Benzhexol Hydrochloride* ,(Diclofenac), (Colpermin), (Ventolin), (Gaviscon), (Reliflex).
L E	15	Selegiline, Sinemet, Artane*.
D B	12	Selegiline, Sinemet-plus, Artane*, (Quinine bisulphate), (Anti-inflamatory drugs).
G R	6	Selegiline, Sinemet-plus, Artane*, (Tenoret).
K B	19	Sinemet-plus, Selegiline, Disipal*, (Lactolose, Frumil).
R H	7	Selegiline, Sinemet-plus, Orphenadrine*.
J D1.	18	Selegiline, Sinemet, Artane*.
F D	2	No Medication.
E G	2	(Nitrazepam).
J P1	5	Madopar, Selegiline, (Prednisolone).

Table A2.2

Binocular Flash VEP :- Controls

SUBJECT	N1 Latency (ms)	P1 Latency (ms)	N2 Latency (ms)	P2 Latency (ms)	Amplitude N1-P1 (μV)	Amplitude N2-P2 (μV)
E B	40.0	66.0	81.0	124.0	4.16	26.89
E B1	41.0	65.0	98.0	135.0	6.82	27.94
W B	39.0	70.0	92.0	117.0	10.34	10.39
B B	56.0	74.0	91.0	113.0	5.35	9.50
E B2	56.0	77.0	85.0	109.0	13.02	8.51
T B	59.0	77.0	95.0	118.0	2.30	6.67
P B	43.0	62.0	96.0	135.0	4.95	29.81
A D	44.0	67.0	110.0	141.0	6.31	17.99
J D	63.0	76.0	96.0	133.0	5.55	18.99
H D	43.0	71.0	95.0	128.0	6.17	10.66
C D	41.0	71.0	89.0	120.0	9.00	13.16
E E	47.0	64.0	96.0	130.0	5.06	11.40
L F	48.0	64.0	105.0	139.0	4.70	11.37
M G	55.0	79.0	92.0	110.0	7.04	6.16
P H	55.0	67.0	83.0	131.0	4.93	33.86
L J	57.0	77.0	84.0	112.0	3.70	23.01
A L	41.0	80.0	127.0	156.0	23.52	12.16
T M	57.0	80.0	116.0	142.0	7.59	10.51
A M	47.0	72.0	108.0	148.0	12.08	32.55
K N	43.0	64.0	92.0	127.0	6.32	14.01
N O R	48.0	73.0	107.0	141.0	19.13	23.92
E N	43.0	70.0	120.0	134.0	18.64	6.36
M P	44.0	82.0	111.0	133.0	20.45	5.75
C R	45.0	72.0	90.0	115.0	15.25	8.60
P R	61.0	76.0	92.0	122.0	3.13	18.57
M R	46.0	75.0	104.0	128.0	9.15	10.22
C S	41.0	69.0	103.0	144.0	11.61	17.39
C S1	54.0	77.0	116.0	137.0	4.97	13.46
A S	43.0	78.0	116.0	144.0	8.38	12.47
M S	58.0	78.0	100.0	140.0	5.65	15.39
P W	60.0	82.0	107.0	129.0	1.95	7.95
M W	42.0	62.0	88.0	113.0	14.18	21.91
S W	56.0	80.0	110.0	132.0	11.63	8.03

TABLE A2.3

Binocular Flash VEP :- Parkinson's Disease Patients Taking Dopaminergic Medication.

SUBJECT	N1 Latency (ms)	P1 Latency (ms)	N2 Latency (ms)	P2 Latency (ms)	Amplitude N1-P1 (μV)	Amplitude N2-P2 (μV)
A W	24.0	43.0	69.0	125.0	4.94	13.59
R N	57.0	75.0	97.0	142.0	6.45	5.01
M S	41.0	66.0	109.0	134.0	22.08	25.94
S R	36.0	74.0	100.0	129.0	11.26	8.06
R B	43.0	58.0	109.0	155.0	4.42	29.87
M U	-	-	68.0	104.0	-	16.00
B O	-	50.0	63.0	82.0	-	28.03
F A	48.0	75.0	109.0	127.0	9.98	11.23
I H	40.0	72.0	95.0	130.0	15.15	15.00
M I	48.0	83.0	99.0	137.0	3.78	24.66
A J	45.0	76.0	122.0	141.0	55.14	35.31
J D	46.0	66.0	85.0	130.0	7.78	9.35
A C	41.0	67.0	111.0	181.0	9.41	21.48
I N	39.0	74.0	105.0	120.0	9.05	6.90
M T	66.0	81.0	106.0	141.0	2.40	20.47
P N	48.0	72.0	108.0	140.0	18.00	12.50

TABLE A2.4

Binocular Flash VEP :- Parkinson's Disease Patients Taking Dopaminergic & Anticholinergic Medication.

SUBJECT	N1 Latency (ms)	P1 Latency (ms)	N2 Latency (ms)	P2 Latency (ms)	Amplitude N1-P1 (μV)	Amplitude N2-P2 (μV)
J P	39.00	67.00	89.00	116.00	9.96	27.16
L E	61.00	89.00	108.00	141.00	15.13	11.03
D B	38.00	67.00	103.00	167.00	4.94	16.23
G R	46.00	65.00	99.00	128.00	6.35	20.13
K B	36.00	50.00	94.00	142.00	5.10	21.66
R H	42.00	76.00	104.00	136.00	11.50	11.03
J D	51.00	63.00	109.00	160.00	0.67	14.30

TABLE A2.5

Binocular Flash VEP :- Parkinson's Disease Patients Taking No Medication.

SUBJECT	N1 Latency (ms)	P1 Latency (ms)	N2 Latency (ms)	P2 Latency (ms)	Amplitude N1-P1 (μV)	Amplitude N2-P2 (μV)
M I	36.00	56.00	74.00	136.00	2.91	33.86
F D	40.92	72.17	107.33	134.00	11.00	18.41
E G	40.92	62.41	97.56	134.00	9.59	16.57

TABLE A2.6

Pattern Reversal VEP to a 60′ Check Counterphasing at 2Hz :- Controls (RE).

SUBJECT	N75 Latency (ms)	P100 Latency (ms)	Amplitude N75-P100 (μV)
E B	80.00	104.00	10.35
E B1	60.00	109.00	4.00
W B	78.00	102.00	6.02
B B	80.00	105.00	5.26
E B2	77.00	100.00	4.67
T B	73.00	102.00	3.89
P B	106.00	136.00	3.89
A D	82.00	108.00	4.04
J D	89.00	110.00	3.77
H D	46.00	119.00	5.94
C D	88.00	115.00	7.19
E E	83.00	132.00	6.20
L F	84.00	111.00	7.40
M G	51.00	95.00	10.63
P H	83.00	134.00	15.12
L J	77.00	100.00	9.14
A L	88.00	128.00	7.63
T M	86.00	139.00	3.82
A M	99.00	127.00	3.95
K N	75.00	109.00	9.00
N O R	57.00	101.00	3.48
E N	101.00	135.00	6.11
M P	81.00	111.00	11.94
C R	81.00	105.00	7.93
P R	82.00	109.00	11.45
M R	83.00	120.00	8.00
C S	86.00	125.00	4.00
C S1	65.00	128.00	1.80
A S	79.00	115.00	3.62
M S	86.00	122.00	5.93
P W	77.00	112.00	2.82
M W	75.00	102.00	6.07
S W	78.00	104.00	6.70

TABLE A2.7

Pattern Reversal VEP to a 60′ Check Counterphasing at 2Hz :- Parkinson′s Disease Patients Taking Dopaminergic Medication (RE).

SUBJECT	N75 Latency (ms)	P100 Latency (ms)	Amplitude N75-P100 (μV)
A W	86.00	107.00	7.99
R N	58.00	113.00	3.60
M S	76.00	105.00	8.73
S R	76.00	120.00	6.14
R B	53.00	115.00	8.01
M U	86.00	118.00	8.46
B O	77.00	124.00	10.19
F A	96.00	110.00	2.12
I H	91.00	112.00	2.34
M I	82.00	113.00	8.73
A J	87.00	144.00	12.72
J D	75.00	110.00	10.26
A C	50.00	113.00	8.26
I N	57.00	111.00	15.61
M T	91.00	123.00	5.90
P N	114.00	142.00	4.72

TABLE A2.8

Pattern Reversal VEP to a 60′ Check Counterphasing at 2 Hz :- Parkinson's Disease Patients Taking Dopaminergic & Anticholinergic Medication (RE).

SUBJECT	N75 Latency (ms)	P100 Latency (ms)	Amplitude N75-P100 (μV)
J P	48.00	112.00	4.50
L E	60.00	106.00	16.82
D B	86.00	117.00	9.08
G R	67.00	114.00	7.75
K B	88.00	130.00	10.76
R H	80.00	120.00	5.25
J D	84.00	120.00	4.34

TABLE A2.9

Pattern Reversal VEP to a 60′ Check Counterphasing at 2 Hz :- Parkinson's Disease Patients Taking No Nedication (RE).

SUBJECT	N75 Latency (ms)	P100 Latency (ms)	Amplitude N75-P100 (μV)
M I	81.00	111.00	12.80
F D	93.66	126.86	3.78
E G	105.38	140.53	9.96

TABLE A2.10

Pattern Reversal VEP to a 10′ Check Counterphasing at 2Hz :- Controls (RE).

SUBJECT	N75 Latency (ms)	P100 Latency (ms)	Amplitude N75-P100 (μV)
E B	88.00	108.00	9.71
E B1	78.00	103.00	4.25
W B	83.00	104.00	4.32
B B	86.00	113.00	6.53
E B2	82.00	116.00	2.74
T B	93.00	118.00	4.34
P B	107.00	138.00	3.70
A D	105.00	137.00	3.80
J D	99.00	115.00	3.97
H D	88.00	111.00	3.54
C D	96.00	127.00	10.01
E E	97.00	128.00	7.10
L F	88.00	120.00	3.77
M G	56.00	101.00	9.37
P H	88.00	117.00	15.66
L J	85.00	106.00	3.70
A L	98.00	124.00	10.89
T M	103.00	125.00	6.09
A M	121.00	148.00	2.41
K N	91.00	123.00	7.53
N O R	112.00	150.00	5.29
E N	97.00	125.00	7.04
M P	93.00	120.00	10.93
C R	85.00	113.00	9.00
P R	89.00	126.00	10.14
M R	78.00	124.00	5.02
C S	101.00	140.00	3.44
C S1	93.00	123.00	4.79
A S	121.00	140.00	1.27
M S	93.00	126.00	8.87
P W	80.00	111.00	2.65
M W	86.00	109.00	9.73
S W	90.00	111.00	6.60

TABLE A2.11

Pattern Reversal VEP to a 10′ Check Counterphasing at 2Hz :- Parkinson's Disease Patients Taking Dopaminergic Medication (RE).

SUBJECT	N75 Latency (ms)	P100 Latency (ms)	Amplitude N75-P100 (μV)
A W	+	+	+
R N	90.00	112.00	3.75
M S	95.00	125.00	5.83
S R	96.00	120.00	6.34
R B	100.00	140.00	8.43
M U	78.00	122.00	7.82
B O	102.00	140.00	10.78
F A	100.00	122.00	6.92
I H	93.00	117.00	3.86
M I	90.00	116.00	7.93
A J	90.00	141.00	7.61
J D	72.00	116.00	13.37
A C	89.00	133.00	6.81
I N	100.00	125.00	9.16
M T	98.00	133.00	5.50
P N	120.00	155.00	5.97

TABLE A2.12

Pattern Reversal VEP to a 10′ Check Counterphasing at 2Hz :- Parkinson's Disease Patients Taking Dopaminergic & Anticholinergic Medication (RE).

SUBJECT	N75 Latency (ms)	P100 Latency (ms)	Amplitude N75-P100 (μV)
J P	92.00	115.00	4.15
L E	82.00	119.00	12.65
D B	98.00	125.00	10.73
G R	100.00	143.00	2.97
K B	97.00	138.00	11.07
R H	95.00	130.00	5.49
J D	+	+	+

TABLE A2.13

Pattern Reversal VEP to a 10′ Check Counterphasing at 2Hz :- Parkinson's Disease Patients Taking No Nedication (RE).

SUBJECT	N75 Latency (ms)	P100 Latency (ms)	Amplitude N75-P100 (μV)
M I	93.00	119.00	9.38
F D	105.38	126.86	3.82
E G	109.28	146.39	14.90

TABLE A2.14

Patten Reversal VEP to a 73′ Check Counterphasing at 6 Hz with 30% Contrast (RE).

CONTROLS			PDpx + DA			PDpx + DA + ACH			PDpx (No Medication)		
SUB.	N1-P1 Amp.(μV)	% Pow. 2nd Har.	SUB.	N1-P1 Amp.(μV)	% Pow. 2nd Har.	SUB.	N1-P1 Amp.(μV)	% Pow. 2nd Har.	SUB.	N1-P1 Amp.(μV)	% Pow. 2nd Har.
EB	4.49	45.9%	AW	5.77	20.9%	JP	4.79	5.1%	MI	3.13	53.9%
EB1	-	-	RN	2.60	1.2%	LE	3.64	18.1%	FD	3.20	41.0%
WB	2.15	39.1%	MS	4.30	38.0%	DB	2.01	11.5%	EG	3.14	20.6%
BB	0.33	10.8%	SR	-	-	GR	1.93	50.8%			
EB2	-	-	RB	0.57	11.9%	KB	5.83	35.8%			
TB	1.80	15.5%	MV	4.19	26.6%	RH	2.41	24.2%			
PB	3.48	14.8%	BO	2.71	28.8%	JD	-	-			
AD	1.84	35.2%	FA	3.96	13.5%						
JD	2.28	39.5%	IH	0.68	22.0%						
HD	4.60	7.8%	MI	1.60	46.7%						
CD	2.81	29.6%	AJ	3.77	23.8%						
EE	2.85	25.9%	JD	-	-						
LF	2.17	39.2%	AC	-	-						
MG	3.58	62.1%	IN	5.25	61.6%						
PH	6.05	43.3%	MT	2.72	17.7%						
LJ	1.98	2.2%	PN	6.00	39.3%						
AL	1.74	30.2%									
TM	2.78	29.7%									
AM	4.21	53.5%									
KN	3.17	45.3%									
NOR	1.68	40.3%									
EN	3.39	31.7%									
MP	1.97	23.0%									
CR	2.80	26.5%									
PR	3.80	50.4%									
MR	4.56	54.8%									
CS	2.51	15.4%									
CS1	-	-									
AS	-	-									
MS	3.25	34.5%									
PW	-	-									
MW	7.16	42.2%									

Table A2.15

Patten Onset/Offset VEP to a 6′ Achromatic Check of 85% Contrast Using a 200ms Ramp Time (RE).

CONTROLS		
SUB.	C11 Lat.(ms)	C1-C11 Amp.(μV)
EB	208.80	10.00
EB1	-	-
WB	270.00	5.25
BB	243.00	4.50
EB2	-	-
TB	-	-
PB	307.80	2.50
AD	237.60	4.69
JD	253.80	4.25
HD	208.80	6.10
CD	259.20	3.50
EE	212.40	6.75
LF	-	-
MG	246.60	6.15
PH	216.00	8.50
LJ	203.40	5.20
AL	241.20	6.67
TM	†	†
AM	246.60	6.00
KN	239.40	6.80
NOR	†	†
EN	248.40	6.75
MP	223.20	3.35
CR	279.00	5.00
PR	280.80	5.30
MR	252.00	5.00
CS	352.80	3.00
CS1	-	-
AS	237.60	6.50
MS	289.80	3.00
PW	295.20	2.15
MW	316.80	4.90
SW	261.00	1.50

PDpx + DA		
SUB.	C11 Lat.(ms)	C1-C11 Amp.(μV)
AW	-	-
RN	†	†
MS	239.40	3.20
SR	225.00	4.00
RB	250.20	6.00
MV	230.40	5.00
BO	-	-
FA	201.60	14.00
IH	257.40	4.00
MI	318.60	7.00
AJ	298.80	2.00
JD	280.80	6.00
AC	246.60	2.10
IN	210.60	8.00
MT	309.60	3.00
PN	-	-

PDpx + DA + ACH		
SUB.	C11 Lat.(ms)	C1-C11 Amp.(μV)
JP	-	-
LE	277.20	3.60
DB	275.40	3.80
GR	-	-
KB	259.20	5.00
RH	194.40	3.00
JD	-	-

PDpx (No Medication)		
SUB.	C11 Lat.(ms)	C1-C11 Amp.(μV)
MI	292.60	7.00
FD	231.55	3.30
EG	396.78	6.30

Table A2.16

Patten Onset/Offset VEP to a 4cpd R/G Isoluminant Horizontal Square Wave Grating Using a 200ms Ramp Time (RE).

CONTROLS		
SUB.	C11 Lat.(ms)	C1-C11 Amp.(μV)
EB	293.40	13.00
EB1	-	-
WB	253.80	7.50
BB	286.20	4.50
EB2	259.20	3.00
TB	288.00	2.00
PB	367.00	8.00
AD	288.00	5.00
JD	288.00	7.50
HD	288.00	1.00
CD	277.20	2.50
EE	289.80	6.00
LF	234.00	3.50
MG	280.80	5.25
PH	270.00	5.00
LJ	226.80	7.50
AL	316.80	5.25
TM	†	†
AM	311.40	5.00
KN	270.00	6.00
NOR	†	†
EN	300.60	5.00
MP	302.40	4.60
CR	279.00	4.00
PR.	318.60	5.00
MR	262.00	4.00
CS	-	-
CS1	-	-
AS	295.20	6.00
MS	329.40	3.50
PW	385.00	2.25
MW	313.20	3.77
SW	273.60	5.00

PDpx + DA		
SUB.	C11 Lat.(ms)	C1-C11 Amp.(μV)
AW	†	†
RN	†	†
MS	266.40	5.20
SR	300.60	5.50
RB	293.40	4.50
MV	190.80	6.75
BO	-	-
FA	246.60	6.00
IH	259.20	3.50
MI	315.00	6.70
AJ	352.80	3.80
JD	277.20	4.75
AC	302.40	4.10
IN	282.60	7.00
MT	284.40	5.00
PN	-	-

PDpx + DA + ACH		
SUB.	C11 Lat.(ms)	C1-C11 Amp.(μV)
JP	-	-
LE	275.40	3.40
DB	325.80	3.50
GR	320.40	3.82
KB	300.60	3.50
RH	264.60	4.00
JD	†	†

PDpx (No Medication)		
SUB.	C11 Lat.(ms)	C1-C11 Amp.(μV)
MI	294.00	6.00
FD	259.67	3.22
EG	424.91	2.63

Table A2.17

Example of an EEG spectral parameter output from patient MV.

CHANNEL 1

BAND	PEAK FREQUENCY	% POWER/ EDGE FREQUENCY
1	2.7	26.3%
2	6.3	64.0%
3	12.2	8.7%
4	13.7	1.0%
5	6.3	11.3Hz

CHANNEL 2

BAND	PEAK FREQUENCY	% POWER/ EDGE FREQUENCY
1	1.0	24.5%
2	6.1	64.5%
3	12.2	9.4%
4	13.4	1.6%
5	6.1	11.6Hz

CHANNEL 3

BAND	PEAK FREQUENCY	% POWER/ EDGE FREQUENCY
1	2.9	22.3%
2	6.3	68.4%
3	10.0	8.2%
4	14.2	1.1%
5	6.3	10.3Hz

CHANNEL 4

BAND	PEAK FREQUENCY	% POWER/ EDGE FREQUENCY
1	1.0	38.1%
2	6.1	51.1%
3	8.5	8.6%
4	13.7	2.2%
5	6.1	12.1Hz

CHANNEL 5

BAND	PEAK FREQUENCY	% POWER/ EDGE FREQUENCY
1	2.7	37.9%
2	6.1	47.5%
3	9.0	13.1%
4	14.6	1.6%
5	6.1	12.0Hz

BAND SPECIFICATIONS.

Band 1:	0.25 ----	4.00 Hz
Band 2:	4.00 ----	8.00 Hz
Band 3:	8.00 ----	13.00 Hz
Band 4:	13.00 ----	30.00 Hz
Band 5:	0.25 ----	30.00 Hz

Example of a steady state VEP spectral parameter output from patient MV.

CHANNEL 1

BAND	PEAK FREQUENCY	% POWER/ EDGE FREQUENCY
1	0.0	40.8%
2	0.0	38.1%
3	11.7	16.1%
4	0.0	5.0%
5	11.7	12.7Hz

CHANNEL 2

BAND	PEAK FREQUENCY	% POWER/ EDGE FREQUENCY
1	0.0	17.5%
2	0.0	47.8%
3	11.7	26.6%
4	25.4	8.1%
5	3.9	13.1Hz

CHANNEL 3

BAND	PEAK FREQUENCY	% POWER/ EDGE FREQUENCY
1	0.0	23.5%
2	0.0	47.4%
3	11.7	22.2%
4	19.8	6.9%
5	11.7	13.0Hz

CHANNEL 4

BAND	PEAK FREQUENCY	% POWER/ EDGE FREQUENCY
1	0.0	13.8%
2	5.9	38.5%
3	11.7	35.3%
4	19.8	12.4%
5	11.7	13.4Hz

CHANNEL 5

BAND	PEAK FREQUENCY	% POWER/ EDGE FREQUENCY
1	0.0	18.8%
2	5.9	37.7%
3	11.7	30.5%
4	19.5	13.1%
5	11.7	13.6Hz

BAND SPECIFICATIONS.

Band 1:	0.25 ----	4.00 Hz
Band 2:	4.00 ----	8.00 Hz
Band 3:	8.00 ----	13.00 Hz
Band 4:	13.00 ----	30.00 Hz
Band 5:	0.25 ----	30.00 Hz

APPENDIX 3.

KEY:

- : No response

| : Not done (due to lack of time, technical problems &/or patient fatigue)

Photopic ERG.

CONTROLS				PD + DA Medication				PD + DA + ACH			
SUB.	a (ms)	b (ms)	a-b (μV)	SUB.	a (ms)	b (ms)	a-b (μV)	SUB.	a (ms)	b (ms)	a-b (μV)
EB	16.00	31.60	43.13	BO	15.60	29.60	119.93	JP	14.80	26.40	96.61
MW	16.00	28.00	41.25	JP	16.80	32.80	36.25	RH	16.40	36.00	49.39
AS	16.00	32.80	106.28	RB	24.40	29.20	60.23	GR	15.60	28.00	106.04
TM	16.40	32.80	61.74	FA	23.60	35.20	48.74	DB	22.40	29.20	83.90
AM	19.60	43.20	10.13	IH	22.40	34.80	25.95	LE	16.40	27.20	63.39
JD	14.40	30.80	58.81	AH	17.20	27.60	39.89	KB	14.40	27.60	94.59
MS	17.20	31.60	46.33								
NOR	17.20	32.40	36.67								
EN	25.60	50.00	2.73								
AL	18.40	32.80	28.19								
MP	18.00	32.20	45.53								
CS	18.40	34.40	46.22								
WP	16.40	28.00	42.60								
EE	17.20	36.40	154.21								

TABLE A3.1

Scotopic ERG.

CONTROLS				PD + DA Medication				PD + DA + ACH			
SUB.	a (ms)	b (ms)	a-b (μV)	SUB.	a (ms)	b (ms)	a-b (μV)	SUB.	a (ms)	b (ms)	a-b (μV)
EB	-	-	-	BO	22.00	44.40	394.91	JP	20.80	60.80	326.95
MW	24.40	75.60	408.97	JP	30.00	56.00	179.28	RH	22.40	50.80	135.93
AS	24.40	49.60	296.47	RB	29.20	53.20	239.05	GR	22.40	44.00	228.50
TM	21.60	44.80	236.73	FA	30.00	54.80	307.02	DB	28.00	54.80	282.41
AM	-	-	-	IH	26.40	48.40	217.96	LE	28.40	52.40	285.93
JD	21.60	47.20	226.16	AH	27.60	49.20	222.65	KB	24.40	52.00	376.17
MS	27.60	53.20	297.65								
NOR	25.20	48.00	158.19								
EN	23.60	42.80	141.79								
AL	25.20	50.80	147.65								
MP	29.60	52.80	172.65								
CS	26.40	47.60	128.11								
WP	23.20	46.80	207.41								
EE	24.80	50.00	331.63								

TABLE A3.2

Pattern Reversal ERG to a 48′ Check Counterphasing at 2Hz at 85% Contrast

CONTROLS				PD + DA Medication				PD + DA + ACH			
SUB.	N35 (ms)	P50 (ms)	N35-P50 (μV)	SUB.	N35 (ms)	P50 (ms)	N35-P50 (μV)	SUB.	N35 (ms)	P50 (ms)	N35-P50 (μV)
EB	34.80	57.20	2.12	BO	27.20	50.80	3.65	JP	28.80	52.80	4.54
MW	28.40	54.80	4.83	JP	32.80	57.60	3.20	RH	38.40	58.00	1.71
AS	34.40	50.40	1.85	RB	32.40	57.20	3.73	GR	27.60	54.00	3.66
TM	34.40	54.00	2.13	FA	40.80	60.40	2.45	DB	33.20	51.20	4.36
AM	40.40	64.80	1.53	IH	41.20	56.00	1.66	LE	30.00	53.60	3.20
JD	34.40	58.40	2.49	AH	36.40	58.80	1.58	KB	34.40	52.80	2.79
MS	35.20	57.60	3.29								
NOR	40.80	57.60	1.59								
EN	25.60	50.00	2.73								
AL	38.40	58.00	1.75								
MP	23.60	44.00	2.58								
CS	38.00	58.40	2.05								
WP	36.00	66.00	1.42								
EE	36.00	57.60	3.91								

TABLE A3.3

Pattern Reversal ERG to a 26′ Check Counterphasing at 2Hz at 85% Contrast

CONTROLS				PD + DA Medication				PD + DA + ACH			
SUB.	N35 (ms)	P50 (ms)	N35-P50 (μV)	SUB.	N35 (ms)	P50 (ms)	N35-P50 (μV)	SUB.	N35 (ms)	P50 (ms)	N35-P50 (μV)
EB	40.80	58.00	0.94	BO	33.60	50.00	1.74	JP	31.60	52.40	2.79
MW	28.80	56.40	4.55	JP	34.40	58.00	2.62	RH	39.20	71.60	1.84
AS	36.00	58.00	2.33	RB	33.60	58.00	3.36	GR	35.20	53.20	2.51
TM	34.80	54.40	2.04	FA	42.00	59.20	2.33	DB	34.40	57.60	2.69
AM	48.80	71.60	1.46	IH	44.40	63.20	1.92	LE	28.80	54.80	3.03
JD	40.00	59.60	2.95	AH	42.40	57.60	1.37	KB	27.20	44.80	2.12
MS	25.20	58.80	3.29								
NOR	37.60	58.00	1.15								
EN	25.60	49.20	1.75								
AL	40.00	58.00	1.44								
MP	27.60	52.80	2.67								
CS	37.60	58.00	2.18								
WP	48.40	66.00	0.87								
EE	34.80	58.80	2.05								

TABLE A3.4

Pattern Reversal ERG to a 2° 22′ Check Counterphasing at 6Hz at 30% Contrast

CONTROLS			PD + DA Medication			PD + DA + ACH		
SUB.	A-B (μV)	C-D (μV)	SUB.	A-B (μV)	C-D (μV)	SUB.	A-B (μV)	C-D (μV)
EB	2.50	1.87	BO	+	+	JP	-	-
MW	1.80	1.77	JP	0.90	1.50	RH	-	-
AS	-	-	RB	2.30	2.00	DB	+	+
TM	0.34	2.88	FA	1.80	0.50	LE	1.34	1.97
AM	0.55	0.38	IH	1.87	1.50	GR	1.00	2.50
JD	1.54	0.97	AH	1.50	1.87	KB	-	-
MS	+	+						
NOR	1.47	1.44						
EN	-	-						
AL	-	-						
MP	2.59	1.71						
CS	0.60	0.71						
WP	0.70	0.70						
EE	0.70	0.50						

TABLE A3.5

APPENDIX 4.

KEY:

- : No response

† : Not done (due to lack of time, technical problems &/or patient fatigue)

Subject Details - Alzheimers Patients.

Subjects				Approx. Disease Duration (Years)	Medication
SUB.	AGE	VA	SEX		
DH	57	6/9	M	2	Sodium Valporate, Epilim, Pthyadine.
MC	49	6/5	M	2	Prozac, Atenolol
MS	69	6/7.5	M		
AW	72	6/6	M	1 $^1/_2$	No Medication.
EH	63	6/7.5	M	2	No Medication.
JB	65	6/36*	F	3	No Medication.
UD	74	6/6	M	$^4/_{12}$	Circulation Tablets (cannot remember).
IS	68	6/7.5	F	1 $^1/_2$	Tolectin, Cimetidine.
JT	58	6/36*	M	3	Antidepressants.
MH	66	6/7.5	F	2 $^1/_2$	No Medication.
AL	68	6/9	M	4	No Medication.
MC1	80	6/9	M	1 $^1/_2$	No Medication.
FS	64	6/9	F	2	No Medication.
AE	72	6/7.5	M	4	Ondansitron, Aspirin, Water Tablets.
MP	64	6/7.5	F	3	Prosac.
MC2	61	6/5	M	3 $^1/_2$	Ondansitron.
DT	71	6/7.5	M	$^2/_{12}$	No Medication.

TABLE A4.1

Binocular Flash VEP :- Alzheimer's Disease Patients. (O_1-F_z Channel).

SUBJECT	N1 Latency (ms)	P1 Latency (ms)	N2 Latency (ms)	P2 Latency (ms)	Amplitude N1-P1 (μV)	Amplitude N2-P2 (μV)
D M	44.00	72.00	103.00	143.00	5.03	8.78
M C	44.00	66.00	114.00	163.00	5.68	5.31
M S	68.00	94.00	146.00	235.00	2.34	25.00
A W	62.41	89.75	128.81	167.88	9.50	9.33
E H	40.92	60.45	85.84	124.91	1.50	17.43
J B	42.88	66.31	97.56	132.72	8.93	6.07
U D	62.41	83.89	126.86	162.02	3.49	7.03
L S	40.92	52.64	85.61	124.91	1.34	20.41
J T	-	-	176.00	206.42	-	15.00
M H	46.78	70.22	95.61	128.81	5.98	33.15
A L	42.88	64.36	95.61	136.63	2.76	9.38
M C1	58.50	93.66	189.36	226.47	18.60	6.19
F S	40.92	72.17	97.56	124.91	2.18	9.58
A E	42.88	74.13	107.33	185.45	14.58	7.57
M P	48.73	74.13	99.52	130.77	9.92	17.38
M C2	48.73	70.22	105.38	132.72	4.78	10.52
D T	40.92	81.94	105.38	128.81	11.27	13.30

TABLE A4.2

Pattern Reversal VEP to a 60′ Check Counterphasing at 2Hz (O_1-F_Z Channel) :- Alzheimer's Disease Patients.

SUBJECT	N75 Latency (ms)	P100 Latency (ms)	Amplitude N75-P100 (μV)
D H	84.00	111.00	3.56
M C	81.00	122.00	4.51
M S	91.00	136.00	6.89
A W	93.66	124.91	7.64
E H	64.36	124.91	7.95
J B	74.13	111.23	3.41
U D	60.45	83.89	0.64
I S	97.56	121.00	5.92
J T	74.13	115.14	2.47
M H	89.75	113.19	5.08
A L	97.56	146.39	2.69
M C1	113.19	156.16	4.67
F S	89.75	109.28	2.59
A E	74.13	119.05	8.04
M P	79.98	119.05	12.07
M C2	93.66	126.86	3.11
D T	79.98	124.91	2.21

TABLE A4.3

Pattern Reversal VEP to a 10′ Check Counterphasing at 2Hz (O_1-F_Z Channel) :- Alzheimer's Disease Patients.

SUBJECT	N75 Latency (ms)	P100 Latency (ms)	Amplitude N75-P100 (μV)
D H	91.00	117.00	2.50
M C	96.00	123.00	4.15
M S	73.00	123.00	7.42
A W	93.66	146.39	7.52
E H	87.80	136.63	5.66
J B	93.66	122.95	6.93
U D	99.28	127.81	1.75
I S	97.56	132.72	7.13
J T	+	+	+
M H	95.61	122.95	6.65
A L	99.52	136.63	5.99
M C1	83.89	138.58	4.59
F S	-	-	-
A E	89.75	136.63	12.99
M P	89.75	121.00	13.71
M C2	105.38	136.63	4.97
D T	91.70	130.77	12.83

TABLE A4.4

Pattern Reversal VEP to a 73′ Check Counterphasing at 6Hz and of 30% Contrast (O_1-F_z Channel) :- Alzheimer's Disease Patients.

SUBJECT	Amplitude N1-P1 (μV)	% Power 2nd Harmonic
D H	1.40	8.60
M C	0.80	4.10
M S	-	-
A W	1.06	13.11
E H	-	-
J B	4.54	5.91
U D	-	-
I S	3.21	2.03
J T	+	+
M H	3.26	55.34
A L	2.09	18.81
M C1	2.78	21.29
F S	-	-
A E	1.46	29.97
M P	3.83	40.18
M C2	3.30	16.57
D T	4.38	27.25

TABLE A4.5

Pattern Onset/Offset VEP to a 6′ Achromatic Check of 85% Contrast Using a 200 ms Ramp Time :- Alzheimer's Disease Patients.

SUBJECT	Latency C11 (ms)	Amplitude C1-C11 (μV)
D H	196.20	4.31
M C	219.60	0.95
M S	-	-
A W	199.91	3.98
E H	442.48	5.48
J B	263.19	5.26
U D	-	-
I S	259.67	3.48
J T	+	+
M H	196.39	6.04
A L	242.09	3.25
M C1	305.38	6.64
F S	221.00	0.96
A E	266.70	11.77
M P	249.13	6.10
M C2	284.28	3.37
D T	319.44	4.92

TABLE A4.6

Pattern Onset/Offset VEP to a 4CP Isoluminant Red/Green Horizontal Grating Using a 200 ms Ramp Time :- Alzheimer's Disease Patients.

SUBJECT	Latency C11 (ms)	Amplitude C1-C11 (μV)
D H	244.80	4.50
M C	273.60	1.95
M S	-	-
A W	298.34	5.58
E H	365.14	2.80
J B	291.31	4.01
U D	249.13	1.27
I S	266.70	5.38
J T	+	+
M H	259.67	5.85
A L	301.86	3.24
M C1	354.59	5.25
F S	263.19	1.35
A E	322.95	8.50
M P	277.25	6.41
M C2	389.75	3.41
D T	340.53	13.30

TABLE A4.7

APPENDIX 5.

KEY:

- : No response

| : Not done (due to lack of time, technical problems &/or patient fatigue)

FLASH VEP.

N2 Latency (ms).

SUBJECT	Eye	Control	Run 1	Run 2	Run 3	Run 4
R D	R	56.00	67.00	67.00	68.00	61.00
	L	62.00	76.00	76.00	64.00	61.00
A D	R	59.00	60.00	86.00	60.00	77.00
	L	60.00	58.00	57.00	59.00	58.00
A G	R	70.00	68.00	65.00	68.00	72.00
	L	74.00	67.00	70.00	96.00	71.00
J B	R	69.00	69.00	69.00	70.00	60.00
	L	60.00	60.00	70.00	67.00	71.00
P F	R	99.00	101.00	102.00	101.00	104.00
	L	97.00	99.00	100.00	99.00	99.00
J G	R	47.00	59.00	45.00	42.00	37.00
	L	41.00	40.00	58.00	40.00	56.00

TABLE A5.1

P2 Latency (ms).

SUBJECT	Eye	Control	Run 1	Run 2	Run 3	Run 4
R D	R	114.00	104.00	115.00	109.00	109.00
	L	116.00	110.00	112.00	119.00	112.00
A D	R	106.00	104.00	107.00	104.00	103.00
	L	106.00	104.00	104.00	105.00	106.00
A G	R	122.00	124.00	121.00	125.00	122.00
	L	117.00	120.00	119.00	121.00	121.00
J B	R	111.00	111.00	109.00	113.00	111.00
	L	108.00	112.00	111.00	110.00	107.00
P F	R	110.00	115.00	112.00	101.00	112.00
	L	112.00	114.00	116.00	114.00	109.00
J G	R	114.00	110.00	108.00	107.00	107.00
	L	115.00	106.00	109.00	111.00	102.00

TABLE A5.2

N2-P2 Amplitude (μV).

SUBJECT	Eye	Control	Run 1	Run 2	Run 3	Run 4
R D	R	22.52	19.93	18.84	17.81	20.29
	L	23.09	22.00	17.92	16.41	20.25
A D	R	7.42	6.51	3.48	4.62	2.91
	L	5.32	6.09	6.96	5.44	5.44
A G	R	9.16	8.56	7.41	9.46	8.43
	L	9.48	10.43	8.77	6.93	9.19
J B	R	10.81	8.67	11.20	6.08	10.46
	L	16.18	12.01	8.84	9.39	5.55
P F	R	1.70	0.80	0.49	0.34	0.54
	L	2.22	2.44	2.23	2.33	1.90
J G	R	11.23	10.41	11.30	10.35	8.96
	L	13.88	11.86	9.58	12.01	12.72

TABLE A5.3

PATTERN REVERSAL VEP TO A 60' CHECK COUNTERPHASING AT 1Hz AND 85% CONTRAST.

P100 Latency (ms).

SUBJECT	Eye	Control	Run 1	Run 2	Run 3	Run 4
R D	R	119.00	113.00	115.00	115.00	116.00
	L	119.00	114.00	116.00	114.00	114.00
A D	R	129.00	122.00	131.00	126.00	126.00
	L	128.00	123.00	129.00	129.00	130.00
A G	R	115.00	112.00	115.00	125.00	114.00
	L	113.00	115.00	115.00	121.00	113.00
J B	R	109.00	112.00	124.00	127.00	125.00
	L	112.00	132.00	133.00	134.00	128.00
P F	R	113.00	116.00	113.00	107.00	125.00
	L	113.00	112.00	118.00	112.00	120.00
J G	R	120.00	117.00	115.00	115.00	122.00
	L	118.00	114.00	119.00	112.00	117.00

TABLE A5.4

N75-P100 Latency (μV).

SUBJECT	Eye	Control	Run 1	Run 2	Run 3	Run 4
R D	R	10.37	20.00	9.78	7.88	10.80
	L	12.60	11.50	9.59	12.14	10.14
A D	R	5.87	2.67	4.78	3.92	3.16
	L	4.46	3.03	1.98	3.14	4.61
A G	R	6.55	6.79	6.09	9.46	4.00
	L	7.33	6.55	5.85	6.93	4.65
J B	R	2.83	4.74	4.14	6.84	6.30
	L	7.03	6.34	5.00	6.00	4.70
P F	R	4.99	7.58	5.19	4.74	6.34
	L	7.00	7.09	5.78	5.86	4.38
J G	R	8.61	8.23	6.20	7.77	8.01
	L	10.51	9.97	9.52	6.38	10.05

TABLE A5.5

% Power of 2nd Harmonic (%).

SUBJECT	Eye	Control	Run 1	Run 2	Run 3	Run 4
R D	R	22.10	19.50	37.20	18.80	17.20
	L	21.60	15.40	4.80	15.20	22.40
A D	R	0.00	0.00	0.00	0.00	0.00
	L	0.00	0.00	0.00	0.00	0.00
A G	R	8.30	11.30	10.80	2.70	0.00
	L	2.60	4.70	5.00	6.10	0.00
J B	R	2.50	8.00	0.00	8.60	0.00
	L	5.50	3.80	7.90	9.70	0.00
P F	R	7.70	0.00	0.00	0.00	0.00
	L	0.00	0.00	0.00	6.20	0.00
J G	R	0.00	0.00	0.00	0.00	4.20
	L	0.00	0.00	0.00	0.00	0.00

TABLE A5.6

VEP'S TO A HORIZONTAL 4CPD GRATING PRESENTED AS A PATTERN ONSET/OFFSET STIMULUS USING A 300 MS RAMP.

CII Latency (ms).

SUBJECT	Eye	Control	Run 1	Run 2	Run 3	Run 4
R D	R L	268.40 316.80	332.20 341.00	305.80 301.40	301.40 308.00	295.20 319.00
A D	R L	365.20 396.00	334.40 352.00	370.00 365.20	345.40 350.00	382.00 310.20
A G	R L	341.00 378.40	354.20 -	367.40 360.80	369.60 345.40	376.20 371.80
J B	R L	352.00 332.20	340.00 330.00	370.00 385.00	374.00 374.00	327.80 356.40
P F	R L	334.40 343.20	376.20 387.20	385.00 345.40	370.00 378.40	345.40 380.60
J G	R L	- -	- -	- -	- -	- -

TABLE A5.7

CI-CII Amplitude (μV).

SUBJECT	Eye	Control	Run 1	Run 2	Run 3	Run 4
R D	R L	7.50 6.00	6.18 9.00	7.50 7.50	8.72 4.02	5.13 5.99
A D	R L	1.85 1.69	2.31 1.54	2.00 2.36	2.01 1.75	2.37 2.56
A G	R L	5.50 3.50	2.50 -	3.25 2.50	3.50 3.25	2.00 3.25
J B	R L	5.31 4.10	4.50 5.00	4.60 6.34	7.66 7.26	6.62 4.17
P F	R L	4.29 3.71	3.39 4.17	2.57 3.40	3.50 2.44	3.60 3.57
J G	R L	- -	- -	- -	- -	- -

TABLE A5.8

PERG 48′ CHECK, 2Hz, 85%.

N35 Wave Latency.

SUBJECT	Eye	Control	Run 1	Run 2	Run 3	Run 4
P F	R L	32.80 34.40	26.80 26.40	26.00 28.00	24.80 25.60	25.60 27.60
J G	R L	27.60 27.20	22.80 25.20	25.60 26.80	26.80 27.20	26.80 26.80
A W	R L	29.20 27.60	25.60 28.00	27.60 27.60	† †	† †
R D	R L	27.20 28.00	24.80 28.00	24.80 28.00	25.20 26.40	22.80 22.00

TABLE A5.9

P50 Wave Latency.

SUBJECT	Eye	Control	Run 1	Run 2	Run 3	Run 4
P F	R L	49.60 50.40	44.00 44.40	45.20 45.20	43.60 44.80	45.60 45.20
J G	R L	51.60 51.60	44.40 44.80	46.00 44.40	44.80 44.00	45.20 45.20
A W	R L	53.20 51.60	47.60 48.00	49.20 50.00	† †	† †
R D	R L	53.60 54.00	46.80 50.00	46.00 45.20	45.20 44.40	45.20 44.80

TABLE A5.10

N35-P50 Wave Amplitude.

SUBJECT	Eye	Control	Run 1	Run 2	Run 3	Run 4
P F	R L	3.40 3.17	2.68 3.51	3.59 4.21	2.92 3.05	2.09 1.58
J G	R L	4.85 5.15	5.32 5.09	4.13 5.01	5.07 5.28	6.28 6.20
A W	R L	5.10 5.07	5.53 3.53	4.72 3.80	† †	† †
R D	R L	5.76 3.79	5.63 3.66	5.50 3.87	5.72 3.76	6.46 4.07

TABLE A5.11

PERG 26′ CHECK, 2Hz, 85%.

N35 Wave Latency.

SUBJECT	Eye	Control	Run 1	Run 2	Run 3	Run 4
P F	R L	33.20 34.40	27.20 27.60	26.80 33.60	24.80 27.60	24.00 25.20
J G	R L	27.60 28.00	25.20 24.40	25.20 24.40	26.80 26.40	26.80 26.40
A W	R L	20.40 27.60	26.80 28.00	25.60 27.20	‡	‡
R D	R L	33.20 27.20	26.00 28.00	25.20 26.40	24.40 27.60	26.00 26.40

TABLE A5.12

P50 Wave Latency.

SUBJECT	Eye	Control	Run 1	Run 2	Run 3	Run 4
P F	R L	56.80 57.60	44.80 44.80	44.00 44.40	45.60 45.20	47.20 46.80
J G	R L	52.80 53.60	46.40 46.00	46.00 46.00	47.60 46.80	47.20 44.80
A W	R L	54.00 52.00	48.00 53.20	52.40 46.40	‡	‡
R D	R L	58.00 53.60	47.60 50.00	46.80 50.00	46.00 44.40	47.60 44.00

TABLE A5.13

N35-P50 Wave Amplitude.

SUBJECT	Eye	Control	Run 1	Run 2	Run 3	Run 4
P F	R L	2.89 3.56	2.01 2.39	2.39 2.60	3.00 2.83	1.46 1.22
J G	R L	3.92 4.06	3.44 3.15	3.38 4.06	3.72 4.05	5.09 4.75
A W	R L	4.15 4.98	1.96 3.18	3.52 3.07	‡	‡
R D	R L	3.57 3.50	5.23 3.11	4.01 2.85	4.60 3.24	5.45 2.80

TABLE A5.14

MAGNO ERG 27mm CHECK, 6Hz, 30%.

a-b Amplitude (μV).

SUBJECT	Eye	Control	Run 1	Run 2	Run 3	Run 4
P F	R L	0.65 0.61	1.07 1.81	1.50 1.04	1.29 0.43	0.44 0.33
J G	R L	0.03 0.48	0.71 0.76	0.71 0.70	1.07 0.78	1.06 0.96
A W	R L	1.87 2.00	2.30 1.87	2.50 1.78	‡	‡
R D	R L	1.23 0.50	1.95 1.80	1.87 1.70	1.87 1.56	1.50 1.80

TABLE A5.15

PHOTOPIC ERG.

a Wave Latency (ms).

SUBJECT	Eye	Control	Run 1	Run 2	Run 3	Run 4
P F	R L	14.00 14.00	14.40 14.40	14.50 14.50	14.00 14.00	14.80 14.40
J G	R L	15.20 15.20	14.00 14.40	14.00 14.40	14.00 14.00	14.00 14.00
A W	R L	14.00 15.60	13.60 14.00	14.80 13.60	‡	‡
R D	R L	15.00 15.00	13.60 14.40	13.20 11.60	13.60 14.00	13.20 13.60

TABLE A5.16

b Wave Latency (ms).

SUBJECT	Eye	Control	Run 1	Run 2	Run 3	Run 4
P F	R L	27.60 28.80	27.60 27.60	26.80 27.20	27.20 28.00	27.20 28.00
J G	R L	29.20 30.40	27.60 28.00	28.00 28.80	28.00 29.20	29.20 29.20
A W	R L	26.00 26.40	24.80 25.60	25.60 26.00	‡	‡
R D	R L	35.00 32.00	27.20 25.60	26.40 26.00	27.60 25.60	26.40 26.00

TABLE A5.17

a-b Wave Amplitude (μV).

SUBJECT	Eye	Control	Run 1	Run 2	Run 3	Run 4
P F	R L	73.36 74.00	133.23 116.41	105.87 102.30	118.40 113.78	92.04 100.83
J G	R L	149.87 148.23	167.86 150.23	176.36 155.57	211.58 182.98	201.58 179.76
A W	R L	95.56 92.28	128.78 109.09	80.79 112.49	‡	‡
R D	R L	34.09 18.34	181.86 95.85	141.26 85.48	153.21 89.82	131.71 88.12

TABLE A5.18

SCOTOPIC ERG.

a **Wave Latency (ms).**

SUBJECT	Eye	Control	Run 1	Run 2	Run 3	Run 4
P F	R L	22.40 22.00	21.60 23.60	24.00 23.60	21.60 22.00	21.20 21.60
J G	R L	21.20 21.20	21.60 22.00	21.60 21.60	21.60 20.80	21.20 21.20
A W	R L	20.80 21.20	20.40 20.40	20.80 21.20	‡	‡
R D	R L	21.20 23.60	21.60 22.00	21.60 21.60	20.80 21.60	22.00 22.00

TABLE A5.19

b **Wave Latency (ms).**

SUBJECT	Eye	Control	Run 1	Run 2	Run 3	Run 4
P F	R L	47.60 46.00	38.00 42.00	43.20 41.20	42.40 44.00	38.80 39.20
J G	R L	39.60 38.80	39.60 39.60	38.80 39.60	43.60 40.00	40.40 40.00
A W	R L	41.60 43.20	42.80 51.20	42.00 42.40	‡	‡
R D	R L	54.80 52.40	43.20 37.20	43.20 40.80	53.20 44.40	49.60 40.00

TABLE A5.20

a-b **Wave Amplitude (μV).**

SUBJECT	Eye	Control	Run 1	Run 2	Run 3	Run 4
P F	R L	291.78 311.71	312.88 257.81	273.04 296.48	352.73 314.06	268.36 249.61
J G	R L	301.17 266.01	392.57 383.19	369.13 339.83	461.71 400.83	400.77 358.58
A W	R L	254.28 244.92	325.77 248.43	268.35 283.58	‡	‡
R D	R L	193.35 80.85	345.69 120.70	263.66 167.57	310.54 145.30	305.85 146.47

TABLE A5.21

APPENDIX 6.

BRIEF COGNITIVE RATING SCALE (BCRS).

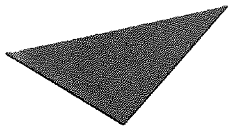
AXIS	RATING (Circle Highest Score)	ORDINAL CLINICAL CHARACTERISTICS
I: Concentration	1	No objective or subjective evidence of deficit in concentration.
	2	Subjective decrement in concentration ability.
	3	Minor objective signs of poor concentration (e.g., on subtraction of serial 7's from 100.
	4	Definite concentration deficit for persons of their background (e.g., marked deficit on serial 7's; frequent deficit in subtraction of serial 4's from 40).
	5	Marked concentration deficit (e.g., giving months backwards or serial 2's from 20).
	6	Forgets the concentration task. Frequently begins to count forward when asked to count backwards from 10 by ones.
	7	Marked difficulty counting forward to 10.
II. Recent memory	1	No objective or subjective evidence of deficit in recent memory.
	2	Subjective impairment only (e.g., forgetting names more than formerly).
	3	Deficit in recall of specific recent events evident upon detailed questioning. No deficit in the recall of major recent events.

	4	Cannot recall major events of previous weekend or week. Scanty knowledge (not detailed) of current events, favourite TV shows, and so on.
	5	Unsure of weather, may not know current president or current address.
	6	Occasional knowledge of some recent events. Little or no idea of current address, weather, and so on.
	7	No knowledge of any recent events.
III.		
Past memory	1	No subjective or objective impairment in past memory.
	2	Subjective impairment only. Can recall two or more primary school teachers.
	3	Some gaps in past memory upon detailed questioning. Able to recall at least one childhood teacher and/or one childhood friend.
	4	Clear-cut deficit. The spouse recalls more of the patient's past than the patient. Cannot recall childhood friends and/or teachers but knows the names of most schools attended. Confuses chronology in reciting personal history.
	5	Major past events sometimes not recalled (e.g., names of schools attended).
	6	Some residual memory of past (e.g., may recall country of birth or former occupation).
	7	No memory of the past.

IV: Orientation	1	No deficit in memory for time, place, identity of self or others.
	2	Subjective impairment only. Knows time to nearest hour, location.
	3	Any mistake in time > 2hr; day of week > 1 day; date > 3 days.
	4	Mistakes in month > 10 days or year > 1 month.
	5	Unsure of month and/or year and/or season; unsure of locale.
	6	No idea of date. Identifies spouse but may not recall name. Knows own name.
	7	Cannot identify spouse. May be unsure of personal identity.
V: Functioning and self-care.	1	No difficulty, either subjectively or objectively.
	2	Complains of forgetting location of objects. Subjective work difficulties.
	3	Decreased job functioning evident to co-workers. Difficulty in travelling to new locations.
	4	Decreased ability to perform complex tasks (e.g., planning dinner for guests, handling finances, marketing, etc).
	5	Requires assistance in choosing proper clothing.
	6	Requires assistance in feeding, and/or toileting, and/or bathing, and/or ambulating.
	7	Requires constant assistance in all activities of daily life.

PUBLICATIONS

Proceedings from the Society for the Promotion of the Visual Sciences, 1993.



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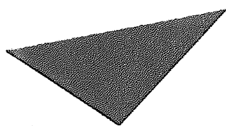
Proceedings from the XXX Symposium of the International Society for Clinical Electrophysiology of Vision, 1992.



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Proceedings from the XIII International Congress of EEG and Clinical Neurophysiology, 1993.

VISUAL EVOKED POTENTIALS IN ALZHEIMER'S AND PARKINSON'S DISEASE.

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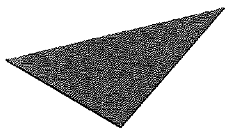

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Proceedings from the First International Meeting on Advanced Methods in Visual Psychophysiology and Electrodiagnosis, 1993.

The effect of Dopamine and Acetylcholine on the Visual Evoked Potential

R. Daniels, G.F.A. Harding and S. J. Anderson
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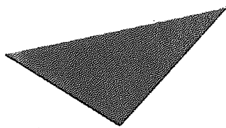

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Electroencephalography and Clinical Neurophysiology, 1993, Volume 87, Number 2, S75.

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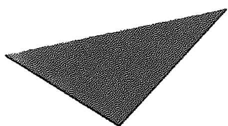
R. Daniels, G.F.A. Harding, S.J. Anderson. *Aston University, Birmingham, UK*



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Effect of dopamine and acetylcholine on the visual evoked potential

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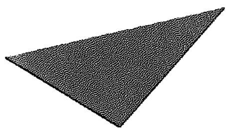

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Visual evoked potentials to flash and pattern reversal stimulation after administration of systemic or topical scopolamine

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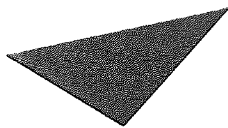
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