Signal Processing of the Auditory Event-Related Potential in Major Psychotic Illness

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ABSTRACT

The P300 waveform of the auditory event-related potential (ERP) was evaluated in studies which examined measurement methodology and which analysed the separate sub-components of the waveform in a group of patients with schizophrenia and manic depressive illness.

Two simulation studies were carried out. One was designed to evaluate a new objective method for measuring P300 latency, the other applied the technique of latency corrected averaging to P300 measurement. A model for the P300 is described which allows the time domain behaviour of the waveform to be predicted when it is subjected to the different high-pass filters used in clinical studies. A new method for measuring the latency of the P300 based on a least-mean-squares (LMS) fit to data is described. A simulation study on the technique of latency corrected averaging showed that the best method for detecting an evoked potential signal like the P300 waveform is based on covariance. The optimum signal pre-filter cut-off frequency and the most suitable type of template were determined.

The first clinical study was a detailed investigation on the measurement methodology in clinical studies of the auditory P300. Data from twenty-three schizophrenics and 26 controls were examined. The proposed model for P300 was evaluated in the frequency domain and the value of the LMS fit in P300 measurement was established.

The second clinical study used novel auditory stimuli as a means of separating the sub-components of the P300 complex. Three clinical tests were used based on the standard auditory "oddball", a standard auditory oddball with additional "distracting" novel stimuli, and a passive paradigm using novel stimuli. The use of the Slow Wave as an index of task difficulty was examined. Twenty-eight controls, 29 schizophrenics and 28 subjects with bipolar depression were studied.

The results from these experiments showed that abnormalities of P300 sub-components in the schizophrenic group are enhanced when using distracting stimuli and that these differences are present even in passive orienting. The bipolar group also showed abnormal P300 sub-components in responses to the distraction task. These results could imply a more widespread disruption in underlying brain structures in schizophrenia than bipolar depression. Used in conjunction with brain perfusion images derived from single photon emission tomography (SPET), the paradigms described have shown great potential for locating the underlying brain structures involved in the genesis of P300, and how they are affected in abnormal pathological states.

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Chapter 1.

Introduction and outline of research

The clinical diagnosis of major mental illnesses including schizophrenia and manic depressive illness is based almost entirely on symptomatology and there is as yet no established place for neuropsychological, neurophysiological, or neuroradiological tests. While the reliability of clinical diagnosis is established, the validity of current diagnostic systems is unknown. In other words, it is not at all certain that existing diagnostic schemes relate to the underlying genetic or neuropathological causes of disease. There is a tremendous need for biological markers of risk to major psychotic illness

Medical imaging modalities such as magnetic resonance imaging (MRI) and single-photon emission tomography (SPET), which look at brain anatomical structures or changes in regional cerebral blood flow, suggest that imaging may have an important role in diagnosis in the future. Some success has been reported with these techniques but, while the information provided has reasonable spatial resolution, the temporal resolution is poor. To study the cognitive processes of the brain good temporal resolution is essential. The limitations with MRI are being improved upon with the genesis of the functional MRI technique (fMRI) but much work is required on control subjects to validate the technique. However, as with SPET, the haemodynamic time-constant associated with tracer and ligand uptake shall prove the limiting factor and other techniques need to be used until these problems are surmounted.

A more promising approach is the use of evoked potentials. This technique has been used to study a range of psychiatric patients with some success. The P300 component of the long-latency event-related potential (ERP) has

been of particular value in the study of schizophrenia, dementia, unipolar depression, and bipolar depression. Differences have been identified not only between healthy control subjects and psychotic patients, but also across different groups of psychotic patients.

The success of this research has been tempered by a failure to consistently replicate results. Indeed, there have been published findings from some research groups which totally conflict with results published by other groups. As a result, there has been much attention recently regarding the methodology and clinical utility of the P300 in patients suffering from the psychoses (Goodin, 1990; Pfefferbaum et al., 1990; Polich, 1992). The need to adopt standard data acquisition and processing methodology to allow the valid inter-comparison of results from different study groups is a common theme. This not a new problem. As early as 1977 guidelines were published listing the basic essential criteria for the publication of data from ERP studies (Donchin et al., 1977). A very recent publication by an international committee has laid down standards for stimulation, recording, and component identification in ERP studies (Goodin et al., 1994).

Schizophrenia and manic depressive illness are particularly debilitating conditions. Accurate diagnosis allows treatment strategies which greatly ameliorate the symptoms of disease. Improvements in diagnostic sensitivity and specificity are desirable goals which could be realistically achieved with improved clinical testing. A sensitive marker which is able to identify subjects who are vulnerable to the development of psychotic illness has much attraction. The criteria for a marker to detect genetic risk for psychosis were outlined by Reider and Gershon (1978). A marker should have the following properties: a greater prevalence in psychotics and their relatives; be independent of medication and clinical state; be stable over time; be associated with "spectrum" disorder in families; be able to predict development of illness in "high risk" individuals and be customer friendly.

The P300 has received much attention due to its potential as a biological risk marker in schizophrenia. P300 latency and amplitude changes have been seen in a proportion of first degree relatives of schizophrenic subjects (Friedman et al., 1988; Blackwood et al., 1991; Schreiber et al., 1991; Schreiber et al., 1992; Kidogami et al., 1992; Roxborough et al., 1993). P300 amplitude reduction is an accepted feature of schizophrenia, but also occurs in dementia and depression. P300 latency delay is also becoming accepted as a feature of schizophrenia. A recent review of published studies in schizophrenia confirms this (Ebmeier, 1991). However, because the statistical distributions for P300 measures in patient groups tend to overlap with those of control groups, more accurate diagnoses, including sub-typing of conditions, are probably required to increase group separation.

There are a number of different techniques in use for making simple measurements of latency and amplitude on ERP features. The high-pass filter setting used to record data can have a significant effect on the appearance of a recorded waveform composed of different underlying frequencies. The peak of the P300 component has a particular scalp topography which will influence the result of amplitude measurements. These seemingly fundamental methodological issues have been a source of anomaly in reports of P300 in clinical studies. A detailed investigation is required to establish the influence of these separate factors on the clinical utility of the P300 as a clinical marker for psychosis.

The most common noise reduction technique used in evoked potential studies is signal averaging. This technique is ideal for stationary signals. If this fundamental requirement is violated the result of the averaging process becomes distorted. The technique of latency corrected averaging was developed to deal with non-stationary neural signals. This technique also allows a more accurate representation of an average waveform from single ERPs to be constructed as it can take account of "physiological jitter". The

amount of physiological jitter between control and patient groups is of interest, particularly if it leads to a deeper understanding of the underlying processes. Analysis of single trial ERPs offers scope for assessing the amount of jitter and reviewing short-term changes in mental state related to cognitive processing. Also, the ERP waveform is thought to comprise of a series of overlapping sub-components, reflecting concurrent underlying neural processes. The technique of identifying such (micro-volt) potentials relies on latency corrected averaging using advanced digital signal processing techniques. Cross-correlation and covariance based template matching techniques have been proposed. An in-depth study of the merits of each and other related issues, such as the optimal pre-filter setting and the "best" template, is required as published studies use a range of techniques making an inter-comparison of results difficult.

There are reports of a family of P300 sub-components, the so-called "P3a" and "P3b", which are evoked or emitted by different stimulus parameters The underlying neural processes that these sub-components reflect is not well understood. Part of the problem in interpreting the meaning of sub-components of the P300 waveform is that the associated cognitive theory is not particularly well developed and remains contentious. We are interested in determining whether P300 measures satisfy the criteria for a clinical marker. The results from the research will be assessed with this aim in mind and reference to cognitive theory will be limited to more widely accepted notions of the amount of cognitive processing resources and their allocation in response to task-relevant and task irrelevant stimuli. The scalp topography and latency of the P300 sub-components are different and different quantities of processing resources and different processing strategies are implied. There also appear to be differences in the measures of these sub-components between normal control subjects and patient groups. The ability to experimentally manipulate these sub-components is particularly attractive if it increases the sensitivity of the measure in detecting subjects with psychosis.

The specific aims of this research are:

i) To investigate the methodology used in the recording and analysis of the P300 component of the auditory "oddball" event-related potential paying particular attention to the high-pass filter setting during recording, the electrode site at which the measurement is made, the method of defining the features of the waveform.

ii) To investigate the digital signal processing methodology used in latency corrected averaging to determine the best method of template matching, the optimal pre-filter setting, and the most suitable template.

iii) To experimentally manipulate the sub-components of the cognitive P300 waveform to assess their utility for deriving a clinical marker in schizophrenia and bipolar depression.

Chapter 2.

Manic Depressive Illness and Schizophrenia

2.1 Introduction

The lifetime prevalence of schizophrenia in most countries of the world is about 1% (Regier et al., 1988) and a further 1% suffer from bipolar and manic depressive illness (Kendall, 1993). Rates for (unipolar) major depressive disorder are much higher with estimates of lifetime prevalence ranging from 5-17% (Blazer et al., 1994).

2.2 Major depressive disorder

2.2.1 Introduction

Affective disorders are disorders of mood and include anxiety, depression and elation, each with clearly recognisable symptoms. The most common form of depressive illness is unipolar depression.

2.2.2 Unipolar depression

There has long been controversy about the best way to classify depressive illness and there is often an overlap with other conditions. For example,. patients with persistent anxiety symptoms may also develop depressive symptoms and depression may also be linked to alcoholism, anorexia and several other states.

The common form of depression encountered in general medical settings is described as unipolar depressive illness. Subjects have bouts of depression but do not experience episodes of elation. Episodes may develop after particularly stressful life events, for example in bereavement, when depression is said to be reactive. Or often depression develops "out of the blue" and is described as endogenous. The classification of depression has been assisted by the independent use of structured clinical interviews, such as the Schedule for Affective Disorder and Schizophrenia (SADS) (Spitzer et al., 1979) and the adoption of standardised diagnostic criteria such as Research Diagnostic Criteria (RDC) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-

IV).

2.2.2.1 Epidemiology

Depressive symptoms are found in between 10% and 16% of men, and between 20% and 24% of women. People with depressive illness are much less common accounting for between 2.4% and 4% of men and between 7% and 8% of women in surveys carried out in London, Canberra and the United States (Kessler et al., 1994).

Depressive illnesses are the commonest diagnosis in a study of inceptions of illness in general practice, accounting for 12% of all new illnesses and 45% of all psychiatric diagnoses made in this setting.

2.2.2.2 Symptoms

These are described under four headings: emotional changes, cognitive changes, motivational changes, and neurovegetative symptoms.

Emotional changes

In the early stages of a depressive illness the patient may notice that there is no longer pleasure to be derived from life. This anhedonia is part of the experience of sadness or unhappiness. Sense of humour is often lost. Eventually the mood becomes one of sadness and misery with tendency to weep and the content of the patient's thought becoming pessimistic and gloomy, in keeping with the underlying mood.

Cognitive changes

These include feelings of low self-esteem with an exaggerated assessment of current life problems and gloomy predictions about the future. Features such as changed self-concept and self-blame become common. Difficulty in making decisions, lack of confidence and, in severe forms of depression, guilt and worthlessness prevail. Suicidal ideas may appear in the presence of such other symptoms. Sleep and appetite may both be impaired.

Motivational changes

Low energy, fatigue, apathy, and inability to concentrate are symptoms of depressed mood. Depressed patients tend to be socially withdrawn and are unable to perform tasks or take responsibility as they normally would. Failure to complete tasks reinforce ideas of self-blame or worthlessness. Patients are often said to be 'dependent' because they become willing to allow others to take over responsibility for giving them guidance.

Neurovegetative symptoms

These include disturbances of appetite, weight, sleep rhythm, libido, energy levels, and posture. Depressive mood may influence the way the patient speaks, walks, and sits. In minor depressive illness increased appetite with weight gain is common, but weight loss predominates in severe depression. There is diminution of sexual interest and performance. Sleep is reduced, interrupted, and unrefreshing. Emotional energy no longer flows outward and the patient becomes lost in miserable self-absorption. In severe depression the patient may report early waking, and diurnal variation of mood, with the worst mood in the morning.

2.2.2.3 Diagnosis

There is no point of discontinuity between normality and depression so the dividing line is arbitrary. The criteria of the American Psychiatric Association enshrined in DSM-IV manual have been established as follows

> a) Depressed mood or inability to experience pleasure to be prominent and persistent, and to have had at least three of the following seven symptoms on each day for the previous two weeks:
>
> b) poor or increased appetite/weight loss or gain; insomnia or hypersomnia; agitation or retardation; loss of energy or fatigue; feelings of worthlessness, guilt, or self-reproach; poor concentration/slowed thinking/indecisiveness; thoughts of death or attempted suicide.

c) the illness is severe enough for the person to seek help.

2.2.2.4 Aetiology - predisposing factors

A genetic contribution has been established in family, twin, and adoption studies. Studies of twins have shown a genetic component in depressive illness, where environmental precipitants may be important and life stress such as early bereavement increase vulnerability of susceptible individuals.

2.2.2.5 Treatment

Anti-depressant treatment has been used successfully in shortening the course of depressive illness. The more severe the depression the more likely that anti-depressants will succeed.

Specific Pharmacological Treatment

There are several classes of anti-depressants many of which operate on monoamine pathways. Their mode of action however remains obscure.

Specific Psychological Treatments

Cognitive therapy is given by some clinical psychologists and is useful in patients as an adjunct to anti-depressant medication.

Electroconvulsive Therapy

This treatment is reserved for severe psychotic depression when a patient is suicidal and other treatments have not worked. After administering a general anaesthetic, a sinusoidal current pulse is applied via temporal lobe and vertex electrodes with the aim of inducing a grand-mal seizure (fit). It is thought that grand-mal seizure activity is necessary for the anti-depressant effect and there is evidence that the therapeutic effect is related to the duration of the induced seizure.

2.2.2.6 Course and Prognosis

There is a large variation in the outcome of depressive illness although many patients

will become symptom free within four to six weeks. Depressive illness associated with abnormal personality is likely to have poor outcome. Depressive illness is highly responsive to treatment but there is a high likelihood of recurrent episodes.

2.2.3 Manic-Depressive Psychosis

The main features of this illness are that patients have alternating episodes of depression and excitement, often of psychotic intensity. In severe cases this illness is called mania and milder cases are called hypomania.

2.2.3.1 Epidemiology

The lifetime morbid risk for bipolar disorders is around 1% with an annual inception rate of about 10 per 100,000 men and 15 per 100,000 women (Weissman et al., 1988).

2.2.3.2 Symptoms

The main features of mania are elevation of mood, increased activity, and grandiose ideas. Mood elevation may range from euphoria to elation or irritability and anger.

2.2.3.3 Diagnosis

DSM-IV criteria include irritable or elevated mood for a period of one week which is severe enough to disrupt work and social activities. At least three of the following must be present: increased activity or restlessness; pressure of speech; subjective increase of speed of thought; increased self-esteem or grandiose ideas; decreased sleep necessity; abnormal distractibility; disinhibited behaviour.

2.2.3.4 Aetiology

Genetic Factors

Family and twin data suggest that this disorder is distinct from unipolar depression. The genotype underlying bipolar illness may sometimes produce unipolar illness or cyclothymic personality. No specific mode of inheritance has been established.

Personality

Patients with cyclothymic or depressive traits are at greater risk of bipolar disorder.

Drugs

Some patients have their only episode of manic illness during treatment with anti-depressant drugs for a depressive episode. Amphetamines have been implicated in the causes for this disorder although some people may tolerate very high doses while others develop manic illness in relatively small doses.

Stressful life events

The pattern for the development of mania often follows that for the development of depression and can be precipitated by the same sort of stressful life events, although once established, bipolar mood swings tend to be independent of life events.

2.2.3.5 Treatment

Drug treatment

Major tranquilisers are preferred in mania to deal with symptoms of excitement and hallucinations (e.g. haloperidol and chlorpromazine). Lithium carbonate is used to reduce the recurrence rate and severity of attacks.

In recurrent illness, prophylactic lithium is used for both manic depression and psychotic unipolar depression.

Electroconvulsive treatment

May be used in cases that do not respond to drug treatment.

Hospital admission

Is often necessary to contain episodes of mania.

2.2.3.6 Course and prognosis

Patients will have episodes of increasing duration and frequency during life.
Lithium has had some degree of success on the impact of the disorder, by reducing the

frequency and intensity of attacks.

2.3 Schizophrenia

Schizophrenia is regarded as a group of disorders rather than a single entity. The main groupings of the established illness were originally described by Emil Kraepelin (1856-1926) as paranoid, hebephrenic and catatonic and are still used today.

2.3.1 Epidemiology

Approximately 1% of adults are diagnosed as schizophrenic at some time during their lives (Regier et al., 1988). Onset is usually between the ages of 16 and 36 years of age.

2.3.2 Clinical features

Schizophrenia is a term used to describe a combination of symptoms. There is frequently a prodromal stage in which non-specific and mild affective symptoms precede psychotic phenomena. The duration of these symptoms may last months or years. The diagnosis is made only when it cannot be established that an organic factor initiated and maintained the disturbance. Psychotic symptoms occur in several spheres and are divide into positive and negative symptoms.

Positive symptoms

The following specific symptoms can be identified: auditory, visual, tactile, or olfactory hallucinations; thought disorder; delusions which are often paranoid or quite bizarre; affective symptoms including depression and excitement resembling mania.

Negative symptoms

These cover four areas: poverty of speech; slowness of thought and movement; emotional flatness; loss of volition. These particular symptoms are exacerbated in an under-stimulating environment.

2.3.3 Diagnostic criteria

In the absence of epilepsy, mania, intoxication or evidence of other gross cerebral damage, the presence of one or more of the following symptoms for a period of longer than one month indicates a likely diagnosis of schizophrenia:

a) disorders of thought possession; auditory hallucinations; passivity experiences; persistent delusions and delusional perception, and the diagnosis should also be considered if the patient has two or more of the following:

b) persistent hallucinations in any modality; incoherent or irrelevant speech and mannerisms; catatonic phenomena; negative symptoms.

Additionally, it is necessary to differentiate between schizophrenia and mania as recent studies have shown some overlap of symptoms. The presence of pronounced elation of mood assists in categorizing mania. Repeated episodes of illness in mania and schizophrenia are common but the gradual accumulation of negative symptoms in the course of the illness is symptomatic of schizophrenia.

2.3.4 Aetiology

A number of factors are implicated in the development of the illness. Perhaps the most important is genetic followed by environmental especially, it is believed, influences on the early development of the individual.

Genetic causes

A number of studies now have shown that this is a major factor in the development of the illness. The risk associated for one person who has a sibling or one parent suffering from schizophrenia is about 12% (Gershon, et al., 1976). The risk for a child with two parents suffering from schizophrenia is about 40% (Gottesman and Shields, 1982). This is underlined by the fact that the risk holds even for twins who have been raised apart or adopted offspring reared apart from a schizophrenic parent (Stabeneau, et al., 1969).

Environmental factors

There is some evidence that suggests this is also a factor in the development of the illness because of:

i) the lack of 100% genetic concordance in monozygotic twins;

ii) the excess of winter births in schizophrenic patients;

iii) the increased incidence of birth complications.

2.3.5 Course

The characteristic course of the illness is relapsing and chronic and the patient often becomes progressively more disabled. The outcome for schizophrenia is however variable and it is possible to make a complete recovery from a single episode of the illness.

2.3.6 Treatment

Long-term treatment for schizophrenia as a hospital in-patient has gradually been replaced by brief hospital treatment for the acute phase followed by sustained treatment in the community.

Acute phase

In-patient admission or day-unit attendance is usually accompanied by medication. Oral neuroleptics such as chlorpromazine are used to suppress psychotic behavioural disturbances. Nursing support and occupational therapy is given to encourage the patient to maintain a normal daily routine.

Long-term treatment

Medication is usually changed to long acting injections of flupethixol or fluphenazine, given every two to four weeks. The patient may move to accommodation, either at home or supported by qualified care staff, to allow them to adopt a place in the community.

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Chapter 3.

Evoked potentials and the Event-related potential (ERP)

In this chapter an outline is given of the source of brain electrical signals in relation to the underlying cell structure and anatomy. The methodology for recording brain-originating scalp potentials is covered, with particular emphasis on evoked and event-related potentials. The cognitive event-related potential (ERP) is considered in depth with a review of its clinical application. Results from a study on the effect of time domain high-pass filtering on the appearance of the ERP is presented and a model of the P300 component of the ERP is proposed.

3.1 The Central Nervous System

The brain and spinal cord constitute the central nervous system (CNS), as in figure 3.1.

The fundamental unit of the CNS is the nerve cell, or neuron. There are many different types of neuron found in different areas of the CNS. For example pyramidal cells within the cerebral cortex; association cells within the thalamus; motor neurons in the spinal cord; somatosensory cells in the skin and Purkinje cells within the cerebellum. The structure of these neurons is similar and most comprise a cell body which has an axon attached to it and dendrites radiating from the axon. The radiating dendrites terminate in synapses and these act as the interface for communication between adjacent neurons.

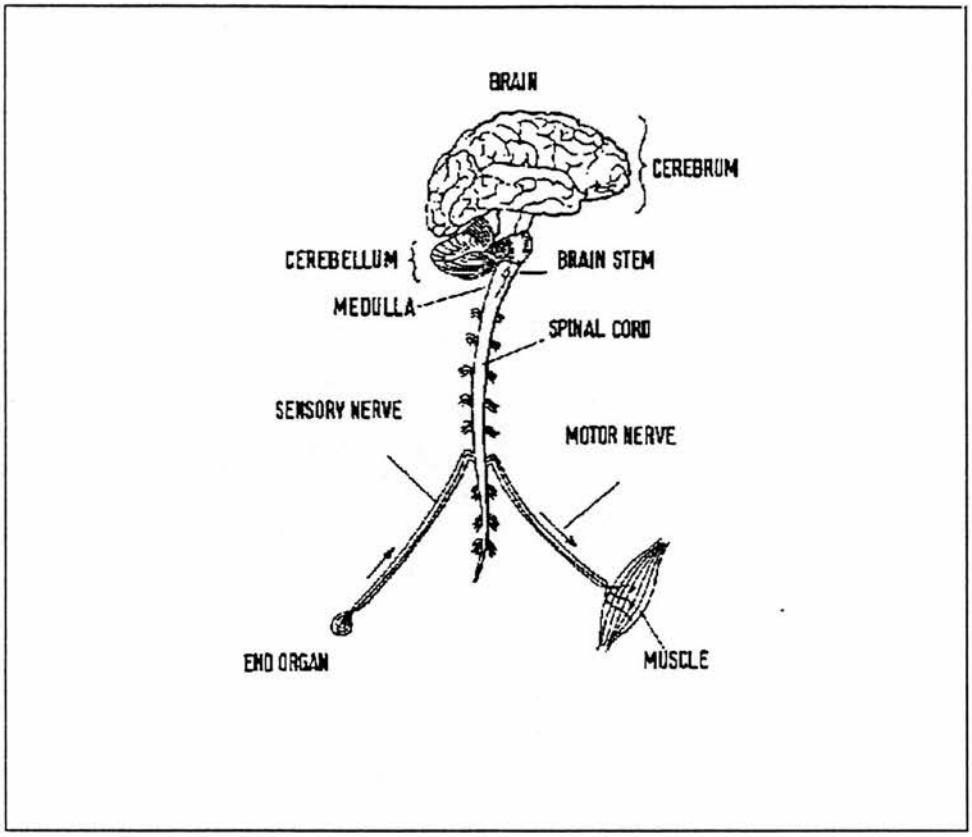


Figure 3.1 The human central nervous system

3.2 Structure of the human brain

The human brain can be divided into three main areas: the brainstem, the cerebellum and the cerebrum. The brainstem is connected to the spinal column and passes afferent and efferent signals from the sensory nervous system to and from higher brain centres. An important region for relaying all the sensory information is the thalamus, which is comprised of two egg-shaped structures anterior to the mid-brain. The olfactory sense is the only sensory system which is independent of the thalamus. The cerebellum is involved in motor function and exerts fine control over muscle movements. The cerebrum is the largest brain structure and is composed of "grey matter", or unmyelinated axons, and "white matter" which is composed of myelinated fibres. The cerebral cortex is associated with higher brain functions such as thought and cognitive processing while the white matter forms association

tracts involved in passing information between different processing areas within the brain (Kolb and Whishaw, 1990; Nieuwenhuys et al., 1988).

In the spinal cord, neuron cell bodies form nuclei in a central core which is surrounded by fibres known as neuron axons. In the cerebrum and cerebellum the neuron cell bodies form a layer of two-three millimetres thickness and the whole cerebral cortex contains about 10^{10} neurons. Association neurons predominate below, in the white matter and there are around 10^7 per cm^2 under the cortex. Around 5% of the nerve fibres that enter the underside of the cortical surface radiate from the thalamus and other subcortical structures (Nunez, 1989).

3.3 Brain electrical activity

Most of the electrical activity of the human brain originates from neurons in the cortex. Coordinated communication between neurons in the cortex occurs by the transmission of action potentials along the axon and across localised synaptic junctions. Figure 3.2 is a stylised diagram of a neuron from the cerebral cortex showing the two different sources of brain electrical activity.

Cortical neurons are heavily interconnected by synapses and there are around 10^5 synapses on the surface of each. The synaptic inputs to the neuron may excite or inhibit it causing either excitatory synaptic potentials or inhibitory synaptic potentials. Excitation of the neuron causes the generation of an axonal action potential. Local measurement of this potential would give a value of around -100 mV for the inner surface with respect to the outer surface of the cell. Action potentials generate circulating currents in the cortex in the vicinity of the neurons and the cerebral cortex. When large groups of neurons depolarise in a coordinated manner the resulting circulating currents generate electrical potentials detectable on the surface of the scalp.

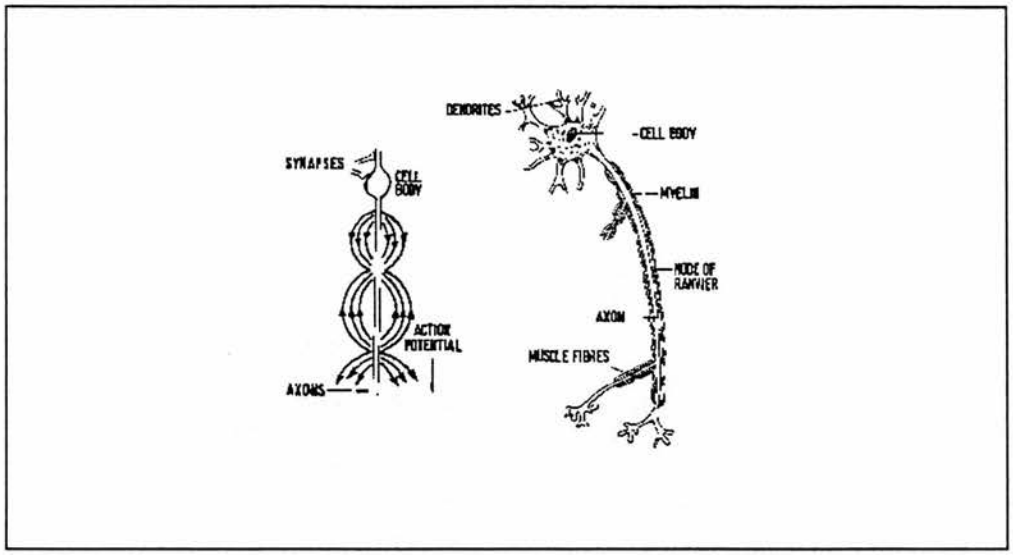


Figure 3.2 The structure of a neuron (right) and the generation of a neuronal action potential (left). Extra-cellular communication is by electrical potentials generated at the synapses, which may be excitatory or inhibitory. A nerve action potential is generated along a fibre by external current flow, induced by electrical fields in the Nodes of Ranvier.

The electrical properties of the human skull determines the path that circulating currents take to the surface of the scalp. The resistivity of the brain and scalp are approximately the same order of magnitude (200-400 Ohm cm) while the resistivity of the skull is approximately 80 times greater (16,000 Ohm cm, Nunez, 1989).

The electrical activity of the brain can be divided into three categories i) spontaneous potentials ii) evoked potentials iii) single neuron potentials.

3.3.1 Spontaneous potentials

The alpha rhythm in man was discovered by Hans Berger in 1928, a German psychologist, who measured the spontaneous electrical brain activity on the surface of the human scalp. The electroencephalograph in its simplest form means a graph of electrical changes from the *enkephalos* (Greek, for brain).

The EEG is classified using a widely accepted convention which describes its activity in terms of particular frequency bands. There are five principal bands of EEG activity called delta, theta, alpha, beta-1, and beta-2 with equivalent frequency bands 0.5-4 Hz (δ), >4-7 Hz (θ), >7-12 Hz (α), >12 -17 Hz (β_1), and >17-30 (β_2). These frequency bands occur in different circumstances and from different brain regions. There has been extensive research on their anatomical source and how pathology modifies their behaviour. The amplitude of these signals is usually around 10's of micro-volts. The dominant rhythm generated in the posterior cortex of the brain is alpha and is maximal when the eyes are closed. The dominant rhythm in the pre-central and post-central sensorimotor area and tertiary frontal areas covers the beta band. The EEG is a valuable clinical tool and in the diagnosis of brain tumours, epilepsy, mental retardation and head injury, among others.

3.3.2 Evoked Potentials.

There are two distinct categories of evoked potential (EP) :transient and steady-state.

EPs are in general considered to be transient, limited representations of the brain's response to a stimulus. Strictly speaking, a transient EP is one which occurs once. The brain is normally in its resting state when such activity is evoked and there is a range of methods for evoking it. Such stimuli could be electrical, mechanical, heat, light, gaseous, or chemical. Some stimuli are designed to excite auditory, visual and somatosensory brain regions while cognitive evoked potentials can be generated from tasks which require a subject to respond to task-relevant stimuli, generating a long-latency, event-related potential (ERP). Tests aimed at examining the response in specific brain regions normally adopt the name associated with it, e.g., the brainstem evoked potential (BSEP), visual (cortical) evoked potential (VEP), auditory (cortical) evoked potential (AEP), somatosensory evoked potential (SSEP). It is also possible to generate transient evoked potentials to missing auditory,

visual or somatosensory stimuli, although these are normally referred to as emitted rather than evoked potentials.

As the name suggests, a steady-state evoked potential is one which may, at least for the duration of the stimulation, achieve a predictable and unambiguous level. Steady-state and transient EPs are normally generated by repetitive stimuli but the original distinction between them was derived from the appearance of the response in the frequency domain (Regan, 1989). The visual steady-state EP is one of the best known steady-state responses. The stimulus repetition rate of the transient evoked response is usually much longer than for the steady-state evoked response. The stimulus repetition rate is important when considering the frequency passband. At high repetition rates only a few harmonics of the stimulus fall within the brain's passband so that the steady-state EP is simpler than at low repetition rates. Long delays between stimuli allow a higher range of harmonics within the brain's passband to develop and the signal is more complex.

3.3.3 Single neuron potentials

These potentials are normally measured across the membrane of a single neurone and require special microelectrodes. The technique is valuable for studying the behaviour of the constituent components of the brain at microscopic level, particularly with regard to the chemical properties and interactions within the neurone.

3.4 Evoked potential recording techniques

The techniques for recording scalp potentials have been refined over many decades and the standard methodological approaches are now discussed.

3.4.1 Electrodes and measuring systems

Recording methodology for the EEG and EPs is now well developed. Silver-silver-chloride electrodes are the most commonly used in EEG and EP

studies and their characteristics are suitably stable over the duration of a recording session. Used in conjunction with modern electronic differential amplifiers it is possible to make satisfactory recordings of very low amplitude (micro-volt) potentials down to nearly d.c. Very low frequency potentials associated with these electrodes drying out are a problem and the effect of these polarisation potentials can normally be minimised with high-pass filters. The technique of recording EEG and EPs has now developed to such an advanced level that the electronic amplifiers can be built into the recording electrode (Taheri, 1994). The requirements of an EEG/EP recording system, the relative size of signals and noise, and noise reduction techniques are addressed in more detail in the next chapter.

The Ten-Twenty electrode system is now universally used in EEG and EP studies (Jasper, 1958). This system is based on the identification of consistent anatomical features on the skull and developing i) an anterior-posterior line between the nasion and inion ii) a coronal line between the left and right preauricular points. The length of these lines are used to define points at distances of 10% and 20% separation, which overly identifiable brain anatomical regions.

3.4.2 The reference electrode in EP and ERP studies

There are many alternative views regarding the best reference site for recording unipolar signals from the scalp. Average and common reference electrode arrays have been proposed for EEG studies where the assumption is that the EEG is produced from many randomly orientated current dipoles. The reference electrode site is more crucial in EP and ERP studies, where this assumption is not valid. The selection of scalp site for the reference electrode in unipolar signal recording in EP and ERP studies can have a significant effect on the appearance of the signal (Wolpaw and Wood, 1982; Denoth et al., 1986; Faux et al., 1990). One of the best descriptions of this problem is given by Nunez (1981) who showed how the current paths from

cortical dipole sources behave under normal circumstances and how they are affected by linked ear reference electrode sites. The suggestion from this work was that, while linked ear reference electrodes are preferable to scalp electrode sites a potential divider circuit is necessary to prevent "short-circuiting" any real voltage asymmetry between the two hemispheres of the brain. This conclusion was challenged and shown to be imprecise for the situation in practice when the impedance at the skin-electrode interface is taken into account (Andino et al., 1990). The argument Nunez used against deriving a reference by simply linking the ear electrodes did not take account of these impedances, which in fact assist to preserve symmetry in the same fashion that a potential divider would.

3.5 The event-related potential (ERP)

The term "event-related potential" refers to an EEG response to a particular type of meaningful stimulus, and can be evoked by a range of sensory modalities. The ERP is a complex waveform with a number of sub-components and it was first reported by Sutton et al., in 1965. The authors reported it in response to both auditory and visual stimuli and noted how measures of the certainty or uncertainty of the stimulus modulated its appearance. They also noted that the most important feature of the event-related potential was a positive-going deflection that occurred 300 ms after the stimulus.

Subsequent studies have concentrated mainly on this, the "P300" component, particularly with a view to understanding its role in reflecting both normal and abnormal cognitive processes, as seen in mental illness. P300 has been intensely studied for almost thirty years using auditory "oddball" tasks particularly in studies of cognition and the results from hundreds, if not thousands, of studies have been published. There is speculation that the P300 may have a role as a biological trait marker for schizophrenia and other major mental illnesses (Blackwood et al, 1991).

3.5.1 Auditory oddball ERP experimental paradigms

The simplest and most frequently used ERP experimental paradigm is the auditory oddball one designed to evoke a P300 response. There are, however, equivalent paradigms that use somatosensory or visual stimuli.

The subject is presented with a train of two different auditory stimuli, one occurring frequently the other rarely and at random. The stimuli are normally single frequency tones. The instruction is to attend to the rare oddball sound and to either keep a mental count of the number of occurrences or to press a button in response to it. Most research groups use frequent stimuli at a frequency of 1 kHz and a rare target response at a frequency of 1.5 kHz. Target-to-non-target probability varies between 0.33:0.67 - 0.5:0.95 (Fabiani et al., 1987) and the stimulus duration is normally 40 ms. The target and non-target responses are usually saved and averaged separately prior to analysis. The ERP evoked in an auditory oddball paradigm shall be the focus for this thesis.

3.5.2 ERP components and their topography

Compared to other evoked brain potentials the ERP complex occurs a considerable time after the stimulus and is often referred to as the long-latency ERP. A common practice in evoked potential terminology is to label particular features of the waveform with names reflecting both their polarity and time of their appearance after stimulus, the latency. Figure 3.3 shows a typical ERP complex and its constituent components, recorded from three scalp locations at Fz, Cz and Pz, from a control subject. In keeping with the accepted terminology, the ERP complex has five main features : N100 (N1), P200 (P2), N200 (N2), P300 (P3), and the Slow Wave (SW). Guidelines published in 1977 (Donchin et al.) specific to ERPs addressed many issues of nomenclature and EP waveform polarity convention. The convention for using "positive up" in reference to EP waveform diagrams was accepted, and this convention is adopted throughout in any diagrams of

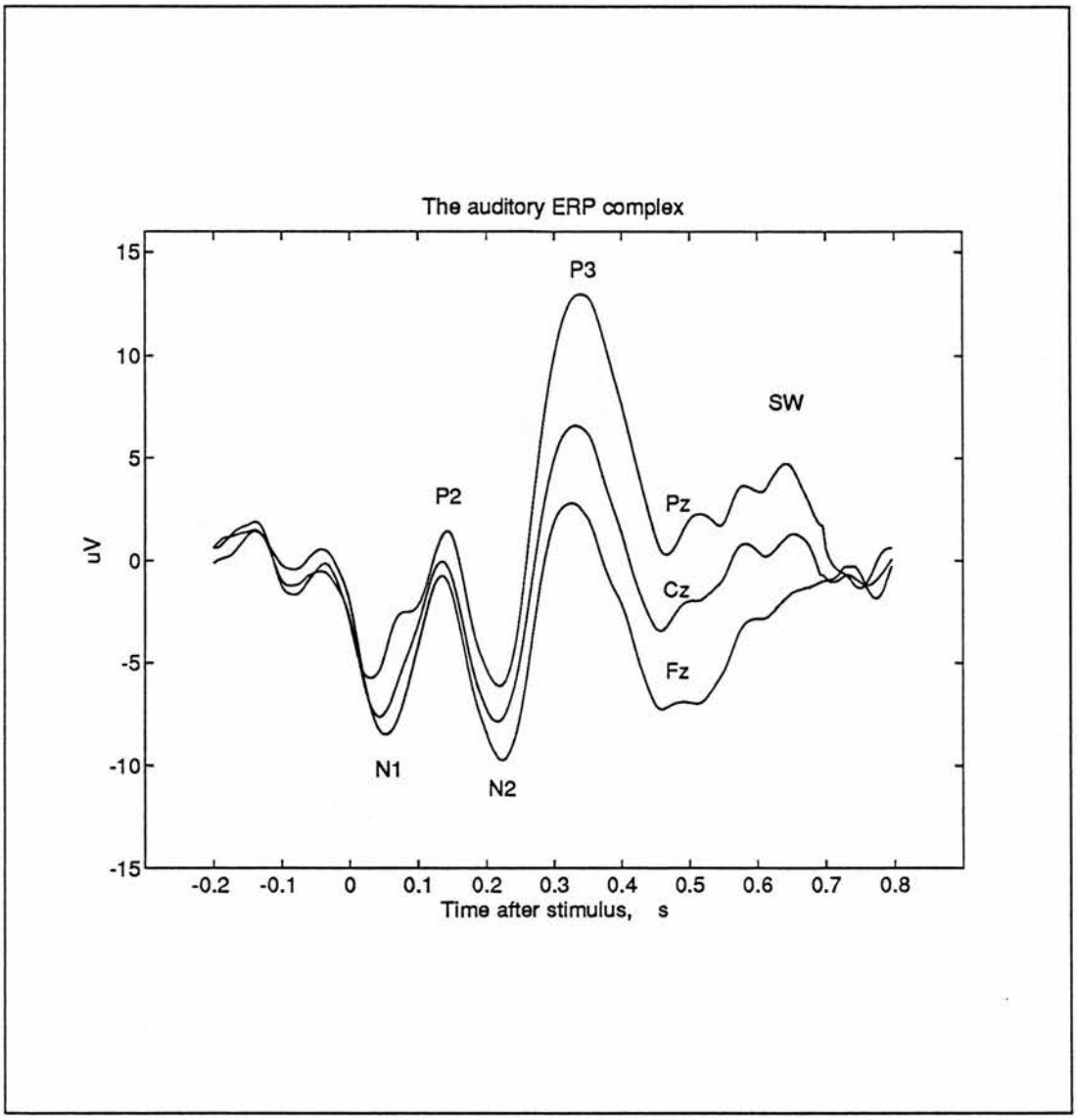


Figure 3.3 The auditory oddball ERP complex.

ERP waveforms. The topography of the ERP changes from the front to the back of the head. As can be seen from figure 3.3, the P300 component has a parietal maximum and a frontal minimum while the Slow Wave is negative frontally and positive parietally. This topography suggests that there is a dipole associated with SW which is orientated along the mid-line of the skull. The Slow Wave is thought to occur at the same time as the P300 but its duration is much longer, continuing beyond 700 ms. The components of the ERP waveform fall into two categories: exogenous and endogenous.

3.5.3 Exogenous ERP components:the N100 and P200

An exogenous component in a biological system is one whose features are determined by influences external to the organism in which it is measured. The exogenous components of the ERP are the N100 and P200 which are automatically elicited regardless of whether a task-relevant stimulus is present i.e. in response to both rare and frequent stimuli. The presence of these components reflect the auditory processing response and are related to the physical characteristics of the stimulus. The N100 component in a selective attentional auditory task was shown to be larger to attended than ignored sounds (Hillyard et al., 1973) but it was later shown that the increased size was due to a processing negativity which is superimposed at the same time as N100 (Näätänen and Michie, 1979). Both N100 and P200 are affected by the intensity of the stimulus, increasing in amplitude with increasing intensity and *vice versa* (Picton and Hillyard, 1974). It was also shown that directing attention towards an auditory stimulus increases the amplitude of the N100 and P200 components (Picton and Hillyard, 1974). A detailed study on the effect of ageing on all ERP components (Pfefferbaum et al., 1984a) showed the amplitude topography for N100 has a Cz > Fz > Pz pattern, while the P200 amplitude topography has a Cz > Fz=Pz pattern. The latency of the N100 and P200 components were not affected by age while N100 and P200 amplitude topography appeared to change with age showing an increase at the Cz electrode site. The inter-stimulus-interval (ISI) appears to affect the N100, with increasing ISI producing a larger and later N100 using both auditory and somatosensory stimuli (Miltner et al., 1991).

3.5.4 Endogenous ERP components: the N200, P300, and SW

When Sutton et al. (1965, 1967) discovered the late positive complex they proposed that it was "endogenous", related to the psychological reaction of the subject to the stimulus, rather than the physical characteristics of the stimulus. Subsequent investigations revealed that there are three main endogenous ERP components: N200, P300, and the SW. The P300 complex,

N200, and SW are thought to have overlapping sub-components and these will be considered in turn. The N400 and contingent negative variation (CNV) are also endogenous ERPs but will not be considered here

3.5.4.1 The N200

The N200 is often observed in the presence of the P300 and it has been shown that the two are highly correlated in an analysis of single trial data in control subjects (Michalewski et al., 1986). The N200 component is thought to comprise of two sub-components, which were labelled "mismatch negativity" (MMN, N2a) and N2b (Näätänen and Gaillard, 1983). The MMN precedes the N2b. Earlier work had shown that N200 may reflect the state of arousal (alertness) of a subject, with increasing levels of arousal producing a smaller N200 (Picton et al., 1974). A dependent relationship between N200 and the early component of the P300, which was called "P3a", has also been suggested (Squires et al., 1977). The N200 component is widely distributed across the scalp with a maximum being measured at fronto-central regions.

3.5.4.2 The P300 and its sub-components

The P300 complex is thought to consist of possibly three sub-components, labelled P3a, P3-novel, and P3b.

The initial report of a late positivity suggested that there was a single maximum peak in the region of 300 ms. A study two years later by the same authors using an auditory paradigm with varying probability and missing rare stimuli resolved an earlier and smaller P300 component than previously observed by Sutton et al. (1967). A more detailed study was carried out by Squires et al.(1975) using loud and soft tones or tones of different frequencies. Probability and task were varied; rare stimuli were counted or ignored. The results from this experiment led to a redefinition of the P300 complex. The response to the "ignore" condition or to occasional shifts in

pitch and loudness was called "P3a", occurring between 220 and 280 ms. This component had a fronto-central maximum. When the subject actively attended to stimulus shifts, the component which appeared in response was called "P3b", occurring between 310 and 380 ms with a parietal maximum. However, it was noted that both P3a and P3b components sometimes appeared in response to the attended rare stimuli. At the same time as an early P300 component was produced in response to "unattended" auditory stimuli another early P300 component was observed in response to novel visual stimuli (Courchesne, 1975). While the response was maximum at the Cz electrode, it was referred to as a "frontal" P300. Here, the author noted that his observed frontal P300 and the previously reported P3a differed in latency and amplitude. Strictly speaking this sub-component should be referred to as the "P3-novel". A further study using "missing" rare auditory stimuli led to the related P300 component being labelled "evoked" in response to rare attended stimuli, and the smaller amplitude "emitted" P300 labelled in response to the missing rare auditory stimuli, although they occurred in the same latency range (Ruchkin and Sutton, 1978). The effect of prefrontal lesions on the early P300 component in response to a novel auditory stimulus was reported by Knight in 1984. The novel stimulus was a simulated dog bark, which the subjects were instructed to ignore. There was no difference in the appearance of the response to attended rare stimuli in controls or patients, both showing a parietal maximum. The response to the rare novel stimulus produced a "fronto-central maximum", although the response was bigger at Cz than Fz, while the topography for the patient group was the same as for the response to the rare attended stimulus. A rapid habituation to the novel stimulus was noted in controls but not patients.

From the above summary it is obvious that there is much discrepancy in the literature regarding the roles, topography, and nature of these early P300 components. Also, the simple auditory "oddball" P300 paradigm is complicated by the fact that 20-30% of subjects will demonstrate a bifurcated

P300 complex, comprising of both early and late components as described above (Polich, 1991).

3.5.4.3 Factors affecting the appearance of P300

The latency of the P300 is thought to reflect the stimulus evaluation time when the single trial P300 latency is measured against individual reaction times to the rare visual stimuli (Kutas et al., 1977). These authors showed that, when responding with accuracy, the P300 latency was correlated to reaction time but was not correlated to P300 latency when responding with speed.

P300 amplitude is influenced by experimental factors such as task difficulty, stimulus probability and inter-stimulus-interval and may reflect the amount of resources available to process the stimulus (Polich, 1987). The stimulus probability was shown to affect the amplitude of the late positive wave in an inverse relationship, with amplitude decreasing as stimulus probability increases (Sutton et al, 1965; Polich, 1990). Polich also showed in this work that the latency of P300 increased as target probability decreased and that amplitude increased for a low probability target at a shorter ISI. He suggested that the P300 amplitude therefore reflects the amount of processing resources available when it is produced.

Most EP components tend to decrease in amplitude with stimulus repetition due to habituation. The effects of habituation have been studied in depth in the context of the P300 and many studies reviewed (Teuting and Levit, 1979). The rate of habituation has caused some debate, with some groups reporting different rates from others, but this may be a function of the experimental variation. A review of studies of the effects of habituation showed that there are two discrete stages: a fast, short-term habituation over several seconds and a slow, long-term habituation over several minutes (Picton and Hillyard, 1988). The effect of habituation on novel visual stimuli

was studied and it was shown that the response which was initially maximal at the Fz electrode shifted after only eight stimuli to become maximum at the Cz and Pz electrodes (Courchesne, 1978).

The discriminability of the target will affect task difficulty. Auditory discriminablity can be varied by making the difference between the frequencies of frequent and target sounds more or less obvious. It was shown by this method that there is an increase in latency of both N200 and P300 components and reaction time as discrimination reduces (Ritter et al., 1979). A later study reported the effect of both discriminability and speed versus accuracy, in response to identifying the target (Pfefferbaum et al., 1983). The P300 latency was shortened and amplitude increased during the speed compared to accuracy regime. P300 latency was delayed in the difficult compared to easy discrimination task, while amplitude was unaffected. The suggestion here is that the task is more demanding, increasing processing time, hence the latency increase.

The instruction to refrain from blinking during the recording of P300 appears to significantly affect the amplitude of N100 and P300, particularly in subjects who having been instructed not to blink, then blink during the experiment (Verleger, 1991). P300 latency was not affected. The author suggested that the instruction not to blink constitutes a second task, along with counting the target, therefore stretching the processing resources over two concurrent tasks.

The effect of age on latency of P300 has been studied by many groups. A review of such studies concluded that, while results are conflicting, there appears to be an average increase in latency of about 1.3 ms per year after the age of 18 (Picton, 1992).

The effects of medication on the P300 amplitude and latency have been

concisely summarised (Picton, 1992). The main changes appear to be induced by the anticholinergic drug scopolamine which appears to affect both amplitude and latency.

The neural generation of the scalp recorded P300 is not completely understood. Several lines of evidence, including topographic analysis (Lovrich et al., 1988), depth electrode recording (Halgren et al., 1980; Meador et al., 1987; Smith et al., 1987; Stapleton and Halgren, 1987; Richer et at., 1989; Smith et al., 1990) and studies on patients with discrete neural lesions (Knight et al., 1988; Knight et al., 1989) have suggested that the auditory cortex and associated areas in the superior temporal and inferior parietal regions are critical for P300 generation.

However, the anatomical source(s) of P300 is a subject of much debate and controversy.

3.5.4.3 The Slow Wave (SW)

The SW was first commented on by Squires et al. (1975). It was seen to have positive polarity over the parietal electrode site and negative polarity over the frontal electrode site. It was only seen in response to rare attended stimuli and varied in a similar manner to stimulus parameters as P3b.
The role of SW was examined in detail in 1980 (Ruchkin et al.) where it was concluded that, while speculative, the SW amplitude (and possibly duration) reflects the amount of processing required by the eliciting rare event.
A study of N200, P300, and SW in an auditory oddball task using different stimulus probabilities, discrimination levels, and missing stimuli concluded that while SW covaried with P300 it had a different site of origin because it was not present at the nasopharynx (Perrault and Picton, 1984). Ruchkin and Sutton have concentrated on studies of SW and these are reviewed by Fabiani et al. (1987). They propose that SW represents further or additional processing activities continuing after P300. When task difficulty increases

SW will increase. Like the P3b, the amplitude of SW is affected by attention, increasing with increasing attention level (Picton, 1992).

3.5.5 Comments on the terminology for defining ERP components

ERP component terminology has been the source of much controversy, mainly because the theoretical definition of the P300 component is still under development.

Experimental measures become "psychophysiological" when they are derived from physiological experiments where the independent variables may be psychological in nature. The major problem with the ERP is the fact that its major components overlap in the time domain. The implication that a waveform comprised of overlapping components can be decomposed, thus allowing the underlying independent psychological processes to be determined remains contentious.

A number of papers have commented on the problems of relating the theoretical and observational definitions of a "component" in psychophysiological studies and are succinctly reviewed (Fabiani et al., 1987). An example of the problem of labelling P300 components was made as early as the time when a sub-component of the P300 complex was first elicited experimentally (Squires et al., 1975). The authors labelled the early component "P3a" and the later component "P3b". At the time they stated that they did not wish these terms to become "institutionalized", but subsequent literature appears to have adopted these names. The subsequent, perceived problems of accepting nomenclature as standard as a result of "institutionalization" are covered by Fabiani et al. (1987). A recent comment quantifies the three most common fallacies with psychophysiological component classification as "biophysical, morphological, and lackadaisical" (Donchin et al, 1994).

The main problem with using scalp voltage potentials to model psychological processes relates partly to the poor spatial information available from studies of brain potential topographic maps used to identify dipole sources. For such a model to succeed these components must reflect independent neural processes. It is essential that such information should reveal whether these sources originate superficially in the cortex or deeper in the limbic system, for example. Currently, brain voltage topographic mapping techniques are not sensitive enough to provide a unique solution to the problem and it is possible that surface potential maps could originate from either superficial or deep-lying sources (Nunez, 1981). A recent review of the field highlights this as the outstanding unresolved problem in ERP research, suggesting that magnetoencephalography and other imaging modalities may surmount the constraints of source analysis (Picton, 1992). However, another recent study implies that a multi-modal imaging approach may improve the prospects for resolving this dilemma. The relationship between grey matter volume, measured using magnetic resonance imaging (MRI), and P300 amplitude suggests that this reflects a functional rather than topographical relationship (Ford et al., 1994).

3.6 ERPs in clinical studies

There have been many clinical studies which used ERP experimental paradigms. Aside from schizophrenia, unipolar and bipolar depression, which are given below, the P300 has been measured in studies including dementia, (Goodin et al., 1978; Polich, 1991; Goodin and Aminoff, 1992), pre-senile dementia and alcoholic Korsakoff syndrome (St Clair et al., 1985), idiopathic Parkinson's disease (Ebmeier et al., 1992), borderline personality disorder (Blackwood et al., 1986); autism (Cieselski, 1990); prefrontal lesions (Knight, 1984). These are some examples from a range of studies which show changes of P300 features concomitant with clinical features.

3.6.1 Schizophrenia

There have been many studies of P300 in schizophrenia, the first auditory P300 study being reported in 1972 (Roth et al.). This study found a significant reduction in P200 and P300 amplitude compared to controls but no latency differences. The amount of chlorpromazine was reported to correlate in a negative fashion with P200 amplitude. The next reported study used auditory and visual stimuli with changing stimulus sensory modality in schizophrenic, psychotic depressed and control subjects (Levit et al., 1973). A difference in amplitude was noted in the N100-P300 components across groups, with controls > depressives > schizophrenics. In this study chlorpromazine did not appear to affect any of the N100-P300 components of the ERP. A study on the effect of habituation on P300 amplitude, elicited by auditory and visual stimuli, in schizophrenics, unipolar depressives and a control group found that N100 showed a significant reduction in controls and depressives but not schizophrenics (Teuting and Levit, 1979). No significant P300 habituation was noted, only a trend for such in the visual response of the schizophrenics, accompanied by an increase in latency. The reported reductions in P300 amplitude were then studied on a trial-by-trial basis to assess whether this was due to greater variance of P300 latency in schizophrenia (Roth et al., 1980). It was concluded that, while the variance was greater, this did not account for the reduced amplitude. A dichotic listening task was used in a study of a group of schizophrenics and controls to assess their selective attention ability (Baribeau-Braun et al., 1983). The P300 amplitude was significantly reduced in schizophrenics compared to controls. No differences in evoked potential measures were noted in schizophrenic sub-groups of medicated versus unmedicated, apart from N100 amplitude, which was reduced in the medicated group.

These quoted studies are probably the most frequently referenced in reports of P300 in schizophrenia and there is general agreement that P300 amplitude reduction is a feature of schizophrenia. More recently a P300 amplitude asymmetry has been reported as a feature of schizophrenia. Three studies by

the same research group on medicated schizophrenics reported that P300 was attenuated in the left temporal compared to right temporal region and are reviewed (McCarley et al., 1991). A further study by the same group on unmedicated schizophrenics confirmed these findings (Faux et al., 1993). These results have not been replicated by any other group and may be due to the methodology employed. These authors also found that left sylvian fissure enlargement correlated with P300 amplitude at the T3 electrode site (McCarley et al., 1989) and that there was significant correlation between reduced P300 amplitude at the T3 left and a reduction in volume of the left superior posterior temporal gyrus (McCarley et al., 1993).

The case for P300 latency has produced conflicting results and much controversy regarding whether or not it is delayed. A review was carried out of P300 studies in schizophrenia (Roth et al.,1986). Of 14 studies done between 1972 and 1984 only 4 reported a significant delay in schizophrenia compared to controls. However, a more recent meta-analysis of 15 published studies between 1977 and 1990 concluded that P300 latency is delayed in schizophrenia (Ebmeier, 1991).

Abnormal neuropsychological measures have been found to correlate with P300 abnormalities in schizophrenia, particularly measures of frontal lobe function (Roxborough et al., 1993). This study also confirmed an amplitude reduction and latency delay in the P300 of schizophrenics compared to controls. These results were confirmed in a later study (Souza et al., in press).

One or two studies have focused on the P3-novel response in schizophrenia. The amplitude of both the P3-novel (labelled P3a in this work) and P300 was found to be reduced in an auditory oddball task with additional novel sounds (Grillon et al., 1990). In a study using auditory and visual stimuli in attend and ignore paradigms, the reduction in P300 amplitude in schizophrenics was

greater when the stimuli were attended to - differences between controls and schizophrenics of the "emitted" P300 were relatively smaller (Grillon et al., 1991).

3.6.1.1 P300 as a biological marker for schizophrenia

Bearing in mind the criteria for a biological marker to detect genetic risk for psychosis (as outlined in chapter 1 of this thesis) the P300 would appear to offer much promise of fulfilling many of the required criteria.

An important related question is whether such a psychophysiological measure is indicative of a biological trait or reflects clinical state only. A trait marker should be independent of the effects of medication. A report which addressed this question looked at P300 measures, derived from auditory and visual paradigms. The study comprised a group of schizophrenics, classified as being either undifferentiated or paranoid in both medicated and unmedicated states, and controls (Duncan et al., 1987). This initial report concluded that visual P300 measures reflected clinical state, as P300 amplitude correlated highly with neuroleptic medication. A more recent report examined auditory P300 measures in schizophrenics and their first degree relatives. It was concluded that because low P300 amplitude is a feature of both schizophrenics and their relatives it is a trait marker for schizophrenia (Kidogami et al., 1992).

However, subsequent studies have shown that a more robust candidate may be the P300 latency. In particular, an auditory P300 study of schizophrenic patients and their relatives revealed a bimodal distribution for the P300 latency of the relatives (Blackwood et al., 1991). This study was followed up by repeating the auditory P300 paradigm in parallel with extensive neuropsychological testing in both schizophrenics and their first degree relatives. The results were replicated (Roxborough et al., 1993).

3.6.2 Depression: unipolar and bipolar

There have been many studies of P300 in unipolar depression, some carried out in parallel with the studies of schizophrenia commented on above. There are relatively few published studies specifically on bipolar depression however, and Muir et al., (1991) have shown the importance of separating unipolar from bipolars in P300 studies. Unipolars show no changes in P300 latency whereas bipolars have a prolonged P300 latency.

The first study of P300 in psychotic depression (assumed unipolar) reported that ERP measures were similar to those for control subjects, but were significantly different from schizophrenics (Levit et al., 1973). An auditory P300 paradigm with button-press reported no significant differences in P300 measures in unipolar depression compared to controls, but the depressives had longer reaction times (Giedke, et al., 1981). A review of published studies of P300 in schizophrenia and depression between 1972 and 1984 concluded that there was no significant difference between unipolar depressed patients and controls for the P300 (Roth et al., 1986). Subsequent studies have found little or no significant P300 changes between unipolar depressed patients and controls (Pfefferbaum et al., 1984b; Gordon et al., 1986, Blackwood et al., 1987;Patterson et al., 1988; Kraiuhin et al., 1990).

The first notable report of P300 in bipolar depression combined unipolar depressed, schizophrenic subjects and controls in the study (Muir et al., 1991). This was a large study of 96 schizophrenics, 99 bipolar depressives, 44 unipolar depressives and 213 controls. The study used a simple auditory oddball paradigm and the results showed a distinction in P300 between unipolar and bipolar depression which was similar to the changes found in schizophrenia. The P300 latency was significantly prolonged in schizophrenia and bipolar depression compared to controls and unipolars. All patient groups had significant reduction in P300 amplitude compared to controls. Psychophysiological recordings were made from one electrode only, at Cz, so

it was not possible to comment on the topographical patterns of the patient groups. An auditory P300 study of melancholic depression (assumed unipolar) showed that subjects experiencing hallucinations and/or delusions had significantly smaller P300 amplitude than controls (Santosh et al., 1994). There were significant correlations between psychotic features and P300 amplitude.

Finally, a very recent study looked at auditory P300 features and neuropsychological performance in schizophrenia and bipolar depression (Souza, et al, in press). There was a significant delay in P300 latency of both schizophrenic and bipolar depressed subjects compared to controls, at central and temporal leads. The P300 amplitude was not significantly different from the control group, however.

Chapter 4.

Evoked potential models

A number of models have been proposed for evoked potentials ranging from a simple additive model to an inverse filter model. The inverse filter is one of a number of new approaches using autoregressive techniques to model brain dynamics (Wright et al., 1990; Kaminski and Blinowska, 1991). This approach is still being validated and models are under development for clinical studies of EPs. Their potential use in clinical studies is unknown at present and will not be considered further.

4.1 The additive and phase re-ordering models for evoked potentials

The EEG can be modelled on n harmonically related generators which have a random phase, θ, and amplitude relationship, as shown in figure 4.1. This model fits well with the observed EEG.

The simple additive model of the EP suggests that its appearance among random EEG is due to an additional generator of a particular frequency and phase switching on for a limited period. This model was first

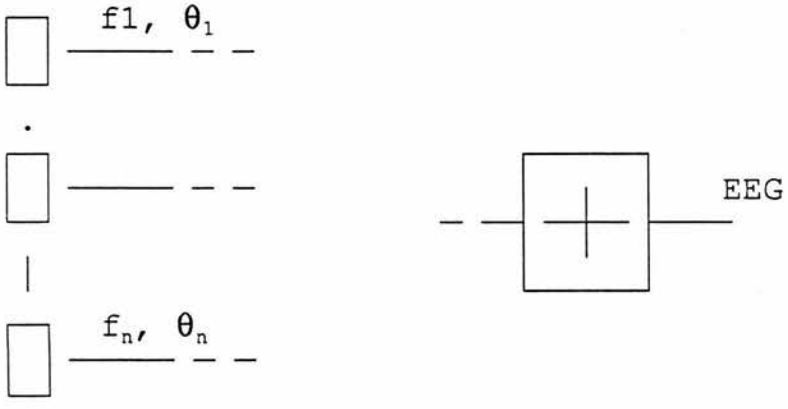


Figure 4.1 The additive EEG model

challenged in 1974 when it was noted that the average power in the signal pre- and post-stimulus was not significantly different (Sayers et al.). The authors studied the EP phase and amplitude contributions in the frequency domain and concluded that it was possible for an EP to be generated by simply re-ordering the phases of the harmonics of the background EEG. Thus an EP model based on phase re-ordering was proposed. Subsequently, both additive and phase re-ordering models were further tested but the results were conflicting (Reviewed : Jervis et al., 1983). This group then went on to test further the proposed models and concluded that large harmonic EP components were generated by additional additive frequencies, as in the proposed additive model, but that they are also accompanied by some degree of phase re-ordering. Small amplitude components were thought to exhibit both additive and phase re-ordering behaviour, but the additive components were undetectable.

4.2 The effect of high-pass filters on the P300

An additive model for the ERP appears valid as the waveform comprises overlapping temporal components. The P300 complex in particular would fit such a model as it has two components and an overlapping Slow Wave, as previously described.

The effect of filtering a composite waveform might lead to unexpected effects in the post-filtered waveform, particularly for frequency components in the transition band of the filter (Maccabbee et al., 1985).

A number of studies have used different high-pass filters in ERP studies and it has been suggested that this may be a reason for conflicting results in studies of schizophrenia (Ebmeier et al., 1990). A review of studies using auditory oddball paradigms showed that a low, low-pass filter is associated with negative findings whereas higher low-pass filters are associated with positive findings.

It was a hypothesised that, because schizophrenics have a smaller Slow Wave than controls, this might lead to differential filtering effects, accounting for the reported group differences.

4.2.1 A proposed model of P300

It was decided to test such a hypothesis on data provided from a clinical ERP study by the Department of Psychology, University of Aberdeen. The study groups comprised 18 schizophrenics, 16 patients with idiopathic Parkinson's disease and two groups of matched controls. The full results from this study have been published (Ebmeier et al., 1992) and a summary of the important points is now given. The summary concentrates on the results of processing P300 data acquired from Cz and Pz electrode sites in an auditory oddball task.

4.2.1.1 Methods

Data were processed using a range of digital infinite impulse response (IIR) low-pass filters which emulated the characteristics of the (optimally flat) analogue 1-pole, -6db/octave, Butterworth filter (Appendix 1). The data were originally recorded at different high-pass filter settings across the two studies with the Parkinson's disease patients at 0.54 Hz (-3 dB) and the schizophrenics at 0.16 Hz (-3 dB). So for the schizophrenic patients the data were filtered in 3 separate passes at 0.54, 1, and 2 Hz while the Parkinson's disease patient data were filtered at 1 and 2 Hz in 2 separate passes. The P300 peak was identified as the maximum positive deflection in the window between 250 and 480 ms for schizophrenics and their controls and between 280 and 490 ms for Parkinson's patients and their controls. Manual measurements were made on traces of the data at each of the filter settings. The filters were synthesised in the PC-MATLAB (™The Mathworks Inc.).

4.2.1.2 Results

Lead	Filter	Controls	Schizophrenics
Cz	0.16	322 (21)	363 (60)
	0.54	315 (20)	357 (61)
	1	309 (19)	354 (63)
	2	303 (19)	350 (56)
Pz	0.16	337 (49)	368 (62)
	0.54	321 (37)	363 (63)
	1	317 (39)	360 (64)
	2	312 (41)	356 (64)

Table 4.1 P300 latency (±SD) : control and schizophrenic groups.

Lead	Filter	Controls	Parkinson's
Cz	0.54	350 (49)	354 (43)
	1	344 (50)	351 (44)
	2	340 (52)	349 (44)
Pz	0.54	366 (48)	374(53)
	1	360 (49)	372 (53)
	2	356 (50)	369 (52)

Table 4.2 P300 latency (±SD) : control and Parkinson's disease groups.

A significant number of recordings from both leads exhibited a bifurcated P300 peak. By progressively increasing the high-pass filter cut-off the maximum peak was seen to change from the later to the earlier peak. An example of this peak change phenomenon is given in figure 4.2 below.

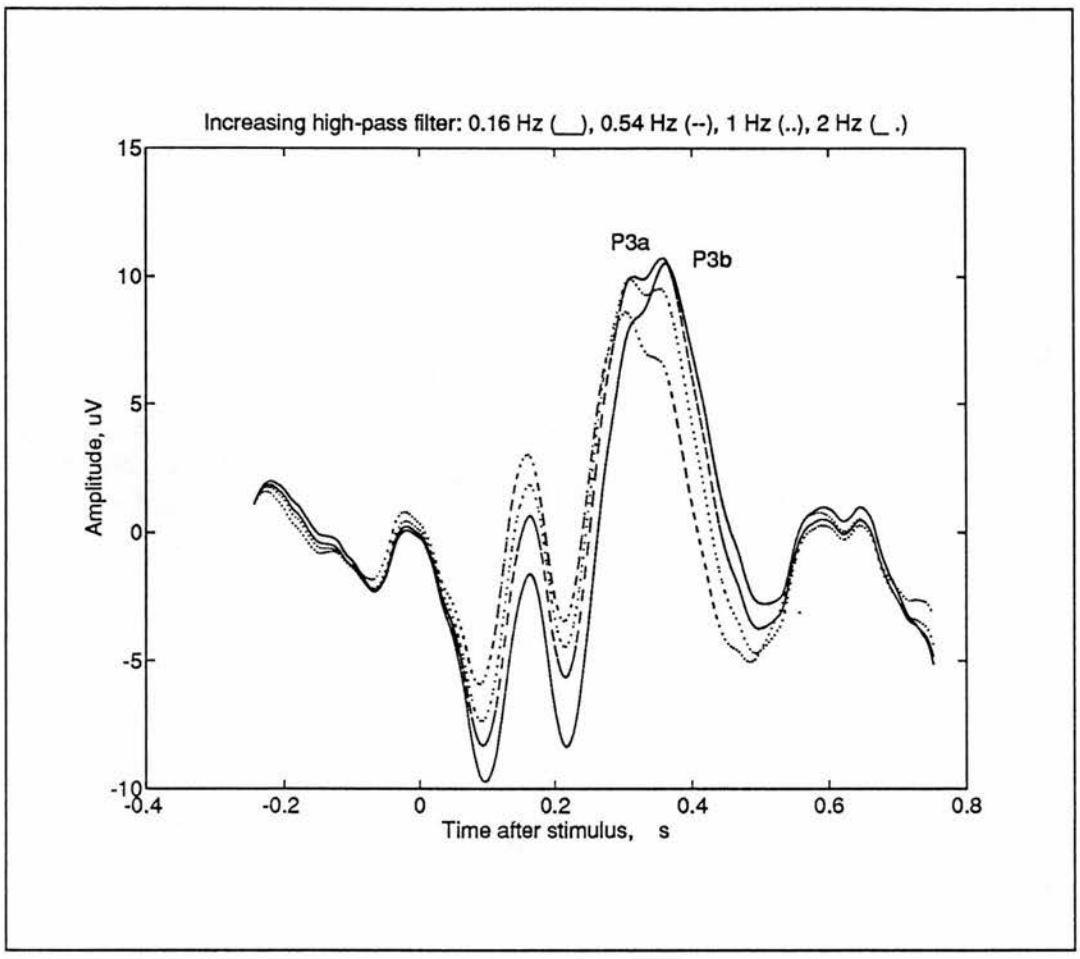


Figure 4.2 The peak change phenomenon in P300 due to high-pass filtering

Here the P3b sub-component would be identified as the maximum peak in the window at the 0.16 Hz filter setting. As the filter cut-off increases the P3a sub-component becomes dominant. An explanation for this is given in the data simulation below. To prevent the effect of this phenomenon biasing the results, the peak identified at the lowest low-pass filter setting was tracked in subsequent filtering stages so that measurements were consistent.

Schizophrenics and controls

A repeated measures analysis of variance gave a significant group x filter interaction ($F=6.25$, $p < 0.01$), with the control group showing a greater reduction in latency than schizophrenics (Table 4.1). It was noted that in the schizophrenic group, 15 data sets from 36 (42%), from either Fz or Cz

electrode sites exhibited a peak change when filtering from 0.16 to 2 Hz. For the control group only 7 from 36 (19%) recordings showed a peak change, across the same filter range.

Parkinson's disease and controls

Statistical analyses showed a significant group x filter interaction ($F=12.11$, $p < 0.001$) with the control group showing a greater reduction in latency than the parkinsonian patients (Table 4.2). Across the filter range 0.54 Hz to 2 Hz it was noted that in the patient group, 17 from 64 recordings (27%) exhibited a peak change while only 1 from 32 (3%) control recordings did.

4.2.1.3 The P300 model

From analysis of the above data it became clear that the effects of the filter would become predictable if an additive two-frequency model for the P300 complex were adopted. By inspection of the data, the P300 complex was modelled with a sinusoidal component of 7.5 Hz representing the P3a and P3b, while the Slow Wave was modelled by a component at 2.5 Hz. Figure 4.3 shows how 2.5 Hz and 7.5 Hz components sum in a ratio of 1:1 to form the simulated P300 complex.

Figure 4.4 shows the effect of the digital filters on the 7.5 Hz component (upper panel) and the 2.5 Hz component (lower panel). The digital filters are linear and time invariant and will act on the individual components of a summed waveform exactly as they will operate on the summed waveform. This simulation shows how the high-pass filters used in the study will induce a larger phase shift left (time-lead) in the 2.5 Hz component compared to the 7.5 Hz component. So the measured time shift will vary, depending on the ratio of the two components in the composite waveform. The phase lead, θ, induced in a pure sinusoid of frequency f with filter cut-off f_c is given by

$$\theta = 90 - \tan^{-1}\left[\frac{f}{f_c}\right]$$

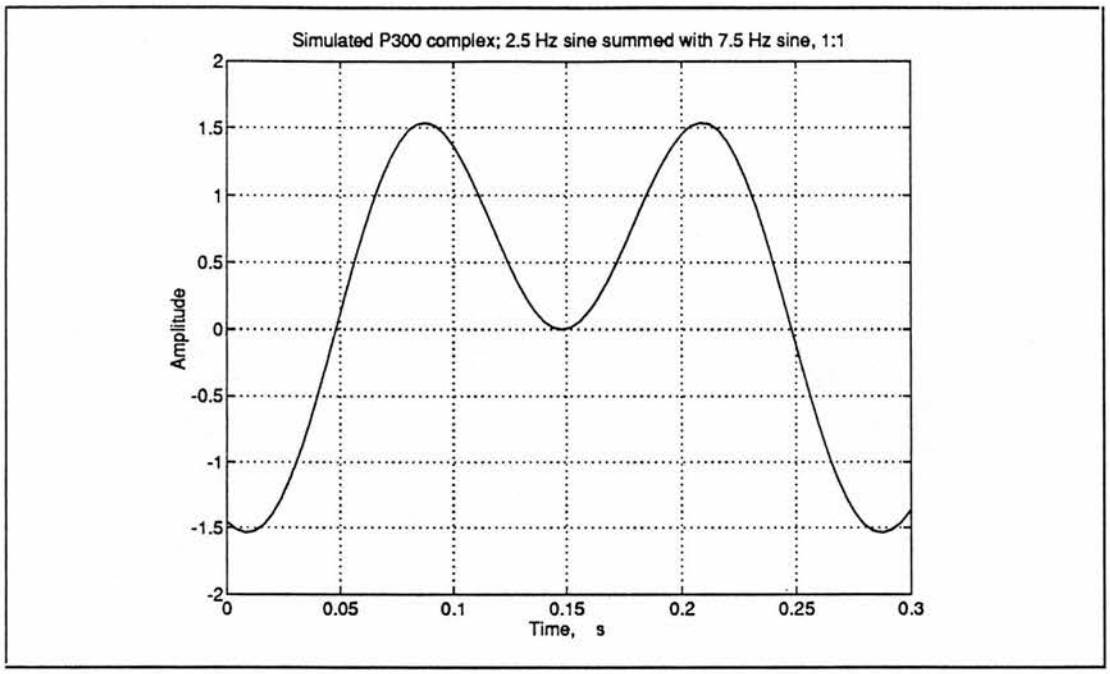


Figure 4.3 Simulated P300 complex made from summed 2.5 Hz and 7.5 Hz sinusoids

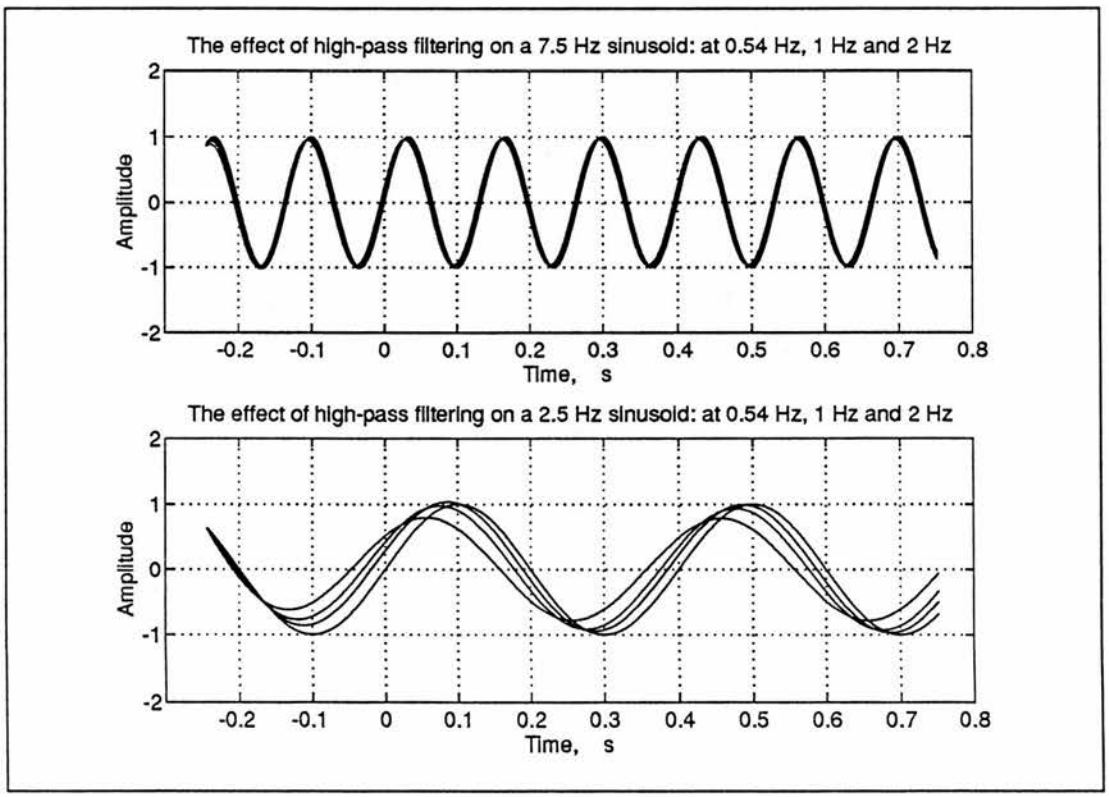


Figure 4.4 The effect of high-pass filtering on 7.5 Hz and 2.5 Hz sinusoids.

For frequency, f, the equivalent shift in the time domain is defined as,

$$\Delta t = [\ \frac{\theta}{360}\ ]\frac{1}{f}$$

It is possible that a composite waveform which consists of a relatively higher ratio of the 2.5 Hz component may have a larger induced phase shift than a composite with relatively more of the higher frequency at 7.5 Hz if measurements are made on the maximum peak.

Further evidence has emerged from this study regarding the role of P300 latency as a marker for schizophrenia and that P300 measures are sensitive in the study of idiopathic Parkinson's disease. From the results it appears that the schizophrenic subjects did have a smaller P300 and Slow Wave as has been previously reported.

The problem with this study is that the conclusions are based on a limited data set. Data from a larger range of electrodes coupled with spectral analysis should allow this model to be more precisely tested and defined. A more detailed study is required to quantify exactly the ratios in which these two modelled components add and whether this in turn could become a sensitive marker for schizophrenia or other major psychiatric disorders. A further study was carried out and is reported in chapter 7 of this thesis.

Chapter 5.

Digital signal processing methodology in measurement of the P300 component of the auditory Event-related potential (ERP)

Digital signal processing methodology in the field of EP and ERP research has expanded extensively over the past 15 years reflecting the improvements in processing power and speed brought about by the new generation of digital microprocessors and the advent of the personal computer. The amount of published literature is therefore significant and a comprehensive review of all published work would be beyond the scope of this thesis. However, a selection of the most important techniques ranging from the basics of signal averaging through to the more complex adaptive filtering methods plus recent advances in the field will be covered. The depth of the review will then be kept within reasonable limits.

There are a number of comprehensive reviews of digital signal processing techniques in use in EP and ERP research and the progress made using them (Aunon et al., 1981; Callaway et al.,1983; Gevins and Remond, 1987; Fabiani et al., 1987; Basar, 1988; Ruchkin, 1988; Regan 1989; Rohrbaugh et al., 1990; Polich, 1991). Despite the publication of guidelines on methodology and publication criteria as early as 1977 (Donchin et al.) methodological issues still dominate published literature in the field of ERPs. In particular, recent publications focus on how methodology will affect the clinical utility of the ERP (Denoth et al., 1986; Celesia, 1990; Pfefferbaum et al.,1990; Goodin, 1990; Polich, 1992; Picton, 1992). Very recently published guidelines (Goodin, et al., 1994) on recording and measurement techniques show that this theme is likely to continue into the future. The need to adopt standard recording and measurement techniques across research groups to allow inter-comparison of data is a common theme.

This chapter reviews the different approaches taken in signal processing of the EP's and ERP's and covers some of the most salient issues, dealing in particular with the problems of making time domain measures on the P300 component of the ERP. Finally, a new method is proposed for measurement of the P300 complex in the time domain.

5.1 Signals and noise in evoked potential studies

Evoked brain electrical activity measured on the surface of the scalp will be corrupted by other sources of electrical activity from within and extraneous to the human body. These additional signals are considered sources of noise when their frequency spectrum overlaps that of the signal and, in general, any signal which is not of interest is classified as such. All active muscles and nerves in the human body generate spontaneous electrical activity which can interfere with concurrent recordings of evoked potential activity. A measure of the root-mean-square (rms) voltage contributions from a desired signal and any unwanted noise components in an observed signal is defined as the signal-to-noise ratio (SNR), which is usually expressed in dB

$$SNR = 20\log_{10}\left[\frac{Vs_{rms}}{Vn_{rms}}\right]$$

where Vs_{rms} and Vn_{rms} are the rms contributions of signal and noise respectively, across the same bandwidth.

The important sources of noise from within the human body are i) electromyographic (EMG) from muscles in the region of the recording electrode (up to 10 mV, peak) ii) electro-oculographic (EOG) activity originating from the dipole current source in the eye (a few mV peak from horizontal, vertical and blinking movements) iii) electrocardiographic (ECG) activity from the heart (a few mV peak) iv) spontaneous electroencephalographic (EEG) noise (10's of μV), particularly time-locked

alpha activity.

External sources of electrical noise originate from mains operated electrical equipment. Electric, magnetic, and radio-frequency fields can all be generated by laboratory equipment and if they are in the vicinity of the human body significant levels of mains interference at 50 Hz and higher order harmonics may become apparent. These sources will induce currents to flow through the body via capacitive coupling and alternating root-mean-square (rms) currents of the order of only 0.2 μA can produce potentials of around 20 Volts (rms) across the human body (Brown and Smallwood, 1981, p268). These are the biggest sources of interference in any studies of human electrophysiological activity. Modern electronic amplifier design can remove most of the effect of these sources particularly the differential input amplifier which has the ability to reject very high levels of external electrical interference common to both inputs. The ability of a differential amplifier to reject sources of interference common to both its inputs is called the Common-Mode Rejection Ratio (CMRR), expressed in decibels (dB), and is given as

$$CMRR = 20 * \log_{10}\left[\frac{V_{CMi}}{V_{CMo}} * gain\right] \quad (dB)$$

where V_{CMi} is the common mode input voltage and V_{CMo} is the common mode output voltage measured at the amplifier, and gain is the amplifier gain. For evoked potential studies a CMRR of 120 dB is normally required. So for an amplifier with a gain of 10,000, a common mode input voltage of 1 volt p-p would produce a common output voltage of 10 mV p-p.

Consideration of the bandwidth of the signals and noise allows the use of bandpass amplifiers as a simple means of reducing the influence of external electrical noise sources. The combined frequency bandwidth of EEG, EOG,

and ECG sources is from about 0.5 - 100 Hz while EMG bandwidth is from 10 Hz - 5 kHz. The bandwidth of the ERP is from about 0.5 - 10 Hz so the influence from these sources can be minimised by judicious selection of filters on the input signal. For ERP studies the bandwidth of the filters were set from 0.16 - 30 Hz (-3dB).

It is important to ensure that the sampling rate of any analogue-to-digital conversion system is not allowed to sample signal frequencies which are higher than half the sampling rate. This is known as the Nyquist Criterion. This basic rule will prevent the appearance of another source of interference from aliased signals. The upper frequency limit of bandpass filters are normally chosen with this in mind and would be set such that signal sources near the Nyquist frequency were reduced to around -60dB of their value in the pass-band.

The use of sound-proofed, electrically screened recording booths can minimise the effects of mains-originating noise and EMG noise generated in response to external sounds. Comfortable seating and low background light levels are effective in further reducing artifacts from EOG and EMG sources. Avoiding large loops in recording electrode wiring also reduces the possibility of currents being induced in the recording system due to sources of strong magnetic fields. Recent advances in EEG electrode technology propose a new recording system where the amplifier electronics and power supply have been miniaturised to a degree where they are built in immediately under the electrode contact, in close proximity to the scalp (Taheri et al., 1994). Many of the problems associated with extraneous noise should, in principle, be much reduced.

It is desirable to minimise all sources of noise before applying high gain amplification to signals prior to digitisation. When these precautions are taken recordings of less than 1 μV peak are possible in, for example, the

auditory brainstem evoked potential. However, there will always be a problem with noise sources which occupy the same part of the frequency spectrum as the signal of interest. The basics of digital signal sampling in the time and frequency domains are given in Appendix 1.

5.2 Noise reduction methods

5.2.1 Signal averaging

The technique of superimposition was first used by Galton (1822-1911) over a century ago. His aim was to identify common features in the faces of criminals with the hope that potential offenders could be identified prior to committing a crime. This technique was not successful but its use in identifying the features of a successful racehorse was. The first reported attempt to use this technique in medicine was reported by Dawson (1947) in the recording of somatosensory evoked potentials. The superimposition on a CRT of consecutive sweeps of EP and background EEG led to the identification of components associated solely with the desired evoked activity. The next logical step to superimposition was averaging as the effects of random noise are not cancelled in superimposition.

An observed waveform g(t) contains two components : the signal or evoked potential, s(t), and the noise or ongoing EEG, n(t). It is assumed that the noise component is additive so that a model

$$g(t) = s(t) + n(t)$$

is valid. The success of the technique depends on the signal being stationary in time while the additive noise source is random, non-stationary, and has a mean value of zero. It is assumed that the signal is deterministic i.e. present in every data sweep. Appendix 1 covers the statistical treatment of signal averaging theory. The result is that an ensemble average formed from N consecutive data sweeps will improve the SNR by a factor of $(N)^{1/2}$ for zero-

mean noise. This technique is also known as stimulus synchronised averaging (SSA) because the ensemble average is produced by lining up the individual trials. The common start time for each trial, the "zero" time, is the stimulus onset.

There are problems with this technique if the basic assumptions are not met i.e. the signal is not deterministic. This is the case in the auditory ERP and other forms of evoked potential. Studies have shown that the latency of somatosensory evoked potentials varies from sweep-to-sweep (Brazier, M., 1964), that the latency of the auditory ERP in control subjects (Ruchkin and Sutton, 1979), and control and schizophrenic subjects also varies as a function of data sweep (Roth et al., 1980).

The effect of such non-stationarity is to smear the peak of the resultant average across time, effectively reducing the amplitude of the average representation of the signal. It has also been reported that the latency of an averaged signal is not the same as the average of the individual latencies (Callaway, et al., 1984). Other important problems with averaging have been reviewed and are well documented (Aunon and Childers, 1981; Ruchkin, 1988; Regan,1989).

External and internal periodic noise sources such as mains interference and alpha activity may be particularly problematic. Averaging these stationary noise sources will not reduce their influence on the final result to the same degree as zero-mean random noise. It has been shown that the complete removal of periodic noise is highly improbable when using signal averaging (Evanich et al., 1972). Simulations of averaging with aperiodic sinusoidal noise sources revealed that even at reasonably high numbers of ensemble sweeps (n=256) the amplitude probability distribution of the residual noise adopts a Rayleigh distribution. The main source of periodic noise in EP recording is alpha activity. Alpha activity is classified as falling between 8

and 13 Hz within the EEG spectrum. A study on the amplitude probability density for all EEG activity (Elul, 1969; McEwan and Anderson, 1975) and alpha activity only (Saunders, 1965) revealed that EEG activity follows a Gaussian distribution for 66% of the time, while alpha activity adopted a skewed distribution, the envelope following the Rayleigh distribution. This implies that alpha activity can become as problematic as truly periodic noise from external sources such as mains interference.

The presence of alpha activity during ERP recordings is part of the price exacted when subjects are asked to close their eyes to reduce the influence of EOG artifacts. In the case of 50 Hz mains noise, digital notch filters have been successfully used to remove its effect when the signal and noise bandwidths overlap. When this is not the case, band-limiting the upper frequency recorded can be achieved using low-pass filters. But perhaps the simplest method of minimising the effect of periodic noise sources is to introduce an additional random inter-stimulus interval which will range between 0 ms and the period of the lowest frequency of noise. So, to remove the influence of alpha activity from ERP recordings, an additional random delay between 0 - 125 ms is introduced.

Signal averaging is now one of the most widely used techniques in recording milli- and micro-volt potentials from the human body in the ECG (bundle-of-His activity) auditory, visual, and somatosensory evoked potentials. Its main attractions are that it is a fast and convenient method of reducing noise.

5.2.2 Latency corrected averaging

The first proposed method for identifying variable latency neuroelectric signals used cross-correlation between a template (the average waveform) and individual responses which then allowed the responses to be moved in the time domain until they aligned to the same point (Woody, 1967). This procedure was repeated recursively until convergence. Three iterations were

used between the new corrected average, updated after each iteration, and individual responses. A subsequent report showed that one iteration was sufficient (Wastell, 1977).

Latency corrected averaging is a method of producing an average of many evoked potentials while taking account of latency "jitter". Jitter is a physiological uncertainty caused when individual components of the signal vary as a function of stimulus application. The technique was first proposed by McGillem and Aunon (1977). Data are pre-processed with a minimum mean square error (mmse) filter which takes account of the finite duration of the transient evoked potential. Pre-processed individual responses are then aligned with a triangular template using a cross-correlation maximum to find the best alignment. Histograms of single trial latencies then allow proper statistical classification methods to decide whether one or more sub-groups of averages should best represent the data set. This technique is particularly valuable in the analysis of multiple-peaked evoked potential data within an analysis epoch.

There have been many variations on this type of filter and different templates and alignment techniques are used. The Woody Filter and modified versions are the most widely used form of adaptive filter in ERP research. The field is extensively reviewed in the next chapter of this thesis. Some proposals are made based on a study of simulated data regarding the best method of template matching, best template and the optimum low-pass filter setting in chapter 5 of this thesis.

5.2.3 Weighted Averaging

This technique produces an average representation of single-trial responses by assigning different weights to each trial. For an ensemble of M single-sweep waveforms, $X_m(t)$,

$$X[t] = \begin{bmatrix} x_1(t) \\ x_2(t) \\ \cdot \\ \cdot \\ \cdot \\ x_m(t) \end{bmatrix}$$

$x_i(t)=s_i(t) + n_i(t)$ are the respective additive signal and noise components of the *i'th* waveform. The averaged ensembles of the signal and noise components, S(t) and N(t), formed from identical matrices, sum such that the weighted ensemble average is given by $w^TX(t)$, where $w^T=[w_1, w_2, ..., w_M]$ is the M-by-1 weight vector. The optimal weight vector is set to the standard deviations of the signal components. The weights are designed to maximise the SNR by satisfying a generalized eigenvalue value problem involving correlation matrices of the underlying signal and noise components (Davila and Mobin, 1992). The results from this technique claimed an improvement in SNR of up to 25% compared to conventional averaging. The strength of this approach is that it can cope with signals which vary in amplitude from sweep-to-sweep but its weakness is that it is unable to deal with non-stationary signals, subject to latency jitter. An earlier published approach (Hoke et al., 1984) attempted to deal with noise between trials which was non-stationary, assigning weights of varying magnitudes. A simple model for non-stationary noise was adopted, based on a multiplicative model. Trials with high SNR estimates are weighted more heavily than low SNR trials. This approach does not take account of latency jitter or a signal of varying amplitude. It did perform better than conventional averaging however.

5.2.4 Exponential Averaging

The exponential averager has been used to track both latency and amplitude changes on single trial responses (Svensson, 1993). Two algorithms are used based on an adaptive LMS-filter. One algorithm combines exponential

averaging after filtering while the other doesn't. The estimator which combines exponential averaging and filtering can detect latency changes faster than the estimator based on exponential averaging only. In an exponential average, the exponential filter operates on the average thus

$$\hat{s}_n(k) = (1-\gamma)\, y_n(k) + \gamma\, \hat{s}_{(n-1)}(k)$$

where $\hat{s}_n(k)$ is the *n'th* estimate of the response s(k) and $y_n(k)$ the recorded signal after the *n'th* stimulus. The weight factor γ controls the influence of the old response. The averager assigns higher weights to the most recent responses.

5.2.5 Bispectrum Averaging

This technique was developed to specifically deal with non-stationary signals. It does not however return estimates of the time domain position of the signal but returns frequency domain information regarding either the Fourier amplitude or Fourier phase (Nakamura, 1993). The process is based on cross-correlation matching of single responses with a template of the average using triple correlation and the bispectrum

$$I^{(3)}(a,b) = \int I(t)\, I(t+a)\, I(t+b)\, dt$$

where I(t) is a time signal. It can be shown that the bispectrum is given by

$$\hat{I}^{(3)} = \iint I^{(3)}(a,b) \exp[-2\pi j(ua+vb)]\, da\, db$$

The bispectrum is defined as the Fourier Transform of the third-order cumulant.

5.2.6 Principal component analysis

A multivariate statistical approach would appear to be a more valid approach to analysing signals with overlapping components compared to time domain measures on the single most obvious feature. The basis of this approach assumes that the observed EP is a linear sum of components. This linear sum is then decomposed into a set of variables with different loadings. There are two stages to deriving principal components; generation of the cross-product, covariance, or correlation matrix of the averaged signal; rotating the principal components using a Varimax rotation criterion. The advantages and disadvantages of this approach have been reviewed (Wood and McCarthy, 1984; Regan, 1989) but the main problem is that there is poor discrimination between amplitude changes and incorrect variance can result from the non-stationary components of the signal.

5.2.7 Frequency domain filtering

The process of time domain averaging has the effect of acting as a comb filter in the frequency domain (Dawson, 1951). This filter will selectively enhance frequency components at the fundamental frequency F, which is the data sweep repetition rate, and higher order harmonics at 2F, 3F ...NF, where NF is the Nyquist Frequency. An explicit frequency domain approach to averaging was proposed by Arpaia et al., (1989), using the Fast Fourier Transform (Appendix 1). This filter performs exactly the same function as the Woody filter to produce a latency corrected average but runs approximately twice as fast. The speed advantage gained by this approach is in the pre-filtering stage of the data, which can be performed in the frequency domain by multiplying Fourier coefficients with a weighting factor between 0..1. The maximum cross-covariance between the single trial and template found in the time domain has an identical equivalent in the frequency domain by calculating the complex conjugate product of the Fourier Transforms (Elliot and Rao, 1982). So for two time series f(t) and g(t) with Fourier Transforms F[f(t)] and F[g(t)] respectively

where $z(\tau)$ is the cross-covariance between the two time-series, and F[g(t)]*

$$F^{-1}\{F[f(t)]F[g(t)]^*\}=z(\tau)$$

is the complex conjugate of F[g(t)]. Another reported method for separating components of overlapping waveforms using Fourier analysis and aimed at ERP applications had limited success (Hansen, 1983). The effectiveness of the proposed solution depended on the signal being purely deterministic and the latency of the overlapping components being known *a priori*. The result gave information relating only to the underlying waveshapes and not their latency. Its use in ERP research is therefore limited.

5.2.8 Adaptive filters

These filters are used principally to provide estimates of single trial responses but have also been used to pre-process data prior to ensemble averaging. A linear filter is one in which the filter output is a linear function of the observations applied to the input of the filter. For an observed data sequence {y(n)} which is a distorted or noisy version of the signal {x(n)} a linear filter will operate on {y(n)} to give an estimate { $\hat{x}(n)$ }.

The normal approach to linear filter optimization is to minimize the mean-square value of the error signal, e(n), defined as the difference between the desired filter response, x(n), and the actual response, $\hat{x}(n)$ such that

$$e(n) = x(n) - \hat{x}(n) \qquad (5.1)$$

is a minimum. The mean-square error (mse), or cost function, for the filter is defined as

$$\xi(n) = E[e^2(n)] \qquad (5.2)$$

Thus the optimal filter is defined as that filter of the set of all possible linear filters which minimise the mse.

A solution to the problem of a stationary signal buried in noise was proposed by Wiener (1949), which is said to be optimum in the mean-square sense. In problems where either the signal or noise is non-stationary, the Wiener filter is unable to provide a satisfactory solution. A time-varying filter is more suited to dealing with non-stationary signals and the Kalman filter was proposed more recently as the optimum solution (Kalman,1960).

One of the most commonly used adaptive filters in ERP research is the Wiener filter. There has been much debate concerning the validity of this filter to non-stationary evoked potential signals, and this along with an outline of the time domain representation of the filter are briefly described here.

5.2.8.1 The Wiener Filter

For the Wiener filter, the output of a finite impulse response (FIR) filter can be considered a convolution of the filter impulse response, h_i, with the input sequence y_i. This convolution is given as a finite summation of N products

$$\hat{x}(n) = \sum_{i=0}^{N-1} h_i \; y(n-i)$$

where N-1 is the filter order and h=0 for $n \geq N$, $n < 0$. The finite sum of products is compactly expressed as the vector inner product

$$\hat{x}(n) = \underline{h}^T \underline{y}(n) = \underline{y}^T(n) \; \underline{h} \qquad (5.3)$$

If the input sequence, x(n), and output sequence, y(n) are wide sense stationary (wss), i.e. constant mean for all time, then the cost function is derived by substituting equations 5.1 and 5.3 into 5.2 and reducing the solution to

$$\xi = E[x^2(n)] - 2\underline{h}^T\Phi_{xy} + \underline{h}^T\Phi_{yy}\,\underline{h}$$

The cross-correlation vector is given by Φ_{xy} and the auto-correlation vector is given by Φ_{yy}. The optimum impulse response for the filter, h_{opt}, which minimises the mse is a solution to the set of N simultaneous linear equations

$$\Phi_{yy}\underline{h}_{opt}\, n = \Phi_{yx}$$

Thus it is possible to define the Wiener filter in the time domain. An estimate of the signal $\hat{x}_a(n)$ can be provided by ensemble averaging x(n) assuming the residual noise contribution is small. The auto-correlation function of the signal can be derived from this. The cross-correlation function is derived from this estimate of the signal and the observed signal y(n), which may be a single trial response. The process for deriving the impulse response of the filter would be to calculate the auto- and cross- correlations of signal and signal plus noise. This would be carried out for each single trial response.

The application of the Wiener filter to evoked potential processing was first proposed as a means of reducing the number of waveforms required to produce an ensemble average (Walter, 1968), hence shortening the total data acquisition time. There have been a number of publications subsequently, many challenging the validity of this approach with non-stationary signals such as ERPs. Doyle (1975) noted that the transfer function in the frequency domain had been incorrectly defined in relation to published findings of visual evoked potentials. Further criticism of the validity of the filter was published: Ungan and Basar (1976), relating to information loss in non-stationary signals; further comment on the validity of the spectral estimates

made by Walter (Albrecht and Radil-Weiss, 1976); that the effect of inter-stimulus interval on the final error estimate is more important for the Wiener filter compared to averaging (Albrecht et al., 1977). Then a series of papers was published underlining the problems with the Wiener filter in processing non-stationary signals with spectral overlaps between signal and noise (Carlton and Katz, 1980; Wastell, 1981; de Weerd, 1981a, 1981b). A filter was then proposed to deal with non-stationary signals, based on the Wiener filter (Cerutti et al., 1986). The main difference in this approach was that an estimate of the EEG noise was made independently of the signal. An estimate of the (assumed stationary) noise is made by recording EEG activity prior to the stimulus. This approach was recommended only for single trial visual evoked potentials. The arguments regarding the utility of the Wiener filter appear to have gone full circle now with suggestions that the filter has some utility when used on single trials prior to ensemble averaging as a means of further improving the SNR (Thakor, 1987). This idea was further extended in 1991 (Furst and Blau) who proposed that the MSE filter is still valid but only over a small number of sweeps, with the implicit assumption that the signal is therefore stationary.

5.2.8.2 Other adaptive filters

Filters which attempt to take account of non-stationary signals whose spectra overlap those of noise have been proposed and have achieved varying degrees of success. The first proposed time-varying filters (de Weerd, 1981a) had problems due to overlapping signal and noise spectra and performed only slightly better than averaging while matrix-filtering (Yu and McGillem, 1983) was successful but required intense statistical computation. Another disadvantage is that it relies on post-stimulus EEG segments to provide noise estimates. A more recent theoretical proposal uses parametric modelling and a Kalman filter (von Sprecklesen and Bromm, 1988). The filter appears to deal with variable latency simulated signals.

5.2.9 Neural networks

The potential for neural network analysis in the automatic processing of signals from the brain has been explored for nearly 10 years (Rumelhart and McClelland, 1986; Gevins and Morgan, 1988) and applied to ERP research (for a recent example see Slater et al., 1994). A parallel distributed model, built on neural networks, was recently proposed as a model for schizophrenia (Hoffman and McGlashan, 1993).

The success of neural network analysis algorithms depends on the extraction of unique waveform features then "training" a software algorithm with a normal data set. The network may have a number of layers of interconnected "perceptrons", which mimic excitatory neurons in the human brain. Perceptron excitation or inhibition levels are modified by weights which are assigned by adaptively processing the characteristics of normative data while in the learning mode. An excellent discussion of this approach in the field of cognitive processing has been published (Rumelhart and McClelland, 1986).

5.2.10 Wavelet analysis

Wavelet analysis is one the most recently proposed method for analysing EPs and uses a completely different approach to previous methods. (Bartink and Blinowska, 1992). The method is unique in that its effectiveness is not degraded by the departures from the normal restrictions concerning the signal - the need for a deterministic signal, purely random characteristics of the EEG, and independence of the signal from noise.

Wavelet analysis is based on the the scaling function called $\Phi(t)$ which has a remarkable property: the set

$$[\,(2^j)^{-1/2}\phi(t-2^jn)\,]_{n\in Z}$$

is an orthogonal family in the $L^2(R)$ norm, for any $j \in Z$. An orthonormal basis function can be built by dilating the function $\Phi(t)$ with a coefficient 2^j, then translating the resultant function on a grid with intervals proportional to 2^{-j}. This basis can be used to analyze signals with resolution 2^{-j}. To extract the difference of information between the approximation of the function f(t) at resolution 2^j and 2^{j+1} one uses the orthogonal wavelet $\psi(t)$. This has the remarkable property of defining an orthonormal basis in $L^2(R)$:

$$[\,(2^j)^{-1/2}\psi_{2j}(t-2^jn)\,]_{j,n\in Z} \quad .$$

Functions $\Phi(t)$ and $\psi(t)$ can be used to define i) a discrete approximation of f(t) at resolution 2^j :

$$A_{2j}f=\langle f(t)\,,\phi_{2j}(t-2^{-j})\,n\rangle$$

ii) discrete detail signal at resolution

$$D_{2j}f=\langle f(t)\,,\psi_{2j}(t-2^{-j})\,n\rangle$$

The $A_{2j}f$ can be interpreted as the low-pass filtered signal. The detail of the signal describes the difference between $A_{2j}f$ and $A_{2j+1}f$, so it is a measure of the irregularity of the signal resolution 2^{j+1}. D_{2j} can be considered a bandpass signal. This multi-resolution decomposition has many advantages over the discrete Fourier Transform whose spectral resolution and upper limit are set by the duration of the sampled signal and the sampling frequency. Distinguishing characteristics can therefore be derived from single trial EP signals using discriminant function analysis. This makes the technique particularly valuable in the study of EPs evoked by non-periodic stimuli, thus avoiding the limitations of conventional averaging.

These last two techniques (neural network and wavelet analysis) have yet to have their clinical utility fully explored in ERP research but represent perhaps the most exciting recent advances in the field.

5.3 Time domain measurement of the amplitude and latency of the P300 component of the ERP

The important time domain features of a representative evoked potential, either a single trial or an averaged waveform, are normally classified using measures of latency and amplitude on important peaks of positive or negative polarity. As discussed in chapter 3, the ERP has 5 features of interest, the N100, P200, N200, P300, and Slow Wave components. Amplitude measurements are normally referred to some baseline derived from the pre-stimulus region. Normally the pre-stimulus region of the averaged frequent response is used. This is because the pre-stimulus baseline of the averaged target responses may be noisier, due to the lower number of responses in the average, and the confounding effect of activity left over from the preceding stimulus.

The identification of the P300 complex of the ERP is relatively easy as it is much bigger than the other components. In principle this should make amplitude and latency measurements easy. However, in practice the P300 complex can be a particularly difficult signal to make measurements on as it may have more than one peak of the same amplitude. A common approach from a number of research groups is to assign a window of a particular width then search for the maximum peak within this window calling it the P300. Table 5.1 lists a by no means definitive selection of windows from some published studies. Note that some studies simply report that the "P300" is the complex being measured. In such cases, unless explicitly stated otherwise, reported P300 measurements are classified as referring to P3b.

Table 5.1 Some published ERP data processing windows, all times in ms.

Study groups	N1	P2	N2	P3a	P3b	SW	Ref
C and S	< 150	< 255	1st -ve post P2		250-480		Ebmeier et al., 1992
PD	< 170	150-280	1st -ve post P2		270 - 550		"
C and S				270 - 550	270 - 550		Grillon et al., 1990
C	80 - 100	140 - 190	150-215 (P3a) 170-250 (P3b)	220 - 280	310-380	mean 400-500	Squires et al., 1975
C				250-500	250-500		Holdstock & Rugg, 1992
	80-200	170-300			320-650		Courchesne, 1978
PF and C			1st -ve 150-250	250-450	250-450	mean 400-700	Knight 1984
C	48-148	100-248	200-400		280-800 (Pz)	max post-P3 -ve Fz +ve Pz	Pfefferbaum et al., 1984
C			150-350		250-500	max -ve post-P3 in Fz	Perrault & Picton, 1984
C,D,S	70-120	140-230	-ve pk pre-P3		265-500		Blackwood et al., 1987
C	80-120	100-200	160-240		240-400		Polich, 1990
C	50-150	N1-250	P2-350		290-450	mean 500-700	Roth et al., 1980

C=control, D=depressed, PD=Parkinsons Disease, PF=Prefrontal lesions, S=schizophrenic

Quite often, the P300 complex will have two peaks and sometimes, particularly in patient groups, more than two peaks. There is no explanation as to why this phenomenon should be more pronounced in some subjects than others although the functional nature of multi-peaked P300 components is thought to relate to specific task requirements (Polich, 1988). It was also suggested in this study that P3a and P3b sub-components may be distributed in the population in an asymmetric fashion. Normally, unpredictable, task-relevant stimuli will generate a small fronto-central P3a and larger parietal P3b. The P3a is associated with a passive auditory oddball paradigm (Sutton et al., 1967). Another early component, sometimes also called P3a, but more correctly the P3-novel, is evoked in tasks designed to elicit an orienting response using novel stimuli (Courchesne, 1975). This sub-component has different latency and amplitude but similar topography as P3a, thus the confusion in terminology. It was first evoked by passive novel visual stimuli rather than emitted in a passive auditory oddball paradigm. However, if a subject initially perceives an auditory stimulus as having some significant degree of novelty the contribution from the P3-novel generator may be considerable. This is the case when different novel auditory stimuli are used, as there is no habituation effect (Holdstock and Rugg, 1992). It is possible that in the early part of a recording session of an auditory oddball paradigm, where the degree of novelty perceived by the subject may initially be high, that the rare attended oddball stimulus will also generate a significant P3-novel sub-component. This may lead to the appearance of a bifurcated P300 peak with a significant contribution from the P3-novel sub-component. Schizophrenic subjects also demonstrate a greater number of additional peaks which are more difficult to describe in terms of the currently understood P3a and P3b terminology. These peaks are possibly due to more diffuse utilisation of processing resources of a cognitive task in schizophrenia. They may also be partially caused by higher levels of EMG noise reflecting the fact that schizophrenic subjects are more restless than control subjects when performing tasks for any duration of time.

The topography of the Slow Wave component of the ERP, as described in chapter 3, is also important. The effect of the parietally maximum positive component of Slow Wave will enhance the amplitude of any peaks at that region of the scalp. So the topography for the P300 complex may vary significantly from frontal to parietal regions of the scalp with the early P3a being dominant at the Fz electrode site and the P3b becoming dominant at the Pz electrode site. Figures 5.5, 5.6, 5.7, and 5.8 in the next section give graphic examples of this problem. Each of these figures, two from control subjects and two from schizophrenic subjects, show a P300 complex with two main peaks. In each case the maximum peak value changes when moving from the frontal (Fz) to parietal (Pz) leads. Thus, moving from the front to the back of the head gives a maximum evoked potential peak from different sources.

There are significant differences in the peak latencies between the frontal and parietal sites in all the examples given. A technique was devised by Goodin et al., (1978) to deal specifically with the multi-peak P300 complex. This technique involves visually determining a point of intersection derived from the intersection of the slopes of the rising and falling edges of the P300 complex. The peak latency is derived from the intersection of two manually drawn lines and the amplitude is taken as the maximum peak value of the complex. The method is prone to error, is not free from sources of observer bias, and is likely to have poor repeatability.

A method of dealing with bifurcated P300 complexes was proposed by Polich (1988). Here a "P3MAX" measurement technique was derived from taking the maximum P300 peak amplitude across all the electrode sites studied. This method used the pre-stimulus baseline as the reference point and is not ideal for the reasons outlined above.

The method of *t*-statistical probability mapping (t-spm, Duffy et al., 1981)

was used by Morstyn et al., (1983), for calculating group differences based on the amplitude of the P300 complex. The procedure calculates the Students-t value at every electrode site at different time intervals with the aim of maximizing differences between groups.

A proposed method of dealing with multi-peak EP complexes is to derive representative measures of the energy of the complex. This is derived by integrating the area of the waveform under consideration. This technique is only successful if the SNR is the same across study groups otherwise the effect of noise on the integrated area will lead to significant errors. One method used in studies of schizophrenia (Morstyn et al., 1983; Faux et al., 1990) is based on the mean value of the P300 amplitude in the time window between 300 and 400 ms. The effect of different SNRs on these measures was not evaluated, however.

A more robust, objective, and repeatable technique would be of major benefit when making measurements on noisy and multi-peak P300 data. Such a technique, using a least-mean-squares approximation to data is proposed in the next section of this chapter.

5.4 The least-mean-squares peak definition method

5.4.1 Introduction

The problems of making measurements on a P300 complex with a number of peaks of the same amplitude were outlined in the previous section. There is a requirement for a simple, repeatable and objective technique to deal with this problem. The most widely used technique, the slope-intersection method, is perhaps the one most prone to error due to the subjective nature of the measure. This technique is a crude version of a more exact least-squares approximation to data. It was decided to investigate the merits of such a technique for making measurements on the type of signal present in the P300

complex.

5.4.2 The least-mean-squares algorithm

Least-mean-squares (LMS) fitting is used principally as a means of smoothing noisy data to identify underlying trends. The technique involves generating a solution which returns a minimum value of the summed error between data points and their fit calculated using the LMS algorithm. For a set of data points (x,y), the least-mean-squares approximation must be a linear combination of a set of basis vectors. It is therefore possible to define the functional form of the approximate solution for a polynomial function. The solution may generate a fit to data with a number of turning points reflected by the number of terms in the solution. For a set of m data points (x,y), an m x n matrix ($m \geq n$), A, is constructed where n is the number of basis vectors in the approximation. The elements of the matrix are

$$A[i,j] = V_j(X_i)$$

where $V_j(X_i)$ is the jth basis vector evaluated at data point $X[i]$. A vector Y is constructed that contains the y-values of the data points. The coefficients of the basis vectors that form the LMS approximation will be the n vector C, such that the Euclidean norm of $(AC-Y)$, represented by $\| AC - Y \|$, is a minimum. This requirement is converted to the requirement that

$$\|BC-Z\|_2 + \|R\|_2$$

be a minimum. here B is an n x n matrix, Z is an n vector, and R is an $(m - n)$ vector. The equations $BC=Z$ are the normal equations. This expression is minimised when C solves the equation $BC=Z$. Gaussian elimination (Burden and Faires, 1985) with partial pivoting is used to solve the normal equations if they form a system of linear equations. The Borland Turbo Pascal numerical methods toolbox allows the user to define the type of

approximate LMS solution (polynomial, power, logarithmic, exponential or Fourier).

The simplest form of least-squares fit to a data array X of i samples, X_i, is a linear regression generated by a least square line where Y_i where

$$Y_i = a * X_i + b$$

and parameters a and b are known. Non-linear influences or experimental error mean that there are no values for a and b that hold exactly. For our data the P300 complex requires an approximate solution with at least one turning point and a polynomial of the type

$$y = c_n x^{n-1} + c_{n-1} x^{n-2} \ldots c_2 x + c_1$$

is appropriate. The degree of the polynomial is defined as the number of terms in solution. The turning points, or peaks, of this solution can be found by differentiating the expression and setting the result equal to zero

$$\frac{dy}{dx} = (n-1)\, c_n x^{n-2} + (n-2)\, c_{n-1} x^{n-3} + \ldots c_2 = 0$$

The solution to this equation are its turning points and they are found using Laguerres method (Ralston and Rabinowitz, 1978) which is also available as part of the Borland Turbo Pascal numerical methods toolbox.

A measure of the goodness-of-fit of the solution is found by calculating the minimum-mean-square error (mmse). The mmse for data array X_i and the LMS fit array Y_i generated to match it is given by

$$mmse=\sqrt{\frac{\sum_{i=1}^{i=n}(X_i-Y_i)^2}{n-1}}$$

where the mmse converges to zero in a perfect fit. It is not desirable to generate a fit which matches data perfectly but which reveals the trend.

5.4.3 Assessment of the optimal polynomial degree of the LMS solution

Ideally, the LMS fit to our data should track the main peak of the P300 complex and resolve one main peak. This should then become a definitive and repeatable solution compared to the previous visual slope-intersection method. To assess which degree of polynomial would give the best fit to P300 data a simulation was carried out.

5.4.3.1 Methods

A synthesised P300 complex was constructed according to the modelled P300 in chapter 4, using the PC-MATLAB. A Slow Wave, simulated by a 2.5 Hz sinewave, was added to a P3a/b complex, simulated by a 7.5 Hz sinewave. The sample separation was set to 4 ms and 101 samples were generated to define a 400 ms window. To smooth the edges of the composite waveform, the data were multiplied by a Hanning window of peak amplitude 1 (Figure 5.1). A range of composites was formed by varying the summed ratios of synthesised SW and P3a/b peak amplitudes at 1, 0.7, 0.3, 0.1, 0.05 (SW:P3a/b). To attempt a realistic simulation of data and to test the robustness of the solutions, the 7.5 Hz component was shifted progressively, one sample at a time, to the left until it had traversed 100 ms of the 7.5 Hz sinewave. This results in a range of simulated P300 complexes starting with both 7.5 Hz peaks symmetrically straddling the 2.5 Hz peak at the start until one of the 7.5 Hz peaks exactly overlays the 2.5 Hz peak. An example of a simulated P300 complex at the start of the simulation, for SW:P3a/b ratios of

1:1, and with a shift left of 9 samples is given in Figure 5.2. Here it can be seen that initially the composite has two main peaks of equal amplitude (upper panel) and one where the later peak dominates (lower panel) to give an asymmetrical complex. There was a total of seventeen different waveforms for each of the five SW:P3a/b ratios.

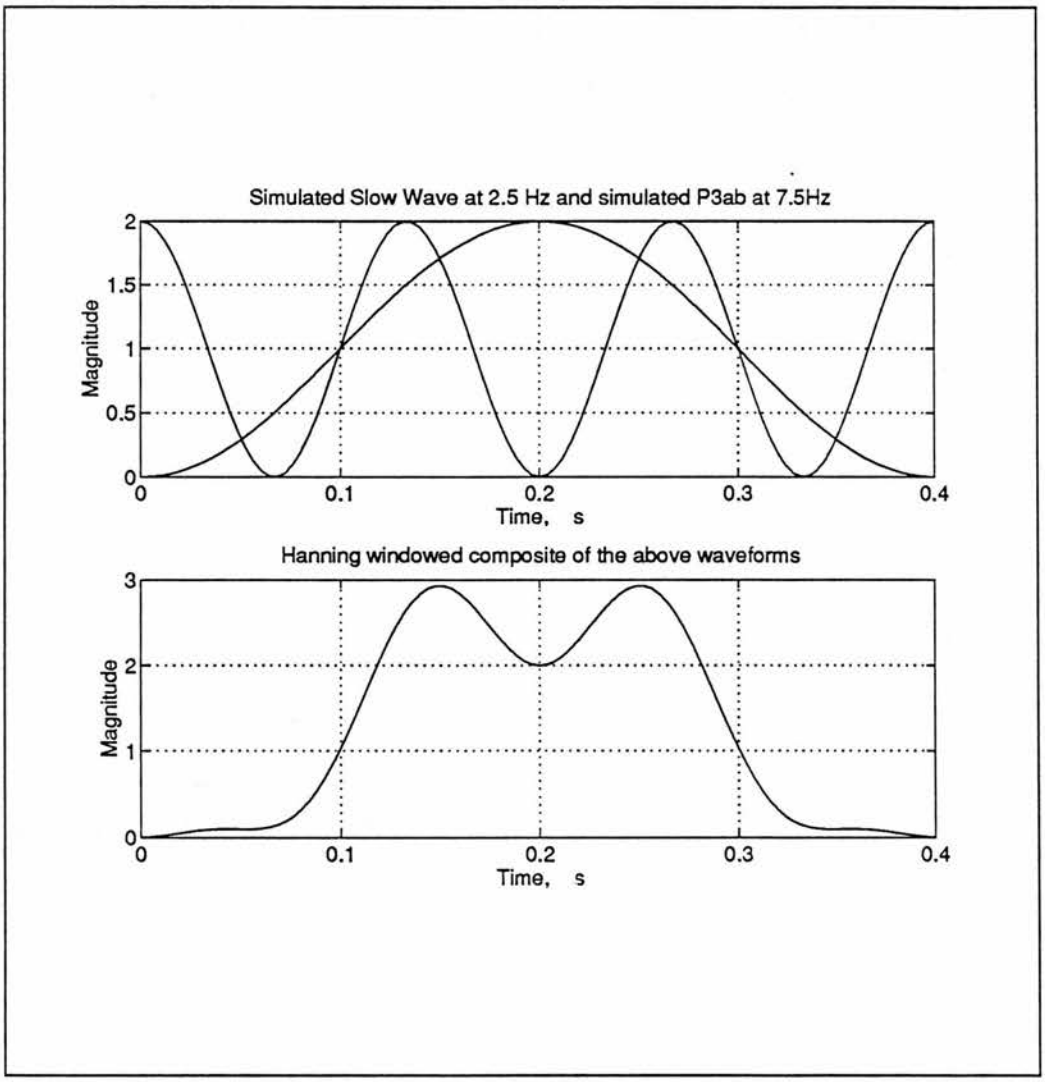


Figure 5.1 Simulated P300 complex.

Three LMS fits were then generated for each complete data set, derived from a third-degree, fourth-degree and fifth-degree polynomial. To further test the robustness of the technique, the LMS polynomials were generated to fit a more restricted data window, between 80 and 320 ms. These inflection points would be equivalent to the N200 and N300 points of the ERP. The amplitude and latency associated with the peaks of these solutions to each of the seventeen waveform matches were recorded. Two figures of merit were derived using these values and the amplitude and latency of the actual peak of the synthesised complex

$$msea = \frac{\sqrt{\sum_{1}^{17} (A_{LMS} - A_{peak})^2}}{17}$$

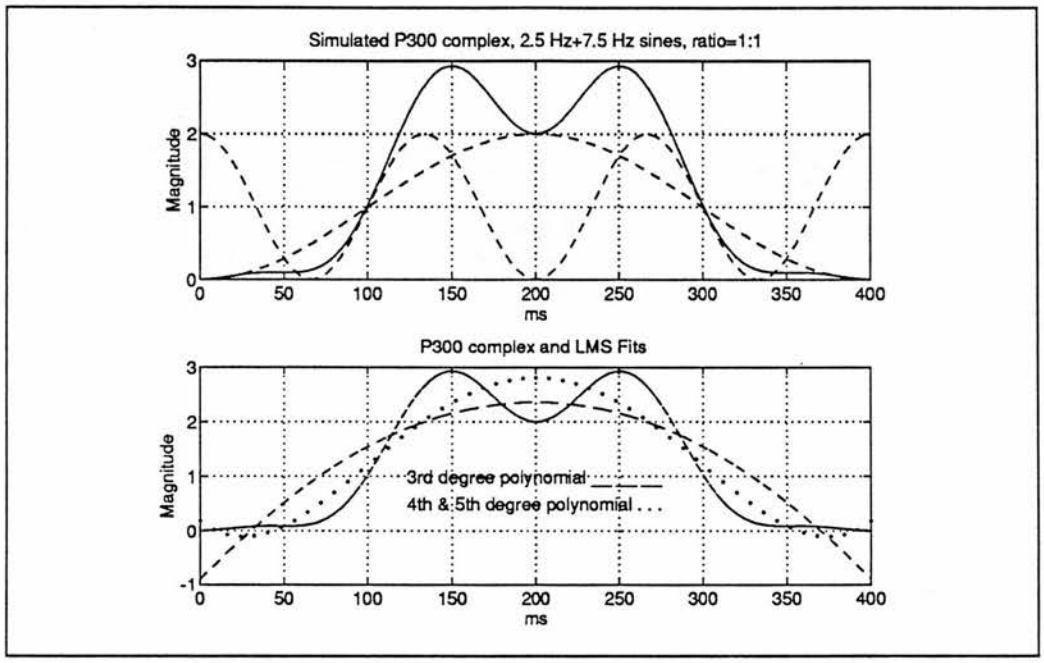
for the amplitude, where A_{LMS} is the amplitude of the LMS fit peak and A_{peak} is the actual peak amplitude, and

$$msel = \frac{\sqrt{\sum_{1}^{17} (L_{LMS} - L_{peak})^2}}{17}$$

where L_{LMS} is the latency of the LMS fit peak and L_{PEAK} is the latency of the actual peak.

Finally, P300 data from the Fz, Cz, and Pz leads of two control subjects and two schizophrenic subjects which demonstrate splitting of the main P300 complex were assessed, using the results from the simulation.

Figure 5.2 3rd-, 4th-, and 5th-degree polynomial fits to composite (1:1), ***full data window***, no phase shift (upper panel) and 9 samples phase shift (lower panel).



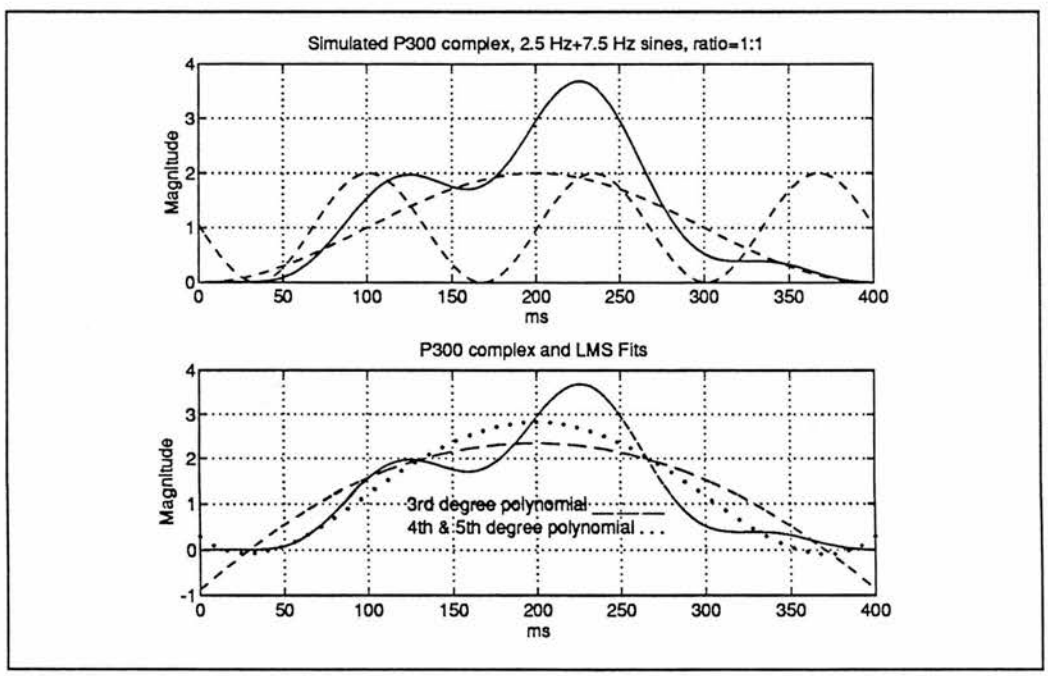
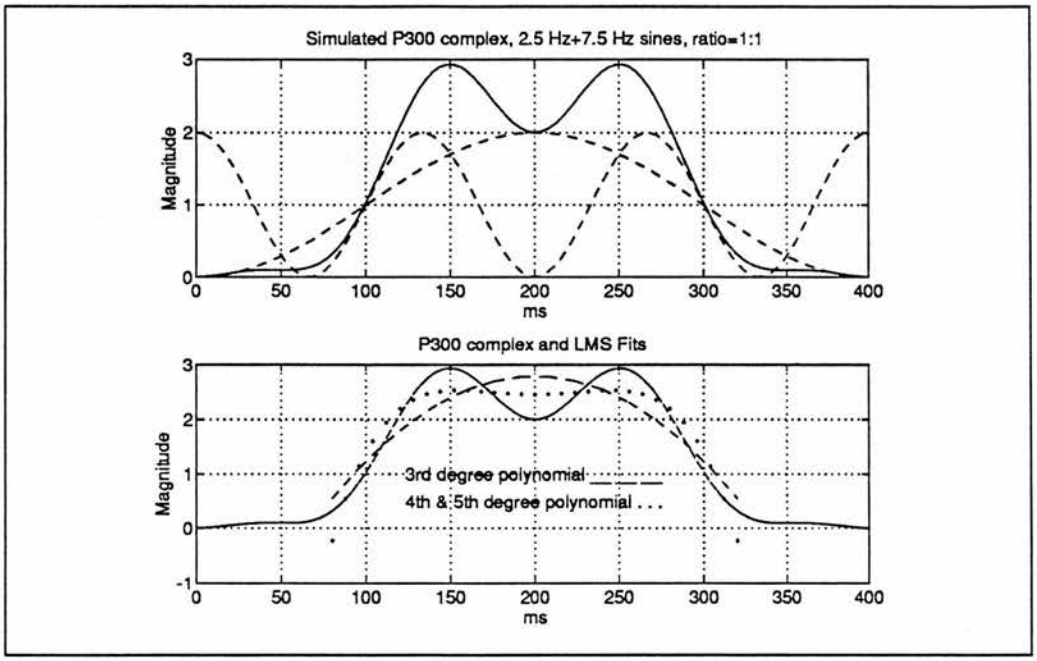


Figure 5.3 3rd-, 4th-, 5th-degree polynomial fits to composite (1:1), ***limited data window*** (80-320 ms). No phase shift (upper panel) and 9 samples phase shift (lower panel).



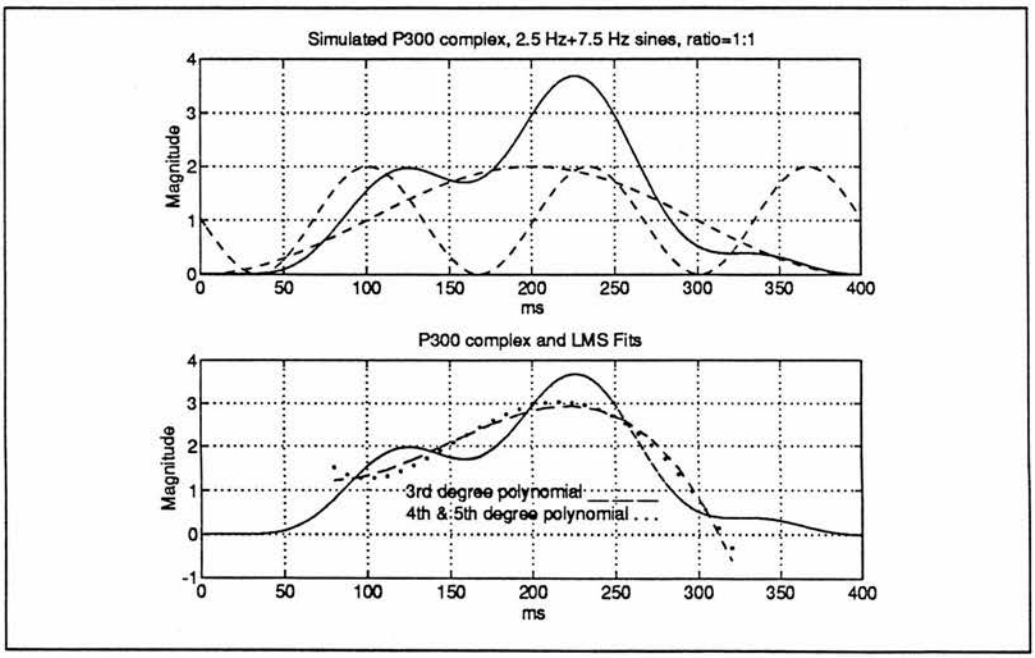
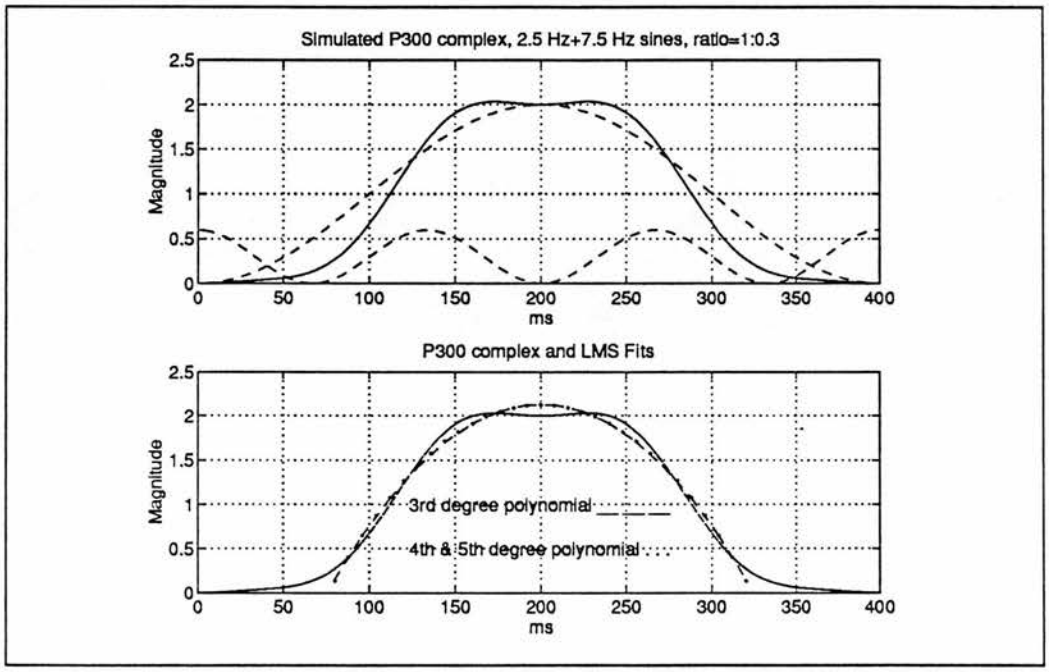


Figure 5.4 3rd-, 4th-, and 5th-degree polynomial fits to composite (1:0.3), ***limited data window*** (80-320 ms), no phase shift (upper panel) and 9 samples phase shift (lower panel).



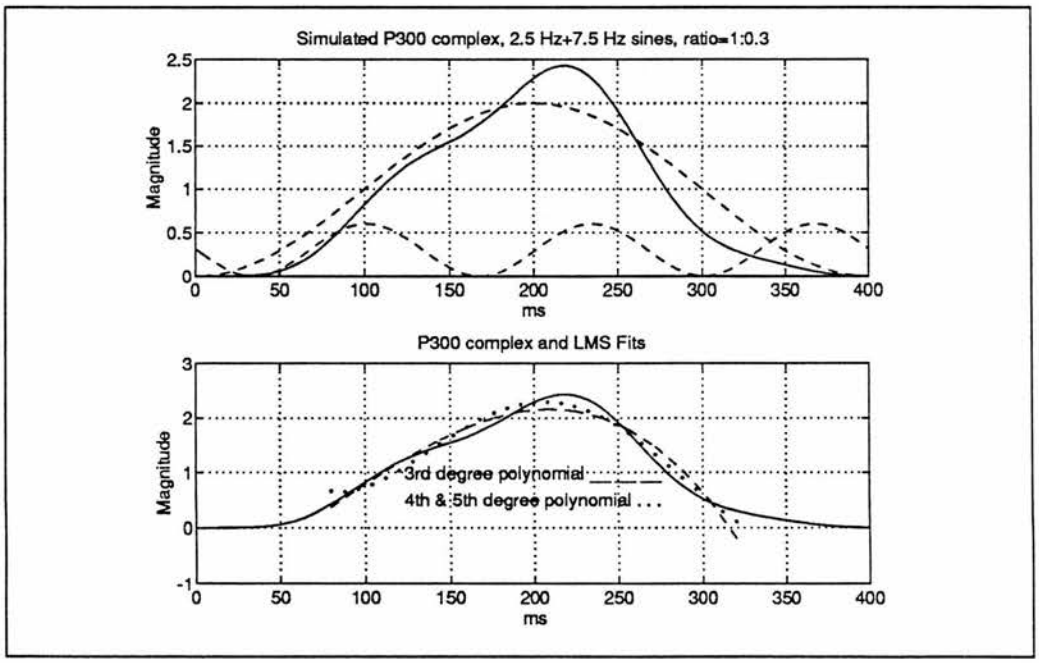
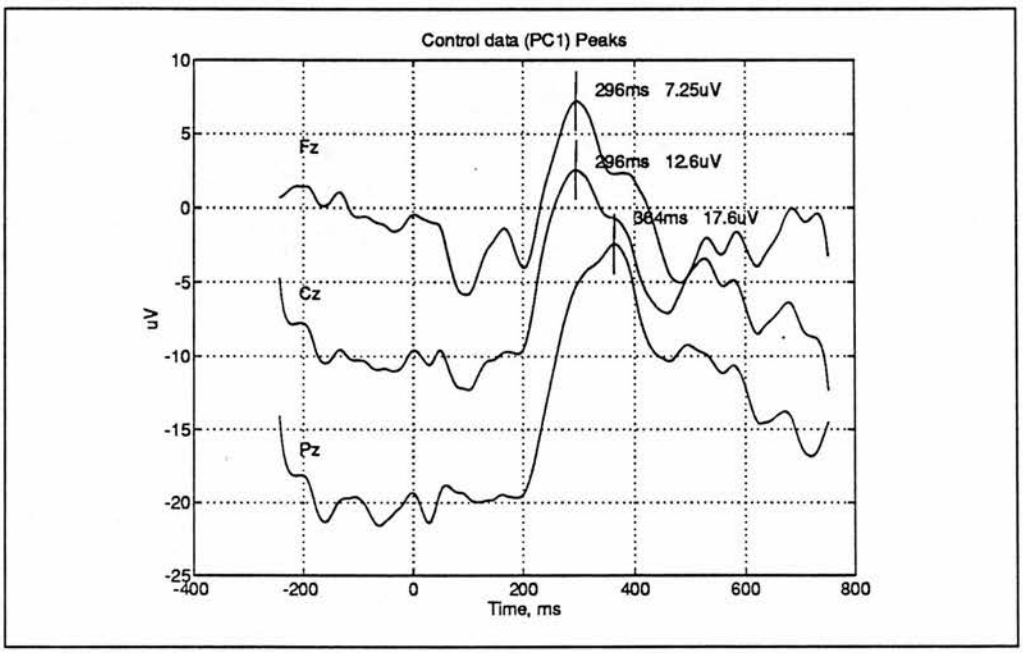


Figure 5.5 Example of control subject PC1 with split P300 complex. Peaks defined using peak search (upper panel). Peaks defined with 3rd- and 4th-degree polynomial LMS fits (lower panel).



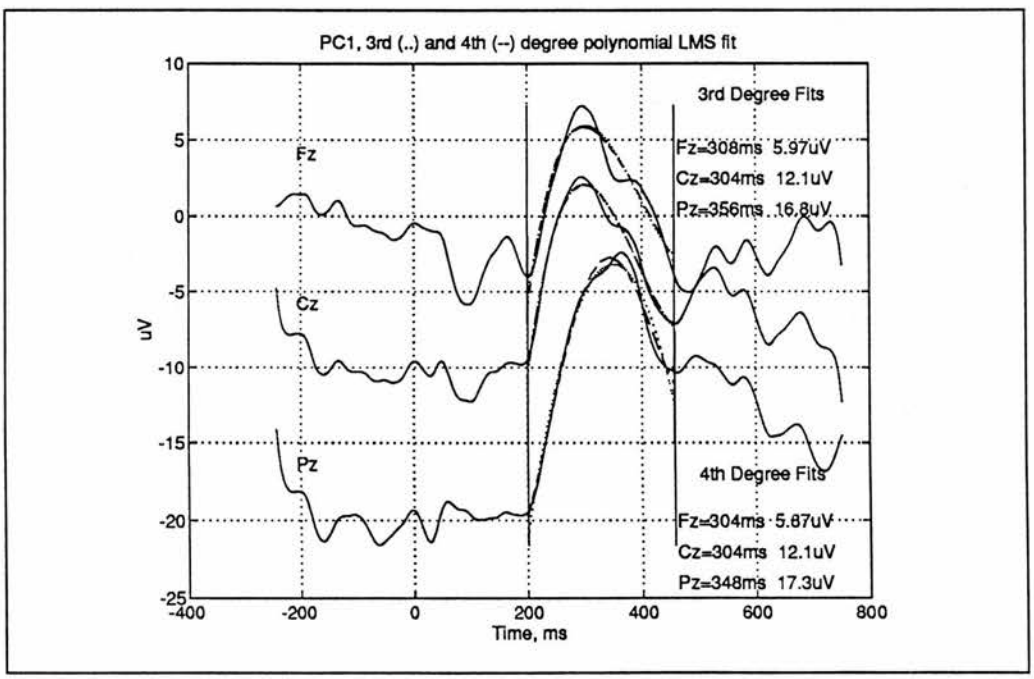
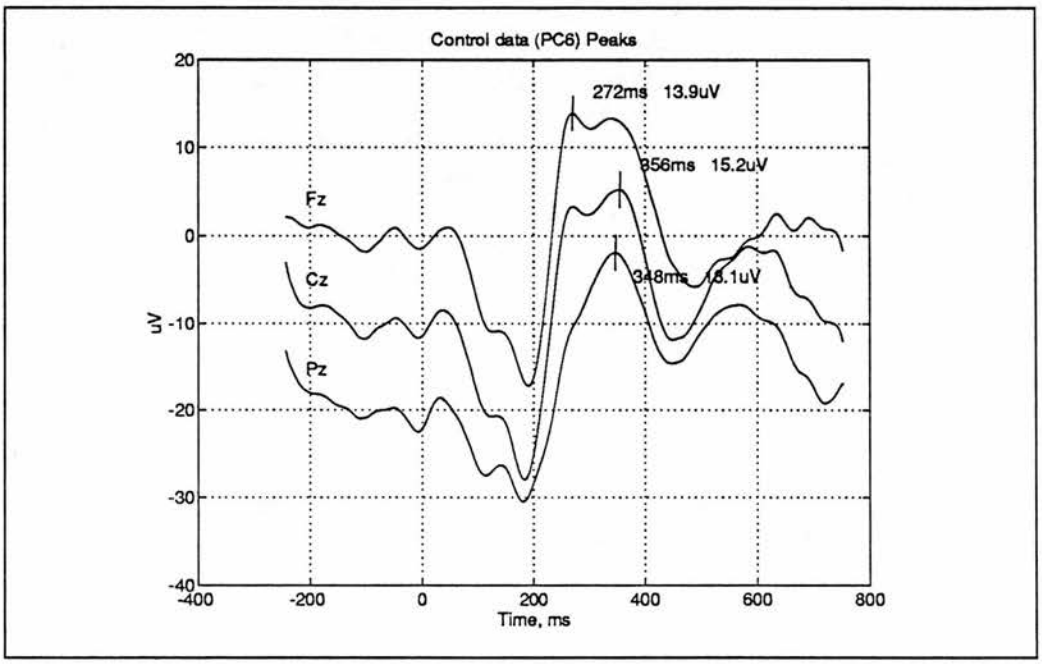


Figure 5.6 Example of control subject PC6 with split P300 complex. Peaks defined using peak search (upper panel). Peaks defined with 3rd- and 4th-degree polynomial LMS fits (lower panel).



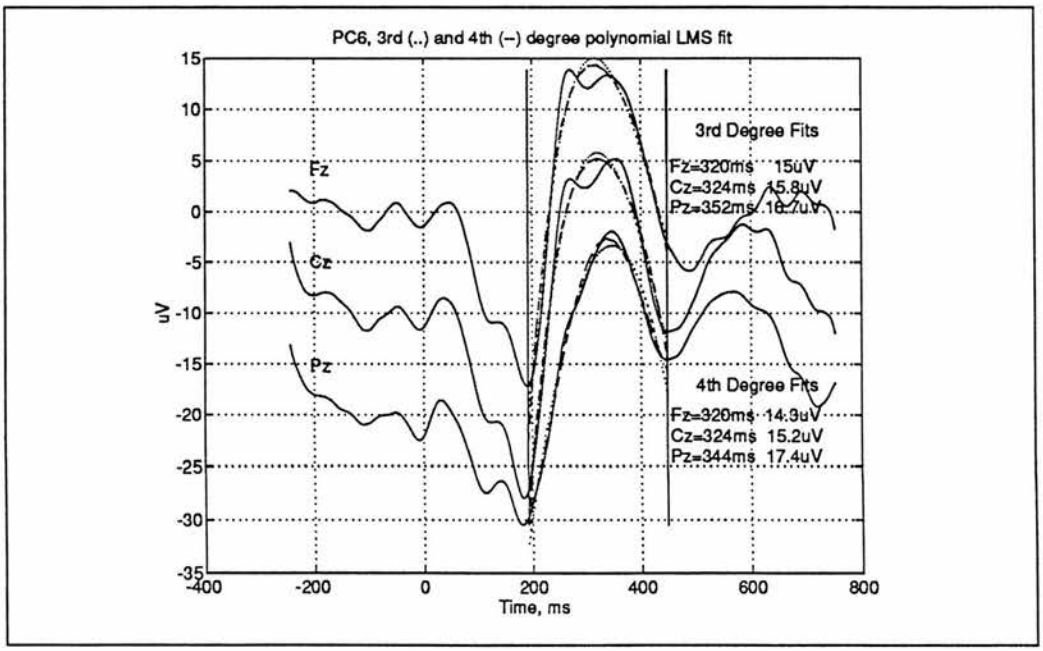
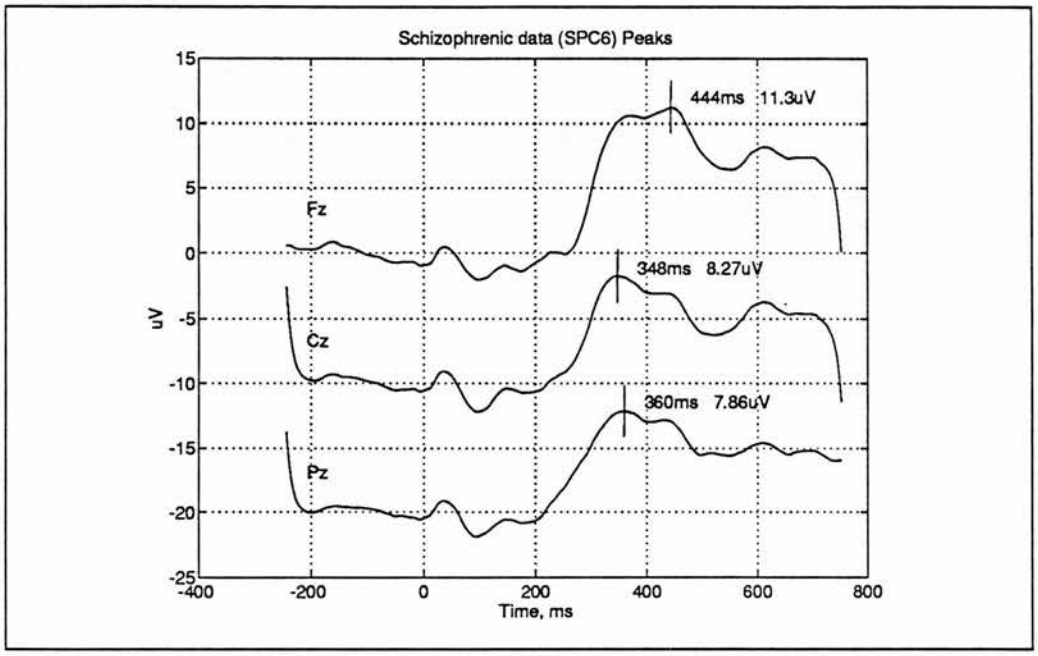


Figure 5.7 Example of schizophrenic subject SPC6 with split P300 complex. Peaks defined using peak search (upper panel). Peaks defined with 3rd- and 4th- degree polynomial LMS fits (lower panel).



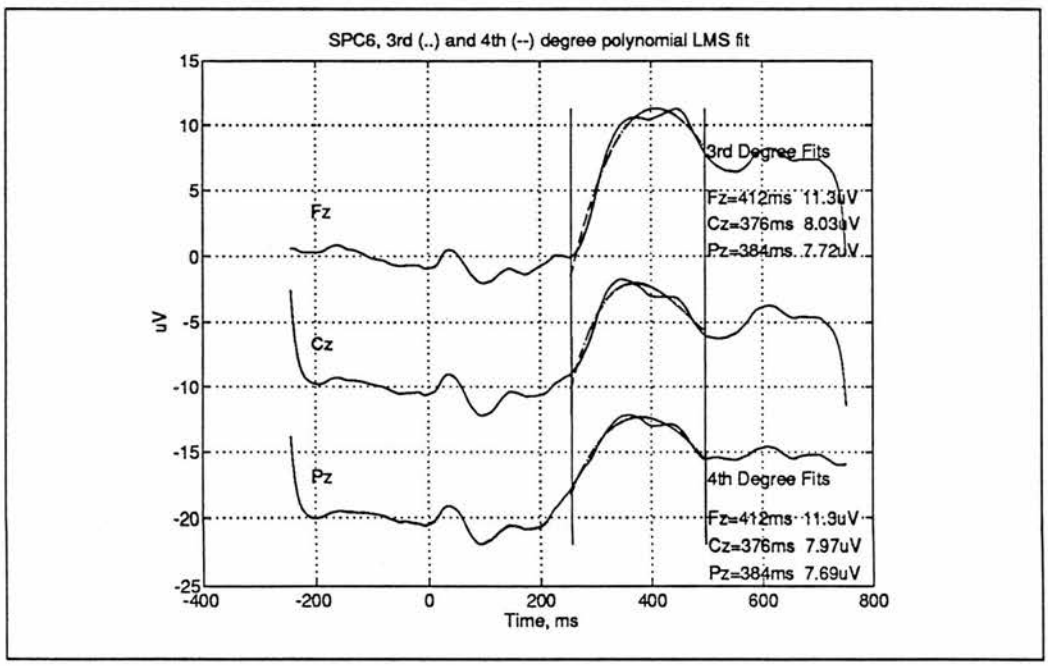
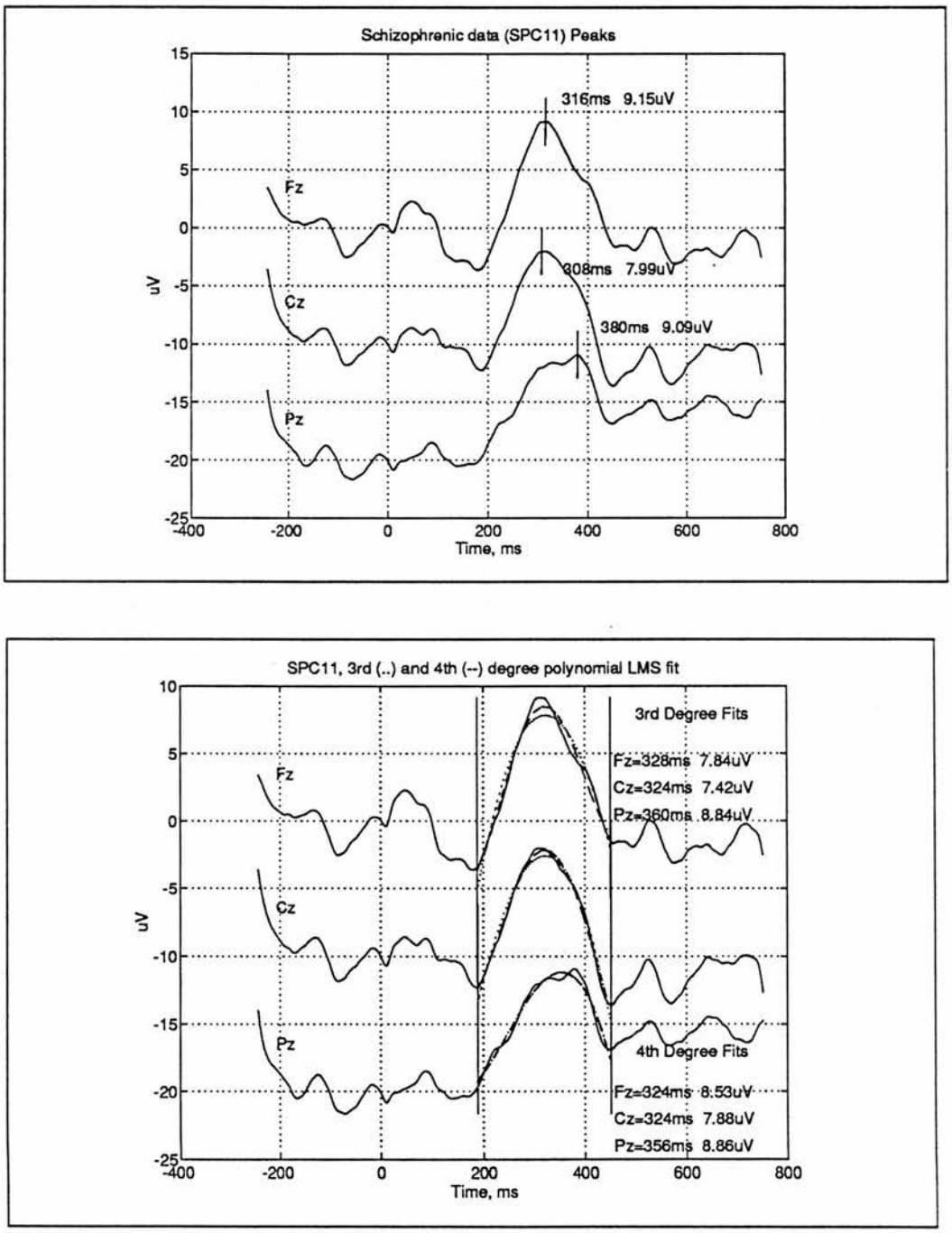


Figure 5.8 Example of schizophrenic subject SPC11 with split P300 complex. Peaks defined using peak search (upper panel). Peaks defined with 3rd- and 4th-degree polynomial LMS fits (lower panel).



5.4.3.2 Results

Tables 5.2 and 5.3 give the mean-square-errors for amplitude and latency as a function of SW:P3a/b ratio. Table 5.2 shows that for amplitude there was no difference between the fourth- and fifth-degree LMS fits. The latency error was the same for each solution. An example of how the three polynomials fit to synthesised data is given in the lower panel of figure 5.2. The fourth- and fifth-degree solutions are identical. From table 5.2, the amplitude error is greater for the third-degree fit compared to fourth- and fifth-degree fits at all ratios, while the latency error is identical for all three as seen in table 5.3.

Table 5.2 Mean-square ***amplitude*** error for third-, fourth-, and fifth -degree polynomial LMS fits for the ***full data window.***

			SW:P3	Ratio		
		1	0.7	0.3	0.1	0.05
DEGREE OF	3	1.31	1.03	0.683	0.561	0.564
POLYNOMIAL	4 & 5	0.844	0.604	0.308	0.184	0.167

Table 5.3 Mean-square ***latency*** error for third-, fourth-, and fifth-degree polynomial LMS fits for the ***full data window.***

			SW:P3	Ratio		
		1	0.7	0.3	0.1	0.05
DEGREE OF POLYNOMIAL	3, 4 & 5	30.12	27.92	19.26	6.22	3.36

Tables 5.4 and 5.5 give the mean-square errors for amplitude and latency measures on the restricted data window.

Table 5.4 Mean-square ***amplitude*** error for third-, fourth-, and fifth -degree polynomial LMS fits for ***narrow data window***.

			SW:P3	Ratio		
		1	0.7	0.3	0.1	0.05
DEGREE OF	3	0.78	0.563	0.289	0.17	0.154
POLYNOMIAL	4 & 5	0.567	0.373	0.126	0.041	0.024

Table 5.5 Mean-square ***latency*** error for third-, fourth-, and fifth-degree polynomial LMS fits for the ***narrow data window***.

			SW:P3	Ratio		
		1	0.7	0.3	0.1	0.05
DEGREE OF	3	87.97	89.52	98.12	83.09	82.84
POLYNOMIAL	4 & 5	82.87	88.32	90.96	84.99	82.84

Table 5.4 shows that the third-degree solution gives a higher amplitude error than either the fourth- or fifth-degree solutions, which are identical. In table 5.5 the mean-square latency error for the third-degree solution is greater than most of those for fourth- and fifth-degree errors, which are again identical. The upper panel of figure 5.3 shows how the fourth- and fifth-degree solutions track both peaks of the original data when there is no phase shift in the P3a/b component for a composite of ratio 1:1. The third-degree solution resolves a single peak. The lower panel of figure 5.3 shows virtually no

difference between solutions. Another example is given in figure 5.4, where the composite ratio is 1:0.3. The upper panel shows a composite with no phase shift of the P3a/b complex and the polynomial solutions are identical while in the lower panel the P3a/b component has been moved left by 9 samples (36 ms). Again there is virtually no difference in the appearance of third-, fourth- and fifth-degree solutions.

Because there was no difference in the fourth- and fifth-degree solutions with the simulated data sets, only third- and fourth-degree solutions were generated for the real P300 data. Tables 5.6 and 5.7 summarise the difference in amplitude and latency between the solutions and the actual P300 peaks, expressed as a percentage of the actual value returned by the maximum peak definition.

Table 5.6 Percentage difference in ***LATENCY*** between 3rd- and 4th-degree polynomial LMS solutions and actual P300 data.

		Polynomial		LEAD	
		Degree	Fz	Cz	Pz
	PC1	3	4	2.7	-2.2
	PC1	4	2.7	2.7	-4.4
	PC6	3	17.6	-9	2.3
CASE	PC6	4	17.6	-9	-1.1
	SPC6	3	-7.2	8	6.7
	SPC6	4	-7.2	8	6.7
	SPC11	3	3.8	5.2	-5.2
	SPC11	4	2.5	4.9	-6.3

Table 5.7 Percentage difference in ***AMPLITUDE*** between 3rd- and 4th-degree polynomial LMS solutions and actual P300 data.

		Polynomial		LEAD	
		Degree	Fz	Cz	Pz
	PC1	3	-17.6	-4	-4.5
	PC1	4	-19	-4	-1.7
	PC6	3	7.9	3.9	7.7
CASE	PC6	4	6.5	0	-3.9
	SPC6	3	0	-2.9	-1.8
	SPC6	4	5.3	3.6	-2.2
	SPC11	3	14.3	7.1	2.7
	SPC11	4	-6.8	-1.4	-2.5

The latency errors given in table 5.6 show that there is very little difference in the accuracy of the third- and fourth-degree polynomial solutions. For the amplitude errors, shown in table 5.7, it appears that the third-degree polynomial performs, in general, as well as the fourth-degree solution but there are bigger differences at the Fz lead for PC1 and SPC11. Figures 5.5, 5.6, 5.7, and 5.8 show how the LMS fits were matched to the original data. In all cases the differences between the amplitude and latency values for the third- and fourth-degree solutions were very close, apart from the differences noted above.

5.4.3.3 Conclusions

There was no significant difference in the accuracy of the solutions produced by fourth- and fifth-degree polynomial fits to simulated data sets for either amplitude or latency. With the simulated data, in most cases, there was little

or no difference in the latency error returned for third-, fourth and fifth-degree solutions. The main differences were noted in the errors accumulated using the third-degree solution compared to the fourth- and fifth degree solutions. There were also some problems with the fourth- and fifth-degree solutions when a limited data window was used and the solution resolved two peaks. In the analysis of real P300 data there was little to choose between a third- and fourth-degree polynomial solution. The biggest differences occurred in the error associated with the amplitude values returned by the LMS fits, where the fourth-degree solution produced smaller errors. Practically the third-degree solution will be used to provide a latency measure only on P300 data. The P300 amplitude will be taken from the actual amplitude of the complex which will be windowed for an LMS fit between the N2 and N3 points.

Chapter 6.

Latency corrected averaging

The technique of latency corrected averaging is perhaps the most widely used in studies of the ERP aside from conventional ensemble averaging and offers the potential for extracting additional information not available from an ensemble average. Latency corrected averaging was briefly covered in the last chapter and will be reviewed in more detail, covering its evolution since being originally proposed for use in the analysis of neuroelectric data and its use in the field of ERP research. The results from a simulation study which examine some pertinent issues and complement recent advances in the field are also presented.

6.1 Cross-correlation and covariance

The cross-correlation function, R(t), used to calculate the best match between two continuous time domain functions f(t) and g(t), random or periodic is

$$R(t) = \lim_{T\to\infty} \frac{1}{T} \int_{-\frac{T}{2}}^{\frac{T}{2}} f(t)\ g(t-\tau)\ dt$$

where T is the duration of functions f(t) and g(t), τ is the time-shift prior to cross-multiplication (Connor, 1982). It can be seen that if f(t)=g(t) the product will be maximum for zero-lag (the auto-correlation function), and will gradually decrease, possibly reaching zero or becoming negative. If the function is correlated with its exact mirror-image about the time axis, there will be a maximum negative correlation at zero lag.

For two discrete data sets such as sampled time domain signals, x(t) and y(t) represented by the sets $\{x_i, y_i : i=1,...,N\}$ the covariance between them, s_{xy}, is defined

$$s_{xy} = \frac{1}{N}\sum_{i=1}^{N} (x_i-\bar{x})\ (y_i-\bar{y}) \qquad (6.1)$$

The bracketed terms represent the deviations from the respective means for each data set. The product of the standard deviations of x_i and y_i, s_x and s_y is defined

$$s_x s_y = [\frac{1}{N}\sum_{i=1}^{N} (x_i-\bar{x})^2\ (y_i-\bar{y})^2]^{1/2} \qquad (6.2)$$

The correlation coefficient, r_{xy}, is defined from 6.1 and 6.2 above as

$$r_{xy} = \frac{s_{xy}}{s_x s_y}$$

The correlation coefficient will have a value ranging from -1 to 1 while the covariance value is a function of the actual range of data values. Aside from this there is an important difference in the property of the covariance and correlation functions. In the case of two waveforms of magnitudes y and 2y, the covariance between the two will be sensitive to the shape of the waveforms while the correlation coefficient is relatively insensitive to shape. Figure 6.1 below is used to illustrate a simple example of this.

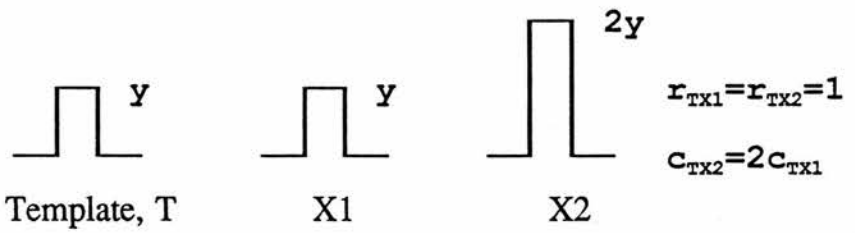


Figure 6.1 Correlation and covariance example.

If the correlation coefficient, r_X, and covariance, c_X, are calculated between the template and X1 then X2, the r value returned will be 1 for both but the c value for X2 will be double that for X1.

6.2 The Woody filter

The genesis of the technique of latency corrected averaging grew from the desire to correct an ensemble average with component signals which violate the fundamental requirement for stationarity. Woody's (1967) initial proposals were to allow the latency of a pseudo-stationary signal buried in significant levels of noise to be estimated using the technique of cross-correlation.

The technique uses a template formed from the ensemble average of an array of single sweep responses. This is aligned with a single trial response to find the best fit to data corresponding to the maximum cross-correlation, returning a latency "jitter" for each trial. If an averaged evoked potential AEP(i), formed from the set $\{x_{ki}\}$ where k refers to the response number, is correlated with a signal x_{ki} the correlation coefficient, r, is given as

$$r_k = \frac{\frac{1}{N}\sum_{i=1}^{N} (x_{ki}-\overline{x_k})\,(AEP(i)-\overline{AEP})}{\left[\frac{1}{N}\sum_{i=1}^{N} (x_{ki}-\overline{x_k})^2 \;\frac{1}{N}\sum_{i=1}^{N} (AEP(i)-\overline{AEP})^2\right]^{\frac{1}{2}}} \qquad (6.3)$$

Successive single trials are aligned for a correlation maximum then shifted in time by the associated jitter value to form a new, latency corrected average (LCA). Three iterations of the filter were necessary before convergence.

Using this approach Woody was able to extract stationary sinusoidal signals from limited, wide-band noise. It was shown that the filter was capable of improving the SNR fivefold, from an input SNR of 0.2 to an output SNR of

1. The filter performance degraded rapidly at lower SNRs. The filter also demonstrated its ability to separate waveforms consisting of multiple synthetic signals using a modified procedure which ranks the correlation coefficients to help identify the different components. Variable latency neuroelctric signals were then processed successfully with the filter. The major weakness in the filter was seen as its inability to distinguish between signals and noise which occupy the same region of the spectrum. A critical evaluation of the Woody filter (Wastell, 1977) with visual EP data suggested that only one iteration of the filter was necessary to produce a new LCA. A narrow template was used, made from the averaged EP and the selection of the template was seen as crucial to the success of the filter. Frequency distributions of the latencies determined by the filter on i) signal only and ii) noise only, showed that a normal distribution is returned for the signal while the noise distribution was uniform. This study hinted at the use of the cross-correlation function as a means of determining the SNR. A theoretical paper by Bershad and Rockmore (1974) had earlier shown that the correlation coefficient could be used as an estimator of SNR. They proposed the maximum likelihood estimator of the SNR, α_r, based on the correlation coefficient, r, between two data sets

$$\hat{\alpha}_R = A\left(\frac{r}{1-r}\right) + B$$

where A is given as

$$A = \exp\left(-\frac{2}{N-3}\right)$$

and B is

$$B = -\frac{1}{2}\left[1-\exp\left(-\frac{2}{N-3}\right)\right]$$

N is the number of samples. The estimator was proposed for use with two

consecutive trials of data. The signal must be present in each trial for the technique to be effective. This technique was further explored by Coppola et al., (1978), who suggested that averaging α_r across pairs of single trials would give an average estimate of the SNR. This group also proposed using the averaged ensemble of the evoked potentials, AEP, as in equation 6.3. to calculate r_k for each trial. The distribution of r_k is skewed and is made normal using the z-transform

$$z_k = \frac{1}{2}\log_e\left[\frac{1+r_k}{1-r_k}\right]$$

The normally distributed average correlation coefficient ZA is then calculated as the mean of all individual coefficients, z_k. The relationship between ZA and SNR was determined empirically for a range of SNRs in a synthesised data set and for the particular template used, which was a limited swept-frequency from 1.5-4.8 Hz, of 400 ms duration. Using these techniques it was possible to quantify the mean SNRs for auditory and visual EPs. The study showed that the SNR for the EPs studied varied on a trial-by-trial basis. The authors suggest that the technique has clinical utility. However, there is a limitation in that the template window must be exactly 400 ms. A fixed temporal relationship between individual ERP components within this fixed window is necessary for such a technique to be successful.

Further refinements to the LCA technique were made by McGillem and Aunon (1977). Woody suggested in his original paper that the effect of noise could be reduced by pre-processing the data with a suitable filter. These authors pre-processed visual EP data with a mmse filter, which was the Wiener filter. This approach allowed detailed analysis of separate signal components in the time domain using a template of 24 ms duration which represented an isosceles triangle. A sign test of the component polarities is used to determine that the intervals in which the peaks are present would not

be produced by ongoing EEG only. Histograms of the separate time domain components allowed the most likely latencies to be identified with each. An LCA was computed for each component. By this method the authors were able to determine the spectral composition of the early and late components of the visual EP. The limitations of the Wiener filter in dealing with non-stationary signals was commented on in chapter 4, and would be valid in this reported method. A study by Aunon and Sencaj (1978) then looked at the effectiveness of this method compared with traditional averaging and simple cross-correlation averaging using the Woody filter on 20 normal subjects who produced visual EPs. They confirmed that the major problem with the Woody filter is when it locks onto the largest peak in the trial, signal or noise. The major problem with this technique is that the resultant LCA bears no resemblance to a conventional average and when the individual components are adjusted, the waveform is disjointed with significant discontinuities in the data.

A significant landmark in ERP research was reached in 1967 (Sutton, et al.) when it was noted that the P300 component in an auditory oddball experiment was still emitted in the absence of a stimulus and that this emitted P300 complex was smaller in amplitude than the evoked P300 complex to a target sound. An important question arose as to whether this difference was due to a smaller emitted potential or whether the variance of the emitted potential was greater than the evoked potential. This issue was addressed using the Woody filter (Ruchkin and Sutton, 1979) to provide an LCA for both emitted and evoked potentials and the result showed that the cause was due to a smaller amplitude emitted potential.

The first published study of the latency corrected average method applied to ERPs in schizophrenia appeared in 1980 (Roth et al). The authors wanted to discount latency jitter as the cause of reduced P300 amplitude as seen consistently in this patient group. The application of the Woody filter with

three iterations to produce an LCA revealed that the amplitude of the P300 was still significantly reduced compared to controls. Another early clinical application of the Woody filter was to produce single trial latencies of P300 for correlation with their individual reaction times (Pfefferbaum et al, 1980; Pfefferbaum et al., 1983). A 250 ms template comprising 1/2 a cycle of a synthesised 2 Hz signal was used. An interesting methodological change to the application of the Woody filter was introduced by this group. They commented on the use of covariance rather than cross-correlation as a means for detecting the best template match, noting that covariance is more sensitive to the shape of the waveform than cross-correlation.

A published study then investigated the individual components of the ERP in control subjects. The aim was to examine the association of the N100, P200, N200, and P300 components (Michalewski et al., 1986). This study used a range of templates derived from the SSA, one for each of the individual ERP components. The study showed that the N200 and P300 components were correlated to a high degree but the exogenous ERP components were dissociated from the endogenous ERP components. This is a very important result and indicates that when latency corrected averaging ERP studies, a template covering the whole complex is not appropriate due the dissociation of the early components (N100, P200) from the late components (N200, P300). The authors also found that the optimum correlation coefficient values for control subjects was between 0.65 and 0.75. This group then went on to perform a similar study on elderly demented subjects, depressed subjects, and elderly controls (Patterson et al., 1988). The use of the LCA on individual components showed that the P300 peak was best at discriminating group latency differences, but component latency variability did not significantly increase diagnostic sensitivity.

The LCA technique was further refined (McGillem et al., 1985) in the context of the ERP. A comparison of conventional averaging, cross-

correlation averaging, latency corrected averaging, continuous latency corrected averaging and enhanced averaging. The continuous LCA technique was introduced to solve the problem of discontinuities in the resultant average using the LCA technique, and produce a continuous waveform. A weighted least-squares function was used successfully for this. Enhanced averaging is a technique using time domain deconvolution to restore the continuity of the LCA. The result of this study showed that the continuous, or fitted, LCA gave the best result.

A comment published on methodology using the Woody filter to process the single trial P300 in clinical applications noted the need for a well done study of the critical low-pass filtering parameters and acceptable signal-to-noise ratios (In : Donchin, 1984, p267). A notable reliability study on single trial analysis of P300 compared the efficacy of a number of techniques based around the Woody filter (using both cross-correlation and covariance measures), area measures, peak-picking and principal component analysis (Fabiani et al., 1987). Optimal pre-processing low-pass filters were not assessed and the main results were conflicting. A subsequent study replicated this assessment but this time studied the effect of SNR and the optimal pre-filter for data on a data set simulating both endogenous and exogenous components of the ERP (Gratton et al., 1989). A template was derived from the simulated ERP complex. The authors concluded that SNR is the most important factor when estimating single trial latency but that it did not appear to interact with other effects, i.e., accurate latency estimators work well at good and bad SNRs. The effect of low-pass filters did not appear to significantly improve cross-correlation averaging but it was noted that the best filter cut-off appeared to be at 1.76 Hz. Cross-correlation signal detection appeared to be a more accurate method than peak-picking with increased sensitivity when the duration of the signal is known. A previously reported result was confirmed: that only one iteration of the Woody filter is necessary for producing an LCA with the optimum SNR. A contentious

finding with this study was the authors' claim that a template which is wider than the P300 complex produces a better result than a template which is equal to or less than the P300 duration. It has been shown in studies on real P300 data noted above that the endogenous and exogenous components are dissociated in single trial analysis. One would therefore expect that a template covering all components would not perform as well as one which focuses on the P300 complex only. Further, it is difficult to assess the importance of these findings in relation to current methodology, where the template used for the Woody filter is either derived from the SSA of the data or a synthetic template, normally a half-cycle of a 2.5 Hz sinusoid.

With this in mind it was decided that a rigorous study would be conducted on simulated data to attempt to address some of the issues covered above.

6.3 Single trial peak detection: a simulation study

The aims of the simulation were to assess

i) the best method of template matching for signal detection : cross-correlation or covariance;
ii) the optimal low-pass pre-filter setting;
iii) the most suitable type of template for optimum signal detection.

All data were synthesised in software written in Turbo Pascal and the programs were run on an Intel 486-DX2 processor based PC.

6.3.1 Methods

A data set was synthesised using the additive signal plus noise model. A one second data epoch, with samples at 4 ms spacing, was generated. The signal was synthesised by the positive half-cycle of a 2.5 Hz sinusoid of width 400 ms. The EEG noise was simulated by applying a digital FIR filter to zero-mean Gaussian noise (Nakamura, 1993). Figure 6.2 shows how this

filter affects zero-mean Gaussian noise in the time domain.

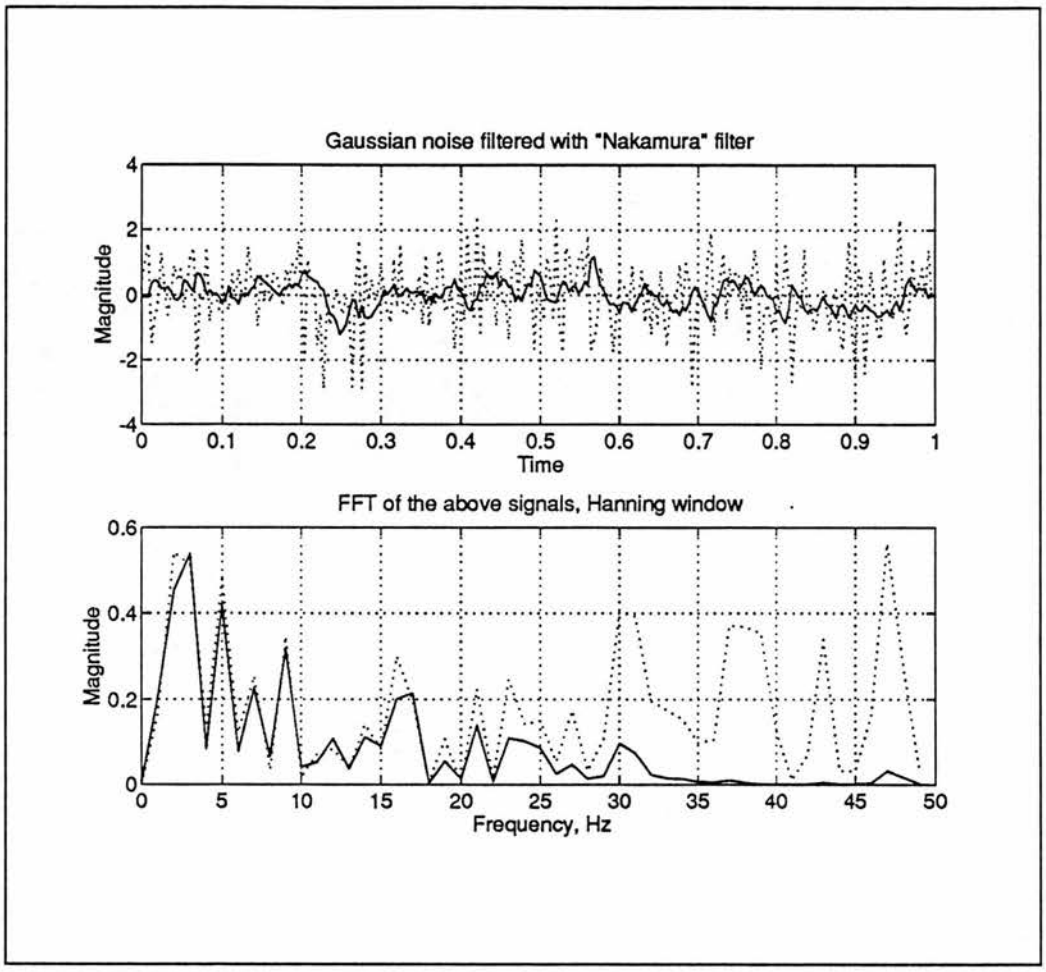


Figure 6.2 The effect of the digital smoothing filter on Gaussian noise in the time domain.

The variance approximates the power of the signal across time (Coppola et al., 1978) and the SNR was determined by calculating the variance of the signal, σ_s^2, and noise, σ_n^2

$$SNR = \frac{\sigma_s^2}{\sigma_n^2}$$

A program ("P3sim", Appendix 2) was written to generate 40 responses, each with 5 different SNRs: 4, 2, 1, 0.5, 0.25. A unique noise set was generated for every trial. The SNRs were set by calculating the variance of the synthesised EEG over the same epoch as the signal then scaling the noise appropriately. Ten data sets were generated to give a total of 400 different responses at each SNR. Figure 6.3 gives an example of the synthesised signal plus noise at SNR of 4.

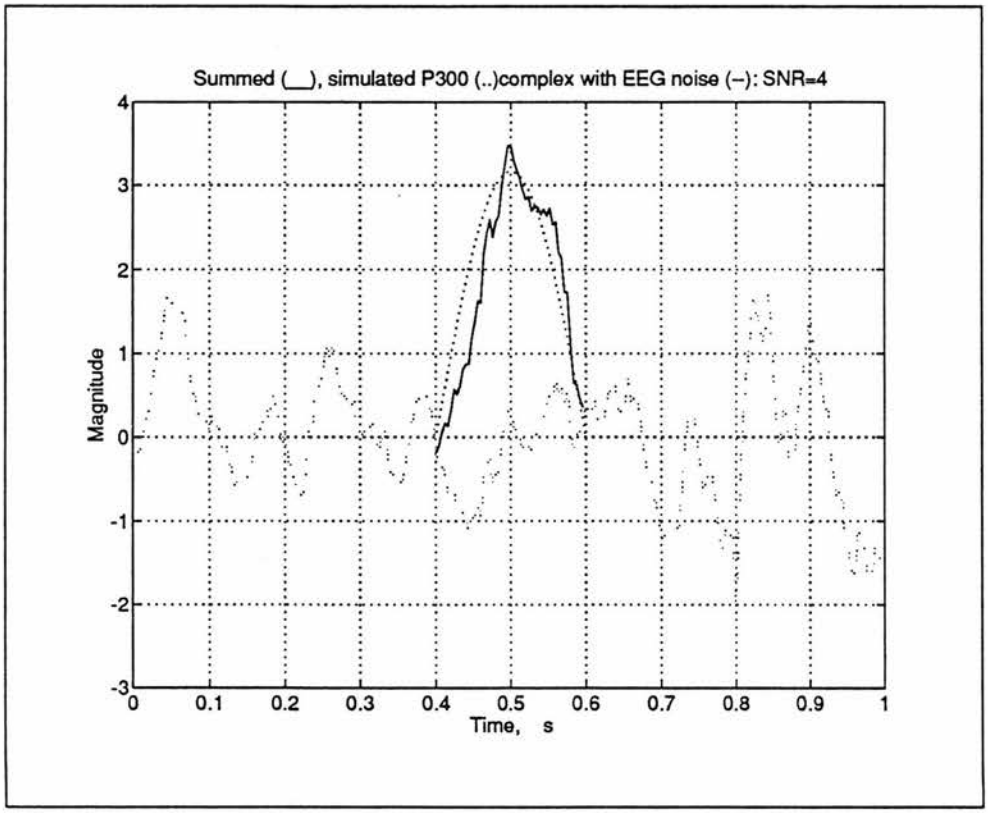


Figure 6.3 Synthesised P300 and EEG noise at SNR of 4.

The spectrum of the synthesised EEG was compared to real EEG sampled using the custom built EEG/EP system described in the next chapter. The EEG was sampled at 250 Hz over a one second epoch. Figure 6.4 shows the spectra from synthesised EEG and the EEG from a control subject.

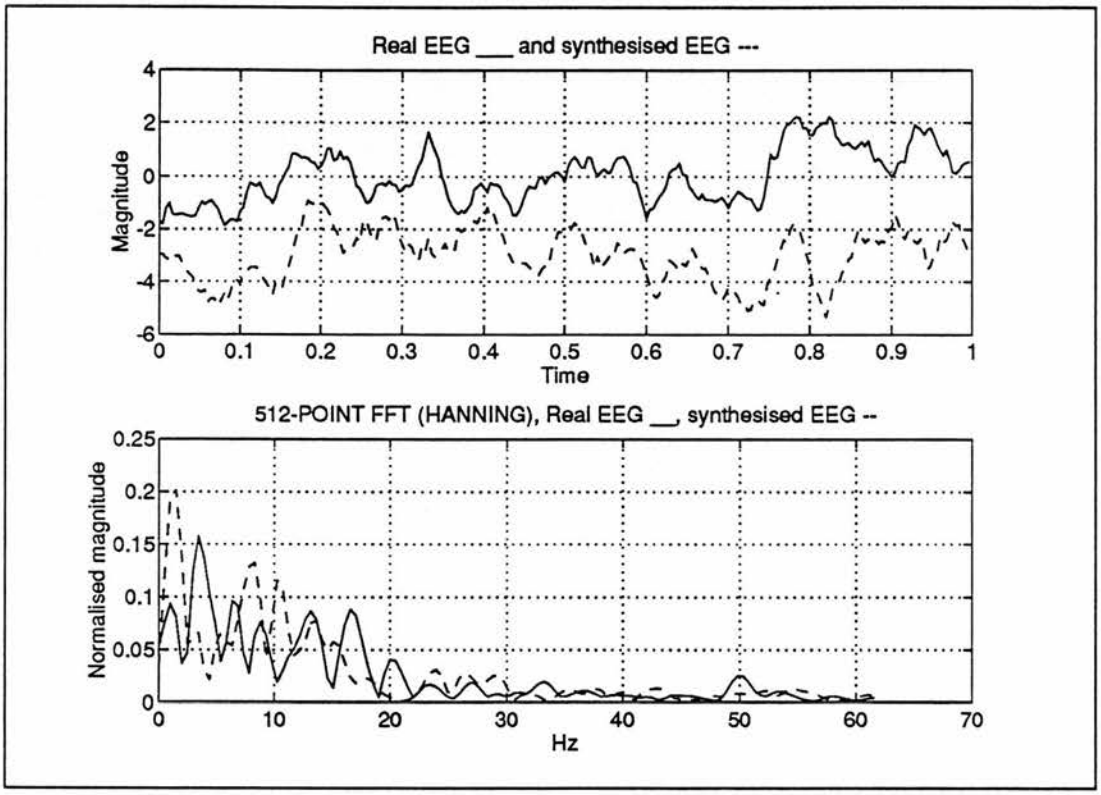


Figure 6.4 Spectra of synthesised EEG and EEG from a control subject.

For each of the ten data sets, an ensemble averaged waveform was computed for each of the five SNRs. The average was stored with the un-averaged data.

6.3.1.1 Templates

It was decided that three different templates would be used for the maximum cross-correlation or maximum covariance search. Two of these templates are currently in use by other research groups - the SSA and a 2.5 Hz half-sine. It was decided to use a new template, not previously evaluated for this

application. The template is based on a least-squares fit to the SSA using a third-degree polynomial, as described in the last chapter. This approach has several potential advantages. If the SSA has a number of peaks, it is conceivable that this might lead to sources of alignment error, with the alignment becoming biased toward a particular peak in the template. This in turn could lead to significant cumulative errors. The appearance of a number of peaks in the SSA can be caused by either the underlying components of the ensemble being multi-peaked, there being a number of different distributions to the individual responses forming the ensemble average, or a combination of both. A least-mean-squares approximation to the SSA should in theory reduce such errors to a minimum. This will be known as the LMS template.

6.3.1.2 Filters

A range of bi-directional, IIR, low-pass digital filters were used to pre-filter the data. The filters synthesise the frequency response of a Butterworth filter, which is optimally flat in the spectral pass-band and introduces minimum distortion to signals. The filter is applied to the data in one direction (forward time) then in the opposite direction (reverse time) to cancel any phase-shift induced in the first pass. The filter cut-off frequency, normally specified as its -3dB point, is then shifted by this process. By passing the data through the filter twice, the -3dB point then becomes the -6dB point. Five low-pass filters were used:15 Hz, 8 Hz, 6 Hz, 4 Hz and 2 Hz. These filter settings were selected as they operate principally within the bandwidth of the EEG and also the P300 complex.

A Turbo Pascal computer program ("Woody", Appendix 2) was written to perform the digital low-pass filtering, allow selection of one of the three templates and application of either cross-correlation or covariance methods to find the best match between template and synthesised P300 complex.
A figure of merit based on the root-mean-square-error was derived to

estimate the performance of the combination of filter, template, and optimum alignment method for the five SNRs

$$mse = \sqrt{\sum_{i=1}^{N} \frac{(L-L_i)^2}{N}}$$

where L is the actual latency of the simulated P300 peak (300 ms) and Li is the latency estimate returned from the adaptive filter. N is the number of sweeps.

6.3.2 Results

A series of plots were constructed from the mses returned to graphically illustrate the performance of the algorithms. These are given in figures 6.5 to 6.10 below. For each template type there are two plots - one for the cross-correlation the other for covariance methods. Each plot shows five curves which correspond to the five low-pass digital filter settings for which the mse is plotted against the SNR. The units of mse are ms.

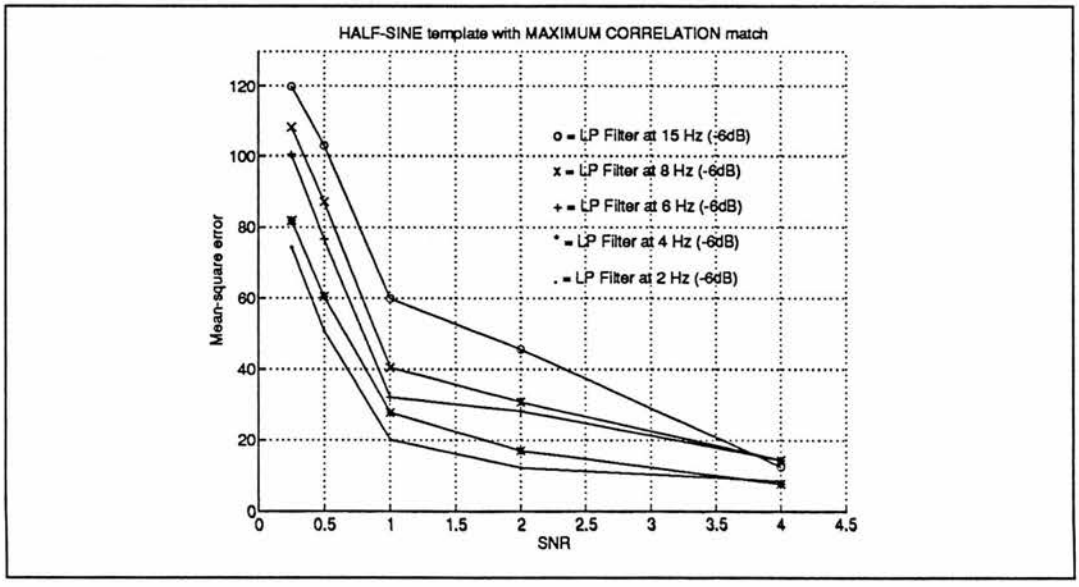


Figure 6.5 Mean-square-error for the ***HALF-SINE*** template at 5 SNRs and 5 L-P filter settings using the ***MAXIMUM CORRELATION*** match.

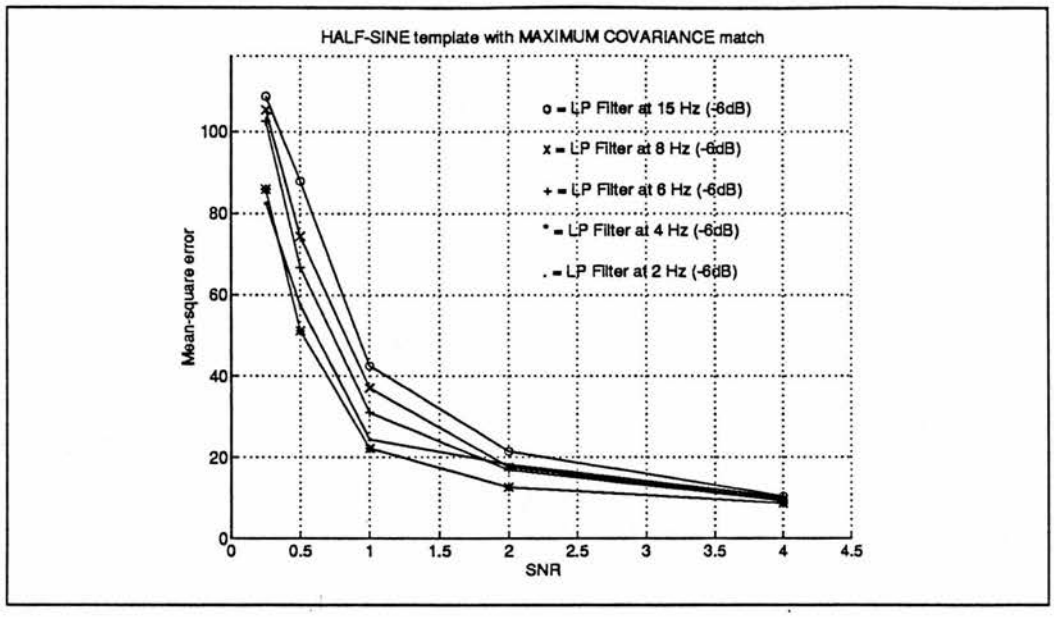


Figure 6.6 Mean-square-error for the ***HALF-SINE*** template at 5 SNRs and 5 L-P filter settings using the ***MAXIMUM COVARIANCE*** match.

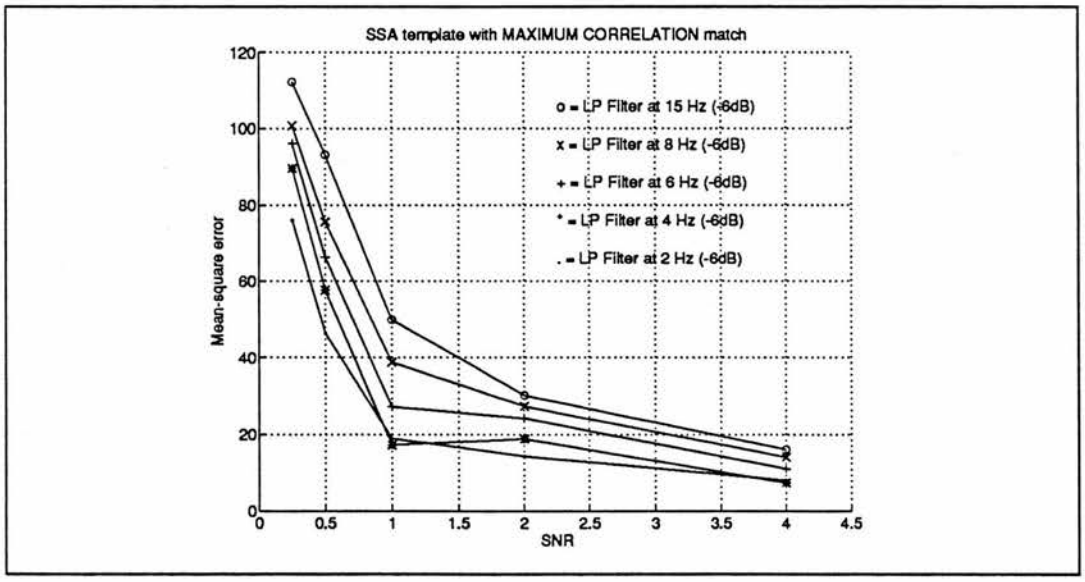


Figure 6.7 Mean-square-error for the ***SSA*** template at 5 SNRs and 5 L-P filter settings using the ***MAXIMUM CORRELATION*** match.

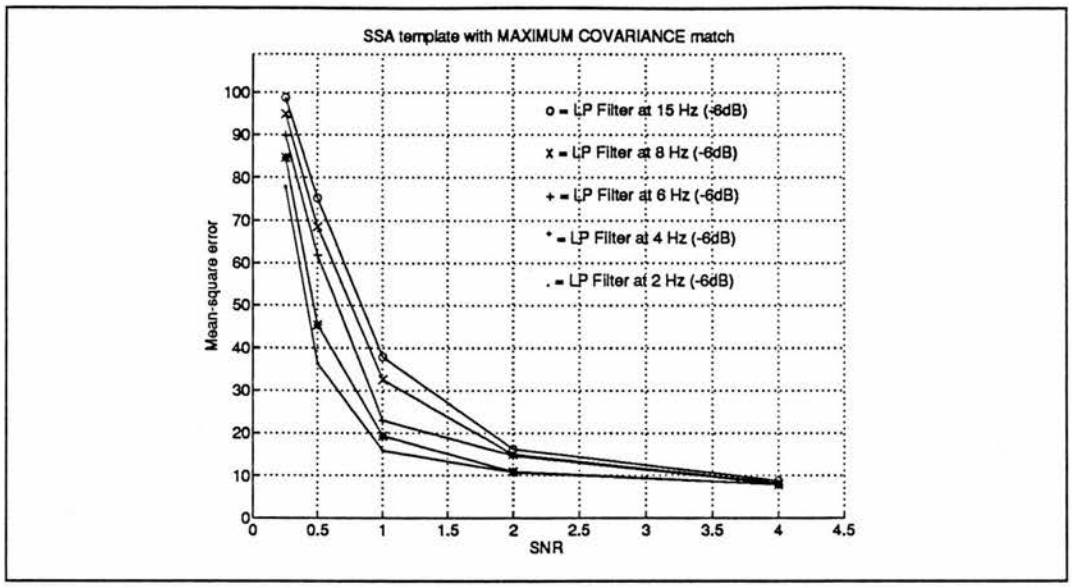


Figure 6.8 Mean-square-error for the ***SSA*** template at 5 SNRs and 5 L-P filter settings using the ***MAXIMUM COVARIANCE*** match.

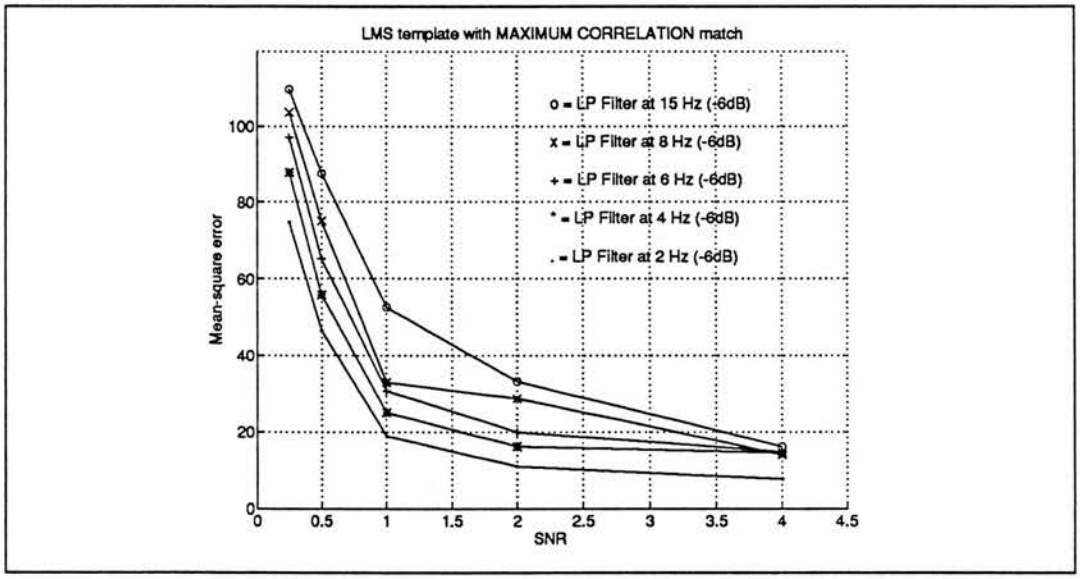


Figure 6.9 Mean-square-error for the ***LMS*** template at 5 SNRs and 5 L-P filter settings using the ***MAXIMUM CORRELATION*** match.

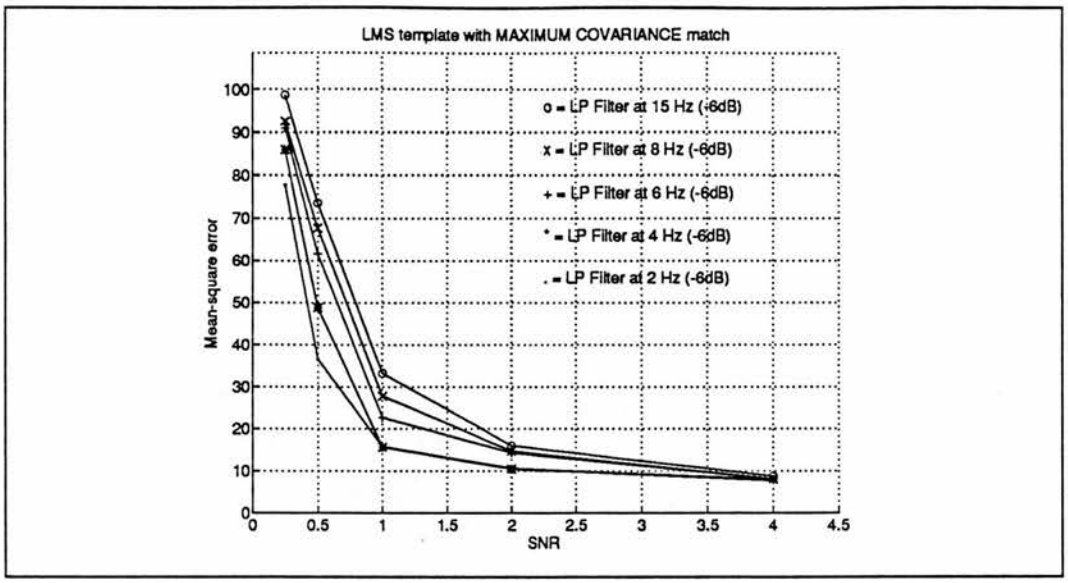


Figure 6.10 Mean-square-error for the ***LMS*** template at 5 SNRs and 5 L-P filter settings using the ***MAXIMUM COVARIANCE*** match.

Also of interest are the mean correlation and mean covariance values returned for the three templates. Figures 6.11 to 6.16 illustrate these values as a function of SNR with curves for each pre-filter setting.

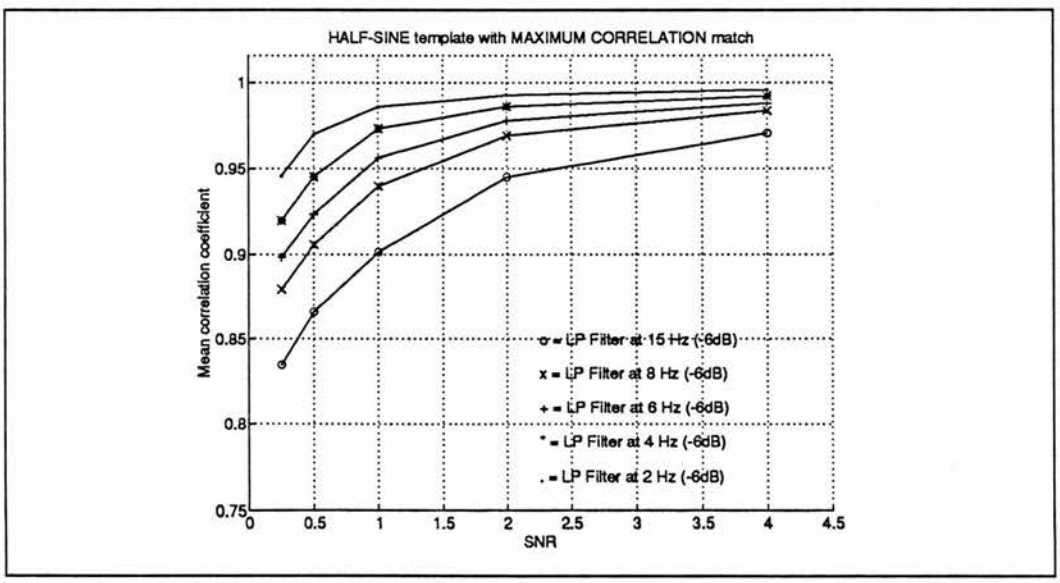


Figure 6.11 Mean **correlation** for the ***HALF-SINE*** template using the ***MAXIMUM CORRELATION*** match at 5 filter settings with 5 SNRs.

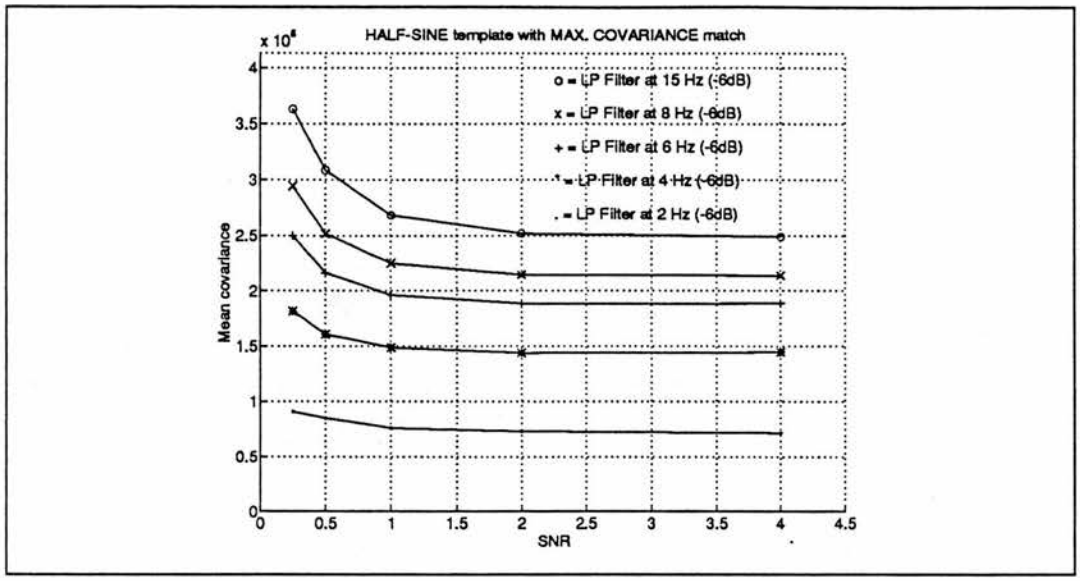


Figure 6.12 Mean **covariance** for the ***HALF-SINE*** template using the ***MAXIMUM COVARIANCE*** match at 5 filter settings with 5 SNRs.

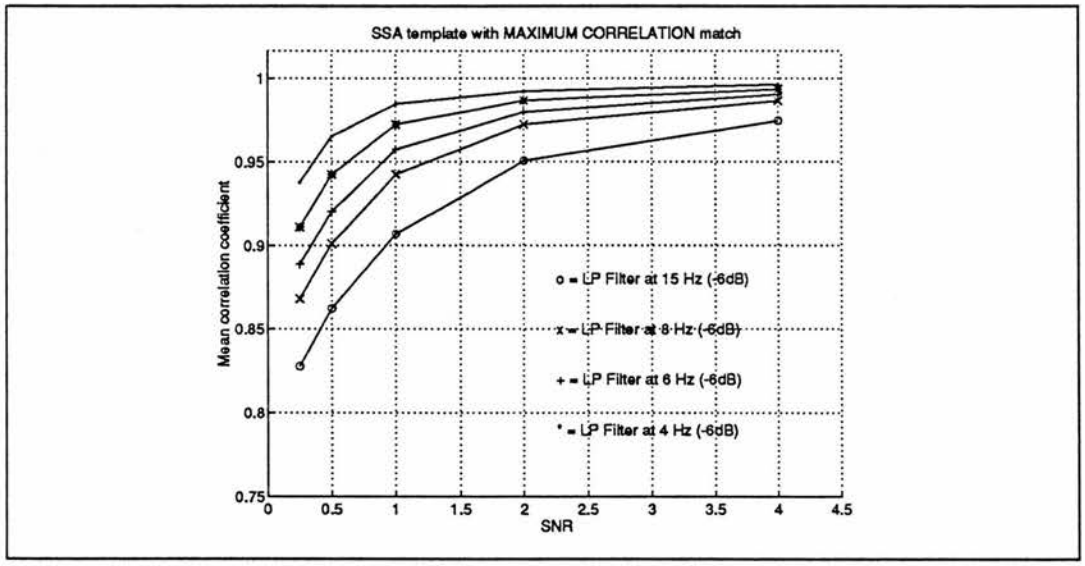


Figure 6.13 Mean **correlation** for the ***SSA*** template using the ***MAXIMUM CORRELATION*** match at 5 filter settings with 5 SNRs.

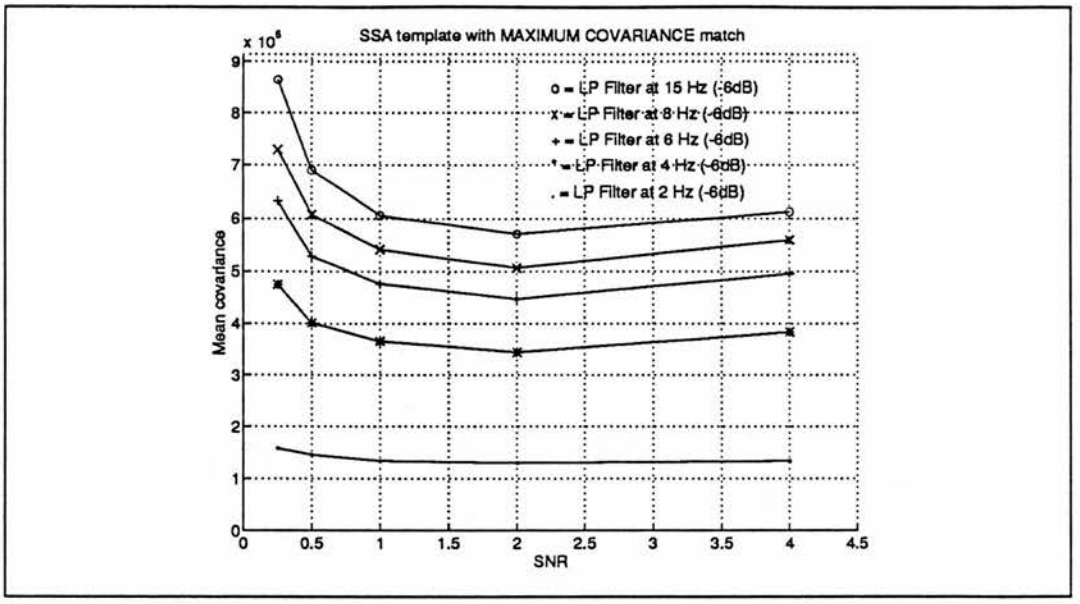


Figure 6.14 Mean **covariance** for the ***SSA*** template using the ***MAXIMUM COVARIANCE*** match at 5 filter settings with 5 SNRs.

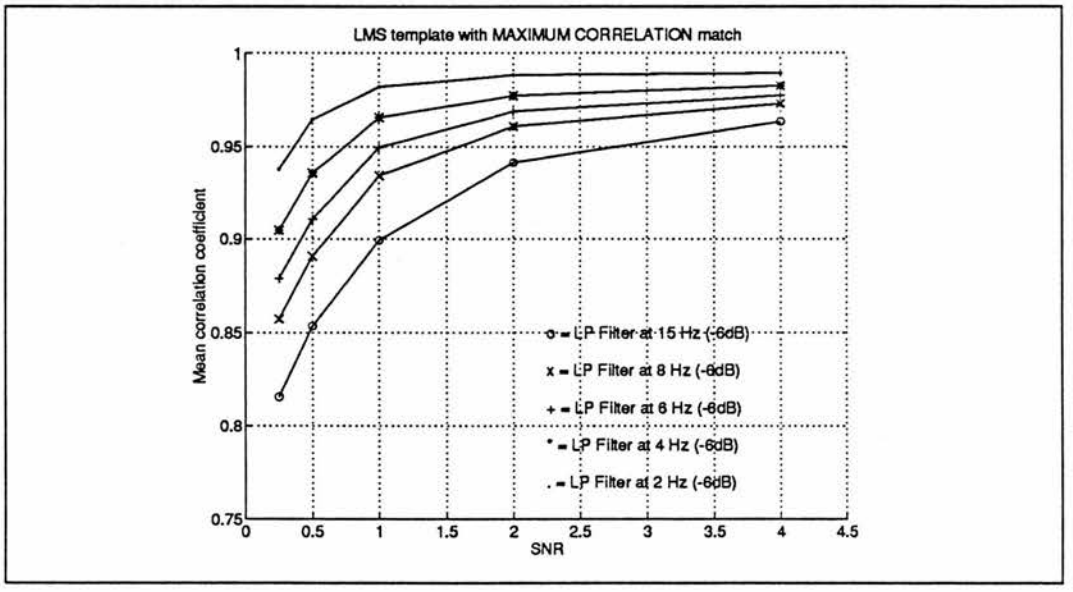


Figure 6.15 Mean **correlation** for the ***LMS*** template using the ***MAXIMUM CORRELATION*** match at 5 filter settings with 5 SNRs.

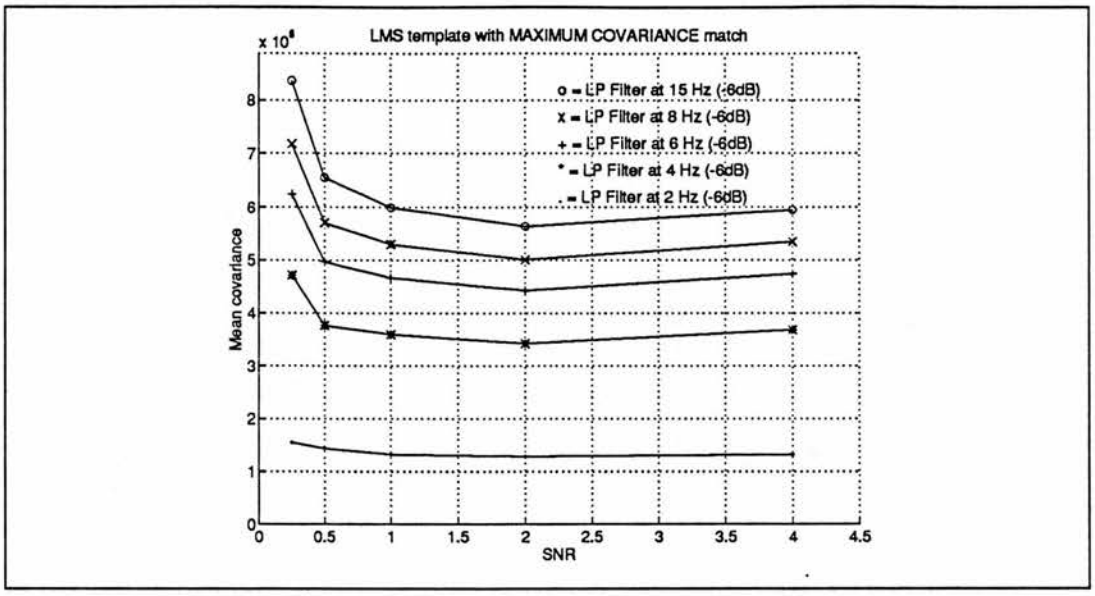


Figure 6.16 Mean **covariance** for the ***LMS*** template using the ***MAXIMUM COVARIANCE*** match at 5 filter settings with 5 SNRs.

These results show that the ability to correctly identify the synthesised P300 complex improves significantly at good compared to poor SNRs when either the correlation or covariance techniques are used with any template type. The effect of pre-filtering data more heavily with a lower low-pass filter gives a significant reduction in the mse as seen in figures 6.5 to 6.10. This reduction appears to be greater using the correlation compared to covariance technique, as seen when comparing the results for each template by either method.

The effect of the low-pass pre-filter in improving signal detectibility is graphically demonstrated when comparing figures 6.5 to 6.10 with figures 6.11 to 6.16, which show a reduction in mse while increasing the mean correlation coefficient and decreasing the mean covariance with filtering. The increase in correlation coefficient with decreasing mse reflects better signal detection while the reduction in mean covariance with decreasing mse reflects better detectibility but also a reduction in amplitude of the single

trials with increased filtering.

It also appears that the mse is generally greater for each template using the correlation technique compared to covariance, suggesting that covariance is better than correlation at detecting the signal. This is possibly due to the correlation method locking onto noise peaks. There is a partial confirmation of this by the observation that there appears to be a bigger improvement (smaller mse) in performance using correlation compared to covariance as more filtering is employed. This is particularly noticeable at the lowest SNR, where the mse for the correlation technique is greater than the mse for covariance by around a factor of 10 for every template. It is noticeable that the covariance mses converge to virtually the same point at high SNR for all pre-filter settings. There is a spread of values for the correlation technique, the lowest errors accumulating with the 4 Hz and 2 Hz filters. The covariance technique also appears to converge to a minimum error at a faster rate with improving SNR than the correlation technique. However, figures 6.12, 6.14 and 6.16 show that at a 2 Hz low-pass filter setting there is a relatively small change in the mean covariance as a function of SNR than at higher filter settings. At the 2 Hz filter setting the mean correlation coefficient also shows less change with SNR as seen in figures 6.11, 6.13, and 6.15. At the same time, there is a fairly large change in the mse with increasing SNR for all templates using both methods. Heavier filtering, while reducing the absolute error accumulated, appears to make the detected signal (true or noise) adopt more of the physical time domain characteristics of the template at low SNRs. The signal and noise must therefore look quite similar at low and high SNRs when heavily filtered. This reflects improving SNR up to a point where both signal and noise spectra are significantly affected by the filter and this result is predictable.

6.3.3 Conclusions

It would appear that the 2 Hz filter offers the best prospect for minimising

errors. This result is in rough agreement with a published simulation, which suggests a low-pass filter around this cut-off is most effective at minimising EEG noise influence in signal detectibility (Gratton et al., 1989). Tables 6.1 and 6.2 summarise the performance of the two template matching techniques using the three template types with the 2 Hz low-pass filter.

			SNR		
	0.25	0.5	1	2	4
Half-sine	74.43	50.82	20.07	12.21	8.44
SSA	76.04	46.43	18.96	14.36	8.04
LMS	74.78	46.48	18.94	11.08	7.81

Table 6.1 Root-mean-square deviation (ms) for three templates at 2 Hz LP filter (-6dB) with a ***maximum correlation*** match.

			SNR		
	0.25	0.5	1	2	4
Half-sine	82.48	57.49	24.42	18.25	10.09
SSA	77.89	36.29	15.89	10.77	7.89
LMS	77.69	36.6	15.75	10.58	7.73

Table 6.2 Root-mean-square deviation (ms) for three templates at 2 Hz LP filter (-6dB) with a ***maximum covariance*** match.

There is very little to choose between the performance of LMS or SSA template using either correlation and covariance, but both perform better than the half-sine template, if the mse is an appropriate index of suitability.

Overall, the covariance method appears to accumulate less total error than correlation across the range of SNR's and templates studied.

The LMS template is a smoothed version of the SSA but the SSA probably bears the closest resemblance to the real underlying signal so should be used in preference to the LMS template.

In this simulation it would be predicted that the half-sine template should perform better than the other two templates, given that it is identical to the true underlying signal. At an SNR of 0.25 with the correlation technique this appears to be the case, but the result for the LMS template is very close. At the same SNR using covariance, the half-sine template accumulates more error than SSA and LMS templates, which give very similar results to each other. As the SNR improves it is noticeable that the half-sine template performs consistently worse than the SSA or LMS templates, except in one instance at SNR of 2 using correlation, where it falls between the other two. This is an interesting and unexpected result.

For this simulation, the implication of such a result is that a template which has no representative influence in its time domain appearance of dominant noise components will be poorer at detecting signals buried in noise than templates that do. For zero-mean noise the SSA should ultimately be a representation of the pure signal, providing the ensemble is constructed from enough trials, as the noise contribution cancels to zero. If the number of trials is relatively small, there may be some residual noise component in the SSA. The LMS template is a smoothed version of the SSA and while the residual noise component may be small, it may be significant in both. For this simulation study it is possible that the characteristics of the noise were such that the amplitude was not normally distributed about a zero mean.

This result raises an important issue with regard to published methodology

which uses synthetic templates, such as the 2.5 Hz half-sine. The validity of applying such a template in ERP studies of the latency distribution of the real P300 data must be questionable. As described earlier in this thesis, a bifurcated P300 complex is a real and accepted phenomenon in the genesis of the ERP. The ability of a synthetic template, to optimally match single, bifurcated trials will be affected and subsequently biased when using a half-sine template. This is because the stability of the early P3a sub-component of the P300 complex is unknown. A template waveform for single trial studies which contains the average representation of the P3a throughout the study is therefore more appropriate.

In conclusion, it appears that an SSA template utilising the covariance method is most appropriate for studies of ERP single trial latency when the data are smoothed with a 2 Hz, bi-directional, low-pass filter.

Chapter 7.

The effect of high-pass filter setting, peak definition method, and electrode site on measurement of P300 amplitude and latency in schizophrenia

As outlined in chapter 1, the main objective of this thesis is to assess how P300 measurement methodology may influence the utility of the auditory P300 as a biological marker for major psychotic illness. We have reviewed both the clinical utility of P300 in psychiatric settings and the signal processing methodology from which the psychophysiological measures are derived. In chapter 4 the effect of high-pass filtering on the appearance and subsequent definition of peak measures was briefly covered. A model for P300 was proposed in chapter 4 with which the effect of high-pass filters on the waveform can be predicted. At the same time it was acknowledged that these data were derived from a limited number of scalp locations and that a more precise model might be derived from additional electrode sites, and by applying spectral analysis techniques. In chapter 5 a new method for objectively measuring the P300 (the LMS fit) is described.

The findings from the simulation work and the empirical observations based on the P300 model suggest that an in-depth study on a clinical data set is required to address some basic issues of measurement methodology. These should include the effect of high-pass filtering, the method of peak definition, and the most pertinent electrode site on which to make these measures. The aim of the study is to assess whether these variables affect the sensitivity of the P300 in clinical situations where the aim is to distinguish a patient group from a control group.

It was decided that such a study would focus on a control and schizophrenic group. Schizophrenia research has generated perhaps the most controversial

findings in the study of P300 latency. First, a description is given of the hardware and software tools developed to acquire and process the data, and the details of the data recording procedures are given.

7.1 A data acquisition and processing system for clinical studies of the P300

The specification for the system was based on the need to carry out clinical recordings which were consistent with those already published. A 6-channel system was specified to allow recording from up to five EEG electrode sites and a single EOG site.

7.1.1 EEG amplifier system

A 6-channel high gain system was used to amplify the scalp signals. This was the Digitimer™ physiological amplifier system which allows both gain and bandwidth to be set manually.

7.1.2 Data acquisition system

This was developed around an IBM PS/2 personal computer system with a 16 MHz 80-286 processor and 80-287 maths co-processor. A commercially available data acquisition board was used for sampling the signals and it plugged directly into one of the computer's expansion slots. A DAS-16 Data Acquisition Card, (Metrabyte™), which allows up to 16 channels of unipolar information to be sampled, was used. The board is supplied with its own controlling software programs, which are written in the Borland Turbo Pascal™ programming language. Control of the board is executed through custom-written software designed to run on a microcomputer.

7.1.3 Auditory evoked potential stimulator

An electronic auditory evoked potential stimulator was designed and constructed (circuit diagram 1, Appendix 2). The stimulator is controlled from the software program via a PC-35 input/output card (Amplicon, Ltd)

connected to the input/output (i/o) bus of the PC. Two control lines from the card allow one of two separate frequency generators on the stimulator to be selected. The stimulator generates audio frequencies which can be changed in steps of 500 Hz, from 500 Hz to 2000 Hz. The frequency durations can be changed from 10 ms to 100 ms in 10 ms steps. Stimulus rise and fall times are set to 10 ms. The audio signals were sent to standard audiometry headphones of type TDH-39 (P.C. Werth Ltd.). The headphones were calibrated using a Cirrus ™ Octave Analyzer, via a 6cc auditory coupler. The front panel volume control of the auditory EP stimulator is calibrated for output sound pressure level (SPL) at 70, 75, 80 and 85 dB SPL.

7.1.4 Software

The data acquisition and processing software programs were written in Turbo Pascal. One main program (ER.PAS, Appendix 2) was used to control the data acquisition hardware, store the data on floppy disk, and process the data. The rare:frequent stimulus ratio, inter-stimulus-interval, and random stimulus sequence are controlled by the software program.

Procedures were written to acquire the data, digitally smooth it after averaging, and allow measurement of the P300 peak amplitude and latency. These are the previously described LMS fit algorithm and a peak searching algorithm, which uses a mouse controlled cursor to interactively search for the maximum or minimum turning-point 6 samples either side of it. The single trial data are displayed on the VDU during the data acquisition run to allow monitoring of the EEG. Sampling rate and the number of samples in each trial are fundamental parameters which can be set using the Metrabyte software procedures. These procedures are incorporated into the main program. All software and hardware were tested before use.

7.1.5 Patient recordings

All ERP recordings were made at the Royal Edinburgh Hospital in the MRC

Brain Metabolism Unit where an electrically screened, sound-proofed booth was available. Patients were seated in a comfortable reclining chair and asked to close their eyes during the recording sessions. The lights were normally turned off for the recording sessions. Standard silver-silver chloride electrodes were attached to the subjects' scalp using EEG electrode paste. Scalp/electrode impedance measurements were made using the built-in tester on the amplifier head-box.

7.2 The clinical study of P300 methodology in schizophrenia

7.2.1 Introduction

Much attention has focused recently on how methodological issues may affect the clinical utility of the P300 (Goodin 1990; Pfefferbaum et al. 1990; Polich 1992). A recurring theme has been the need to achieve a widely accepted, standard data acquisition and processing technique to permit comparison of findings from different research groups. Detailed studies on the effect of electrode coupling (Denoth et al. 1986), choice of reference electrode (Denoth et al. 1986; Faux et al. 1990), peak definition method (Callaway et al. 1983; Polich 1991) and high-pass filters (Ebmeier et al., 1992) have all contributed to this growing debate.

A specific issue which continues to generate controversy, and which is of particular interest, is the delayed P300 latency in schizophrenia. While there is almost universal agreement that reduced P300 amplitude is a feature of the disease (McCarley et al. 1991, Ogura et al. 1991, Roth et al. 1986, Barrett et al. 1986, Baribeau-Braun et al. 1983), conflicting results have been published regarding the latency of P300 in schizophrenia (Roth et al. 1986). The reported discrepancies may be due to the small number of subjects included in some of the studies (Ebmeier 1992), but another possibility could be the different methods adopted by researchers. The finding of P300 latency delay in schizophrenia was challenged by Ebmeier et al. (1992) who suggested that these results may have been influenced by the effect of the 1 Hz high-pass

filter used during the recording of data. A differential effect of the high-pass filter was demonstrated, with a greater phase lead (positive time-shift) in P300 peak latency in control compared to schizophrenic data. A "2-frequency" model of the P300 was proposed, with a fundamental at 2.5 Hz representing the Slow Wave and a higher order harmonic at 7.5 Hz representing the P3a/P3b component. It was proposed that the observed differential effect was due to the ratio of the amplitudes of these two frequencies being different in schizophrenia and that spectral analysis could further test the proposed model. Transient evoked potentials have been successfully modelled on the basis of additive signal generators (Jervis et al. 1983), and the 2-frequency model postulated by Ebmeier et al. (1992) concurs with this.

In this study, 2 different high-pass digital filters (1 Hz and 2 Hz) will be applied to a set of data to investigate how the high-pass filter alters the appearance of the P300 complex in schizophrenics and controls. An understanding of this phenomenon is important, because the effect of the filter on a multi-peak P300 complex may have a major bearing on which peak is chosen as representing the P300. Polich (1991) deals specifically with the problem of the multi-peak P300 complex, arguing that a series of observations across central and parietal leads should be made to define P300 latency using his "P3MAX" criterion. Data will be examined in the frequency domain to see if the proposed 2-frequency model offers an additional means of separating control from schizophrenic data.

The standard method of P300 peak identification is to select the maximum data value in a pre-determined window. A multi-peak complex is normally dealt with using the slope-intersection method described by Goodin et al. (1978). The problems with this non-objective approach have been covered. The method of least-mean-squares described in chapter 4 will be now be extensively assessed on clinical data. ERP data will be acquired from the

three electrode sites normally monitored in clinical studies of P300, at frontal (Fz), central (Cz) and parietal (Pz) locations. The data will be high-pass filtered at three different settings and the methodology used by Ebmeier et al., (1992), will be adopted in relation to correctly tracking peaks to assess the filter effects. Data will then be studied in the frequency domain using the FFT (Appendix 1) to attempt to quantify the spectral composition of the ERP complex.

7.2.2 Aims

The aims of the study were

i) to identify a method best suited to define the P300 in clinical studies, with particular emphasis on peak definition method, electrode site and high-pass filter setting;

ii) to attempt a replication of the study of Ebmeier et al. (1992), showing the effect of the high-pass filters on control and schizophrenic P300 data;

iii) to determine whether there are any spectral differences in schizophrenic and control data, if indicated by the above filtering experiment.

7.2.3 Methods I

7.2.3.1 Recording and stimulus parameters

Twenty-six controls and 23 age-matched schizophrenics, meeting Research Diagnostic Criteria (RDC) and DSM III-R, were studied. Data were recorded from 3 scalp locations (Fz, Cz, Pz) using silver-silver chloride electrodes, positioned according to the international 10-20 system. EOG was recorded from a single electrode positioned supra-orbitally from the left eye. A left ear reference (A1) was used and the right ear (A2) was used as the amplifier ground. Skin\electrode impedances were kept below 3 kOhms. Scalp signals were amplified at a gain of 10,000 within a bandwidth of 0.16 - 30 Hz (-3

dB).

A standard auditory oddball P300 paradigm was employed, where rare tones at 1500 Hz (p=0.1) and frequent tones at 1000 Hz (p=0.9) were played to the subjects in random sequence through audiometry headphones. Inter-stimulus interval was 1.1 seconds, tone duration was 40 ms, at 70 dB SPL. Subjects were asked to count the number of rare tones presented, normally 40, and count accuracy was within ± 10% for both the control and patient group.

Data sampling rate was set at 250 Hz, and 250 samples were collected from each channel - 62 pre-stimulus (248 ms) and 188 post-stimulus (752 ms). An on-line artefact rejection procedure rejected data from any channel exceeding ± 45 μV. Raw target and non-target responses were stored on floppy-disc for later processing, off-line. Two consecutive recordings were made from each subject.

7.2.3.2 Data Processing

The stimulus synchronised average (SSA) was formed from the raw target responses for each of the 3 channels for every subject. Data were then digitally filtered and processed using two peak-searching algorithms. All amplitude measurements were referred to the mean pre-stimulus value of the frequent response.

Digital filters

Infinite Impulse Response (IIR) digital filters having the equivalent response to Butterworth, single-pole, analogue filters with slope -6 db/octave, were synthesised using the PC-MATLAB. Data were first smoothed using a bidirectional (zero phase shift) low-pass filter, with -6dB point at 15 Hz. Two different high-pass filters, -3 dB frequencies at 1 and 2 Hz, were then applied separately to the data. The aim was to induce a phase lead (positive time-shift) on the data and assess whether there was a differential effect on

the subject groups. While 0.16 and 1 Hz are filter settings which have been used in practice, data were also filtered at 2 Hz to assist in the evaluation, and hence address the implication of spectral differences between groups.

Peak definition algorithms

Two peak definition algorithms were developed and applied to the data separately:

a) Peak-search (PS). This algorithm searches 6 samples on either side (± 24 ms) of a visually selected data point. The algorithm looks for a maximum or minimum turning-point then classifies the peak as positive or negative. The maximum (positive or negative) data value in this range in μV, is then returned as is the latency in ms, associated with the peak.

b) Least-mean-squares (LMS). A data window is interactively defined using a mouse pointer to select two data points - normally near the N200 and N300 components of the ERP. A least-mean-squares approximation to the windowed data is then generated using a third-degree polynomial as described in chapter 4 of this thesis.

7.2.4 Methods II

7.2.4.1 Filtering and peak definition procedure

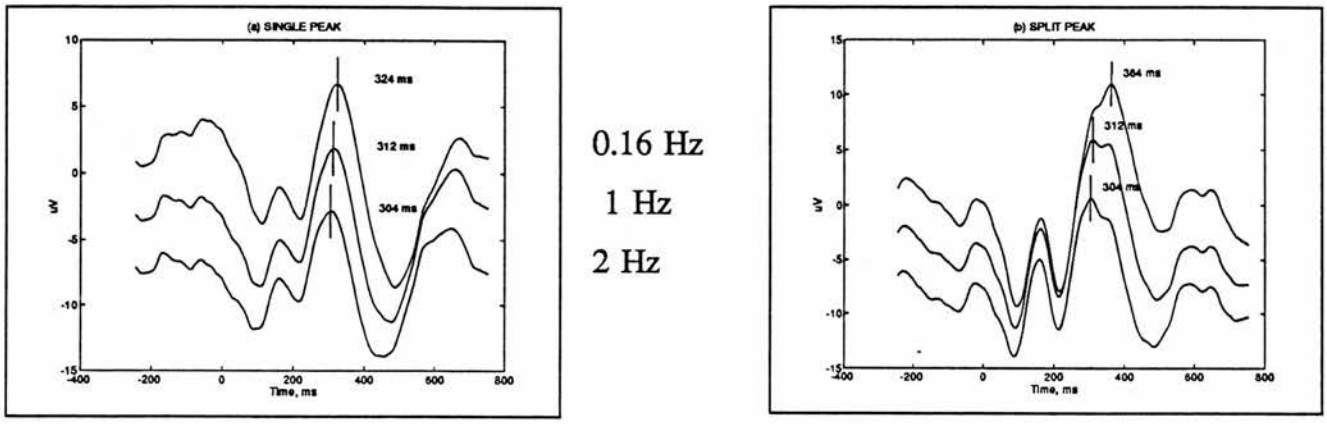
After constructing the SSA for each channel and then smoothing, the data were digitally filtered at the two high-pass settings (1 and 2 Hz), producing two further sets of data for each subject. The peak definition algorithms were then applied to the data in two different ways: i) each data set from each patient was measured independently using both PS and LMS algorithms; ii) Using only the PS algorithm, P300 peaks identified at the 0.16 Hz high-pass filter setting were peak tracked (PT) by examining the data filtered at 1 Hz and 2 Hz at the same time. This was the method adopted by Ebmeier et al. (1992) to assess the effect of the filters.

Data from each study group were separated into two separate sub-groups - one group which showed the peak change phenomenon, described in chapter 3, and the other which showed the more stable, single peak behaviour, when applying the high-pass filters.

Figure 7.1 shows an example of a single lead from two different subjects which exhibit both single peak and peak-changing behaviour when the filters are applied, and how the three methods deal with selecting the P300 peak. The left-hand series of caption (7a,c,e) illustrate how the three methods deal with data which are unambiguous. In each case the peak-search, peak-track and LMS fit have selected the same peak, with a minimal error introduced by the LMS fit. The right-hand side shows a typical example of data which undergoes the peak-change phenomenon after the application of the high-pass filter. In Fig. 7b, the P3b component is dominant and has been selected by the peak-searching algorithm. The application of the high-pass digital filters induces a differential phase shift in the signals and the lower frequency component of the complex moves to the left, causing P3a to increase in magnitude compared to the P3b component. The peak search algorithm will now select the P3a component as representing the P300. In every case where there was a peak change, the error induced was always toward an earlier peak. For the proper assessment of the filter effect, the peak tracking technique was used. Fig. 7d shows how the peak identified at 0.16 Hz high-pass filter setting is tracked at the 2 higher frequency filter settings. Comparing Figures 7b and 7d demonstrates how it is possible to make large errors in latency measurement unless the correct peak is tracked. Six of the 26 controls and 13 of the 23 schizophrenics manifested the peak change phenomenon when the high-pass filters were applied. If peaks were not tracked in the manner described, large errors would have accumulated in the latency measurements, the mean filter effect appearing greater in the schizophrenic group.

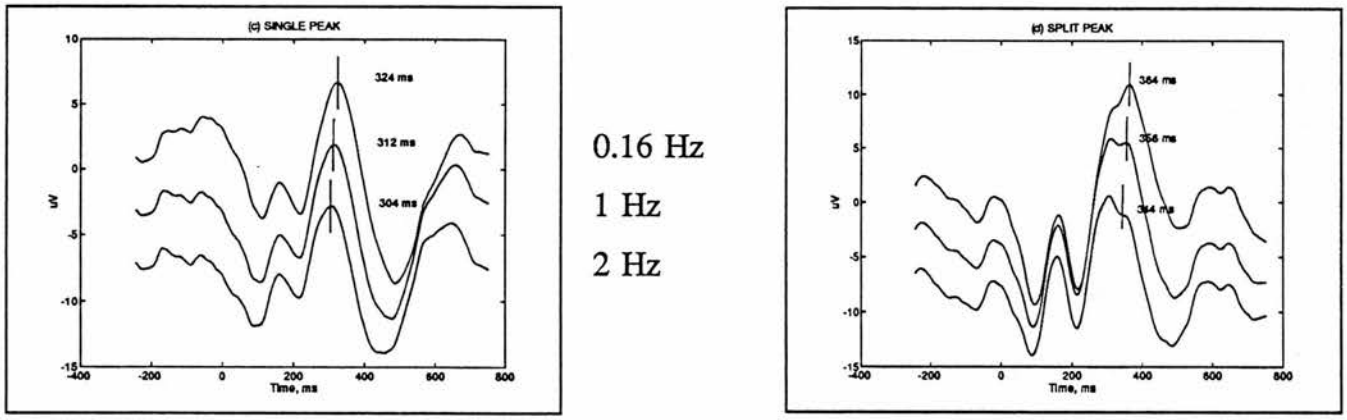
Figure 7.1 Three different methods for peak definition applied to two different types of P300 complex - single peak and split peak.

(a) Single peak PEAK SEARCH (b) Split Peak



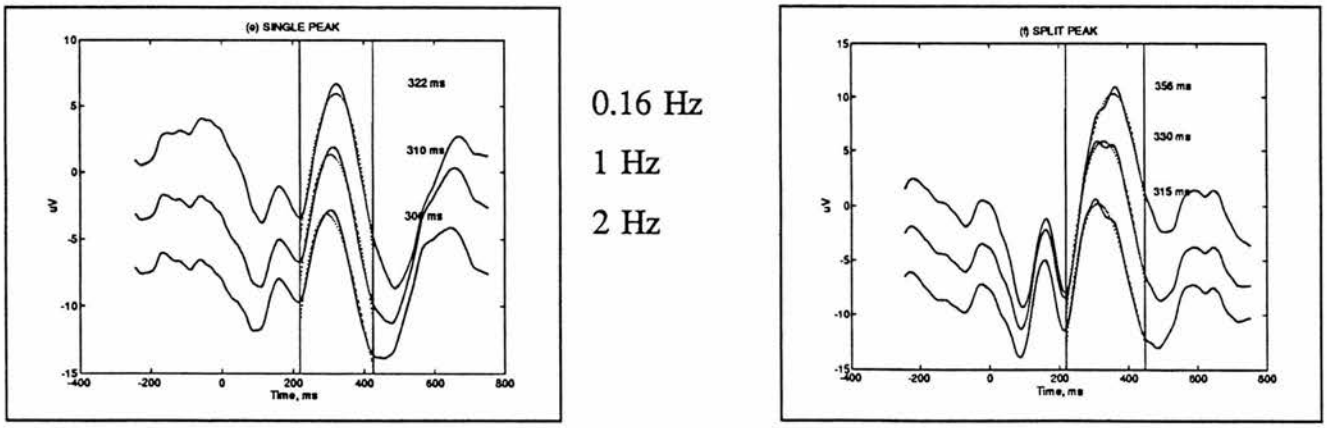
0.16 Hz
1 Hz
2 Hz

(c) Single peak PEAK TRACK (d) Split peak



0.16 Hz
1 Hz
2 Hz

(e) Single peak LMS FIT (f) Split peak



0.16 Hz
1 Hz
2 Hz

7.2.5 Methods III

7.2.5.1 Spectral analysis

The averaged and smoothed data for each lead from each subject were processed using a Fast Fourier Transform (FFT) algorithm (Appendix 1) available in the PC-MATLAB. Initially, any offset was removed then the data were windowed with a Hanning window. The data were then normalised and a 512-point FFT algorithm was then applied. The FFT bin separation was 1 Hz but zero-padding from 250 to 512 points allowed interpolation of intermediate values at approximately 0.5 Hz resolution (Harris, 1978). The spectra from each lead within each group were then summed and averaged to give mean group spectra, which were then plotted. The averaged spectra were scaled to preserve the total mean power relationship between groups. Mean spectrum data were split into 2 frequency bands which on examination appeared to show differences in spectral composition, and which separated the two frequencies postulated in the 2-frequency model: 0.48 - 4.8 Hz and 5.28 - 9.6 Hz. The power in these two bands were summed separately then expressed as a ratio, P_Q:

$$P_Q = \frac{\sum_{h=5.28}^{9.6} P_h}{\sum_{l=0.48}^{4.8} P_l}$$

7.2.6 Results

All statistical testing was carried out using the SPSS software package (SPSS International™, B.V.). Three main, repeated measures analysis of variance (ANOVA) tests were carried out - one on the amplitude data, the other two on latency data. Degrees of freedom (DF) were adjusted using the Greenhouse-Geisser correction where appropriate (Jennings and Wood, 1976). Each ANOVA used 3 leads, 3 filter settings and 2 methods for within-subjects factors. For the latency ANOVAs, one used PS and LMS as the methods, the other used PS and PT as the methods. No amplitude measurements were made with the peak-track method as this was used solely

to assess the effect of high-pass filtering on latency.

7.2.6.1 Latency measurements

Table 7.1 shows the mean P300 latency for both groups at each lead at the three different filter settings, measured by the three methods. The results of independent t-tests between each group of data are also given. Table 7.2 shows the results from the first main repeated measures ANOVA and indicates a significant group, filter and lead effect. The method of peak definition, PS or LMS, was not significant. The indicated group effect was for a significantly delayed P300 latency in schizophrenia (Table 7.1).

Filter effect

The biggest effect on latency was due to the filters, but there was no second-order interaction with group, indicating that the filters affected both sets of data to the same degree. The effect of the filter was, as expected, an introduction of a time-lead to the P300 latency as the filter setting increased (Table 7.1).

Lead effect

The significant lead effect and group x lead interaction was further investigated by three secondary repeated measures ANOVAs, one for each lead. The most significant group effect was found at the Fz lead ($F_{1,47}$=10, P=0.003) compared to Cz ($F_{1,47}$=3.3, P=0.075) or Pz ($F_{1,47}$=4.8, P=0.034). Referring to Table 7.1, it can be seen that, by all methods at all filter settings, the Fz lead gives the greatest significance level (largest t-value) compared to Cz and Pz leads.

Filter-lead interaction

The significant filter x lead interaction was investigated by three secondary repeated measures ANOVAs, one for each filter setting.

Table 7.1 Mean ***P300 Latency***, ms (±SD), and t-tests

Filter & method	Lead	Control	Schizoph.	t*	Two-tailed p
0.16 Hz,	Fz	337 (28)	371 (61)	2.44	0.021
PS	Cz	341 (25)	352 (52)	0.88	0.385
	Pz	353 (22)	372 (54)	1.59	0.122
0.16 Hz,	Fz	338 (23)	378 (51)	3.48	0.002
LMS	Cz	341 (27)	367 (45)	2.37	0.024
	Pz	355 (26)	386 (46)	2.86	0.007
1 Hz,	Fz	326 (28)	353 (50)	2.35	0.025
PS	Cz	324 (27)	343 (54)	1.54	0.133
	Pz	329 (23)	347 (52)	1.53	0.135
1 Hz,	Fz	320 (22)	356 (51)	3.11	0.004
LMS	Cz	320 (24)	340 (45)	1.98	0.059
	Pz	325 (24)	347 (46)	2.09	0.045
1 Hz,	Fz	329 (28)	373 (63)	3.09	0.004
PT	Cz	330 (23)	335 (52)	2.13	0.041
	Pz	337 (25)	368 (55)	2.45	0.02
2 Hz,	Fz	316 (22)	348 (49)	3	0.005
PS	Cz	316 (30)	338 (57)	1.84	0.073
	Pz	316 (26)	337 (52)	1.76	0.087
2 Hz	Fz	311 (21)	349 (55)	3.25	0.001
LMS	Cz	309 (23)	334 (52)	2.28	0.029
	Pz	309 (27)	338 (52)	2.46	0.019
2 Hz	Fz	320 (23)	369 (62)	3.53	0.002
PT	Cz	323 (25)	352 (52)	2.42	0.022
	Pz	329 (27)	363 (57)	2.66	0.012

*separate variance estimates

Table 7.2 **ANOVA** of ***P300 Latency***, for 3 leads with 3 filter settings and 2 methods (PS, LMS fit)

Effects	F value	Hypothesis* (error) DF	p value
Main Effects			
Group (G)	6.2	1, 47	0.016
Filter (F)	190	1.4, 65.3	0.000
Method (M)	0.03	1, 47	0.87
Lead (L)	5.9	1.5, 72.5	0.008
Two-way interactions			
G x F	0.41	1.4, 65.3	0.6
G x M	5.9	1, 47	0.042
G x L	4.8	1.5, 72.5	0.018
F x M	8.9	1.4, 68.2	0.001
F x L	13.3	2.9, 135	0.000
M x L	0.53	1.9, 91.5	0.59
Three-way interactions			
G x F x M	1.5	1.4, 68.2	0.235
G x F x L	0.76	2.9, 135	0.51
G x M x L	0.27	1.9, 91.5	0.76
F x M x L	0.41	2.9, 136.1	0.74
Four-way interaction			
G x F x M x L	0.66	2.9, 136.1	0.57

*Degrees of freedom adjusted for multiple comparisons using the Greenhouse-Geisser correction

The most significant lead effect was found at the 0.16 Hz filter setting ($F_{1.5,72.7}$=11.7, P=0.000) compared to 1 Hz ($F_{1.7,78.2}$=5.3, P=0.01) or 2 Hz ($F_{1.7,82.6}$=3.8, P=0.03). Reference to Table 7.1 confirms that the greatest difference in latencies across the 3 leads occurs at the 0.16 Hz filter setting in both groups, by either method (PS or LMS).

Peak definition

No significant main effect was found between PS and LMS peak definition methods. With a view to assessing the effect of the filters, another repeated measures ANOVA was carried out using PT and PS as the two methods. Similar results to those in Table 7.2 were found, but this time there was a highly significant method effect ($F_{1,47}$=20.3, P=0.000). Two further repeated measures ANOVAs were carried out, one for each method. Both indicated a significant group effect, with PT showing the greatest significance ($F_{1,47}$=8.2, P=0.006) compared to PS ($F_{1,47}$=4.3, P=0.043). There was also a significant group x filter effect for the PT method ($F_{1.2,63.1}$=6.8, P=0.006), replicating previously reported results (Ebmeier et al. 1992). There was no group x filter interaction for the PS method. The results of the two main latency ANOVAs are particularly well illustrated by Figure 7.2, which shows the effect of the filters and peak definition methods at the three electrode sites.

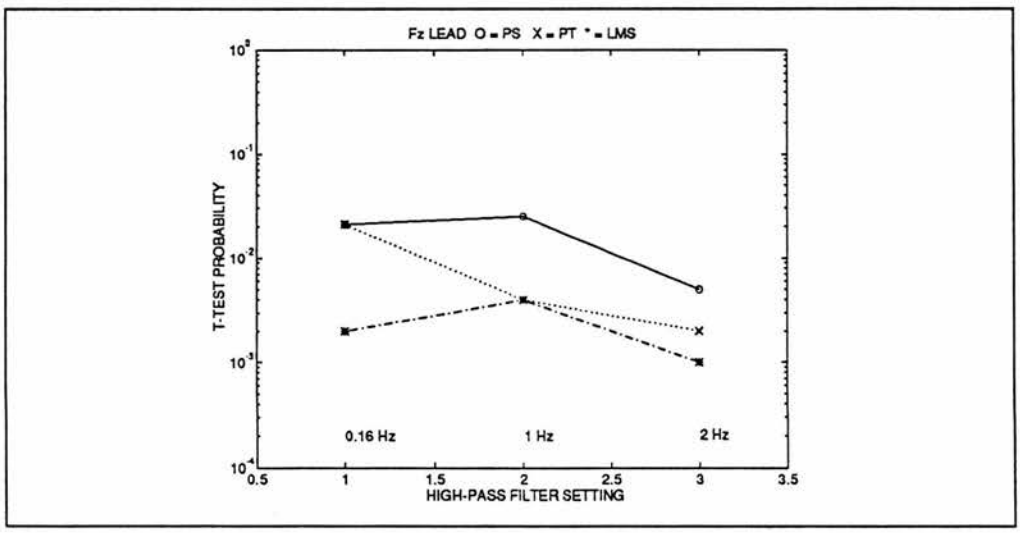


Figure 7.2a. Fz electrode site.

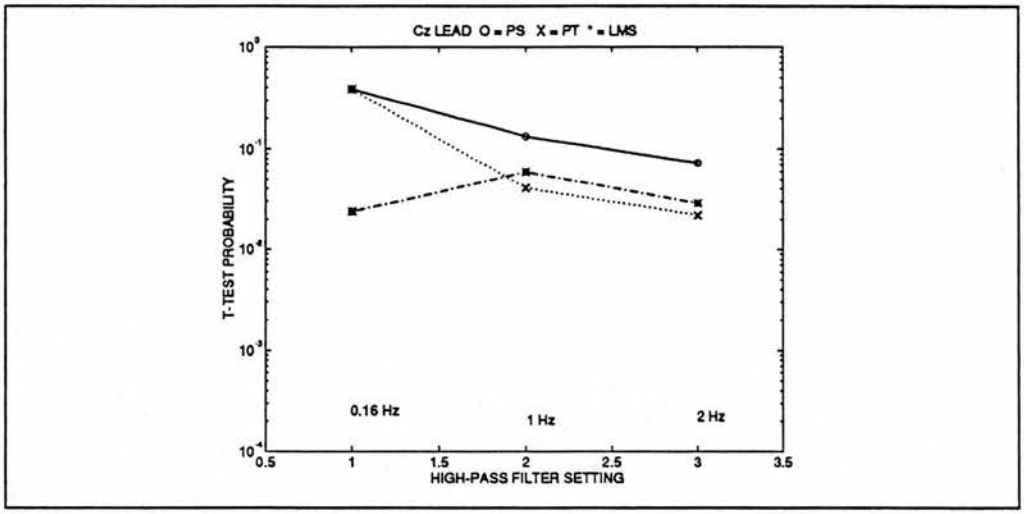


Figure 7.2b. Cz electrode site

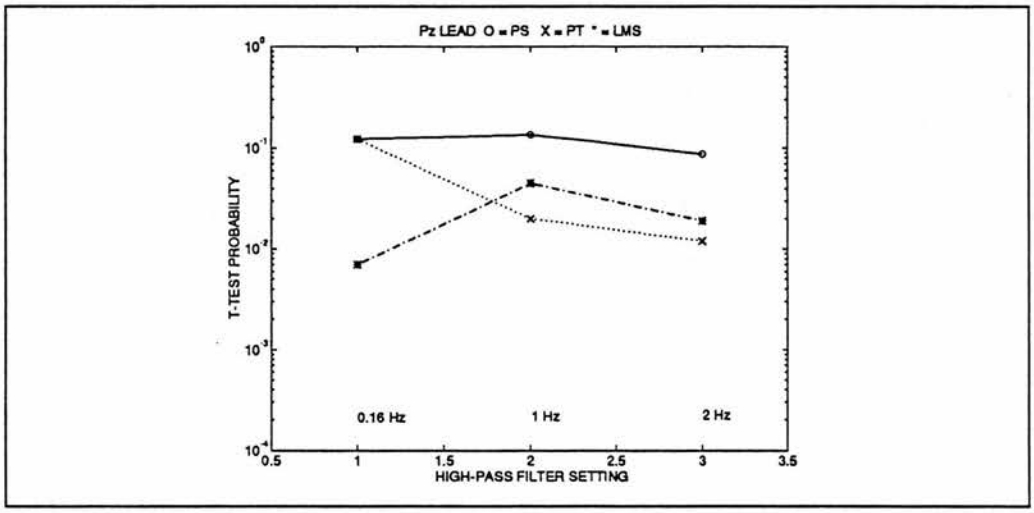


Figure 7.2c. Pz electrode site

Figure 7.2 P value from t-tests on P300 latency of control and schizophrenic groups as a function of high-pass filter setting. The trend for decreasing P value with filter setting is significant by the peak tracking method, for all leads. At 0.16 Hz, the peak-search and peak-track methods will identify the same peak - peak tracking only occurs after the introduction of the 1 and 2 Hz high-pass filters.

7.2.6.2 Amplitude measurements

Table 7.3 gives the mean P300 amplitude and independent t-test results for 3 leads at 3 filter settings by PS and LMS methods. Table 7.4 shows the result of the main repeated measures ANOVA on the amplitude data. Significant group, filter, method, and lead effects are indicated. The group effect was manifested by a significant reduction in amplitude in the schizophrenic group compared to controls at all filter settings by either method at the Cz and Pz leads (Table 7.3).

Table 7.3 Mean ***P300 Amplitude***, μV (±SD), and t-tests

Filter & method	Lead	Control	Schizoph.	t*	Two-tailed p
0.16 Hz,	Fz	8.3 (3.9)	6.8 (4.7)	1.2	0.241
PS	Cz	11.2 (4)	7.7 (3.9)	3.03	0.004
	Pz	12.8 (5.6)	8 (3.7)	3.63	0.001
0.16 Hz,	Fz	7.1 (3.8)	6.1 (4.5)	0.84	0.404
LMS	Cz	10 (3.9)	7.1 (3.8)	2.55	0.014
	Pz	11.7 (5.5)	7.7 (3.7)	2.99	0.005
1 Hz,	Fz	7.5 (4.2)	6 (4.5)	1.2	0.237
PS	Cz	10 (3.9)	6.7 (3.7)	3	0.004
	Pz	11.5 (4.9)	7.2 (3.3)	3.62	0.002
1 Hz,	Fz	6.1 (4)	4.9 (3.7)	1.09	0.283
LMS	Cz	8.8 (4)	5.8 (3.2)	2.96	0.005
	Pz	10.4 (5)	6.3 (3.2)	3.44	0.001
2 Hz,	Fz	5.6 (3.8)	4.9 (3.7)	1.56	0.126
PS	Cz	8.1 (3.5)	5.1 (3)	3.21	0.002
	Pz	8.9 (3.8)	5.5 (2.5)	3.87	0.000
2 Hz	Fz	5.2 (3.2)	4.2 (3)	1.05	0.298
LMS	Cz	7.1 (3.4)	4.5 (2.7)	3.06	0.004
	Pz	8.1 (3.9)	4.9 (2.4)	3.57	0.001

*separate variance estimates

Table 7.4 **ANOVA** of ***P300 Amplitude***, for 3 leads with 3 filter settings and 2 methods (PS, LMS fit)

Effects	F value	Hypothesis* (error) DF	p value
Main Effects			
Group (G)	7.2	1, 47	0.01
Filter (F)	105	1.3, 61.1	0.000
Method (M)	79	1, 47	0.000
Lead (L)	25	1.1, 53.8	0.000
Two-way interactions			
G x F	2	1.3, 61.1	0.15
G x M	25	1, 47	0.047
G x L	7.5	1.1, 53.8	0.006
F x M	0.8	1.2, 55.5	0.4
F x L	22.6	2.1, 98.7	0.000
M x L	4.3	1.3, 61.5	0.032
Three-way interactions			
G x F x M	0.75	1.2, 55.5	0.42
G x F x L	3.9	2.1, 98.8	0.023
G x M x L	0.13	1.3, 61.5	0.8
F x M x L	0.37	2.3, 108.8	0.72
Four-way interaction			
G x F x M x L	2.1	2.3, 108.8	0.12

*Degrees of freedom adjusted for multiple comparisons using the Greenhouse-Geisser correction

Lead effect

The significance of the lead effect becomes obvious when referring to Table 7.3, which shows that the greatest t-value is associated with the Pz lead by both methods at all filter settings, while the Fz lead never gives a significant difference between groups - the group x lead interaction is therefore expected.

Filter-lead interaction

The filter x lead interaction was further investigated by a repeated measures ANOVA carried out for each filter setting. The most significant lead effect was found at the 0.16 Hz setting ($F_{1.2,55.3}$=29, P=0.000). Reference to Table 7.3 shows that the biggest range in amplitude across leads is found at this filter setting, by either method for both groups.

Peak definition

A repeated measures ANOVA was carried out for each of the peak definition methods - PS and LMS. The most significant result was returned for the PS method ($F_{1,47}$=7.9, P=0.007) compared to the LMS method ($F_{1,47}$=6.3, P=0.015). While this result indicates that it may be better to use the PS method to discriminate groups by amplitude measurement, the LMS method was indicated as best for discriminating groups by latency. It would be prudent to adopt the same method for latency and amplitude measurements, however, as the LMS method is best at dealing with data with additional or misleading peaks.

Group-filter-lead interaction

Repeated measures ANOVAs were carried out for each lead, and the greatest filter effect was found at the Pz lead ($F_{1.3,59.5}$=116, P=0.000). It has been shown that the groups are best separated at the Pz lead and the filters appear to further enhance this separation. It is feasible that the gradual reduction in slow wave amplitude is more apparent at this site, and accounts for this

third-order interaction.

7.2.6.3 Spectral Analysis

The mean P_Q for control and schizophrenic groups, calculated for the three leads, gave values as predicted by the 2-frequency model (Ebmeier et al. 1992) - P_Q was greater in the schizophrenic group. The significance of these differences were tested using a Mann-Whitney U-test because the data were not normally distributed. The results for the Fz and Cz leads were not significant. However, the P_Q values returned for the Pz lead were 0.28 (0.14) for controls and 0.46 (0.45) for schizophrenics, and just missed the 5% significance level with a 2-tailed p=0.06. Figure 7.3 shows the mean spectra for the Pz lead.

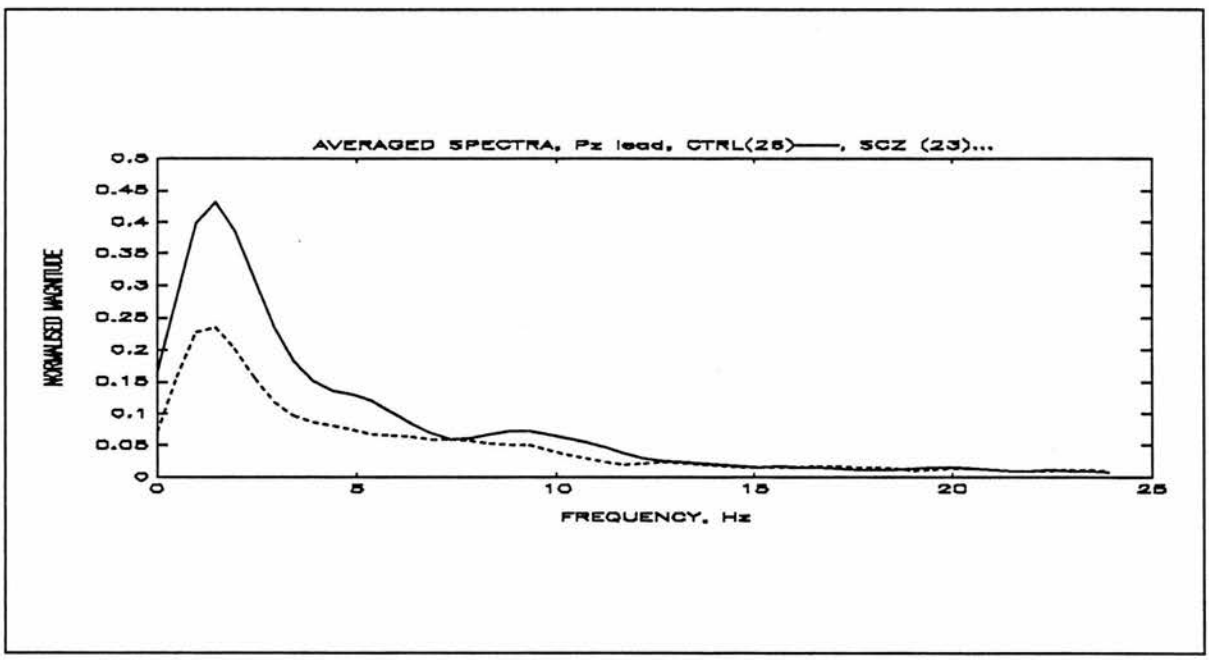


Figure 7.3. Averaged P300 spectra for control and schizophrenic groups at the Pz lead. The total power for control and schizophrenic groups is preserved and spectra are scaled accordingly.

7.2.7 Discussion

The appearance of the P300 complex in the time domain reflects underlying physiological processes, which in schizophrenia are probably less coherent and more diffuse than in normal subjects. While the proposed topography is for a more frontal P3a generator and central/parietal P3b generator (Regan 1989), multi-peak complexes occur more frequently in schizophrenia, particularly in the parietal region. The underlying mechanisms for this are unclear but may be due to different processing strategies. It is also conceivable that the appearance of double-peaked parietal complexes in schizophrenia is due to a reduction in the P3b component, leading to an unmasking of the parietal contribution of the P3a.

The sometimes bizarre appearance of the P300 complex in schizophrenia makes it difficult to acquire meaningful measurements - it is not always possible to identify the P300 as a simple waveform consisting of a slow wave with P3a and P3b components superimposed on it. In such circumstances, the P3MAX measurement proposed (Polich, 1991) is less valid because it is not possible to quantify these additional peaks in the same way as the P3a and P3b components. It is possible that these additional peaks may yet yield important information which will assist in understanding the underlying neuropathological processes. Some of the anomalies associated with multi-peak complexes could also be clarified by producing a latency-corrected average with an adaptive filter (Woody 1967), but at present we are more interested in assessing whether a more global measurement has use as an indicator or trait marker for schizophrenia.

Peak definition method

The least-mean-squares method of peak definition appears to give the most consistent result across all leads at all filter settings. By this method, the groups always showed a significant separation of means. The success of this technique is probably related to the way it smooths out many of the

additional peaks and resolves a single peak. An important conclusion may be drawn from this result with reference to previous results reported by our group and other groups.

At 0.16 Hz, and 1 Hz in particular there is no significant difference between the means of controls and schizophrenics in the Cz and Pz leads when measured by peak-searching. These results become highly significant when the LMS method is used, however. The method of peak definition previously used was slope-intersection, where the intersection of ascending and descending tangents define the peak latency. This technique is an approximation to the more exact method of least-mean-squares fit. This could explain why significant differences have been reported between the latencies of schizophrenics and controls by groups who have used the slope-intersection method (e.g., Blackwood et al. 1987, 1991) and not by others who have used peak-search methods.

Filter setting

Previous criticism of the high-pass filter setting used when recording the P300 now appears invalid. This study has shown that it is possible to separate controls and schizophrenics on the basis of P300 amplitude and latency at 2 filter settings presently and previously used (0.16 Hz and 1 Hz), while also demonstrating that even a 2 Hz high-pass filter would be acceptable, regardless of whether peaks are tracked, as all three methods give a significant group separation for latency.

Electrode site

This study has shown a significant separation of control from schizophrenic P300 data in the three central leads using the least-mean-squares measurement technique. While any of the three leads would be suitable to use for latency discrimination, Fz gave the largest group difference. The Pz lead appears to give the best resolution for amplitude discrimination. It is

well understood that the P3b generator is centro-parietally located, and the Pz lead is probably best sited to maximise the amplitude measurement.

High-pass filter effect and spectral analysis

A significant group x filter interaction occurred only when the peak-tracking technique was used. Peak-tracking is a slightly artificial method of making the latency measurement, as data are not normally filtered at a range of settings, but it is the only way to sensibly evaluate the effect of the high-pass filter on single peaks. The value of adopting this approach is revealed when comparing peak-track and peak-search methods, as shown in Figure 7.2. These figures illustrate the increase in group separation when the homologous peaks are identified. The action of the filter coupled with the effect of peak-changes would tend to reduce the effect size between groups when using the peak-search method, and this is shown particularly well in the Pz lead (Figure 7.2c). The p-value remains almost constant with filtering when peak-searching is used, a consequence of the high number of peak-changes in this lead in the schizophrenic group.

The effect of the high-pass filter on single peaks, when evaluated more correctly with peak-tracking, was to introduce a greater phase lead in controls than in schizophrenics (Figure 7.4).

The degree of time-lead introduced is much greater in the control group, in all leads. This confirms the result previously reported by Ebmeier et al. (1992).

This significant time domain effect implies differences in spectral composition. The 2-frequency model predicts that a time domain difference can be accounted for by spectral power shifts between the fundamental frequency and higher order harmonic. Spectral analysis indicated a trend for this result in the Pz lead only, where the biggest change in control latency

Figure 7.4 Latency shift as a function of high-pass filter setting for the peak-track method in control and schizophrenic P300 latency data. A highly significant lead x filter effect was found using this method.

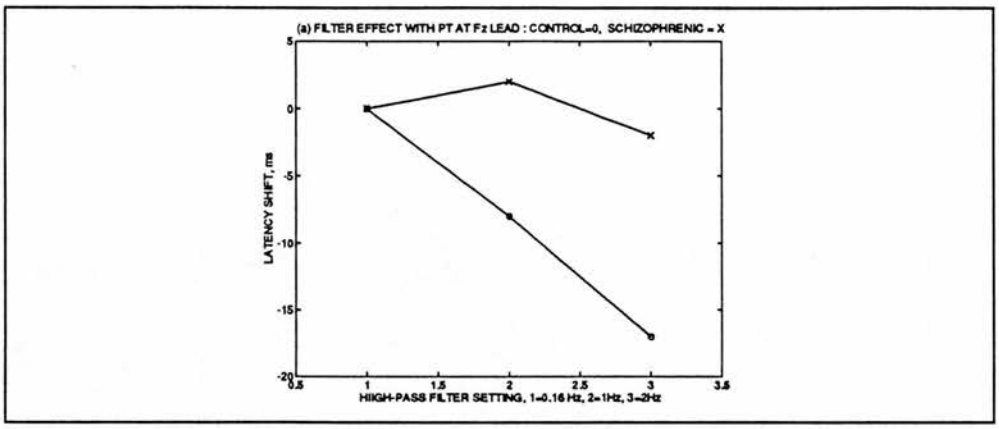


Figure 7.4a. Fz lead

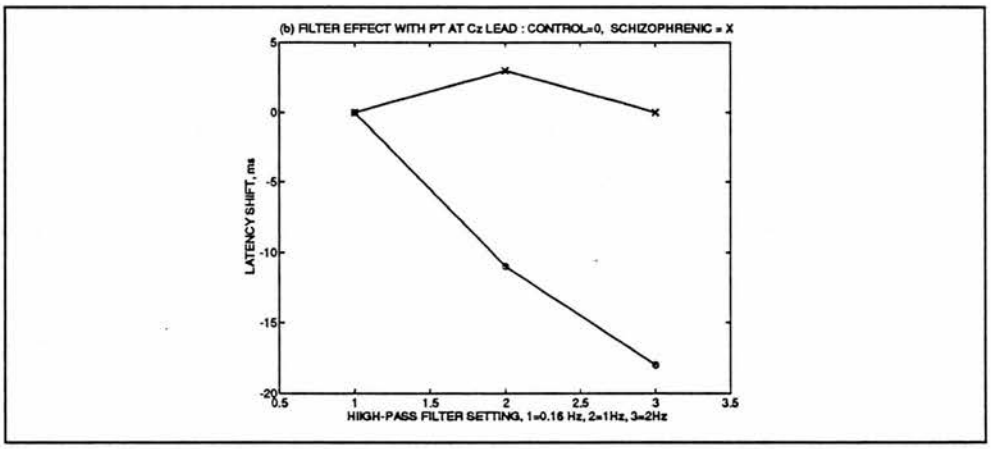


Figure 7.4b. Cz lead

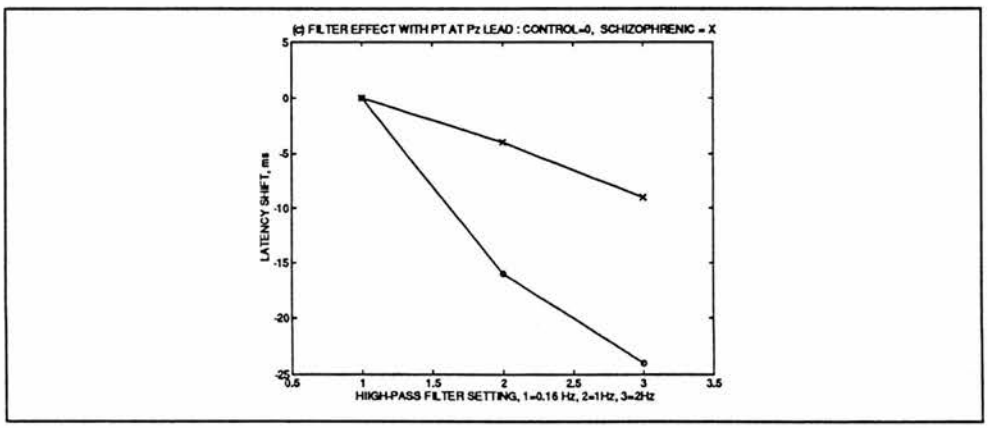


Figure 7.4c. Pz lead

occurs. This is probably due to the fact that the slow wave generator is parietally sited. Figure 7.3 shows that the total power in the averaged schizophrenic spectra is less than in the averaged control spectra (a reflection of reduced amplitude in the time domain) and that there is a trend for the relative distribution of power away from the fundamental towards the higher order harmonic in the schizophrenic group.

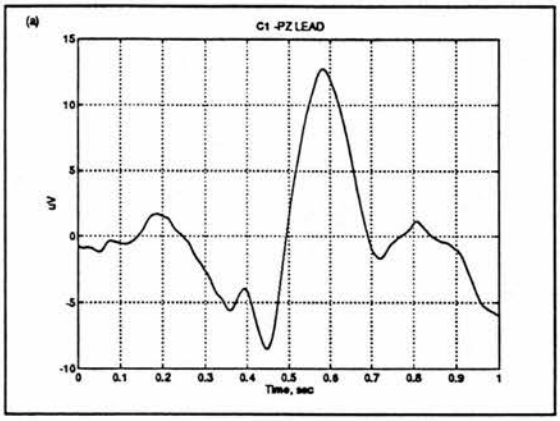
Taking account of the fact that scalloping and spectral leakage, due to windowing data, will reduce spectral resolution (Harris 1978; Jervis et al. 1989), this result shows that the FFT technique is still sensitive enough to allow the viability of the 2-frequency model to be tested. Further, while the model is rather rigid in that two single frequencies are specified, the actual frequencies involved may vary from subject to subject, and some spread of power on averaging spectra is anticipated.

It would be judicious to consider other explanations as to why the result is most significant at the Pz lead. It could be argued that alpha activity generators are sited parietally, and the spectral differences found are due to contamination from these sources. Such activity would be expected to peak in the 8 - 11 Hz band. Reference to Figure 7.3 shows that the main spectral differences are spread across a lower frequency band, between 2 - 8 Hz. The ability of the spectral analysis technique to discern between alpha activity and shifts in power of the slow wave to P3a/P3b complex is demonstrated in Figure 7.5.

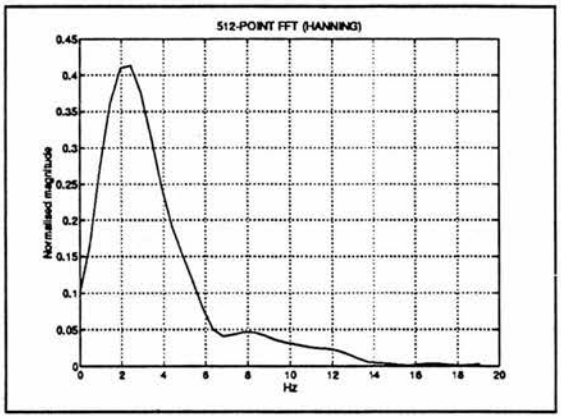
In each set of traces we have a time domain averaged recording of a P300 complex and its decomposition in the frequency domain. The top traces show a dominant P300 complex with low magnitude N100, P200, N200 components. Most of the power is concentrated below the 5 Hz band. In the middle pair of traces, the P300 slow wave component is much reduced and the P3a and P3b components are now clearly resolved. The amplitude of the

Figure 7.5 Time and frequency domain representations of an averaged P300 complex from 2 different subjects - 1 control (a) and 1 schizophrenic (b) - and a synthesised P300 complex (c).

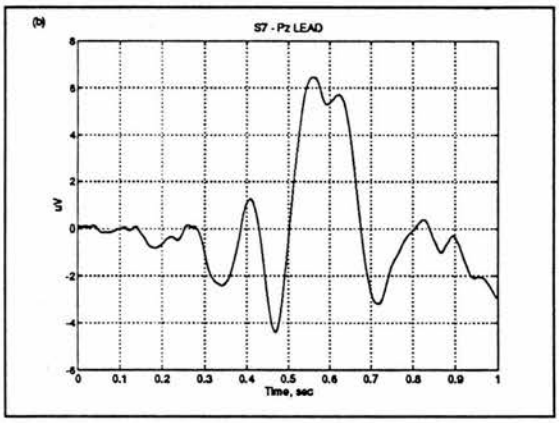
a) C1 - Pz LEAD



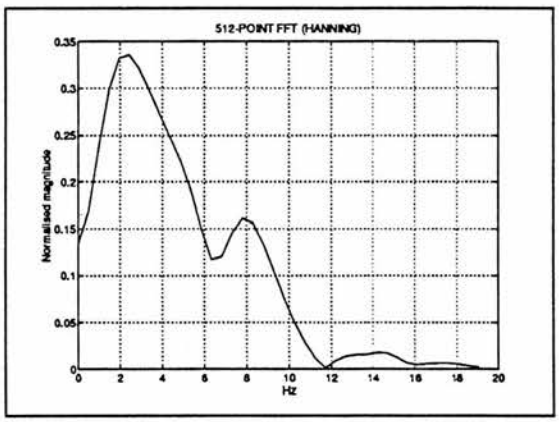
512-POINT FFT of C1



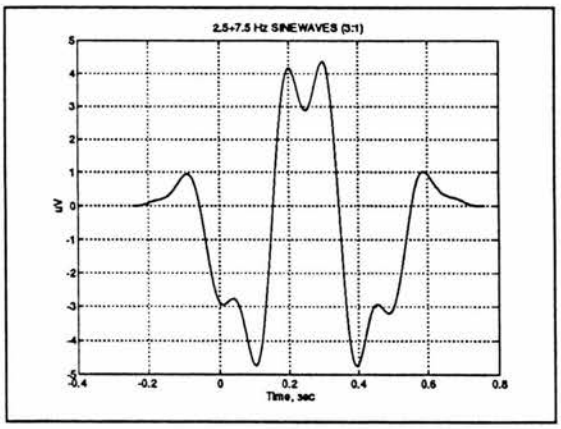
b) S7 - PZ LEAD

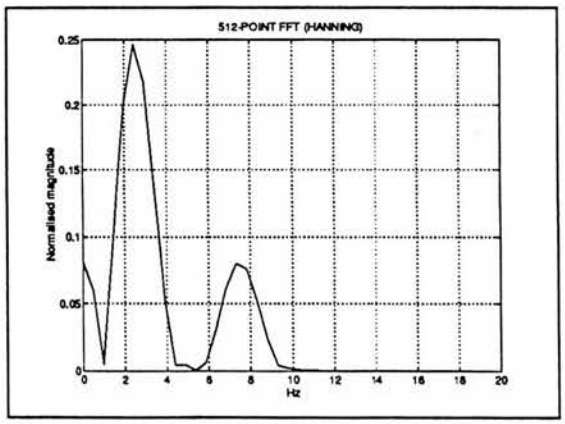


512-POINT FFT of S7



c) 2.5 Hz AND & 7.5 Hz SINES SUMMED 3:1 AND 512 POINT-FFT





exogenous components has increased, and this is reflected by a shift of some power from the middle to the top of the 0 - 5 Hz band. A large peak has also appeared in the middle of the 5 - 10 Hz band. The lower pair of traces were derived by synthesising a P300 complex. Two sine-waves of frequencies 2.5 and 7.5 Hz were summed in a ratio of 3:1. The data were then multiplied by a Hanning window. The time domain features of the complex bear some resemblance to the P300 complex in the middle trace. The effect of spectral leakage and windowing distort the result in the frequency domain, but two clear peaks, corresponding to the constituent frequencies, are well resolved.

It is difficult to speculate whether there is a significant P3a/P3b complex in the top example, or its' contribution in the frequency domain, but the absence of a significant power contribution in the 5-10 Hz band is probably due to the absence of a P3a/P3b complex. The appearance of the P300 complex in the centre set of figures quite clearly allows this distinction to be made by comparison with the synthesised data - the source of the peak in the middle of the 0 - 5 Hz band can be derived by extrapolation, with our knowledge from the synthesised data.

This series of figures demonstrate the spectral differences due to a shift in power between the fundamental and a higher order harmonic of the P300 complex. It is conceivable that because we have observed a trend for a similar shift in power to occur in our data, spectral differences observed are due to different power ratios as hypothesised in the 2-frequency model.

The utility of this information is difficult to determine at present. However, Van Dijk et al. (1992) have demonstrated the use of spectral analysis of P300 in quantifying the contribution of alpha activity during the generation of the evoked response (this was achieved with a very small data window, demonstrating the power of the FFT). A reduced slow wave amplitude in schizophrenia has been reported (Barrett et al. 1986) and frequency domain

analysis may allow the degree of reduction to be quantified, giving an acceptable 2-frequency model. If sufficient numbers can be studied in future, it may be that further evidence for the 2-frequency model of P300 will emerge, which could be used to enhance the prospects of deriving a precise set of markers from the P300 in schizophrenia.

7.2.8 Conclusions

Tables 7.1 and 7.3 support the use of P300 latency, as well as amplitude, as a biological covariate of the disease. The LMS peak definition method appears to be the most suitable algorithm for dealing with multi-peak P300 complexes. The effect of high-pass filtering on the P300 complex in this study of controls and schizophrenics appears to show no differential effect on P300 latency as all of the three filter settings used preserved group differences. Subsequent spectral analysis of the P300 complex revealed a similar spectral composition for P300 in control and schizophrenic groups and this spectral composition appears to fit the 2-frequency model well. The ratio for the fundamental component and its second harmonic appears significantly different in the Pz lead only.

7.2.9 Further work

The genesis of P3a and P3b sub-components in the P300 complex along with the Slow Wave may be different in schizophrenia when compared to other study groups. This may apply to other psychiatric groups with major psychotic illness, such as bipolar depressives. The separation of the P3a, P3b and Slow Wave should in principle allow a detailed study of how the same stimulus parameters affect these overlapping components in different study groups and also allow some insight into the underlying processes responsible for their appearance. The use of passive and novel auditory stimuli in the study of P3a, P3b and P3-novel sub-components of P300 is outlined in chapter 3.

Chapter 8.

The P3-novel, P3-target, and Slow Wave in schizophrenia and bipolar depression

The P300 waveform and its sub-components along with their mode of generation are described in chapter 3. Clinical studies of P300 have tended to focus on the complex derived from auditory oddball paradigms. Such a waveform will normally comprise P3b, sometimes P3a, and the Slow Wave. The accepted terminology appears to be that any early deflection in a bifurcated P300 complex is labelled P3a and the later component as P3b. The propriety of these terms is explored below. The measured contributions of these sub-components to the P300 waveform is partly a function of the electrode site at which the measurement is made. From the published studies reviewed in chapter 3, it would be predicted that measurements at the Fz and Cz electrode sites might show a dominant P3a sub-component while at Pz, the P3b sub-component may dominate. However, this picture is often not consistent, even within a normal control group. Polich (1988) showed an asymmetrical incidence of P300 bifurcation in a large normal control population. The ability to experimentally control the incidence of one or both sub-components is attractive as direct comparisons can be made across control and patient study groups. The benefits of this become obvious if the diagnostic value of the test improves. The amplitude and latency of an emitted P3a component, elicited in "ignore" or "missing" paradigms is smaller, unstable, and therefore less predictable than the P3b. The early P300 component evoked by ignored novel stimuli, the P3-novel, is related to the orienting response and has similar topography to the P3a, however, its amplitude is much greater. Whether the P3a and P3-novel reflect the same underlying neural processes is at present unclear. It is possible that the observed P3a contribution in response to target stimuli is due to some initial novel aspect involved in orienting attention towards a target. The ability to

separate this early component from the P300 complex to targets for analysis is attractive if it reveals more information relating to the underlying cognitive processes.

This chapter describes three experimental paradigms designed to separate the P3-novel from P300 components associated with a task, in the study of schizophrenia and bipolar depression. First, a brief description is given of the auditory evoked potential stimulator that was developed for these experiments.

8.1 The novel auditory evoked potential stimulator

The requirement for the stimulator was that it should be capable of delivering auditory stimuli identical to those used in the experiment described in the last chapter and also be capable of generating additional novel sounds.

The specification for the first auditory stimulator was used to design the tone generator for use in the oddball part of the experiments. The specification for the novel sound generator was produced in consultation with Professor M.D. Rugg, Department of Psychology, University of St. Andrews. On the basis of published results from this group (Holdstock and Rugg, 1992) it was decided to use the same source of novel sounds and the same stimulus durations. The majority of sounds were culled from a BBC sound effects LP and additional sounds were synthesised in the laboratory. Some examples of these sounds are: car horn; duck quack; train whistle; rubber band "twang"; wooden ruler "twang"; metallic resonances from spoons and a thunderclap. A range of 32 novel sounds in total was generated. The limit of the sound range was determined by the technology employed to store the digitised versions of these sounds. The design of the novel sound generator was built around a 32 kByte erasable-programmable read-only memory (EPROM) device (Circuit diagram 2, Appendix 2). The subsequent wiring and controlling electronics were more manageable in the time given to develop

the stimulator. The sounds were sampled with a duration of 100 ms, as in the published work referred to by Holdstock and Rugg and also other published work using this type of stimuli (Grillon et al.,1990a; Grillon et al.,1990b; Grillon et al., 1991).

To control for the effect of stimulus intensity on the amplitude of the response, the novel sounds were normalised to give the same peak intensity as the tones. A program was written in Turbo Pascal to calculate the normalisation factor then scale the data prior to storing it on the EPROM. It was not possible to normalise the novel sounds to deliver the same total energy as the sinusoidal tones because some of them lasted for a shorter duration than the tones (10-20 ms). The scale factor required to make these sounds deliver the same total energy as the tones meant that they would be effectively multiplied beyond the output range of the digital-to-analogue converter.

8.2 The clinical study

8.2.1 Introduction

Many research groups have reported a reduction in the amplitude of the P300 waveform of the long-latency ERP in schizophrenia (Roth and Cannon, 1972; Levit et al., 1973; Roth et al, 1980a, 1980b; Baribeau-Braun et al., 1983; McCarley et al., 1991; Ogura et al 1991), and a delay in latency has been reported (Pfefferbaum et al., 1984; Blackwood et al., 1987; Romani et al., 1987; Muir et al., 1991; Blackwood et al., 1994). While the existence of a latency delay in schizophrenia remains controversial, a recent meta-analysis of fifteen reported studies concluded that P300 is delayed in schizophrenia (Ebmeier, 1991). Asymmetrical P300 topographic patterns are reported in medicated (McCarley et al., 1991) and unmedicated (Faux et al., 1993) schizophrenic subjects. The P300 has also received much attention due to its potential as a biological risk marker in schizophrenia as P300 latency and amplitude changes are observed in a proportion of first degree relatives of

schizophrenic subjects (Friedman et al., 1988; Blackwood et al., 1991; Schreiber et al., 1991; Schreiber et al., 1992; Kidogami et al., 1992; Roxborough et al., 1993).

There have been numerous studies of P300 in unipolar depression. One of the first studies of psychotic depression reported a normal P300 (Levit et al., 1973) and the auditory P300 in depression was found to be normal but with a significantly delayed reaction time (Giedke et al., 1981). A review of published studies of P300 in depression and schizophrenia between 1972 and 1984 concluded that there was no difference between unipolar depressed patients and controls in P300 latency and that P300 amplitude reduction is a rare finding (Roth et al., 1986). One of the studies reviewed was by Pfefferbaum et al., (1984), where it was concluded that while P300 latency delays do occur in schizophrenia, dementia and depression they are not consistently large enough or specific enough to support its use in clinical diagnosis. A replication of this study was carried out, designed to address differences in methodology and analysis from other studies with positive findings (Gordon et al., 1986). A combined group of unipolar depressed (n=12) and bipolar depressed (n=5) subjects was compared to controls, patients with dementia, and schizophrenics. A significant P300 latency delay was found in only 12% of the depressed group, but it was not stated whether they belonged to the bipolar or unipolar sub-groups. P300 amplitude was not reported. There was a suggestion that the latency delay may have been due to anti-depressant medication. Other studies continue to report conflicting results. Reduced P300 amplitude was found in unipolar depression by Blackwood et al., 1987, and Muir et al., 1991, but when retested after recovery from depression, the same patients had normal P300 amplitude suggesting P300 amplitude is a state rather than a trait marker. No P300 abnormalities were reported in a group of unipolar depressed subjects (Patterson et al., 1988) and normal latency is reported (Kraiuhin et al., 1990) while depressed subjects with psychotic symptoms are reported to have

reductions in P300 amplitude which reflect clinical state (Santosh et al, 1994). A visual paradigm using psychologically rated "positive", "negative" and "neutral" word stimuli revealed a P300 amplitude reduction in unipolar depressed and recovered unipolar depressed patients to negative word stimuli (Blackburn et al., 1990). The use of an audiospatial oddball paradigm, to provide a more severe cognitive challenge, and an auditory oddball task showed that only the audiospatial task produced P300 latency delay, in typical depressives but not atypical depressives, while there were no amplitude differences in either task (Bruder at al., 1991). Some of the subjects in this study were classified as bipolar II, and appeared in either the typical or atypical groups.

One of the first EP studies of both bipolar depression and unipolar depression used an augmenting-reducing visual paradigm and found that bipolars from both sexes showed an increasing EP amplitude with increasing stimulus intensity while the male unipolars showed a decrease with increasing stimulus intensity (Buchsbaum et al., 1973). Most studies, as outlined above, have not examined unipolar and bipolar diagnosis separately, usually assuming that these different types of depression formed a single group. However, one of the most notable recent studies looked at 99 bipolar depressives and 44 unipolar depressives along with 96 schizophrenics and 213 controls (Muir et al., 1991). This study reported prolonged P300 latency and reduced amplitude in the bipolar depressed group while the unipolar group had reduced P300 amplitude only, probably reflecting depressed state. This paper commented on the problems of interpreting findings from published work which use different diagnostic criteria. A very recent study of bipolar depressives and schizophrenics reported a significant prolongation of P300 latency in both groups but only the schizophrenics showed a reduced amplitude (Souza et al., in press).

The P300 complex generated by auditory oddball tasks is complicated by the

fact that the waveform may consist of the early P3a component and a later P3b component. Polich (1988) found that 35 out of 100 control subjects studied show a bifurcated P300 complex. Averaged across two trials, the incidence of an overall P300 complex peak maximum occurring in the P3a sub-component at Fz, Cz and Pz was 31.4%, 45.8%, and 44.3% while for the P3b sub-component the incidence was 68.6%, 54.2%, and 55.7%. This suggests an asymmetric distribution for the bifurcated P300 waveform in the normal population. The results from an auditory oddball paradigm can therefore be more difficult to interpret when the underlying distribution pattern of P3a and P3b is unpredictable.

Frontally originating P300 sub-components can be generated by missing target stimuli, unattended target stimuli or by unattended novel stimuli. The published nomenclature for this sub-component has led to some confusion. The first report of an early, low amplitude P300 sub-component in response to missing auditory stimuli was by Sutton et al., (1967). In a study on habituation, there was a report of a positive complex of 210 ms latency in response to ignored rare auditory stimuli (Roth, 1973). A more detailed study by Squires et al., (1975), using loud and soft tones of different frequencies and probabilities in attend and ignore conditions led to the labelling of the early and later P300 sub-components as "P3a" and "P3b" respectively. The authors stressed that they did not wish this nomenclature to be adopted as standard. As well as the latency of the two components being significantly different, the topography was also different with P3b showing a parietal maximum while P3a had a fronto-central maximum. It was noted that sometimes both P3a and P3b components appeared in response to attended rare stimuli. In a study of the latency variability of "presented" and "omitted" single and double click stimuli, the corresponding potentials were labelled as "evoked" or "emitted", which is probably a more precise definition (Ruchkin and Sutton, 1978). A further study by the same authors using visual stimuli showed that the latency of the emitted P300 was longer

than that for the evoked P300 (Ruchkin and Sutton, 1979). There was no comment on the topography of the potentials in either paper. About the same time as the first report of P3a to ignored stimuli a report was published of an early P300 component in response to novel visual stimuli (Courchesne et al., 1975; Courchesne 1978). Passive and active paradigms were used. Attended task-relevant stimuli elicited a parietally maximal "P_3 wave" while the task-irrelevant novel stimuli evoked a "P_3 wave" which was maximum at the centro-frontal scalp, but it was labelled a "frontal variety of P_3 wave". Habituation to the novel stimuli produced a shift in topography to a parietal source with a reduced amplitude, similar to the "ignored" target stimuli. The authors stated that the "*novels* P3" they elicited, while originating from a more frontal location like the P3a described by Squires et al., (1975), it had no other similarities as it was elicited by a visual rather than auditory paradigm; the P3a was elicited in an ignore condition, the P3a does not habituate; the mean latency of P3a is around 100 ms earlier than *novels* P3; P3a amplitude is roughly half that of *novels* P3. There is a suggestion from these data that the *novels* P3, like the P300 to targets described by Squires et al., may sometimes comprise an early and late sub-component equivalent to P3a and P3b in the auditory paradigm. A novel P300 component was generated using somatosensory stimuli (Yamaguchi and Knight, 1991). Task-relevant target and task-irrelevant novel stimuli were generated using taps and shocks respectively. The authors labelled the response to the targets as "P3b" while the response to the novel stimuli was called "P3a". The topography for these components was similar to that derived in auditory and visual paradigms, with P3b being maximal parietally and P3a having a central maximum. Mean P3a latency was nearly 40 ms earlier than mean P3b latency. Compelling evidence for the anatomical area associated with the generation of the response to novel auditory stimuli was reported in a study on P300 in prefrontal lesions (Knight, 1984). One type of distracting novel stimulus, derived from a dog bark, was randomly interspersed within the auditory stimuli of an oddball task. In this study the mean novel P300

waveform in controls was approximately 50 ms earlier than the target P300 and was maximal at the frontal and vertex electrode sites. Habituation to the novel stimulus was again demonstrated. The group with prefrontal lesions had no fronto-centrally originating P3 novel, but the response associated with the novel stimulus measured at the Pz site was earlier than that to the target tones at the same site by around 50 ms. Subjects with temporal lobe lesions (Daruna et al., 1989) showed similar results while subjects with closed head injury showed latency delays in the P3a sub-component (Rugg et al., 1993). The effect of auditory novel stimuli in an oddball task appears to prolong the reaction time to the target stimuli and reduce the amplitude of the targets (Grillon et al., 1990b). The concepts of increased distraction due to the novel stimuli, as indicated by increased reaction time, and increased task difficulty, indicated by reduced target P300 amplitude, were proposed.

The first study of P300 in schizophrenia used an "ignore" paradigm (Roth and Cannon, 1972). White noise and tones were used and their probability swapped from 0.85 between 0.15 in a two-part experiment, designed to produce "temporary dis-habituation of the orienting response". The results showed reduction in the amplitude of the P300 response in schizophrenia. The responses to both attended auditory and visual oddball stimuli and ignored novel auditory stimuli presented amongst attended auditory stimuli have been studied in schizophrenia (Grillon et al., 1990a; Grillon et al., 1991). P300 reduction to attended auditory stimuli was greater than to ignored stimuli in schizophrenia compared to controls and the amplitude of the novel response included in an oddball attend paradigm was reduced in schizophrenics. A reduction in available processing resources in schizophrenia is evidenced by reduced amplitude to task-relevant and task-irrelevant stimuli. It was also suggested that these reductions may be due to either inappropriately increased processing resource allocation or failure to habituate to task-irrelevant stimuli in schizophrenia. A very interesting correlation was noticed in the control group between the amplitude of "P3b"

and "P3a" in the distraction task which was not apparent in the schizophrenic group. It was hypothesised that the amplitude of P3b is a good predictor of P3a amplitude in a distraction task. Note that the authors chose to label the P300 response associated with a task-relevant stimulus as "P3b" while the response associated with the novel stimuli was labelled "P3a". This does not fit with the historical derivation of these terms or their proposed role in reflecting cognitive processes and leads to confusion.

Automatically elicited responses to auditory "startle" stimuli generate a P3b-like component (Putnam and Roth, 1987; Putnam and Roth, 1990). The effects of habituation, stimulus duration and rise time were examined and the maximum P300 response was measured at Pz in three experiments. The automatically elicited P300 response, using intense noise bursts, and the P300 response from "effortful" auditory and visual oddball tasks have been studied in schizophrenia (Pfefferbaum et al., 1989). Reduced P300 amplitude was noted in medicated and unmedicated schizophrenics in both effortful paradigms and in the automatic paradigm while a P300 latency delay was noted in both effortful paradigms for the medicated schizophrenics only. The authors conclude that these results support the hypothesis that schizophrenics are deficient in both effortful and automatic cognitive processing.

The P300 Slow Wave is thought to occur in the same latency range as the P300 waveform and was first reported by Squires et al., (1975). The role of Slow Wave in an auditory oddball task was found to be affected by the same variables as the P300 and was initially thought to reflect the same processes (Squires et al., 1977). Studies of the Slow Wave are reviewed by Fabiani et al., (1987) and Slow Wave is now thought to reflect additional processing activities after P300. Increasing task difficulty is expected to increase the amplitude of the Slow Wave and attention level is directly correlated with Slow Wave amplitude. Slow Wave amplitude is seen to increase in a paradigm designed to elicit the automatic P300 response when subjects are

asked to perform a task (Putnam and Roth, 1990). Recent work by Friedman et al., (1993) studied the topography of the Slow Wave (labelled "$P3_2$ ") and suggested that the pattern may be different in responses to rare novel and target auditory stimuli.

The use of rare novel auditory stimuli mixed at random with frequent stimuli in a completely passive paradigm has many potential advantages in a clinical situation in the study of the psychoses. In a standard auditory oddball task subject compliance may be poor, especially since recording from unmedicated and acutely ill schizophrenic or manic subjects is desirable to minimise the confounding effects of medication. A passive paradigm would be preferred to tasks requiring motor or cognitive responses in studies combining brain imaging with neuropsychological testing.

For clarity, the adopted terminology in this chapter for the P300 response associated with the target in an auditory oddball task will be called the ***P3-target*** and the P300 response associated with the novel stimuli will be called the ***P3-novel.***

8.2.2 Hypotheses

In patient groups with recognised cognitive processing deficits which are reflected in abnormal P300 measures, as outlined above, additional information might be derived by the use of both passive and distracting auditory paradigms where processing demands are different. We would expect to see differences in the responses to both task-relevant target responses and responses to novel distracters in active and passive paradigms. It is hypothesised that the responses to novel sounds would be different when recorded from within an oddball paradigm compared to a passive paradigm and that these differences may be in topography, amplitude, latency, or any combinations of these, reflecting different processing demands and processing strategies.

If task difficulty is reflected in Slow Wave amplitude then an objective measure of perceived difficulty might be observed in differences in this waveform. For example, subjects who experience difficulty in evaluating the relevance of a stimulus would be expected to perceive a task with more difficulty than subjects who do not and hence show increases in Slow Wave amplitude.

8.2.3 Aims

The aims of the study were :

i) to experimentally manipulate the auditory P3-novel, P3-target, and Slow Wave in schizophrenic subjects, bipolar depressed subjects, and control subjects to look for differences between diagnostic groups.

ii) to attempt to reproduce published results for the auditory oddball task in schizophrenia and bipolar depression, paying particular attention to P3-target symmetry in schizophrenia.

iii) to attempt to replicate the findings of Grillon et al., (1990a), regarding the predictive value of P3-target related to P3-novel, and to extend the measures to include latency within a task-relevant with distraction paradigm.

iv) to assess the clinical utility of a passive auditory orienting paradigm.

8.2.4 Methods

Subjects

Twenty-eight control subjects, 28 subjects with bipolar depression and 29 subjects with schizophrenia were studied. Patient groups were interviewed by a trained psychiatrist using the Schedule for Affective Disorders and Schizophrenia (SADS) interview (Endicott and Spitzer, 1978) and met RDC and DSM-IV-R criteria. Patients were in-patients of the Royal Edinburgh

Hospital and controls were recruited from hospital staff and from the local population. Informed consent was obtained from all patients studied. Extensive neuropsychological testing was carried out with ERP measures on weekday mornings over a one year period. Table 8.1 lists the key demographic details of the three groups including the National Adult Reading Test-Revised (NART-R), a measure of pre-morbid IQ, and the Weschler Adult Intelligence Scale-Revised (WAIS-R), a measure of current IQ.

Table 8.1 Demographic characteristics of schizophrenic, bipolar, and control groups (means ± SD).

Demographic data	Schizophrenic (n=29)	Bipolar (n=28)	Control (n=28)
SEX RATIO (M:F)	21:8	13:15	18:10
AGE (RANGE)	35.4 ± 9.4 (18 - 52)	33.8 ± 10.6 (18 -56)	31.2 ± 8.9 (20 - 54)
NART-R (RANGE)	104.1 ± 13.3 (80 - 128)	112.9 ± 12.9 (80 - 129)	112.2 ± 9.5 (96 - 128)
WAIS-R (RANGE)	99.1 ± 18.2 (69 - 138)	110 ± 17.7 (71 - 142)	114.7 ± 8.7 (97 - 130)
EDUCATION (RANGE)	12.3 ± 2.4 (10 - 18)	13.7 (2.7) (10 - 18)	14.5 (2.9) (10 - 21)

One-way ANOVAs with Scheffes analysis across group for each of the demographic variables showed no significant age effect but significant effects for education, ($F(77,2)=3.9$, $p \leq 0.05$, control > schizophrenic), NART-R, ($F(75,2)=4.3$, $p \leq 0.05$, bipolar > schizophrenic) and WAIS-R ($F(78,2)=6.9$, $p \leq 0.05$, bipolar and control > schizophrenic).

Experimental paradigms

Three auditory paradigms were used, two involved responding with a button press to a target tone, the third was completely passive:

i) Auditory oddball task

This was the standard two-tone oddball paradigm designed to evoke a P3-target response and will be referred to as the No-Distraction Task (ND), after Grillon et al., (1990a). A rare tone (p=0.15) at 1.5 kHz and 40 ms duration was presented at random amongst frequent tones at 1 kHz (p=0.85) of 40 ms duration and 10 ms rise/fall time. Subjects were requested to respond as quickly as possible with a button press to the rare target tone.

ii) Auditory oddball task with distraction

The standard two-tone oddball paradigm was extended to include distracting rare novel environmental sounds and is designed to evoke a P3-target and P3-novel response. This will be referred to as the Distraction Task (D) after Grillon et al., (1990a). The tone stimuli had the same frequency and duration characteristics as in task 1 but the probability of the frequent tone was changed to 0.7. The duration of the novel sounds was 100 ms and the stimulus intensity was scaled to match that of the tones. Thirty-two novel stimuli were stored in an EPROM device and presented at random (p=0.15) among the rare and frequent tones. Subjects were instructed to ignore the frequent and novel sounds and to press a button as quickly as possible to the rare target tone.

iii) Passive paradigm

The thirty two novel stimuli used in auditory oddball task 2 were presented at random (p=0.15) among frequent tones at 1 kHz (p=0.85). The frequent tone characteristics were identical to those in the above two tasks. The subject was instructed to ignore all sounds, frequent and novel. The sequence of novel stimuli was the same as that presented in the D task. This will be referred to as the Passive paradigm (P). The order of the first two paradigms was randomised but the P paradigm was always presented to the subjects last. Subsequently, only data from 22 controls, 17 bipolars and 12 schizophrenics was usable. Data from the rest of the subjects was unusable

because of excessive corruption due to movement, or the subjects did not want to complete the test. The initial view by the investigation team that this was an undemanding paradigm which subjects would complete easily, turned out to be wrong.

Data recording

Auditory stimuli at 80 dB SPL intensity were presented binaurally to the subjects via headphones in a sound-proofed booth. Subjects were asked to relax and close their eyes during recording. Unipolar EEG data were derived from silver/silver-chloride scalp electrodes placed at Fz, Cz, Pz, T3 and T4 locations referenced to linked-ears, and the amplifier ground derived from an electrode placed on the forehead. Bipolar electro-oculogram (EOG) was monitored by two electrodes, one supraorbital to and the other at the outer canthus of the left eye. All skin/electrode impedances were below 3 kOhms. Data were amplified at a gain of 10^4 with bandwidth of 0.16 - 30 Hz (-3dB) before being digitally sampled at 250 Hz per channel with 12-bit resolution. Stimuli and resulting responses were generated and stored under the control of a Turbo Pascal program running on an IBM PS/2 desktop computer. Data sweeps with an amplitude exceeding ±50 μV caused the automatic rejection of data from all channels. Data were recorded 244 ms prior to and 752 ms after stimulus presentation and the inter-stimulus-interval was 1.1 seconds plus an additional random period ranging between 0 and 125 ms to attempt to cancel periodic noise due to alpha activity.

Digitised single trial evoked response data were then visually inspected. Trials which appeared on inspection to be corrupted by EOG or EMG contamination were rejected. A stimulus synchronised average (SSA) was then formed for each channel of the resulting data. Forty rare and/or 40 novel responses were collected for each test. The number of rejected P3-targets in the task-relevant paradigms and P3-novel responses in the P paradigm was within 10% for all groups. The reaction times to correctly

identified targets were sampled by the computer and stored.

Data processing

The SSA for the rare, novel and frequent responses were smoothed with a bidirectional digital filter (-3dB, 10 Hz) prior to measuring P3-novel and P3-target amplitude and latency. ERP peak latencies were measured using the method of least-mean-squares described in chapter 4. For the LMS fit, the averaged P3-novel responses and averaged P3-target responses were windowed between the maximum negative turning-points before and after the complex, normally at N200 and N400. The amplitude was selected as the maximum peak value in the ranges 200-320 ms for P3-novel and 280-550 ms for P3-target and referred to the mean pre-stimulus baseline of the averaged frequent response. The mean Slow Wave amplitude was automatically calculated between N400 and 700 ms by visually positioning a cursor at N400. Mean Slow Wave amplitude was measured on the responses from the three mid-line leads only.

Statistical analyses by Repeated Measures analysis of variance (ANOVA)

All statistical tests were carried out using the SPSS software programs (SPSS International™, B.V.). The distributions of amplitude and latency data in P3-novel, P3-target and Slow Wave for all 5 leads were first examined using the SPSS "EXAMINE" procedure, which reports the probability from the Kolmogorov-Smirnov (Lilliefors) test and displays a de-trended Normal distribution. The Lilliefors test is based on a modification of the Kolmogorov-Smirnov test for the situation where means and variances are not known but must be estimated from the data. All data were approximately normally distributed.

Repeated measures ANOVA was applied to the data to address the specific aims of the study. Data from the temporal leads were separated from the mid-line leads for analysis. Because P3-novel, P3-target, and Slow Wave

measures are different dependent variables they were analysed in separate repeated measures ANOVAs across paradigms, for both amplitude and latency. So repeated measures ANOVAs across group (control, bipolar, schizophrenic) with paradigm (ND and D for P3-target, or D and P for P3-novel) and electrode (either Fz, Cz, Pz or T3, T4) as within subjects factors were carried out. Further ANOVAs were applied when indicated from these omnibus analyses to attempt to address the specific aims of the study. It was necessary to apply one-way ANOVAs and Scheffes procedures to quantify group differences within a study.

Degrees of freedom were adjusted using the Greenhouse-Geisser correction for multiple comparisons where appropriate (Jennings and Wood, 1976). Where second-order interactions for amplitude data were to be studied, all data were normalised using the root-mean-square method proposed by McCarthy and Wood (1985) to preserve true topographic differences.

8.2.5 Results

Mean reaction times

The mean group reaction times (ms, ± SD) for the two task-relevant experiments (ND and D) are given in table 8.2. A repeated measures ANOVA across ND and D paradigms for the three groups was carried out. There was no group x paradigm interaction but a significant paradigm effect, $F(1,76)=149$, $p < 0.001$. It can be seen from table 8.2 that the mean reaction times all increased by about 100 ms for each group when the D experiment was performed, compared to the ND experiment.

Table 8.2 **Mean Reaction Times** to the ***P3-target*** response for the ***No-Distraction*** and ***Distraction*** experiments.

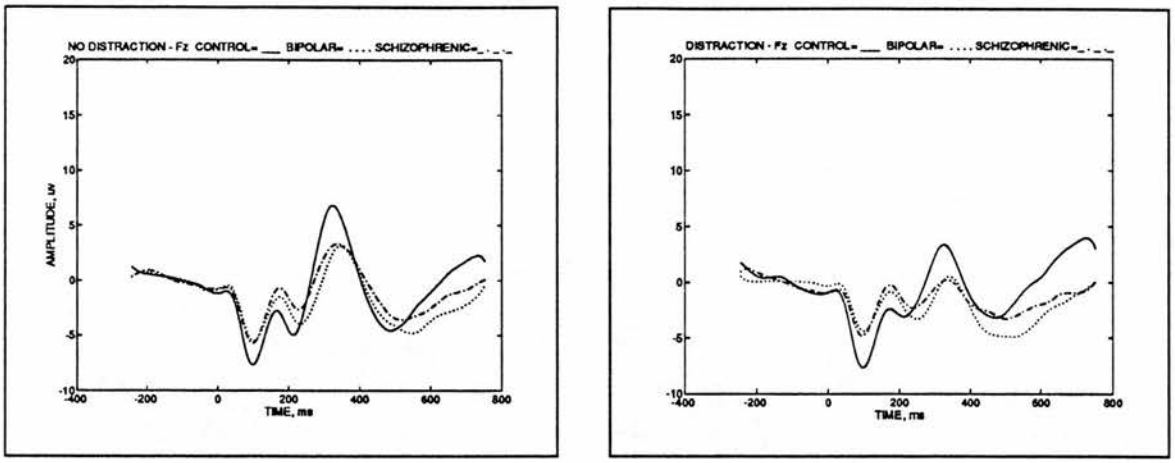
GROUP	ND condition, mean RT (±SD) ms to target tone	D condition, mean RT (±SD) ms to target tone
Control	332 (73.5)	424 (87.4)
Bipolar	362 (97)	461 (83.5)
Schizophrenic	375 (75.8)	463 (71.4)

Figures 8.1 and 8.2, below show the grand averages in the three groups studied for the P3-target and P3-novel responses at all leads, for the ND, D and P tasks.

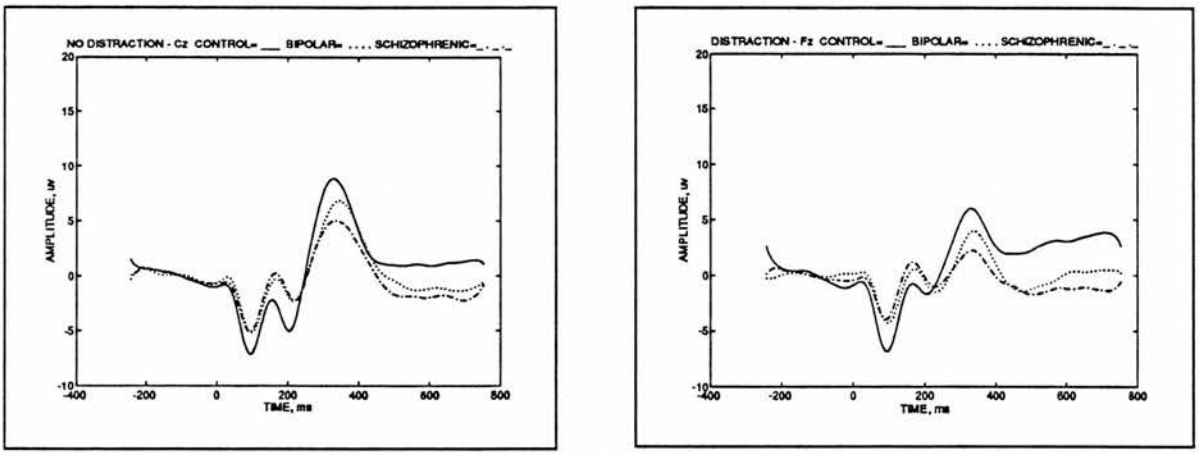
P3-target latency across ND and D tasks

Table 8.3 gives the mean P3-target latency, measured using the LMS-fit, across the ND and D tasks for all groups and tables 8.4 and 8.5 give the results for the repeated measures ANOVAs for these data at the electrode groupings described. The P3-target latency for 1 control and 1 schizophrenic subject was not measurable in the ND paradigm.

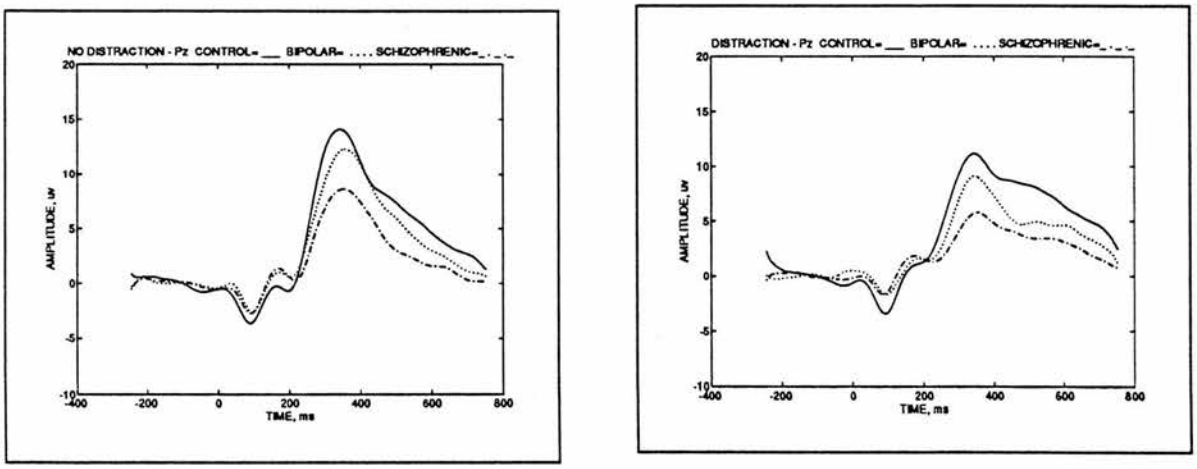
NO DISTRACTION DISTRACTION



Fz ELECTRODE SITE



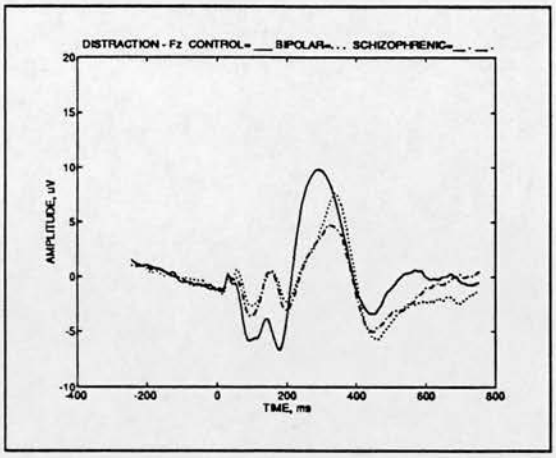
Cz ELECTRODE SITE

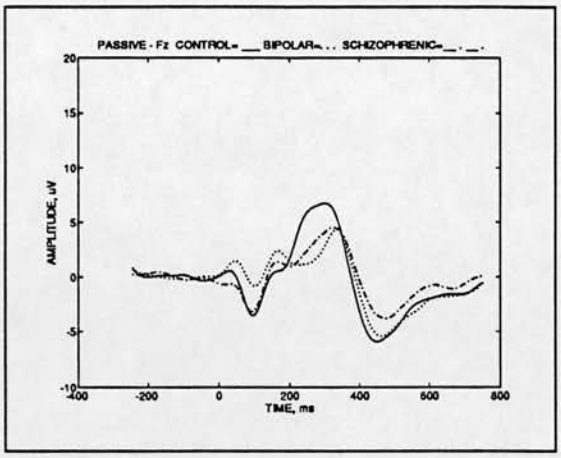


Pz ELECTRODE SITE

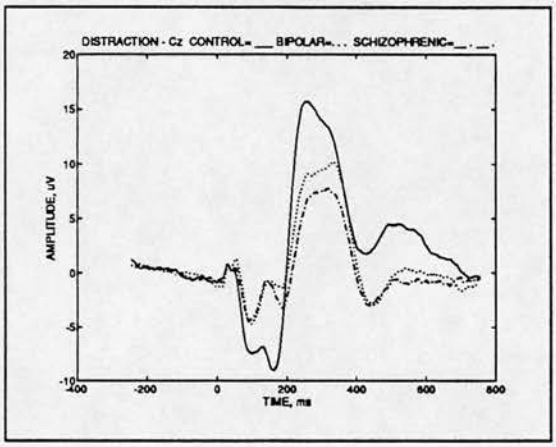
Figure 8.1 Grand averages for the P3-TARGET showing the topography for ND and D tasks in the mid-line leads.

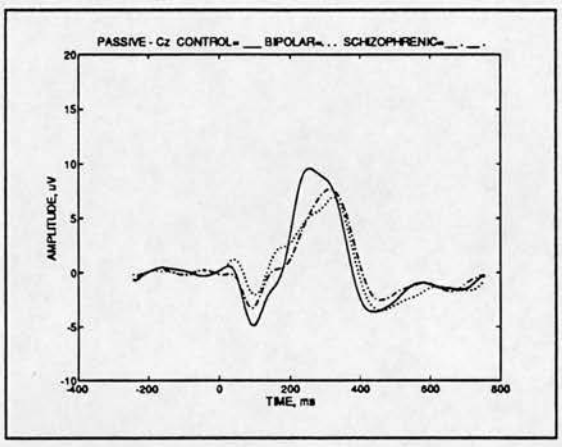
DISTRACTION **PASSIVE**



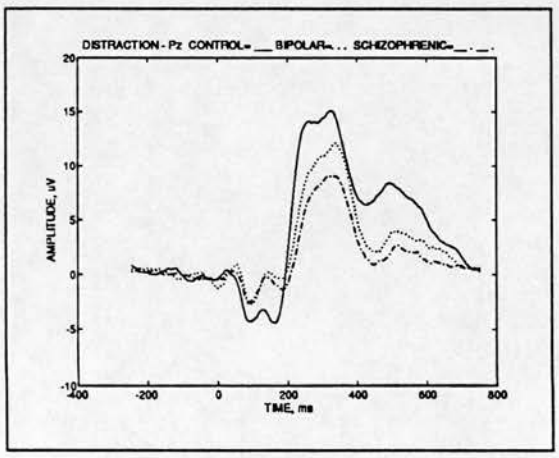


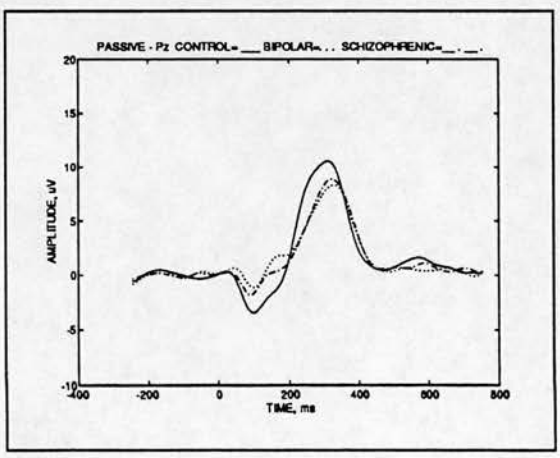
Fz ELECTRODE SITE





Cz ELECTRODE SITE





Pz ELECTRODE SITE

Figure 8.2 Grand averages for P3-NOVEL showing the topography for D and

P tasks in the mid-line leads.

Table 8.3 Mean ***P3-target LATENCY***, ms (± SD), for the three groups across 5 leads in the ***ND and D tasks***.

GROUP	LEAD	NO-DISTRACTION	DISTRACTION
	Fz	327 (25)	326 (39)
	Cz	333 (31)	331 (43)
CONTROL	Pz	345 (27)	348 (36)
(ND: n=27)	T3	335 (24)	337 (36)
(D:n=28)	T4	337 (40)	349 (37)
	Fz	353 (38)	363 (72)
	Cz	351 (36)	365 (80)
SCHIZOPH	Pz	367 (38)	381 (70)
(ND:n=28)	T3	355 (36)	377 (88)
(D:n=29)	T4	352 (41)	365 (68)
	Fz	349 (37)	344 (42)
	Cz	346 (34)	340 (30)
BIPOLAR	Pz	360 (39)	360 (35)
(ND:n=28)	T3	352 (34)	344 (35)
(D:n=28)	T4	361 (38)	347 (54)

Table 8.4 Repeated measures ANOVA across groups on mean ***P3-target LATENCY*** across ND and D tasks for ***Fz, Cz, and Pz*** leads.

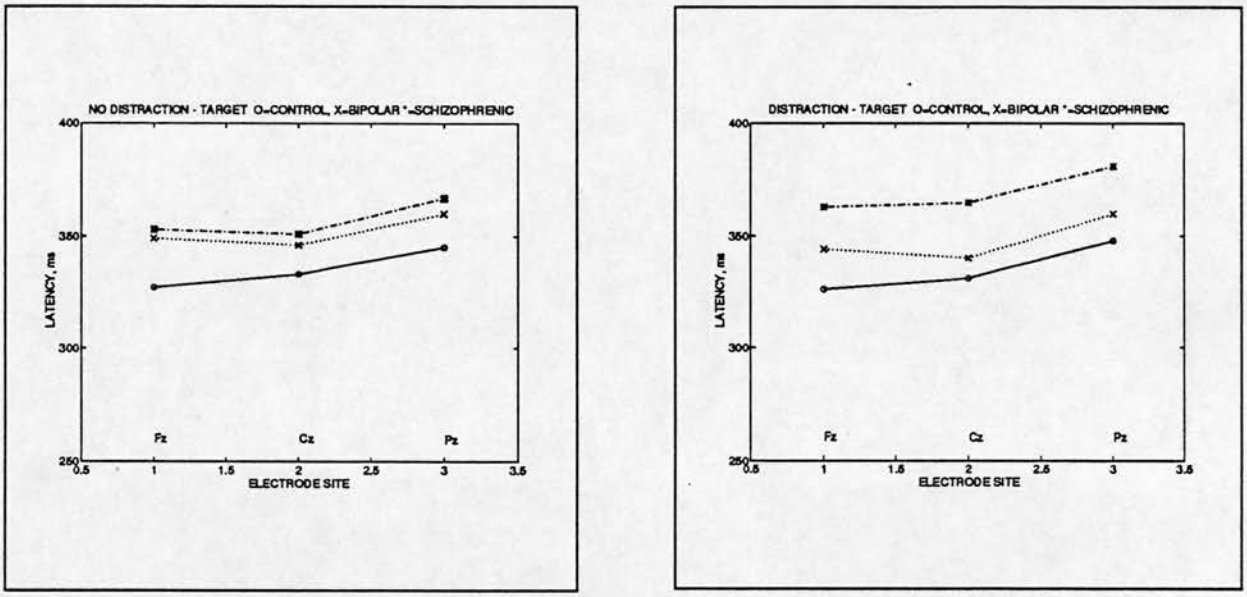
EFFECTS	F-VALUE	P-VALUE	HYPOTHESIS, ERROR,DF
GROUP	4.6	0.013	80, 2
PARADIGM	0.39	0.536	80, 1
LEAD	33	< 0.001	136, 1.7*
G x P	1.37	0.26	80, 2
G x L	0.73	0.55	136, 3.4*
P x L	0.71	0.48	147.3, 1.84*
G x P x L	0.31	0.86	147.3, 3.7*

*Greenhouse-Geisser correction applied

Table 8.5 Repeated measures ANOVA across groups on mean ***P3-target LATENCY*** across ND and D tasks for ***T3 and T4*** leads.

EFFECTS	F-VALUE	P-VALUE	HYPOTHESIS, ERROR,DF
GROUP	3.1	0.052	80, 2
PARADIGM	0.55	0.46	80, 1
LEAD	0.55	0.46	80, 1
G x P	2.48	0.09	80, 2
G x L	3.08	0.054	80, 2
P x L	1.27	0.605	80, 1
G x P x L	1.3	0.28	80, 2

Only group and lead main effects were significant for the mid-line leads and there were no interactions at any level, table 8.4. The lead effect can be seen in figure 8.3 which shows that for each group in either paradigm, P3-target latency is longest at the Pz electrode site, while the differences between the other leads is minimal. For the temporal lead P3-target latency analysis none of the main effects or interactions were significant, table 8.5.



NO-DISTRACTION DISTRACTION

Figure 8.3 P3-target latency from the attended target stimuli in the no-distraction and distraction tasks as a function of mid-line electrode site in the control, schizophrenic, and bipolar groups.

To investigate further the hypothesis that P3-target latency is delayed in schizophrenic and bipolar subjects compared to controls at the mid-line electrode sites, the mean value for the P3-target latencies at each lead across the ND and D tasks was calculated. This is a valid comparison because there was no paradigm effect, and averaging the data improves the accuracy of the estimates and the power of the tests (Hand and Taylor, 1991). So two

further ANOVAs were carried out; one across the control and bipolar groups, the other across the control and schizophrenic groups, using the averaged P3-target latency across ND and D tasks as a within subjects factor for both. For the control v bipolar comparison there was a significant group effect, $F(53,1)=4.56$, $p=0.037$, and significant lead effect, $F(78.9, 1.5)=27.2$, $p<0.001$. There was no interaction between lead and group. These results indicate that the P3-target latency averaged across ND and D tasks is delayed in the bipolar group compared to the controls. Reference to Table 8.3 shows that P3-target latency is longer for bipolars compared to controls at all leads in both experiments. Also, the latency pattern is the same for both groups. For the control v schizophrenic comparison there was a significant group effect, $F(53,1)=7.7$, $p=0.008$, and significant lead effect, $F(94.4, 1.8)=22.9$, $p < 0.001$. There was no interaction between group and lead. These results indicate that the P3-target latency averaged across ND and D tasks is significantly delayed in schizophrenia compared to the controls group at all leads, as there was no group x lead interaction. Reference to table 8.3 confirms that prolonged P3-target latency is a feature of schizophrenia at all mid-line leads averaged across both paradigms, compared to controls. The D task did not significantly increase P3-target latency in any group compared to the ND task.

P3-target amplitude across ND and D tasks

Table 8.6 gives the mean P3-target amplitude using the peak search algorithm across the ND and D tasks for all groups and Tables 8.7 and 8.8 give the results for the repeated measures ANOVAs across these data for the electrode groupings described. The data from one schizophrenic subject was not measurable in the D condition.

Table 8.6 Mean ***P3-target AMPLITUDE***, μV (± SD), for the three groups across 5 leads in the ***ND and D tasks***.

GROUP	LEAD	NO-DISTRACTION	DISTRACTION
	Fz	8.1 (5.6)	4.2 (5.8)
	Cz	11 (5.8)	7.3 (5.6)
CONTROL	Pz	15.8 (4.9)	12.3 (5.5)
(ND:n=28)	T3	5.6 (4.8)	4.6 (4)
(D:n=28)	T4	6.9 (4.1)	5.3 (4.1)
	Fz	5.2 (5.3)	2.6 (3.9)
	Cz	7.1 (6.5)	4 (5.1)
SCHIZOPH	Pz	10.7 (6.4)	7.2 (6.5)
(ND:n=28)	T3	5.1 (3.8)	2.5 (3.3)
(D:n=29)	T4	4.8 (3.6)	2.3 (2.8)
	Fz	5.4 (6.6)	2.4 (5.3)
	Cz	9.3 (5.2)	5.8 (4.4)
BIPOLAR	Pz	14.4 (5.6)	11 (5.5)
(ND:n=28)	T3	5.8 (3.9)	3.8 (4)
(D:n=28)	T4	5.8 (3.3)	3.3 (3.6)

Table 8.7 Repeated measures ANOVA on mean ***P3-target AMPLITUDE*** across ND and D tasks for ***Fz, Cz, and Pz*** leads.

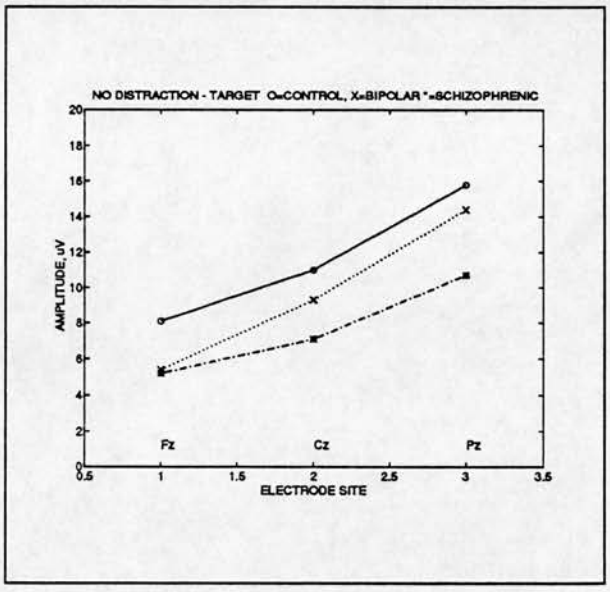
EFFECTS	F-VALUE	P-VALUE	HYPOTHESIS, ERROR,DF
GROUP	4.7	0.012	81, 2
PARADIGM	73.2	< 0.001	81, 1
LEAD	113	< 0.001*	120.4, 1.5*
G x P	0.18	0.833	81, 2
G x L	2.7	0.051*	120.4, 3*
P x L	0.65	0.484*	124.4, 1.54*
G x P x L	0.41	0.75*	124.4, 3.1*

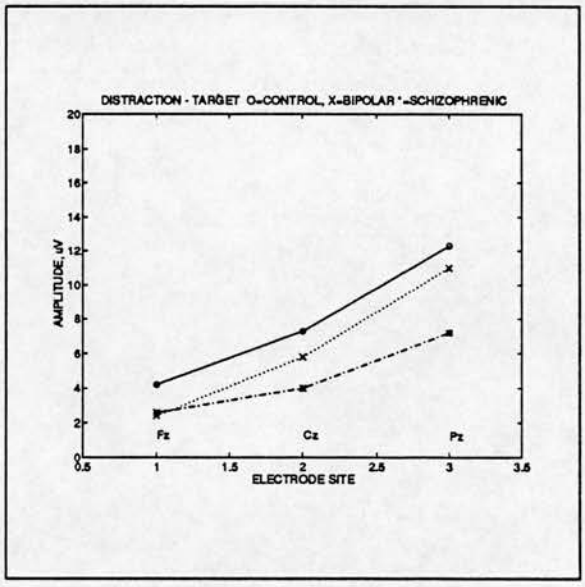
*Greenhouse-Geisser correction applied

Table 8.8 Repeated measures ANOVA on mean ***P3-target AMPLITUDE*** across ND and D tasks for ***T3 and T4*** leads.

EFFECTS	F-VALUE	P-VALUE	HYPOTHESIS, ERROR,DF
GROUP	2.6	0.082	79, 2
PARADIGM	45.4	< 0.001	79, 1
LEAD	0.28	0.6	79, 1
G x P	1.32	0.272	79, 2
G x L	1.84	0.166	79, 2
P x L	0.87	0.355	79, 1
G x P x L	0.46	0.631	79, 2

For the three mid-line leads there were significant group, paradigm, and lead main effects but no significant interactions, table 8.7. The paradigm effect produces a reduction in P3-target amplitude when going from the ND to D task for all groups, as seen in figure 8.4 This reduction in amplitude is constant over groups as the group x paradigm interaction is not significant. The lead effect with no lead x group interaction suggests a similar topography across leads for all groups.





NO DISTRACTION DISTRACTION

Figure 8.4 P3-target amplitude from the attended target stimuli in the no-distraction and distraction tasks as a function of mid-line electrode site in the control, schizophrenic, and bipolar groups.

There was no group difference noted in P3-target amplitude at the two temporal leads, table 8.8 and no further analyses were carried out on these data. The significant paradigm effect replicates the findings in the mid-line leads, with P3-target amplitude decreasing when going from the ND to D condition.

We are interested in P3-target amplitude differences at the mid-line leads between both patient groups and controls and, as a group effect is indicated, three further ANOVAs were carried out across groups, one for each mid-line lead with the two paradigms, ND and D, as within subjects factors. There was a significant main effect for lead at each electrode site studied, which is expected. There was a significant group effect at Cz and Pz only. There was no group x paradigm interaction for any lead. These results indicate that one-way ANOVAs are appropriate across the Cz and Pz leads for each condition to establish the relationships between the three groups. Table 8.9 summarises the results of the ANOVAs and indicates the results of the Scheffes analysis.

Table 8.9 Results from ***ANOVAs at Fz, Cz, and Pz*** electrode site for ***P3-target amplitude*** with two paradigms as within subjects factors (ND and D). The results from subsequent Scheffes analyses are also given.

EFFECTS	Fz	Cz	Pz
GROUP	n.s.	F(81,2)=3.5 p=0.035	F(81,2)=6.5 p=0.002
PARADIGM	F(81,1)=38.1 $p < 0.001$	F(81,1)=57.3 $p < 0.001$	F(81,1)=76.5 $p < 0.001$
G x P	n.s.	n.s.	n.s.
Scheffes analysis ND task		n.s.	Schiz < Control $p \leq 0.05$
Scheffes analysis D task		Schiz < Control $p \leq 0.05$	Schiz < Control $p \leq 0.05$

In the ND task there was a significant reduction in P3-target amplitude in schizophrenics compared to controls at Cz. In the D task there was a significant reduction in the P3-target amplitude in schizophrenics compared to controls at Cz and Pz electrode sites.

P3-novel latency across D and P paradigms

Table 8.10 shows the mean P3-novel latency, using the LMS fit, across the D and P tasks for all groups and tables 8.11 and 8.12 give the results for the repeated measures ANOVAs across these data for the electrode groupings described. Only 22 controls, 12 schizophrenic subjects, and 17 depressed subjects completed the P task. The means used for the repeated measures test in the D task are therefore different from the group means. These figures are shown in parentheses in table 8.10.

Table 8.10 Mean ***P3-novel LATENCY***, ms (± SD), for the three groups across 5 leads in the ND and D tasks.

GROUP	LEAD	DISTRACTION		PASSIVE
	Fz	297 (27)	{301 (26.3)}	284 (28)
	Cz	285 (28)	{288 (28.6)}	279 (33)
CONTROL	Pz	304 (30)	{301 (29)}	299 (28)
(D:n=28)	T3	306 (32)	{312 (32.6)}	288 (26)
(P:n=22)	T4	308 (33)	{315 (32.4)}	298 (26)
	Fz	320 (52)	{319 (33)}	320 (33)
	Cz	313 (48)	{315 (28.5)}	311 (27)
SCHIZOPH	Pz	321 (43)	{329 (27.6)}	309 (34)
(D:n=29)	T3	309 (31)	{318 (18.1)}	311 (18)
(P:n=12)	T4	309 (39)	{319 (30.1)}	315 (26)
	Fz	324 (34)	{318 (32.5)}	311 (48)
	Cz	314 (32)	{304 (28.9)}	302 (43)
BIPOLAR	Pz	326 (37)	{313 (24.2)}	316 (42)
(D:n=28)	T3	321 (36)	{314 (27.3)}	311 (49)
(P:n=17)	T4	320 (35)	{312 (27.8)}	313 (55)

Figures in parentheses are those used in the repeated measures comparison

Table 8.11 Repeated measures ANOVA on mean ***P3-novel LATENCY*** across D and P tasks for ***Fz, Cz, and Pz*** leads.

EFFECTS	F-VALUE	P-VALUE	HYPOTHESIS, ERROR,DF
GROUP	4.8	0.013	47, 2
PARADIGM	1.76	0.191	47, 1
LEAD	13.1	< 0.001	72.5, 1.54*
G x P	0.72	0.49	47, 2
G x L	1	0.39	72.5, 3.1*
P x L	0.28	0.7	74.4, 1.6*
G x P x L	3.17	0.74	74.4, 3.2*

*Greenhouse-Geisser correction applied

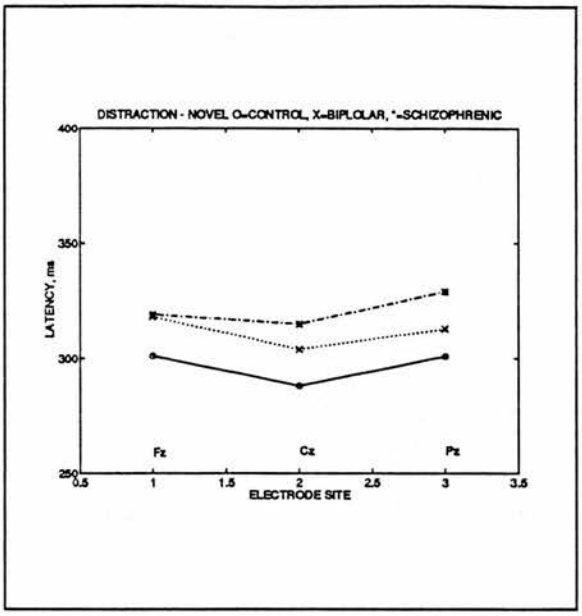
Table 8.12 Repeated measures ANOVA on mean ***P3-novel LATENCY*** across D and P tasks for ***T3 and T4*** leads.

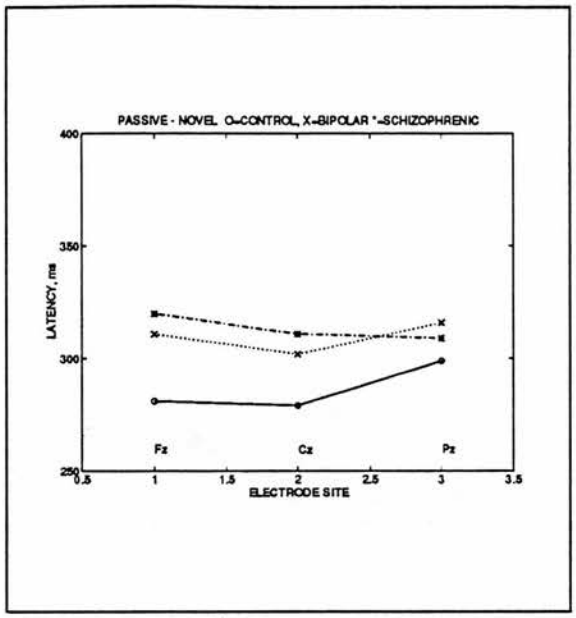
EFFECTS	F-VALUE	P-VALUE	HYPOTHESIS, ERROR,DF
GROUP	1.14	0.33	47, 2
PARADIGM	3.15	0.083	47, 1
LEAD	1.05	0.31	47, 1
G x P	1.78	0.18	47, 2
G x L	0.49	0.62	47, 2
P x L	1.03	0.314	47, 1
G x P x L	0.11	0.9	47, 2

Significant group and lead main effects are noted for P3-novel latency in the three mid-line leads with no significant interactions. The lack of either a paradigm main effect or significant interaction with paradigm allows the mean P3-novel latencies at Fz, Cz, and Pz to be used to establish the group

effect, as for the P3-target latency analysis.

Two further ANOVAs were carried out; one across the control and bipolar groups, the other across the control and schizophrenic groups, using the averaged P3-novel latency across ND and D tasks as a within subjects factor for both. For the control v bipolar comparison there was significant group effect, $F(36,1)=4.5$, $p=0.041$, and significant lead effect, $F(57.3, 1.6)=11$, $p < 0.001$. There was no interaction between group and lead. This result suggests that the P3-novel latency averaged across the D and P paradigms is significantly longer in the bipolar group compared to controls and this is confirmed by reference to table 8.10. The results were similar for the control v schizophrenic analysis. There was a significant group effect, $F(32,1)=11.7$, $p=0.002$, and significant lead effect, $F(47.7,1.5)=9.5$, $p=0.001$. This suggests that the averaged P3-novel latency across D and P paradigms is delayed in schizophrenia compared to controls and this is confirmed by reference to table 8.10. The lead effect in both these comparisons reflects different latency distribution as a function of electrode site and this is illustrated in figure 8.5.





DISTRACTION PASSIVE

Figure 8.5 P3-novel latency (repeated measures values) from the ignored novel stimuli in the distraction and passive paradigms as a function of mid-line electrode site in the control, schizophrenic, and bipolar groups.

There were no significant effects noted in the P3-novel latency measured at the two temporal electrode sites, table 8.12.

P3-novel amplitude across D and P paradigms

Table 8.13 gives the mean P3-novel amplitude, using the peak search algorithm, across the D and P tasks for all groups and Tables 8.14 and 8.15 give the results for the repeated measures ANOVAs across these data for the electrode groupings described. Only 22 controls, 12 schizophrenic subjects, and 17 depressed subjects completed the P task. Therefore the means used in the repeated measures comparison for the D task are different from the group means and these figures are given in parentheses in table 8.13.

Table 8.13 Mean ***P3-novel AMPLITUDE***, μV (± SD), for the three groups across 5 leads in the ND and D tasks.

GROUP	LEAD	DISTRACTION		PASSIVE
	Fz	11.6 (6.8)	{10.9 (7.1)}	8.7 (4.7)
	Cz	18.2 (7.5)	{16.7 (8.1)}	12.2 (4.8)
CONTROL	Pz	17.3 (5.8)	{16.3 (5.9)}	10.9 (7.5)
(D:n=28)	T3	8 (4.7)	{8 (4.3)}	6.6 (3.3)
(P:n=22)	T4	8.4 (4.7)	{8.1 (4.8)}	6.3 (4)
	Fz	6.5 (4.6)	{5.3 (3.5)}	6.2 (5.5)
	Cz	10.2 (4.5)	{10.3 (4.4)}	8.8 (4.9)
SCHIZOPH	Pz	10.5 (4.8)	{11.6 (5.5)}	10.6 (5.6)
(D:n=29)	T3	5.1 (3)	{5.1 {3.5)}	6.5 (4.5)
(P:n=12)	T4	5.9 (3.5)	{6.2 (4)}	5.6 (4.1)
	Fz	7.6 (6)	{8.1 (6.2)}	5.7 (4.3)
	Cz	13.1 (6)	{15.1 (5.2)}	10.3 (5)
BIPOLAR	Pz	13.8 (5.3)	{15.6 (4.9)}	12.3 (3.5)
(D:n=27)	T3	7.1 (3)	{8 (3)}	5.9 (2.7)
(P:n=17)	T4	6.3 (3.5)	{7.1 (3.2)}	5.1 (3.1)

Figures in parentheses are those used in the repeated measures comparison.

Table 8.14 Repeated measures ANOVA on mean ***P3-novel AMPLITUDE*** across D and P tasks for ***Fz, Cz, and Pz*** leads.

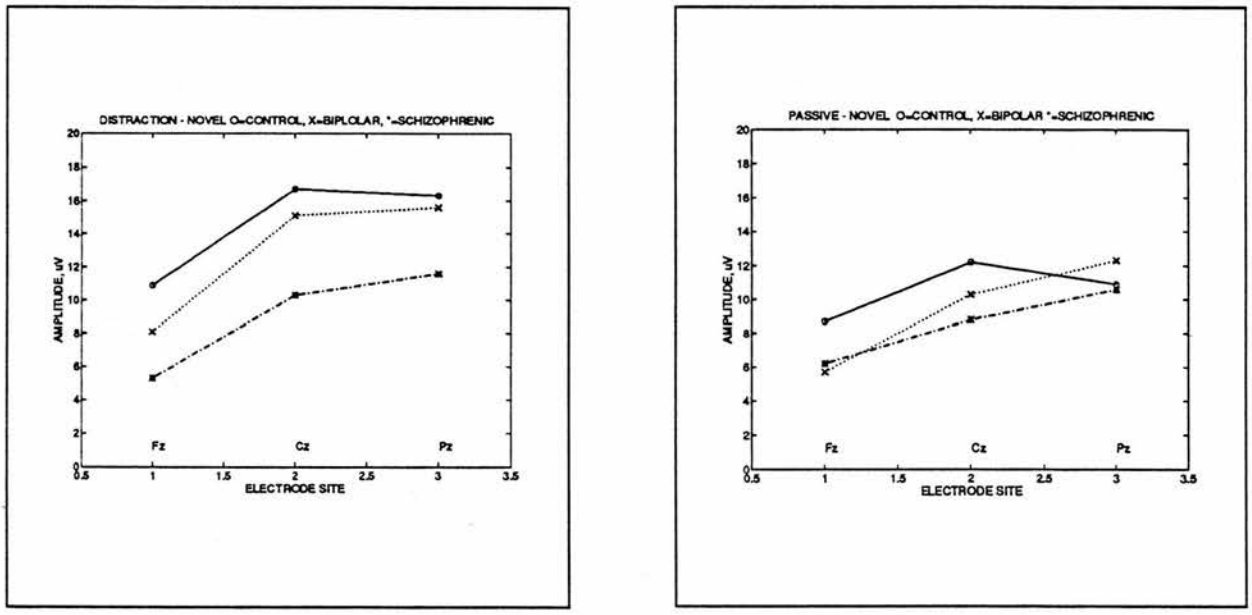
EFFECTS	F-VALUE	P-VALUE	HYPOTHESIS, ERROR,DF
GROUP	3.36	0.043	48, 2
PARADIGM	14.48	< 0.001	48, 1
LEAD	40.16	< 0.001	73.9, 1.64*
G x P	2.06	0.41	48, 2
G x L	1.48	0.226	73.9, 3.1*
P x L	5.84	0.006	81.6, 1.7*
G x P x L	0.46	0.763	81.6, 3.4*

*Greenhouse-Geisser correction applied

Table 8.15 Repeated measures ANOVA on mean ***P3-novel AMPLITUDE*** across D and P tasks for ***T3 and T4*** leads.

EFFECTS	F-VALUE	P-VALUE	HYPOTHESIS, ERROR,DF
GROUP	1.35	0.27	47, 2
PARADIGM	3.6	0.064	47, 1
LEAD	0.45	0.504	47, 1
G x P	1.71	0.193	47, 2
G x L	0.38	0.69	47, 2
P x L	3.2	0.081	47, 1
G x P x L	1.53	0.227	47, 2

There were significant group, paradigm, and lead main effects and a paradigm x lead interaction for the P3-novel amplitude at the three mid-line leads, table 8.14. The paradigm x lead interaction changed to a trend when the data were normalised (F(81,1.7)=3.11, p=0.058) using the method described by McCarthy and Wood, (1985). The paradigm effect reflects a general reduction in P3-novel amplitude when going from a D to P condition at the mid-line electrode sites. The topography for both paradigms in all groups appears to show a centro-parietal maximum and minimum at Fz for P3-novel amplitude, figure 8.6.



DISTRACTION PASSIVE

Figure 8.6 P3-novel amplitude (repeated measures values) from the ignored novel stimuli in the distraction and passive paradigms as a function of mid-line electrode site in the control, schizophrenic, and bipolar groups.

To assess the group effect two further repeated measures ANOVAs were carried out on the three mid-line leads: one on the control and bipolar group the other on the control and schizophrenic group. The same within subjects

factors of lead (Fz, Cz, Pz) and paradigm (D, P) were used. The control v bipolar ANOVA gave significant paradigm and lead effects, as expected, but no significant group effect or interactions. P3-novel amplitude is not significantly different between the control and bipolar group and the topography is similar.

The control v schizophrenic ANOVA gave significant group, $F(32,1)=5.6$, $p=0.025$, paradigm, and lead effects and a significant paradigm x lead interaction. The paradigm and lead effects are expected but the group effect without any interactions indicates that there is a significant difference between the P3-novel amplitude of the schizophrenic and control groups. Re-analysis of the normalised data resulted in the paradigm x lead interaction just missing significance, $F(55.1,1.7)=3.18$, $p=0.057$. Figure 8.6 shows that the topography of the P3-novel appears to change slightly from a central-parietal maximum to a more parietal maximum in the schizophrenic group going from the D to P condition. While there was also no paradigm x lead interaction for the bipolar group, a changing topographic pattern is also suggested from D to P conditions. Reference to table 8.13 confirms that there appears to be a reduction in P3-novel amplitude in the schizophrenic group compared to controls in both conditions.

Slow Wave measured in the P3-target across ND and D tasks

Table 8.16 shows the mean Slow Wave amplitude between N400 and 700 ms measured in the P3-target response across the ND and D tasks for all groups at the three mid-line electrode sites. A repeated measures ANOVA was carried for three groups with paradigm (ND, D) and lead (Fz, Cz, Pz) as within subjects factors.

Table 8.16 Mean ***Slow Wave AMPLITUDE in P3-target***, μV ± SD, for the three groups across ***ND and D*** tasks.

GROUP	LEAD	NO-DISTRACTION	DISTRACTION
CONTROL	Fz	-2.3 (4.8)	-1.3 (7.4)
ND:n=27	Cz	0.2 (3.8)	3.7 (5.1)
D:n=28	Pz	4.4 (2.8)	6 (4.3)
SCHIZOPH	Fz	-2.9 (5.1)	-3 (6.1)
ND: n=28	Cz	-1.9 (3.7)	-1.5 (4.4)
D:n=29	Pz	1.6 (2.7)	2.7 (4.3)
BIPOLAR	Fz	-3 (6.2)	-2.5 (6)
ND: n=28	Cz	-0.9 (4.7)	-0.8 (4.9)
D: n=28	Pz	2.9 (4.8)	4.2 (4.3)

There was a significant group effect only, $F(2,78)=3.7$, $p=0.03$, with no interactions from the repeated measures ANOVA. The group effect was investigated further by taking the mean Slow Wave amplitude across D and P paradigms then performing two further ANOVAs: one for controls v bipolars the other for control v schizophrenics, with three leads as within subjects factors. There was a significant lead effect in both comparisons reflecting the negative frontal and positive parietal amplitude topography. Only the control v schizophrenic comparison gave a significant group effect,

(F(51,1)=8, p=0.007. There were no interactions and this result suggests that the mean Slow Wave amplitude across ND and D conditions is reduced in schizophrenia compared to controls, as seen in table 8.16. This result appears to replicate the finding for P3-target amplitude reduction noted across the same experiments, but extending to all three mid-line leads.

Slow Wave measured in the P3-novel across D and P paradigms

Table 8.17 shows the mean Slow Wave amplitude between N400 and 700 ms measured in the P3-novel response across the D and P paradigms for all groups at the three mid-line electrode sites. Slow Wave could only be measured in 21 controls, 11 schizophrenic subjects, and 17 depressed subjects who completed the P paradigm. Therefore the means used in the repeated measures comparison for the D task are different from the group means and these figures are given in parentheses in table 8.17.

Table 8.17 Mean ***Slow Wave AMPLITUDE in P3-novel***, μV ± SD, for the three groups across ***D and P*** paradigms.

GROUP	LEAD	DISTRACTION		PASSIVE
CONTROL	Fz	-1.8 (5.3)	{-1.2(5.2)}	-3.1 (3.1)
D:n=28	Cz	1.9 (3.9)	{2.2 (3.9)}	-1.7 (3.2)
P:n=21	Pz	5 (4)	{5.3 (4.2)}	0.9 (2.9)
SCHIZOPH	Fz	-2.6 (5.2)	{-4.7 (6.2)}	-2.6 (3.7)
D: n=27	Cz	-1.6 (4.1)	{-3 (4.3)}	-2.3 (2.4)
P:n=11	Pz	1.3 (3.6)	{0.8 (3.4)}	0.13 (3.20
BIPOLAR	Fz	-4 (5.7)	{-4.1 (6.7)}	-3.7 (4.3)
D: n=27	Cz	-1.3 (3.5)	{-0.9 (3.5)}	-2.8 (2.9)
P: n=17	Pz	2.4 (3.2)	{3.1 (3.2)}	0.2 (2.6)

Figures in parentheses are those used in the repeated measures comparison.

Table 8.18 summarises the results from the repeated measures ANOVA.

Table 8.18 Repeated measures ANOVA on ***P3-novel Slow Wave AMPLITUDE*** across ***D and P paradigms*** at Fz, Cz, and Pz.

EFFECTS	F-VALUE	P-VALUE	HYPOTHESIS, ERROR,DF
GROUP	3.1	0.053	46,2
PARADIGM	4.8	0.034	46,1
LEAD	76.1	< 0.001	67.3, 1.5*
G x P	4.4	0.018	46, 2
G x L	1	0.4	67.3, 1.5*
P x L	7.3	0.007	54.5, 1.2*
G x P x L	0.1	0.94	54.5, 2.4*

* Greenhouse-Geisser correction applied

There were significant paradigm and lead main effects and a group x paradigm interaction. The paradigm x lead interaction disappeared when the data were normalised and re-analysed. The lead effect reflects the polarity difference between frontal and parietal electrode sites seen in table 8.17.

A significant group x paradigm interaction suggests that either there is a group difference in one or both experiments or that there is an experiment effect for one or more groups. Because there was no group main effect it is appropriate to test each group separately across experiments. Therefore ANOVAs were conducted on each group for Slow Wave amplitude measures with 2 paradigms (D, P) and three leads (Fz, Cz, Pz) as within subjects factors. The results from these analyses revealed that only the control group showed a paradigm effect, $F(20,1)=23.2$, $p < 0.001$. This result indicates that there is a significant reduction in Slow Wave amplitude in the control group when going from a D to P paradigm.

Correlations between P3-novel and P3-target amplitude and latency within the D task

Table 8.19 summarises the results for Pearsons correlations of P3-novel with P3-target amplitude and P3-novel with P3-target latency within the D task.

Table 8.19. Correlations of P3-novel and P3-target amplitude and latency within Distraction task

CORR.	Lead			Group			
A		Control		Bipolar		Schiz.	
M		r	p	r	p	r	p
P	Fz	0.71	≤0.01**	0.17	n.s.	0.29	n.s.
LIT-	Cz	0.7	≤0.01**	0.4	≤0.05*	0.17	n.s.
U	Pz	0.56	≤0.01**	0.6	≤0.01**	0.4	≤0.05*
D	T3	0.63	≤0.01**	0.59	≤0.01**	0.54	≤0.01**
E	T4	0.7	≤0.01**	0.21	n.s.	0.43	≤0.05*
L		Control		Bipolar		Schiz.	
A		r	p	r	p	r	p
T	Fz	0.32	n.s.	0.5	≤0.01**	0.68	≤0.01**
E	Cz	0.28	n.s.	0.57	≤0.01**	0.51	≤0.01**
N	Pz	0.38	≤0.05*	0.57	≤0.01**	0.36	n.s.
C	T3	-0.13	n.s.	0.6	≤0.01**	0.36	n.s.
Y	T4	-0.03	n.s.	0.05	n.s.	0.43	≤0.05*

Correlation of P3-novel and P3-target amplitude

There were significant correlations in the control group at all leads. The bipolars showed significant correlations at Cz, Pz and T3. The schizophrenics showed significant correlations at Pz, T3 and T4. This result shows more widespread associations between P3-novel and P3-target amplitude in controls than either schizophrenics or bipolars and partially replicates the

findings of Grillon et al., (1990a), in schizophrenia.

Correlation of P3-novel and P3-target latency

There was a significant positive correlation at Pz only in the control group while the patient groups showed significant positive correlations across more leads. In the bipolar group there were significant results at all but the T4 lead. In the schizophrenic group there were significant positive correlations at Fz, Cz and T4.

8.2.6 Discussion

Table 8.20 summarises the findings from these experiments. The differences noted are in comparison to the control group.

Table 8.20. Summary of findings for the schizophrenic and bipolar patient groups across the three experimental paradigms.

	GROUP	
MEASURE	***SCHIZOPHRENIC***	***BIPOLAR***
P3-target latency	**DELAYED: ND, D** paradigms	**DELAYED: ND, D** paradigms
P3-target amplitude	**REDUCED** at Pz in **ND** **REDUCED** at Cz and Pz in **D**	NORMAL
P3-novel latency	**DELAYED: D, P** paradigms	**DELAYED: D, P** paradigms
P3-novel amplitude	**REDUCED: D and P** paradigms	NORMAL

P3-target measures to task-relevant auditory oddball stimuli

There were no significant differences in P3-target latency measured across the ND and D oddball tasks for each group at all electrode sites. However, further analysis of the mid-line electrode sites revealed that P3-target latency averaged across ND and D conditions is delayed in both patient groups compared to controls. These results are in agreement with previously reported findings from other studies which report a delay in latency of P3-target in schizophrenic and bipolar subjects compared to controls. No group latency

differences were noted at the temporal electrode sites.

The P3-target amplitude analysis at the mid-line electrode sites showed a significant reduction when going from an ND task to D task in all three groups studied. Within the ND task, the amplitude of the P3-target was significantly reduced in schizophrenia compared to controls at the Pz electrode site, while in the D task there was a reduction at both Cz and Pz electrode sites. These results are in agreement with previously reported findings in schizophrenia. There were no significant differences in the P3-target amplitude at the electrode sites studied in the bipolar subjects compared to controls and this result replicates the findings of Souza et al., (in press). However, this finding conflicts with that of Muir et al., (1991), who found an amplitude reduction in bipolar depressed subjects. It is not easy to explain this difference in results because data were recorded from only one electrode site, at Cz.

It has been reported that P3-target changes in schizophrenia occur in both medicated and unmedicated states, and there are reports of a similar finding in bipolar depression, as summarised in the introduction. Grillon et al., (1990a, 1991), suggest that amplitude reduction in schizophrenia reflects a reduction in the amount of cognitive processing resources to task-relevant stimuli. The implied reduction in processing resources in schizophrenia is supported by the findings that P3-target amplitude was significantly reduced compared to controls in both paradigms.

P3-target amplitude symmetry in schizophrenia

No significant difference was noted in the amplitude of P3-target at T3 and T4 electrode sites therefore previously reported findings of asymmetry in schizophrenia (McCarley et al., 1991, Faux et al., 1993) are not confirmed.

The reasons for this are unclear but may be due to methodological differences: we used a reaction time task as opposed to target counting; we collected only 40 target responses compared to 60-100 (habituation affects amplitude); for amplitude measurement we used peak maximum as opposed to integrating over a fixed period; we used a different method of statistical analysis. While these authors used Hotellings T-squared analysis, our use of the Greenhouse-Geisser correction for data in multiple comparisons ANOVAs is equally robust.

P3-novel measures in the auditory oddball task with distraction and passive paradigm

The P3-novel latency was significantly delayed at the mid-line electrode sites in both patients groups compared to controls in D and P paradigms. This implies that stimulus evaluation time or, perhaps more accurately, the orienting time, is delayed in the patient groups. However, it has been suggested that delayed "P3a" latency to novel stimuli in head-injured patients may be a reflection of the greater attentional resources allocated to the task of discriminating targets from frequent non-targets (Rugg et al ., 1993).

There was no experiment interaction, so increasing the task difficulty with distracters affects the stimulus evaluation time to novel stimuli to the same degree, for all groups. In the D paradigm there was a significant difference between P3-novel and P3-target latency in all groups, $F(81,2)=73.1$, $p < 0.001$, with P3-novel appearing earlier. There was no group x response interaction.

There was a significant reduction in P3-novel amplitude at the mid-line electrode sites when going from a D to P task in all groups. This reduction was consistent across experiments for all groups as there was no group x

paradigm interaction. However, further analysis showed that P3-novel amplitude is significantly reduced in the schizophrenic group compared to controls and, as there was a lack of group x paradigm interaction, it appears that there is a reduction for both D and P conditions. In the D condition, the amplitude of the P3-novel was significantly larger than P3-target (response, $F(82,1)=107.3$ $p < 0.001$).

Grillon et al., (1990a) suggest that amplitude reductions in P3-target and P3-novel reflect an overall reduction in available processing resources and Pfefferbaum et al., (1989) concluded that schizophrenics are deficient in both effortful and automatic cognitive processing. This was found to be the case for schizophrenics to both target and novel stimuli in this study. The bipolar group did not show significant response amplitude reduction to either novel or target stimuli. If P3-novel amplitude reflects the amount of processing resources available to orient, then it appears that schizophrenics have less available resources than either bipolar or control groups.

In their study of schizophrenia, Grillon et al., (1990a, 1991), derive measures of the amount of processing resources, the "appropriateness" of the allocation of processing resources, and the importance of both task relevance and direction of attention from i) a global reduction in P3-novel and P3-target amplitude in patients; ii) a relatively bigger reduction in the amplitude of P3-target responses compared to the reduction in P3-novel responses in patients iii) a relatively bigger reduction in the amplitude of the P3-target response in an attend condition compared to the reduction in an ignore condition in patients. Both target and novel stimulus response amplitude are thought to reflect the amount of processing resources. The authors suggest that a relatively greater group difference for P3-target amplitude compared to the group difference for P3-novel amplitude (a group x response interaction) indicates an inability to correctly apportion attentional resources (Grillon et

al., 1990a). The effects noted in patients in ii) and iii) imply that P3 reduction is dependent on both task relevance and direction of attention (Grillon et al., 1991). To test the hypothesis that patients are unable to apportion resources correctly in a task-relevant versus task-irrelevant paradigm, an ANOVA was carried out on P3-target and P3-novel amplitude across groups within the D condition. The factors were response (target, novel) and lead (Fz, Cz, Pz). The group x response effect was not significant $F(82,2)=1.9$, $p=0.151$. We have not managed to replicate the reported findings.

Measurements on the P300 response to ignored stimuli in schizophrenia have produced conflicting findings. It has been reported that the P300 response to ignored but intrusive rare stimuli is reduced in schizophrenics (Roth et al., 1980a). The stimuli were tones and white noise bursts of 1 second duration and 100 dB SPL. Also, it has been reported that while the "P3b" to rare target stimuli is reduced in schizophrenia, the "P3a" response to ignored rare stimuli is normal (Scrimali et al., 1988). The findings from this series of experiments suggests that the response to rare, novel events is both reduced and delayed in schizophrenia.

The meaning of the P3-novel response is still unclear at present. Courchesne (1975) suggests that differences in measures of potentials with different topography, the "P3a" and "P3b", imply uniquely separate underlying processes. The result from the correlation analysis on P3-novel and P-target amplitude from this series of experiments appears to imply some association between the two measures, particularly in normal subjects. These two processes probably overlap and are at least partially dependent. However, Holdstock and Rugg (1992) found that there was no "P3a" to a rare ignored tone presented amongst a single novel target tone and frequent, different, novel sounds. The implication from this result is that the resources required

to process a rare ignored "novel" sound are somehow different from those required to process a rare ignored "tonal" sound. It is also possible that using such a stimulus presentation set means that an ignored tone is far more quickly habituated than an ignored novel stimulus in a similar situation. The authors found no long term habituation to the "P3a" generated by ignored novel stimuli, concluding that "P3a" reflects processes leading up to the orienting response.

Novel auditory stimuli and task difficulty

The addition of distracting novel sounds appears to increase task difficulty and this is reflected by the increase in reaction times of about 100 ms in all groups. We did not find a differential increase across groups, so if reaction time is a reasonable index of task difficulty, the D task was perceived with equal difficulty by all groups.

P3-novel and P3-target amplitude topography

P3-novel amplitude was significantly larger than P3-target in all groups in the D task, as shown above. Further analysis on normalised amplitude data showed that the amplitude topography of P3-novel and P3-target is different (response x lead, $F(109, 1.3)=43.5$, $p < 0.001$), but not group dependent (group x response x lead, $F(109, 2.6)=0.25$, $p=0.842$). P3-target amplitude was greatest at Pz in both the ND condition (lead, $F(133,1.64)=97.8$, $p < 0.001$) and D condition (lead, $F(109.7, 1.34)=94.8$, $p< 0.001$) and P3-novel amplitude was greatest at both central and parietal leads than Fz in both the D condition (lead, $F(134.3, 1.6)=72.8$, $p < 0.001$) and P condition (lead, $F(71, 1.5)=17.1$, $p < 0.001$), established by additional post-hoc statistical tests.

These observed topographies fit with those reported in experiments designed

to elicit P3-novel and P3-target, sometimes called P3a and P3b. It is interesting to note that only one of the studies reviewed showed a frontal and vertex maximum to P3-novel (Knight 1984) while the topography for other auditory (Holdstock and Rugg, 1992, Rugg et al., 1993), visual (Courchesne et al., 1975;Courchesne, 1978) and somatosensory (Yamaguchi and Knight, 1991) modalities showed a P3-novel with a centro-parietal maximum. As outlined above, the topography for the P3-novel has sometimes been reported as having a "frontal" maximum when analysis actually showed a centro-parietal maximum. In a bid to prevent further confusion, the P3-novel response appears to be generated from a more centro-parietal region compared to P3-target, which is generated with a parietal maximum.

There is a hint that the amplitude topography of P3-novel is inclined to change when going from the D to P paradigms in the patient groups. The paradigm x lead main effect was not significant in the analysis across D and P conditions but a trend was revealed after data normalisation which is confirmed on inspection of figure 8.6. This effect has been reported in a visual paradigm using novel stimuli (Courchesne, 1978) and was interpreted as being due to habituation. It is likely that we have also observed the effect of habituation as the P paradigm was always given to the subjects last. The observed amplitude reduction and trend for a more parietal topography would appear to support this.

The role of Slow Wave

There was a significant reduction in Slow Wave associated with the P3-target in the schizophrenic group compared to controls in the ND and D tasks, but not across tasks. This reduction is unexpected but may reflect the amplitude reductions seen in the P3-target in schizophrenics. For the Slow Wave associated with the P3-novel there was an increase amplitude when going from a D to P paradigm in the control group only.

It is difficult to interpret these results in light of the understood meaning of Slow Wave supposedly reflecting additional, post-P300, processing (Fabiani et al, 1987). This is only partially confirmed from the result showing an increased Slow Wave in the D compared to P paradigm in the control group. The lack of a positive result in the patient groups suggests that either these groups have a reduction in available "post-P300" processing resources or that these resources are functioning at their limit in the less demanding task, hence increasing task difficulty has no effect.

The role of the Slow Wave in reflecting additional processing was therefore found to be somewhat disappointing.

The clinical utility of the Passive paradigm

In the limited number of subjects studied it appears that there may be some clinical value in the Passive paradigm. Compared to controls, there was a significant latency delay and amplitude reduction of P3-novel in the schizophrenic group while there was a significant delay in the P3-novel latency only in the bipolars. It is difficult to interpret these finding as there are no equivalent published studies. Also, because this paradigm was always presented to subjects last it is possible that the schizophrenic subjects habituate more quickly than controls or bipolars, thus the reduction in P3-novel amplitude. The meaning of a delayed P3-novel latency is more difficult to interpret. If P3-novel reflects processes leading up to the orienting response it seems that groups who demonstrate a delay in P3-target latency might also be expected to demonstrate a delay in P3-novel latency, if these processes are in some way associated as suggested by the correlation analysis.

A tentative conclusion must be that this paradigm may prove to be

particularly valuable when dealing with non-compliant schizophrenic patients and should be further investigated.

Correlations

The correlation analysis between P3-novel and P3-target amplitude showed an association in all groups although it was not so well defined in the patient groups. This result supports the hypothesis that the resources allocated to generate these two potentials are in some way associated. The lack of an identifiable relationship between P3-novel and P3-target latency in the control group but not in the patient group is counter-intuitive, given the demonstrated association between amplitudes. It therefore seems reasonable to hypothesise that the processing options, possibly a combination of serial and parallel processes, are more limited in the patient groups. These options may be limited due to other concurrent processing demands in the patients. Schizophrenic subjects may already have resources engaged with other "inner" tasks. Also, it has been shown that unipolar depressed subjects have a higher expectancy for particular type of stimuli (Blackburn et al., 1990), again suggesting that resources are engaged in processing.

There was no significant correlation between reaction time and P3-target latency in any group. This probably reflects the fact that subjects were instructed to respond to the target tones with speed rather than accuracy as it has been shown that P300 latency becomes un-correlated with reaction time in a speed versus accuracy paradigm (Kutas et al., 1977, Pfefferbaum et al., 1983). The number of incorrectly identified targets was not significantly different across groups in any experiment, but one weakness of this study was that the number of novel distracters incorrectly identified as targets by the subjects was not logged. This would be a useful index of how intrusive the distracters were on the auditory oddball.

8.2.7 Summary and conclusions

Comment on the meaning of P3-novel and P3-target measures

What do these measures of P3-target and P3-novel tell us? It seems reasonable to assume that the neural processes associated with the two events are similar, although they may be at least partially independent. Näätänen (1990) postulates that "P3a" reflects an attentional switch resulting from a mismatch of a stimulus against the passively formed neuronal trace of the frequent stimulus while "P3b" is thought to result from a match between the presented stimulus and a voluntarily maintained attentional trace of the target stimulus. An initial categorisation decision is thus implied - to orient or process? It is possible that subsequent "post-decision" processing is similar, leading to the appearance of either the P3-target and P3-novel responses, or perhaps a combination of both. The amplitude of these potentials appears to reflect the amount of processing resources available. The latency probably reflects stimulus evaluation time for P3-target and orienting time for P3-novel. Processing resource allocation to task-relevant and task-irrelevant stimuli may be reflected in amplitude changes to target and novel stimuli in ND, D, and P conditions.

The amount of resources allocated to process a stimulus must be a function of both the total resources available and the degree to which these resources are already engaged in processing other tasks. It is possible that schizophrenic subjects have an abnormally high demand for processing resources relating to internal auditory or visual hallucinations (Roth et al., 1980a). Bipolar subjects may also have similar internal demands to deal with, relating to their clinical state, which reduces the amount of processing resources they have available to deal with external stimuli.

Conclusions

In summary, tasks involving novel stimuli in addition to the standard oddball paradigm allow separate measurements of the P3-novel and P3-target sub-components of P300 and help identify differences between controls and subjects with schizophrenia and bipolar depressive illness. The schizophrenic subjects compared with controls showed changes of latency and amplitude in both P3-novel and P3-target in all the experimental paradigms while the bipolar subjects showed changes of latency in P3-novel and P3-target. If increased latency and reduced amplitude of event-related potentials are taken to reflect underlying brain structural abnormalities in the psychoses, the results would suggest more widespread disruption in schizophrenia than in bipolar depressive illness.

Chapter 9.

Summary, conclusions, and further work

9.1 Summary and conclusions

The objectives outlined in chapter 1 of this thesis have been achieved and the main findings are now summarised.

A review of exogenous and endogenous P300 components was carried out in chapter 3 and the effect of high-pass analogue filters on the P300 waveform in a clinical situation was studied in chapter 4. The results revealed the as yet unreported behaviour of a bifurcated P300 waveform when subjected to incremental high-pass filtering. The behaviour of the waveform was successfully modelled on an accepted additive evoked potential model. The behaviour of the complex appeared to be different in the two patient groups studied, schizophrenics and parkinsonian patients. Two different two-frequency models were proposed. About the time the results of this research were published (Ebmeier et al., 1992) a report appeared in another journal of a similar, but more limited, study on the effect of two different high-pass filter settings on P300 data from patients who were HIV positive (Goodin et al., 1992). These authors presented findings showing the suitability of a higher high-pass filter cut-off than currently recommended for clinical studies, which we consider to be further support for our findings (Glabus et al., 1994). There was no comment on the effect of the high-pass filter on a bifurcated P300 complex other than to say that a 1 Hz high-pass filter does not cause the appearance of a bifurcated P3 complex, as has been previously claimed.

In chapter 5 the noise reduction methods currently used in evoked potential studies were reviewed. The methods for defining ERP features were also reviewed and a new method, based on a least-mean-squares (LMS)

approximation to data, was developed. A third-degree polynomial solution was found to be most effective at defining a peak in synthesised P300 data and on examples of data from control and schizophrenic subjects manifesting the bifurcated P300 peak phenomenon.

Chapter 6 reviewed the technique of latency corrected averaging in detail. A study was carried out on a data set comprising a synthesised P300 buried in EEG noise, using a modified version of the Woody adaptive filter (Woody, 1967). The optimum pre-filter setting was established along with the most suitable template and the best method of template matching. An important observation was made on the most suitable type of template to use in clinical studies. It appears that a template derived from the stimulus synchronised average (SSA) is better than the 2.5 Hz half-sine waveform most widely used. The justification for this study was based partly on the lack of published research to address these and other fundamental issues. Since this work was completed there have been two published studies on latency corrected averaging methodology. The first study addressed the questions of using either cross-correlation or covariance for template matching and the optimum low-pass filter setting (Smulders et al., 1994). The findings showed that the most suitable template matching technique is based on covariance and this is in agreement with the findings in this thesis. The optimum low-pass filter setting determined was higher, at 3.4 Hz, than that determined in this thesis, at 2 Hz. This study was conducted on data acquired from 13 control subjects. It is difficult to validate a technique unless there is high confidence that the observed result meets the expected result. In an experiment designed to assess the effectiveness of a filter at recovering a signal buried in noise, this can only usually be achieved using synthesised data, where the experimenter has control over the timing and appearance of both signal and noise components. The results of this study should therefore be treated with care as the filter performance was not first assessed on synthesised data. Ideally, a technique should be evaluated and characterised

on synthesised data then applied to real data, using the results from the simulation for guidance. The second study used both synthesised data and data from control subjects (Puce et al., 1994). The Woody filter and a non-correlation based maximum likelihood technique (MLT) were used. The results of the study showed that the MLT was best at tracking time-varying signals. Both the SSA and half-sine templates were used but no comment was made on the relative merits of one or the other. At low signal-to-noise ratio (0.25) there was no major difference between the two methods.

In chapter 7 a detailed study was conducted on P300 measurement methodology with the specific aim of determining which factors affect the utility of P300 in clinical studies. Controls and schizophrenic patients formed the study groups. The value of the LMS technique was established. The effect of high-pass filtering the complex was assessed and it was revealed that group differences are preserved even at a high-pass filter setting of 2 Hz. The model for P300 which was proposed in chapter 4 was investigated further in the frequency domain. Evidence was found which appeared to support the validity of the model, particularly at the Pz electrode site. Both P300 amplitude and latency differences were seen in the schizophrenic group and these findings offer further support for the utility of P300 in clinical studies of the psychoses.

Chapter 8 reviewed the modalities used to elicit evoked and emitted P300 sub-components and the role of Slow Wave was reviewed. A clinical study was conducted on 29 schizophrenics, 28 subjects with bipolar depression and 28 controls. Three experimental paradigms were used which were designed to allow the study of separate P300 sub-components and the Slow Wave. The utility of the LMS technique was further established. Differences were found in the P3-target and P3-novel in both diagnostic groups. The schizophrenics showed delayed latency and reduced amplitude for both sub-components while the bipolar group showed delayed latency in both sub-

components. A passive paradigm designed to evoke a P3-novel response only appeared to show reduced amplitude and delayed latency in the schizophrenic group and a delayed latency in the bipolar group.

In summary, analysis of the P300 waveform and its sub-components using a combination of task-relevant and passive paradigms with novel auditory stimuli offers great promise in the investigation of the psychoses. A particularly useful technique has been established to objectively measure P300 latency. The investigation of the latency corrected averaging technique produced findings which should improve the accuracy of the technique.

The prospect of P300 satisfying the requirements for a biological marker for the psychoses is further enhanced by this work.

9.2 Further work

The findings in chapter 6 on the latency corrected averaging technique were based on a synthesised data set. A study is required on real ERP data derived from control subjects, initially. Once the findings are established then ERP data acquired from patients can be studied. Further work on a larger group of patients is also required to replicate the findings from the Passive paradigm. An accurate recording of the number of novel stimuli, falsely identified as targets will give a better insight into how "distractable" patients are with these sounds.

As a post-script to this thesis, the no-distraction oddball (ND) and distraction oddball (D) paradigms were used in a study of control subjects who also underwent investigation using single-photon emission topography and ^{99m}Tc-Exametazime. A brief summary is now given.

Twenty control subjects were studied at rest and 10 were studied on two occasions, once during the ND task and once during the D task. The aim of

the study was to investigate the differential effects of target detection and the orienting of attention to novel stimuli during target detection. Subjects were scanned with a high resolution single slice multi-detector head scanner (Neuro 900, Strichman Medical Equipment Inc., Boston, USA). Subjects had their eyes closed during administration of the radioactive tracer, which was injected as they listened to the auditory stimuli through headphones. The tracer is almost fully bound within 1 minute of injection.

Images were analysed on a pixel-by-pixel basis using the Statistical Parametric Mapping (SPM) technique developed by Professor Karl Friston at the MRC Cyclotron Unit at the Hammersmith Hospital, London (Friston et al., 1989; Friston et al., 1990; Friston, 1994). This technique spatially normalises the images and elastically transforms them so that they are all orientated in the same 3-dimensional space, aligned along the intercommisural line. Differences in global brain activity are removed after analysis of covariance. The difference between the resting and ND condition and the difference between the ND and D conditions are then calculated using the t-statistic, on a pixel-by-pixel basis. Figure 9.1 shows the SPM{t} map of statistically significant increases in regional cerebral perfusion in the ND condition compared to rest. Figure 9.2 shows the SPM{t} map of statistically significant increases in regional cerebral perfusion in the D condition compared to the ND condition.

During the ND task there was a bilateral posterior (occipito-) temporal and medial frontal activation, a left pericentral increase, and posterior cingulate suppression. During the D condition activation was again found in posterior (occipito-) temporal, medial frontal cortex, left pericentral, with small non-significant reduction in posterior cingulate uptake. This work has been submitted for publication (Ebmeier et al., submitted).

The combination of high spatial resolution imaging techniques, such as

SPET, in parallel with high temporal resolution techniques such as ERPs offers great potential for understanding the underlying neural mechanisms associated with cognitive processing in normal and abnormal subjects.

FIGURE 9.1

SPM {t} maps showing increase in rCBF in the NO-DISTRACTION task compared to REST.

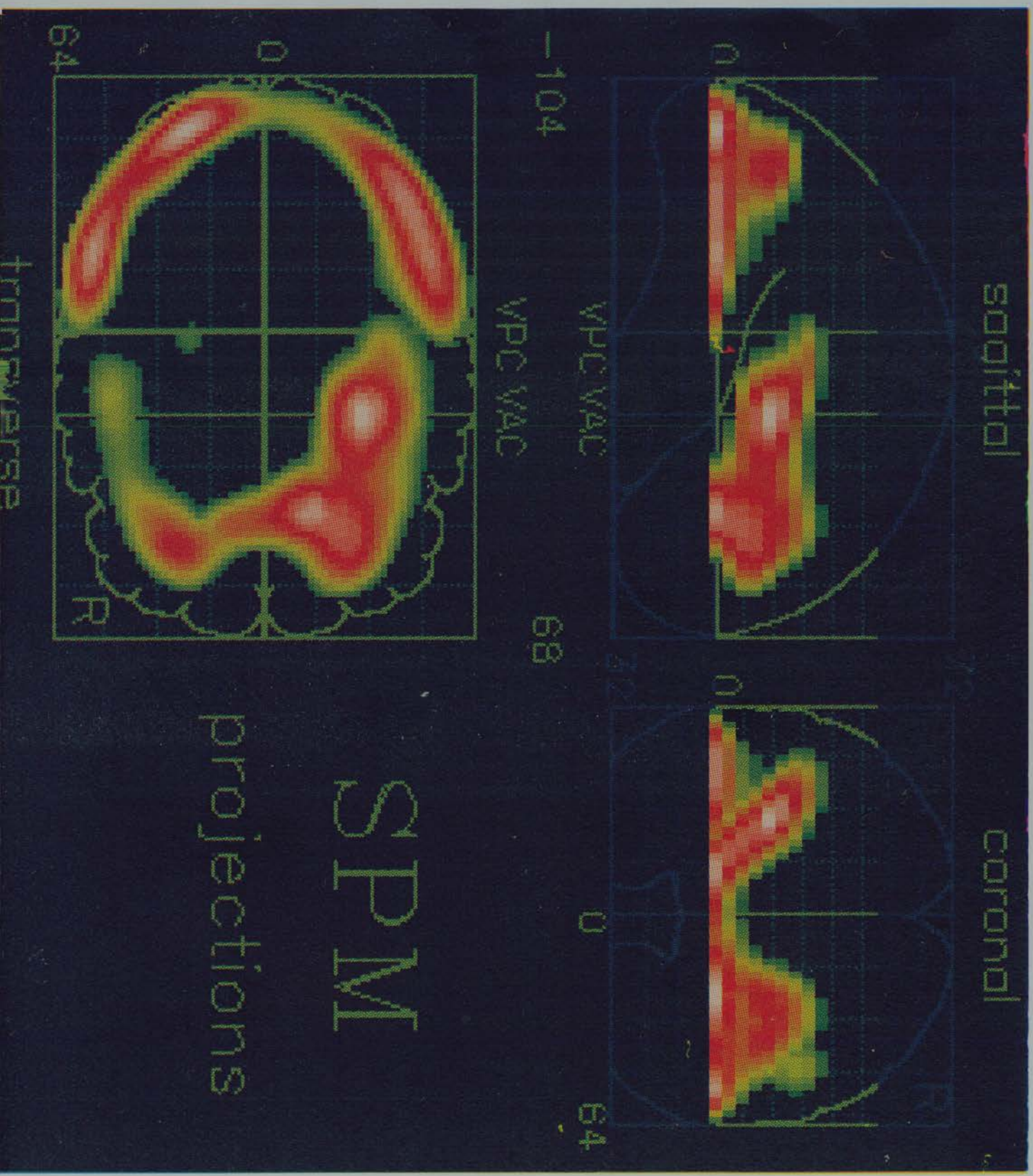
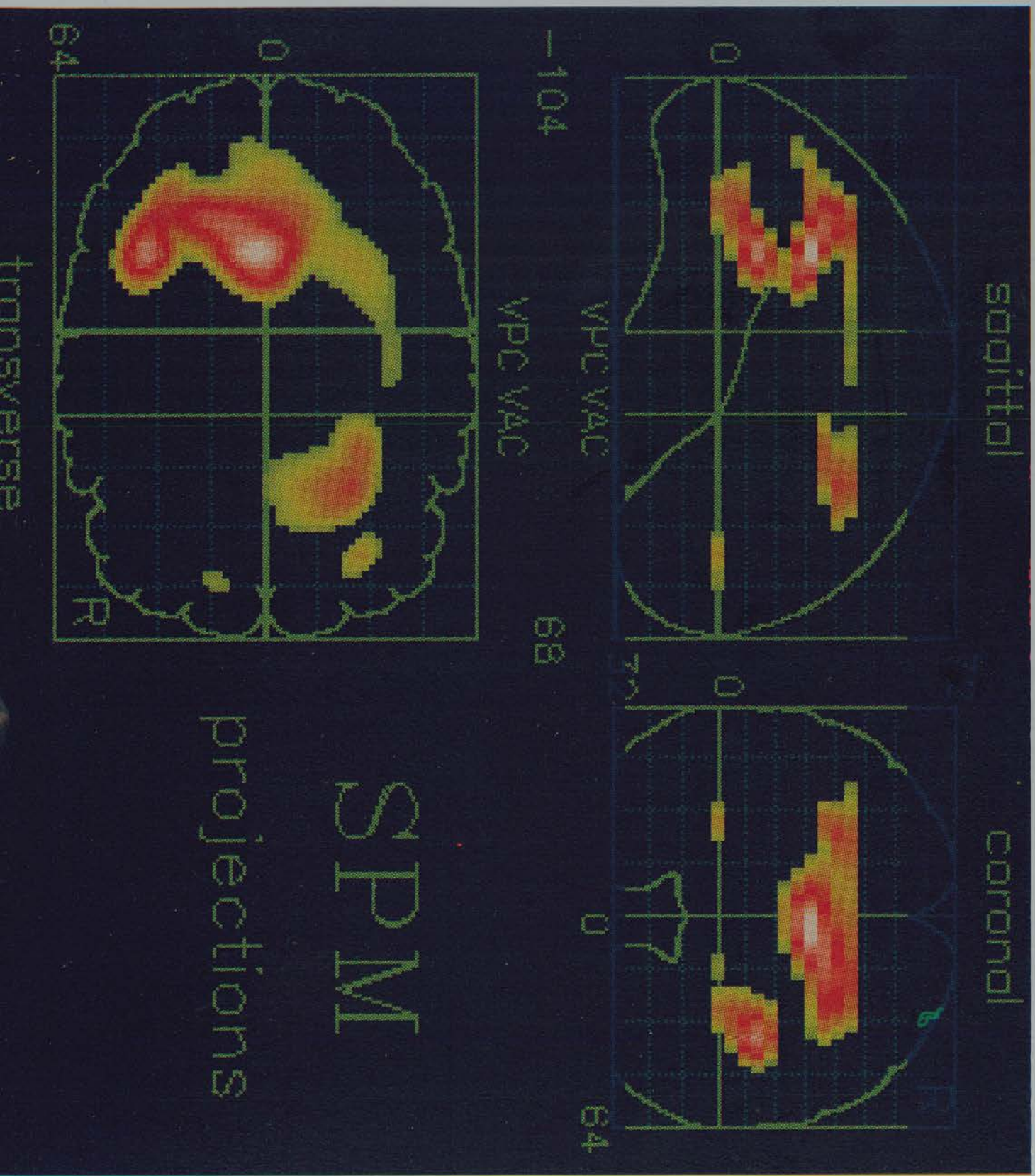


FIGURE 9.2

SPM {t} maps showing increase in rCBF in the DISTRACTION task compared to the NO-DISTRACTION task.



Appendix 1

A.1 Sampled signals:time and frequency domain representations

Scalp potentials are normally amplified and digitised prior to storage for processing. Here, the basic ideas behind sampling are given and these principles are used throughout this thesis when referring to digitally sampled data. The following summary is derived from published work on time domain sampling, spectral analysis, spectral analysis applied to the EEG, and the use of windows within the DFT (Grant et al., 1989; Jervis et al., 1989; Harris, 1978).

A.1.1 Digital sampling

The "real world" is analogue where physical quantities such as air temperature or the sunlight incident on a photomultiplier vary continuously in the time domain. Analogue variables, whatever their origin, are most frequently converted by transducers into electrical currents or voltages which also vary continuously in the time domain. Analogue signals are most commonly digitised using an analogue-to-digital-converter (ADC), which gives a discrete time domain representation of a continuous signal. Analysis and processing of these signals has become routine with the development of the digital computer.

The mathematical process of digitising a continuous function is based on the Dirac delta impulse function, $\delta[n]$, which has the value of unity at n=1 and 0 everywhere else. The process of converting a continuous function, x(t), into a discretely sampled version, x[n] involves multiplying that function by a train of shifted unit impulse functions, spaced at the sampling period. The resultant digitised function, x[n], is a weighted sum of unit impulse functions.

So x[n] is given by

$$x[n] = \sum_{k=-\infty}^{\infty} x[k]\ \delta[n-k] \qquad \text{A.1}$$

k is an integer on all values between $\pm\infty$ so x[n] is a completely general digital signal.

A.1.2 Continuous and discrete frequency domain representation of signals

The generalised, continuous cisoidal signal x(t) can be described using the relationship $x(t) = A\, e^{st}$, where $s = \sigma + j\omega$, the complex frequency, σ represents signal growth or decay, and ω is the continuous angular frequency. It is possible therefore to describe all transient signals in this manner.

The phasor representation of signals is derived from the function $e^{j\theta}$ which describes a unit amplitude vector at angle θ, in polar coordinates. When $\theta=\omega t$, the vector rotates at ω radians per second. The complex conjugate of $e^{j\omega t}$ is $e^{-j\omega t}$, an identical phasor rotating in the opposite direction. Real sinusoidal signals can be considered as the vector sum of two complex conjugate phasors and the real and imaginary parts are given by

$$\cos(\omega t) = \frac{1}{2}(e^{j\theta} + e^{-j\theta})$$

and

$$j\sin(\omega t) = \frac{1}{2}(e^{j\omega t} - e^{-j\omega t})$$

A.1.2.1 The Fourier series

A simple periodic time domain waveform f(t) can be expanded in terms of a complex Fourier series using phasors

$$f(t) = \sum_{n=-\infty}^{\infty} F(n)\ e^{jn\omega_o t}$$

where F(n) is given by

$$F(n) = \frac{1}{T}\int_{-\frac{T}{2}}^{\frac{T}{2}} f(t)\ e^{-jn\omega_o t}\ dt$$

where T is the period of the signal and ω_o is the fundamental frequency. The periodic signal contains frequency components which are integer multiples (harmonics) of the fundamental frequency only.

A.1.2.2 The Fourier transform

The Fourier transform is a development of the Fourier series where the period T increases and the spectral lines become closer until the spectrum eventually becomes continuous. When this occurs the forward Fourier transform, F(ω) is given by

$$F(\omega) = \int_{-\infty}^{\infty} f(t)\ e^{-j\omega t}\ dt \qquad \text{A.2}$$

The inverse process which takes us back into the time domain, the inverse

Fourier transform is given by

$$f(t) = F^{-1}(F(\omega)) = \frac{1}{2\pi}\int_{-\infty}^{\infty} F(\omega)\ e^{j\omega t}\ d\omega \qquad \text{A.3}$$

Equation A.2 holds for any deterministic waveform and is not limited by the need for the waveform to be periodic. For a periodic waveform the Fourier transform pair in equations A.2 and A.3 become: for the forward Fourier transform

$$F(k\omega_o) = \int_{-\infty}^{\infty} f(t)\ e^{-jk\omega_o t}\ dt\ . \qquad \text{A.4}$$

and the inverse Fourier transform

$$f(t) = \sum_{k=-\infty}^{\infty} F(k\omega_o)\ e^{jk\omega_o t} \qquad \text{A.5}$$

A.1.2.3 The discrete Fourier transform

The discrete Fourier transform is now defined for a periodic signal as the fundamental component at ω_o and higher order harmonics of ω_o. A valid discrete transform can be obtained for a periodic waveform by reducing the span of the integration in A.4 to any integer multiple of the fundamental period, from $-T_o/2$ to $+T_o/2$.

For a function f(t) discretely sampled at a period T the corresponding sampled function is f(nT). From A.1 above, the time-shifted Dirac delta function is denoted $\delta(t-nT)$ which, when multiplied by the sampled function replaces f(t) in A.4 by $f(t)\delta(t-nT)$, and the Fourier transform in A.4 becomes

$$F(k\omega_o) = \sum_{-\frac{T_o}{2}}^{\frac{T_o}{2}} f(nT)\ e^{-jnk\omega_o T}$$

where f(nT) = f(t)δ(t-nT). So for an N sample waveform sampled over a fundamental period of f(t), the N-point discrete Fourier transform (DFT) becomes

$$F(k) = \sum_{n=0}^{N-1} f(n)\ e^{-j\frac{2\pi nk}{N}}$$

The fast Fourier transform (FFT) is an algorithm that invokes the DFT in the most efficient computational sense (Cooley and Tukey 1965).

A.1.2.4 Windowing and spectral leakage

The FFT of a set of sampled data is not the true FFT of the process from which the data were obtained because the (signal) process is continuous whereas the data representation is truncated. Data in the total sampled window, T, is obtained by multiplying all the sampled values in the interval by unity while values outside the window are multiplied by zero.
This is equivalent to multiplying, or windowing, the signal by a rectangular window of width T and amplitude 1.

The case for a sampled data set, f(i), is given by the product of the data values s(i) with the window function w(i) so that f(i) = w(i)s(i).

This time domain product is the equivalent of convolution in the frequency domain, so that the FFT value for the *nth* harmonic is given by

$$F(\omega_n) = \sum_{k=-N}^{k=N} W(\omega_n - \omega_k)\ S(\omega_k)$$

where ω_n is the angular frequency of the *nth* harmonic; $F(\omega_n)$ is the complex DFT component at frequency ω_n; $W(\omega_n)$ is the amplitude spectrum of the window at frequency ω_n; $S(\omega_k)$ is the true amplitude spectrum of the signal at frequency ω_k.

So the expression for $F(\omega_n)$ above represents the true spectrum of the signal convolved with the spectrum of the window. The amplitude spectrum of the rectangular window $S_R(\omega_n)$ is given as

$$S_r(\omega_n) = \frac{T \sin\left(\frac{\omega_n T}{2}\right)}{\frac{\omega_n T}{2}} = S_a\left(\frac{\omega_n T}{2}\right)$$

$S_a(\omega_n T/2)$ is known as the sampling function of $\omega_n T/2$. It has the characteristic envelope of a sinc function (Figure A1). The sampling function will therefore have a main lobe and an infinite number of sidelobes.

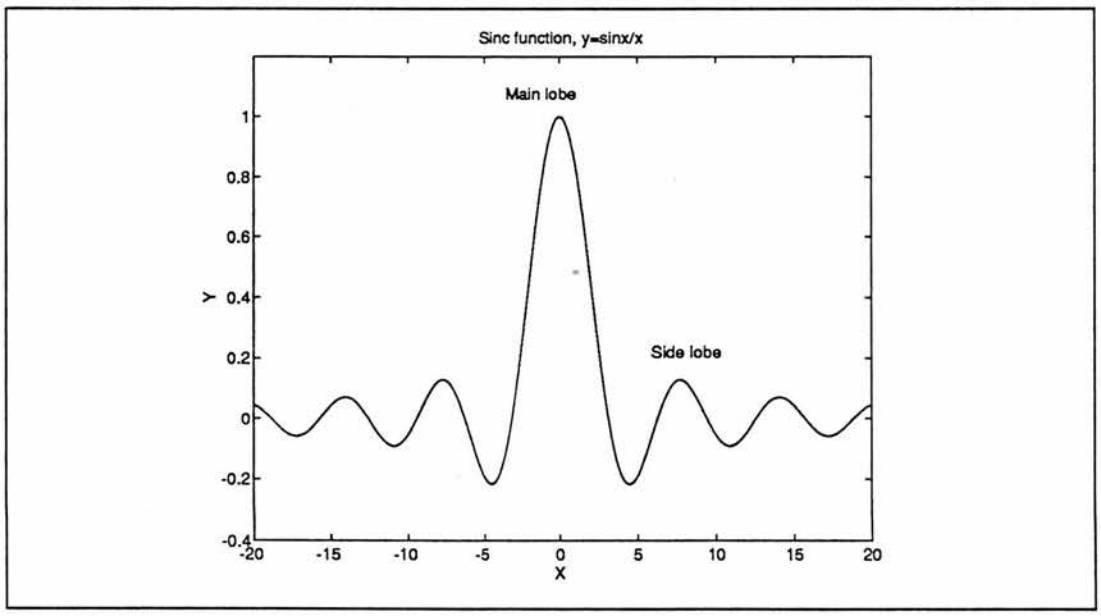


Figure A.1 Sinc function

For a single frequency the spectrum will be two impulses, corresponding to the "positive" and "negative" values of the frequency. Convolving these impulses with the spectrum of the rectangular window, above, will smear the single frequency across a number of neighbouring FFT-bins and introduce spurious peaks due to the sidelobes. This will be true for every spectral component for a multi-frequency signal. This is known as spectral leakage

The effect of this can be reduced by tapering the edges of the data window. There are at least 23 different windows, each with their own merits. In general, there is a trade-off in reducing the effect of the sidelobes against the thickening of the main lobe. One of the simplest and most commonly used, windows is the Hanning window, used throughout this thesis. This window comes from a family of "cosine windows" and for the DFT is described by

$$W(n) = \sin^{\alpha}\left[\frac{n}{N}\pi\right], \quad n = 0,1,2,\ldots,N-1$$

The Hanning window is identified with α equal to 1 or 2.

A.2 The Butterworth filter characteristics

The output of the filter may be defined as $V_o = |H(\Omega)| V_{in}$ where V_{in} is the input and $|H(\Omega)|$ is the filter transfer function.

The complex transfer function for a 1-pole Butterworth filter is given as:

$$|H(\Omega)| = \frac{j\Omega\tau}{1+j\Omega\tau} \quad \text{(A2.1)}$$

where τ, the time constant of the filter is defined as

$$\tau = \frac{1}{2\pi f_c}$$ with f_c the filter cut-off frequency, and $\Omega=2\pi f$.

Expanding equation A2.1 gives:

$$|H(\Omega)| = \frac{1}{1 + (\Omega\tau)^2} [\ (\Omega\tau)^2 + j\Omega\tau]$$

The magnitude of the filter output is the vector sum of the real and imaginary terms inside the brackets multiplied by the real part outside the bracket. The phase relationship of the filter output with respect to the input is derived from the angle between the vector sum and the real axis.

$$\frac{\Omega\tau}{[1 + (\Omega\tau)^2]^{1/2}} \quad \angle\ \theta$$

(magnitude) (phase)

The phase angle between the vector sum and the real axis can be defined as $\Theta = 90 - \tan^{-1}(\Omega\tau)$. For a high-pass filter this angle is positive and the filter

output leads the input by angle Θ.

The phase angle may now be calculated as a function of frequency for any selected cut-off frequency,

$$\theta = 90 - \tan^{-1} [\frac{f}{f_c}]$$

For a frequency, f, the equivalent shift in the time-domain may be defined as,

$$\Delta t = [\frac{\theta}{360}] \frac{1}{f}$$

A.3 The statistical basis of averaging

Adapted from Aunon et al., 1981.

For a measured waveform f(t) comprising two components, s(t), the signal and, n(t), the noise, it is assumed that these components add in a linear fashion such that $f(t) = s(t) + n(t)$.

Conventional averaging involves adding successive epochs comprising continuous signal with additive noise then taking the mathematical average of the sum. A continuous analogue signal, such as the EP, is evoked among background noise (the EEG) by a stimulus, at certain times. The digitized, transient signal can be expressed as

$$f_i(t) = \sum_{m=1}^{M} f_i(t_m)[\delta(t-t_m-t_d)] \qquad \textbf{(A3.1)}$$

$f_i(t)$ is the sampled waveform following presentation of the *ith* stimulus; $\delta(t)$ is the unit impulse sampling function (see A.1); t_m is the sampling time; $f_i(t_m)$ is the value of the continuous waveform at the sampling time; t_d is the sampling duration and can usually be ignored and M is the number of samples per stimulus presentation.

The averaging process is represented by the summation of N waveforms of the type given in A3.1

$$f(t) = \frac{1}{N} \sum_{i=1}^{N} \sum_{m=1}^{M} f_i(t_m) \ [\delta(t-t_m)]$$

At a time t_m the average value becomes

$$f(t_m) = \frac{1}{N} \sum_{i=1}^{N} f_i(t_m)$$

The assumption that the monitored signal f(t) is composed of a signal s(t) and noise term n(t) can be expressed

$$f(t_m) = \frac{1}{N} \sum_{i=1}^{N} [s_i(t_m)+n_i(t_m)] = \frac{1}{N} \sum_{i=1}^{N} s_i(t_m) + \frac{1}{N} \sum_{i=1}^{N} n_i(t_m) \quad \text{(A3.2)}$$

and $f(t_m) = s(t_m) + n(t_m)$, so the average waveform is nothing more than the average signal plus the average noise. The assumption is that the signal is deterministic so that $s(t_m) = s_i(t_m)$ for all i.

From A3.2, the SNR will improve significantly if the noise term is not time locked to the signal. This is usually a valid assumption and the signal may be extracted from the noise by increasing N, the number of stimulus repetitions. The performance of the summation technique can be assessed by looking at the power SNR. The average power in any time locked signal, s(t), is given by

$$P_s = \frac{1}{m} \sum_{j=1}^{m} s^2(t_j)$$

and the average power of the sum of N such potentials is given by

$$\bar{P}_s = \frac{1}{m} \sum_{j=1}^{m} [\sum_{i=1}^{N} s_i(t_j)]^2 = \frac{1}{m} \sum_{j=1}^{m} [N^2 s^2(t_j)]$$

Simplifying

$$\bar{P}_s = N^2 \frac{1}{m} \sum_{j=1}^{m} s^2(t_j) = N^2 P_s$$

The following assumptions are made for the noise:
i) the expected value is zero; ii) the noise is uncorrelated across epochs; iii) the average noise power is the same in each epoch.

With these assumptions the average noise power contribution in the sum of N potentials is given by

$$\bar{P}_n = \frac{1}{m} \sum_{j=1}^{m} [\sum_{i=1}^{N} n_i(t_j)]^2 = \frac{1}{m} \sum_{j=1}^{m} [\sum_{i=1}^{N} [n(t_j)]^2]$$

which can be simplified to

$$\bar{P}_n = \sum_{i=1}^{N} \frac{1}{m} \sum_{j=1}^{m} [n(t_j)]^2 = N P_n$$

Therefore the addition of N single evoked potentials will cause the signal power to increase by a factor of N^2 while the noise power will increase by N.

The standard deviation of the average, σ_{AV}, can also be calculated. First the expected value of an estimator $E[\hat{s}(t)]$ of the signal s(t) is given

$$E[\hat{s}(t)] = E[\frac{1}{N} \sum_{i=1}^{N} f_i(t)] = E[\frac{1}{N} \sum_{i=1}^{N} s_i(t)] + \frac{1}{N} \sum_{i=1}^{N} E[n_i(t)]$$

Since $s_i(t) = s(t)$ for all i (the assumption of signal invariance) and $E[n_i(t)] =$

0 for all i then $E[\hat{s}(t)] = s(t)$. The variance, σ^2_{AV}, can now be computed as

$$\sigma^2_{AV} = E[\hat{s}(t)-s(t)]^2 = E[\ \frac{1}{N}\sum_{i=1}^{N} n_i(t)\ ]^2$$

$$= \frac{1}{N^2}\sum_{i=1}^{N}\sum_{j=1}^{N} E[n_i(t)n_j(t)] = \frac{1}{N^2}\sum_{i=1}^{N} E[n_i^2(t)]$$

This expression holds as long as $E[n_i(t)\ n_j(t)] = 0$ for all $i \neq j$, the case for uncorrelated noise. Therefore

$$\sigma^2_{AV} = \frac{1}{N^2}\ N\ \sigma^2$$

where $\sigma^2 = E[n_i^2(t)]$ and

$$\sigma_{AV} = \frac{\sigma}{\sqrt{N}}$$

Thus averaging decreases the noise in a manner directly proportional to the standard deviation of the noise and in a manner inversely proportional to the square root of the number of replications.

APPENDIX 2

TURBO PASCAL PROGRAM LISTINGS AND CIRCUIT DIAGRAMS

A2.1 PROGRAM "P3SIM.PAS"

```
{$A+,B-,D+,E+,F-,I+,L+,N+,O-,R-,S+,V+}
{$M 16384,0,655360}
Program P3sim;
(* Add 2.5 Hz half sine signal to "noise" of
   i) varying sine-frequencies  with  'random' phase
   ii) EEG noise, generated from coloured Gaussian
   then construct a simulated "P3 file" with 40 responses *)
(************************  MFG  20/2/89..8/93..4/94 ************************)

uses
Dos, general, graph, common, crt;

const
ratios:array[1..5] of real = (4,2,1,0.5,0.25);

type
channel                                 =1..10;
cur_num                                 =1..8;

var
store_block                     : array[1..3000] of longint;
noise_buffer                    : array[1..1500] of integer;
signal_buffer                   : array[1..250] of integer;
ioerr                   : boolean;
dummy                    : char;
file_name                : string;
disk_file,raw_file,av_file      : file;

f_head : record
                pt_name                 : string[20];
                t_type          : string[10];
                year,month,
                day,dow                 : word;
                channels        : byte;
                rate            : real;

                samples,
                fs_eeg,
                fs_eog,
                eog_gain,
                n_tgt1,
                n_tgt2,
                n_nontgt,
                n_rej           : integer;
```

```
                eeg_gain        : longint;

            proc_flg        : boolean;

            tgt1_mag,
            tgt2_mag,
            ntgt_mag        : array[channel,cur_num] of single;

            tgt1_ltncy,
            tgt2_ltncy,
            ntgt_ltncy      : array[channel,cur_num] of single;

            r_times                 : array[0..99] of single;

            comments        : string[200];
        end;{record}
(*****************************************************************************)
procedure io_err(var f_name:file);  {report runtime disk errs}

begin
    case ioresult of
        103:begin
                sound(1000);delay(200);nosound;
                   outtextxy(0,200,
                'Must enter a filename !! - enter then try again ');
                ioerr:=true;
                repeat until keypressed;dummy:=readkey;
                readln(file_name);
            end;
        101:begin
                sound(1000);delay(200);nosound;
                   outtextxy(0,200,
                'DISK FULL !! - Load new disk and ENTER');
                ioerr:=true;close(f_name);erase(f_name);
                repeat until keypressed;dummy:=readkey;
             end;
        105:begin
                sound(1000);delay(200);nosound;
                   outtextxy(0,200,
                'CANT OPEN FILE - ENTER and try again');
                ioerr:=true;repeat;until keypressed;dummy:=readkey;
            end;
        150:begin
                sound(1000);delay(200);nosound;
                   outtextxy(0,200,
                'DISK WRITE-PROTECTED - Correct then ENTER');
                ioerr:=true;repeat;until keypressed;dummy:=readkey;
          end;
    end;{caseof}
end;
(*****************************************************************************)
```

```
procedure Draw_xax(x_1st,y_1st,n_xax,x_stp,x_tic:integer);
{start position(x,y), no of steps, size of steps, width of xtics}
        var
        x_step_count, x_inc,x_pos, y_pos : integer;
begin
        x_inc:=x_stp;
        moveto(x_1st,y_1st+x_tic);lineto(x_1st,y_1st-x_tic);  {draw 1st xtic}
        moveto(x_1st,y_1st);
                FOR x_step_count:=1 TO n_xax do       {draw x-axis}
                begin
                        x_pos:=x_1st+x_inc;y_pos:=y_1st-x_tic;
                  lineto(x_pos,y_1st);moveto(x_pos,y_pos);
                  lineto(x_pos,y_pos+(2*x_tic));moveto(x_pos,y_1st);
                  x_inc:=x_inc+x_stp;
                END; {for}
end;
(*************************************************************************)
procedure set_graphics(dvr,mde:integer);
begin
    Initgraph(dvr,mde,'d:\tp7\bgi');
end;
(*************************************************************************)
procedure create_dummy_file_head(name:string;sweeps:integer);
begin
  with f_head do begin
    n_tgt1:=sweeps;
    n_nontgt:=sweeps;
    eeg_gain:=10000;
    eog_gain:=10000;
    samples:=1500;
    fs_eeg:=1;
    fs_eog:=1;
    channels:=6;
  end;
  {create dummy file on disk}
  {$I-}
  repeat
        ioerr:=false;
        assign(disk_file,'a:\'+name+'.fhd');
        rewrite(disk_file,1);
        io_err(disk_file);
        blockwrite(disk_file,f_head,sizeof(f_head));
  until not ioerr;
  {$I+}
end;
(*************************************************************************)
procedure zero_store_block;
begin
    Fillchar(store_block,sizeof(store_block),0);

end;
```

```
(*************************************************************************)
procedure generate_signal(var sig_var:longint);
var mean,sum,x_stp,y_stp,count:integer;
scale,rad_f:real;
diff:longint;
begin
   rad_f:=2*pi*2.5;  {2.5 Hz '1/2 sine' signal, peak at 300 ms}
   for count:=1 to 250 do
      signal_buffer[count]:=0;
   sum:=0;
   for count:=100 to 150 do begin
      signal_buffer[count+12]:=round(1000*(sin(rad_f*(count/250))));
      sum:=sum+signal_buffer[count+12];
   end;
  {get signal variance}
  mean:=sum div 51;sig_var:=0;
  for count:=113 to 161 do begin
    diff:=signal_buffer[count]-mean;
    sig_var:=sig_var+sqr(diff);
  end;
  sig_var:=sig_var div 49;

{view synthesised signal}
   setcolor(yellow);
   draw_xax(20,175,10,50,5);
   setcolor(white);
   scale:=1;
   for count:=1 to 250 do begin
     x_stp:=21+2*count;
     y_stp:=175-round(signal_buffer[count]*scale);
     if count=1 then moveto(x_stp,y_stp);
     lineto(x_stp,y_stp);
   end;delay(200);
  repeat until readkey='z';
end;
(*************************************************************************)
procedure generate_sine_noise(sig_var:longint;freq,sweep:integer);
{'phase shift' sim. noise at 1 sample/sweep by adding sweep no to ct}

var
rad_f,sc_rat:real;
mean,s_n,count:integer;
diff,sum,noise_var:longint;
begin
  rad_f:=2*pi*freq;
  for s_n:=1 to 5 do begin
     {generate sine noise}
     sum:=0;mean:=0;
     for count:=1 to 250 do begin
       noise_buffer[count+((s_n-1)*250)]:=
       round(1000*sin(rad_f*((count+sweep)/250)));
```

```
      sum:=sum+noise_buffer[count+((s_n-1)*250)];
    end;

    {remove offsets}
    mean:=sum div 250;
    for count:=1 to 250 do
    noise_buffer[count+((s_n-1)*250)]:=noise_buffer[count+((s_n-1)*250)]-mean;

    {get noise variance}
    noise_var:=0;
    for count:=1 to 250 do begin
       diff:=noise_buffer[count+((s_n-1)*250)]-mean;
       noise_var:=noise_var+sqr(diff);
    end;
    noise_var:=noise_var div 250;

    {recalculate noise level to give required snr - actual/reqd. snr}
    sc_rat:=sqrt((sig_var/noise_var)/ratios[s_n]);

    {adjust noise for required snr}
    for count:=1 to 250 do
        noise_buffer[count+((s_n-1)*250)]:=
        round(sc_rat*noise_buffer[count+((s_n-1)*250)]);

 {for testing - recalc. noise variance - first get new mean (should be 0!)}
   sum:=0;
   for count := 1 to 250 do sum:=sum+noise_buffer[count+((s_n-1)*250)];
   sum:=sum div 250;
   noise_var:=0;
   for count:=((s_n-1)*250)+1 to ((s_n-1)*250)+250 do begin
      diff:=noise_buffer[count]-sum;
      noise_var:=noise_var+sqr(diff);
   end;
   noise_var:=noise_var div 250;

 end;
end;
(*************************************************************************)
procedure generate_eeg_noise(sig_var:longint);
{Uses NAKAMURA filter coeffs to generate EEG spectrum from white-noise}
const
f_wt:array[1..21] of real = (-36, -12.7, 9, 27.9, 44, 57.7, 69, 77.8,
                             84, 87.7, 89, 87.7, 84, 77.8, 69, 57.7, 44,
                             27.9, 9, -12.7, -36);
nakam_scale:real=1.104e-3;
var x_stp,y_stp,ch_ct,prev_val,ct:integer;
tmp_buf:array[1..271] of longint;
diff,new_n_var,noise_var,sum,temp_res:longint;
sc_rat:real;
begin
 Fillchar(noise_buffer,sizeof(noise_buffer),0);
```

```
for ch_ct:=1 to 5 do begin
   randomize;
    {high range to accommodate filter}
    for ct:=1 to 271 do tmp_buf[ct]:=random(10000);

      {now filter to approx. eeg spectrum}
    prev_val:=0;
    for ct:=1 to 250 do begin
    temp_res:=round( ( (f_wt[1]*tmp_buf[ct])+(f_wt[2]*tmp_buf[ct+1])+
    (f_wt[3]*tmp_buf[ct+3])+(f_wt[4]*tmp_buf[ct+4])+(f_wt[5]*tmp_buf[ct+5])+
    (f_wt[6]*tmp_buf[ct+6])+(f_wt[7]*tmp_buf[ct+7])+(f_wt[8]*tmp_buf[ct+8])+
    (f_wt[9]*tmp_buf[ct+9])+(f_wt[10]*tmp_buf[ct+10])+(f_wt[11]*tmp_buf[ct+11])+
    (f_wt[12]*tmp_buf[ct+12])+(f_wt[13]*tmp_buf[ct+13])+(f_wt[14]*tmp_buf[ct+14])+
    (f_wt[15]*tmp_buf[ct+15])+(f_wt[16]*tmp_buf[ct+16])+(f_wt[17]*tmp_buf[ct+17])+
    (f_wt[18]*tmp_buf[ct+18])+(f_wt[19]*tmp_buf[ct+19])+(f_wt[20]*tmp_buf[ct+20])+
    (f_wt[21]*tmp_buf[ct+21])-prev_val)*nakam_scale);
    noise_buffer[ct+((ch_ct-1)*250)]:=temp_res;
    prev_val:=noise_buffer[ct+((ch_ct-1)*250)];
    end;

    {now set noise to zero mean}
    sum:=0;
    for ct := 1 to 250 do sum:=sum+noise_buffer[ct+((ch_ct-1)*250)];
    sum:=sum div 250;
    for ct:=1 to 250 do begin
       noise_buffer[ct+((ch_ct-1)*250)]:=noise_buffer[ct+((ch_ct-1)*250)]-sum;
    end;

    {get noise variance - first get new mean (should be 0!)}
    sum:=0;
    for ct := 1 to 250 do sum:=sum+noise_buffer[ct+((ch_ct-1)*250)];
    sum:=sum div 250; {mean noise value}

    noise_var:=0;
    for ct:=1 to 250 do begin
       diff:=noise_buffer[ct+((ch_ct-1)*250)]-sum;
       noise_var:=noise_var+sqr(diff);
    end;
    noise_var:=noise_var div 250;

     {recalculate noise level to give required snr - actual/reqd. snr}
    sc_rat:=sqrt((sig_var/noise_var)/ratios[ch_ct]);
    for ct:=1 to 250 do
       noise_buffer[ct+((ch_ct-1)*250)]:=
       round(sc_rat*noise_buffer[ct+((ch_ct-1)*250)]);

    {view data as it's created}
    setcolor(yellow);
    draw_xax(20,175,10,50,5);
    setcolor(ch_ct+1);
    for ct:=1 to 250 do begin
```

```
      x_stp:=21+2*ct;
      y_stp:=175-round(noise_buffer[ct+((ch_ct-1)*250)]*0.1);
      if ct=1 then moveto(x_stp,y_stp);
      lineto(x_stp,y_stp);
     end;
     delay(200);
  end;
end;
(*************************************************************************)
procedure add_signal_to_noise;
var x_stp,y_stp,count,channel:integer;
begin
    for channel:= 1 to 5 do  begin
      for count:=1 to 250 do
        noise_buffer[count+((channel-1)*250)]:=
        noise_buffer[count+((channel-1)*250)]+signal_buffer[count];

      {view data as summed}
      setcolor(yellow);
      draw_xax(20,175,10,50,5);
      setcolor(white);
      for count:=1 to 250 do begin
        x_stp:=21+2*count;
        y_stp:=175-round(noise_buffer[count+((channel-1)*250)]*0.1);
        if count=1 then moveto(x_stp,y_stp);
        lineto(x_stp,y_stp);
      end;
      delay(200);

   end;
end;
(*************************************************************************)
procedure build_average;
var count:integer;
begin
    for count:=1 to 1500 do
    store_block[count]:=store_block[count]+noise_buffer[count];
end;
(*************************************************************************)
procedure create_composite_file(f_name:string);
begin
{$I-}
    repeat
         ioerr:=false;
         assign(raw_file,'a:\'+f_name+'.trw');
         rewrite(raw_file,2);
         io_err(raw_file);
    until not ioerr;
{$I+}
end;
(*************************************************************************)
```

```
procedure create_average_file(f_name:string);
begin
{$I-}
    repeat
        ioerr:=false;
        assign(av_file,'a:\'+f_name+'.t10');
        rewrite(av_file,4);
        io_err(av_file);
    until not ioerr;
{$I+}
end;
(*****************************************************************************)
procedure save_average(var f_name:string);
begin
   create_average_file(f_name);
   blockwrite(av_file,store_block[1],1500);
   close(av_file);
end;
(*****************************************************************************)
procedure save_composite;
var
channel,count,x_stp,y_stp:integer;
begin
   blockwrite(raw_file,noise_buffer[1],1500);
  {view data as stored}
  for channel:= 1 to 5 do  begin
   setcolor(yellow);
   draw_xax(20,175,10,50,5);
   setcolor(channel+1);
   for count:=1 to 250 do begin
     x_stp:=21+2*count;
     y_stp:=175-round(noise_buffer[count+((channel-1)*250)]*0.1);
     if count=1 then moveto(x_stp,y_stp);
     lineto(x_stp,y_stp);
   end;
   delay(200);
  end;
  cleardevice;
end;
(*****************************************************************************)
procedure create_composite(var freq,sweeps:integer;n_type:char);
var swp_count:integer;
sig_var:longint;
begin
     generate_signal(sig_var);
     for swp_count:=1 to sweeps do begin
         case n_type of
         'S':generate_sine_noise(sig_var,freq,swp_count);
         'E': generate_EEG_noise(sig_var);
         end;{case}
        add_signal_to_noise;
```

```
        save_composite;
        build_average;
      end;
end;
(*************************************************************************)
procedure main;
var
sweeps,freq:integer;
ans:char;
name:string;
 begin
 cleardevice;
 repeat
   color_box(180,120,500,190,lightblue);
   outtextxy(200,130,'Do you wish to construct P3 plus');
   outtextxy(200,150,'i) Sinusoidal noise          (S)');
   outtextxy(200,170,'ii) Synthesised EEG noise    (E)');
   ans:=upcase(readkey);
 until (ans='S') or (ans='E');
 cleardevice;
 sweeps:=40;
 If ans='S' then begin {creates 6 files with f from 8-13 Hz}

    for freq:= 13 to 13 do begin
         zero_store_block;
        name:='f'+int_str(freq);
        create_dummy_file_head(name,sweeps);
          create_composite_file(name);
          create_composite(freq,sweeps,ans);
        save_average(name);
          close(raw_file);
    end;  {for}
  end else   {ans='E'}
  begin
       zero_store_block;
       outtextxy(100,20,'Input the filename to create');
       gotoxy(13,3);
       readln(name);
       create_dummy_file_head(name,sweeps);
       create_composite_file(name);
       create_composite(freq,sweeps,ans);
       save_average(name);
       close(raw_file);
  end;

 end;
(*************************************************************************)
begin
        set_graphics(vga,vgamed);
        settextstyle(0,0,1);
          main;
```

```
        closegraph;
end.
```

A2.2 PROGRAM "WOODY.PAS"

```
{$M 16384,0,655360}
Program Woody;
{ Performs iterative adaptive filter according to Charles Woody's method}
{****************************** ver 1.1 2/89 MFG ******************************}
{latest version 1/94}
uses
Dos, General, Graph, Common, Crt, Rootsequ, Leastsqr;

type
        channel                         = 1..10;
        cur_num                          = 1..8;
        template                        = array[1..250] of longint;
        comp_array                       = array[1..250] of longint;

const   chans : array[1..6] of string   =('Fz','Cz','Pz','T3','T4','eog');
       mid_scr=320;
var
        mouse                           : registers;
        dummy                            : char;
        scale,Z_r                         : real;
        ch                              : channel;
        disk_err,ioerr                   : boolean;
        file_name,f_name,global_f_n     : string;
        tave,ntave,
        tdat,ntdat,hdr_file,disk_file   : file;
        cc_file,lcy_file,cv_file        : text;
        dirinfo                         : searchrec;
       rej_array                       : array[1..40] of char;
       temp_buf                         : array[1..1500] of integer;
       raw_av                          : array[1..1500] of longint;
        store_block                      : array[1..3000] of longint;
        lca                             : array[1..1500] of longint;
        dat_out                          : array[1..1500] of longint;
        buffer2                          : array[1..1500] of integer;

        filter_store                    : data_array;

f_head : record
                pt_name         : string[20];
                t_type          : string[10];
                year,month,
                day,dow         : word;
                channels        : byte;
                rate            : real;

                samples,
                fs_eeg,
                fs_eog,
                eog_gain,
```

```
                n_tgt1,
                n_tgt2,
                n_nontgt,
                n_rej           : integer;
                eeg_gain        : longint;

                proc_flg        : boolean;

                tgt1_mag,
                tgt2_mag,
                ntgt_mag        : array[channel,cur_num] of single;

                tgt1_ltncy,
                tgt2_ltncy,
                ntgt_ltncy      : array[channel,cur_num] of single;

                r_times         : array[0..99] of single;

                comments        : string[200];
        end;{record}
(*************************************************************************)
procedure Draw_xax(x_1st,y_1st,n_xax,x_stp,x_tic:integer);
{start position(x,y), no of steps, size of steps, width of xtics}
        var
        x_step_count, x_inc,x_pos, y_pos : integer;
begin
        x_inc:=x_stp;
        moveto(x_1st,y_1st+x_tic);lineto(x_1st,y_1st-x_tic);  {draw 1st xtic}
        moveto(x_1st,y_1st);
                FOR x_step_count:=1 TO n_xax do      {draw x-axis}
                begin
                  x_pos:=x_1st+x_inc;y_pos:=y_1st-x_tic;
                  lineto(x_pos,y_1st);moveto(x_pos,y_pos);
                  lineto(x_pos,y_pos+(2*x_tic));moveto(x_pos,y_1st);
                  x_inc:=x_inc+x_stp;
                END; {for}
end;
(*************************************************************************)
procedure Draw_yax(x_1st,y_1st,n_yax,y_stp,y_tic:integer);
{start position(x,y), no of steps, size of steps, width of ytics}
        var
        y_inc,x_pos, y_pos, y_step_count : integer;

begin
        y_inc:=y_stp;
        moveto(x_1st-y_tic,y_1st);lineto(x_1st+y_tic,y_1st);  {draw 1st ytic}
        moveto(x_1st,y_1st);
                FOR y_step_count:=1 TO n_yax do   {draw y-axis}
                begin
                  x_pos:=x_1st+y_tic;y_pos:=y_1st-y_inc;
                  lineto(x_1st,y_pos);moveto(x_pos,y_pos);
```

```
                lineto(x_pos-(2*y_tic),y_pos);moveto(x_1st,y_pos);
                y_inc:=y_inc+y_stp;
              END; {for}
end;
(*****************************************************************************)
procedure set_graphics(dvr,mde:integer);
begin
   Initgraph(dvr,mde,'d:\tp7\bgi');
end;
(*****************************************************************************)
procedure Zero_storage_mem;
{zeros storage memory block}
var
count : integer;
begin
        FOR count :=1 TO 3000 do
        store_block[count]:=0;
       for count:=1 to 1500 do
       raw_av[count]:=0;
end;
(*****************************************************************************)
procedure dir_error;    {reports disk errors}
begin

  case doserror of
      0: begin      {no error}
            {outtextxy(0,100,'Disk OK :');}
         end;
      18:begin      {no more files}
            outtextxy(0,150,'Disk not empty!!!');
         end;
      152:begin     {disk not in drive}
            sound(1000);delay(200);nosound;
            outtextxy(0,200,'NO DISK !!!!!');
            outtextxy(0,240,'Insert disk and press key to continue');
            repeat until keypressed;dummy:=readkey;
         end;
      162:begin     {unformatted disk}
            sound(1000);delay(200);nosound;
            outtextxy(0,200,'DISK NOT FORMATTED');
            outtextxy(0,200,
            'Load a formatted disk then press key to continue');
            repeat until keypressed;dummy:=readkey;
         end;
      end;{caseof}
end;
(*****************************************************************************)
procedure io_err(var f_name:file;var file_end:boolean);  {report runtime disk errs}

begin
   case ioresult of
```

```
        100:begin ioerr:=false;file_end:=true; end;
         103:begin
                  sound(1000);delay(200);nosound;
                  outtextxy(0,200,
                  'Must enter a filename !! - enter then try again ');
                  ioerr:=true;
                  repeat until keypressed;dummy:=readkey;
                  readln(file_name);
             end;
         101:begin
                  sound(1000);delay(200);nosound;
                  outtextxy(0,200,
                  'DISK FULL !! - Load new disk and ENTER');
                  ioerr:=true;close(f_name);erase(f_name);
                  repeat until keypressed;dummy:=readkey;
              end;
         105:begin
                  sound(1000);delay(200);nosound;
                  outtextxy(0,200,
                  'CANT OPEN FILE - ENTER and try again');
                  ioerr:=true;repeat;until keypressed;dummy:=readkey;
             end;
        150:begin
                 sound(1000);delay(200);nosound;
                 outtextxy(0,200,
                 'DISK WRITE-PROTECTED - Correct then ENTER');
                 ioerr:=true;repeat;until keypressed;dummy:=readkey;
          end;
    end;{caseof}
end;
(*************************************************************************)
procedure io_er(var f_name:text);  {report runtime disk errs on text files}

begin
    case ioresult of
         103:begin
                  sound(1000);delay(200);nosound;
                  outtextxy(0,200,
                  'Must enter a filename !! - enter then try again ');
                  ioerr:=true;
                  repeat until keypressed;dummy:=readkey;
                  readln(file_name);
             end;
         101:begin
                  sound(1000);delay(200);nosound;
                  outtextxy(0,200,
                  'DISK FULL !! - Load new disk and ENTER');
                  ioerr:=true;close(f_name);erase(f_name);
                  repeat until keypressed;dummy:=readkey;
              end;
         105:begin
```

```
                sound(1000);delay(200);nosound;
                outtextxy(0,200,
                'CANT OPEN FILE - ENTER and try again');
                ioerr:=true;repeat;until keypressed;dummy:=readkey;
            end;
        150:begin
                sound(1000);delay(200);nosound;
                outtextxy(0,200,
                'DISK WRITE-PROTECTED - Correct then ENTER');
                ioerr:=true;repeat;until keypressed;dummy:=readkey;
            end;
    end;{caseof}
end;
(*****************************************************************************)
procedure filter_data(alpha:real);      { takes data from array buffer2,
                                          places output in dat_out }
const
  points = 1500;
                    { for 1st-order Butterworth section, Fc = 15 Hz
                    if sample rate = 250 Hz ( omega =21.6 degrees,
                    (15/250)*360 ). When used in bi-directional form,
                    3dB point moves down to approx. 10Hz

                    Note !      alpha's       -3db

                                  0.6796        15
                                  0.7757        10
                                  0.8167        8
                                  0.8595        6
                                  0.9042        4
                                  0.9510        2          }
var
  point   :integer;
  v :array[1..points] of longint;       { for intermediate data }
  past_x, past_y :longint;              { past values }

begin

    {Filter forward}

  past_x := 0;
  past_y := 0;

  for point:=1 to points do begin
    v[point] := round( (alpha*past_y+(buffer2[point]+past_x)*(1-alpha)/2) );
    past_x := buffer2[point];
    past_y := v[point];
  end;    { for point:=1 to points }

  past_x := 0;
  past_y := 0;
```

```
    {Filter in reverse direction}

  for point:=points downto 1 do begin
    dat_out[point] := round( (alpha*past_y+(v[point]+past_x)*(1-alpha)/2) );
    past_x := v[point];
    past_y := dat_out[point];
  end;    { for point:=points downto 1 }

end;   { filter_data }
(*************************************************************************)
procedure template_start_stop(var start,finish:integer);
var sample_no,count:integer;
begin

   setcolor(white);
   WITH MOUSE DO begin

        AX:=0;Intr($33,mouse);                {reset all mouse drivers}
        AX:=7;CX:=23;DX:=521;Intr($33,mouse); {define horizontal limits}
        AX:=4;CX:=23;DX:=200;Intr($33,mouse); {define start}
        AX:=15;CX:=4;DX:=8;Intr($33,mouse);   {set mickey/pixel ratio}
        AX:=1;Intr($33,mouse);                {show cursor}

        For count := 1 to 2 do begin
          repeat
             AX:=3;Intr($33,mouse);    {monitor for button press}
          until (BX=1) or (BX=2);
          If BX=1 then begin
             AX:=4;CX:=CX+10;Intr($33,mouse);delay(300);
             moveto(CX-10,100);lineto(CX-10,250);
             sample_no:=round((CX-31)/2);
          end; {if}
          case count of
              1 : start :=sample_no;
              2 : finish:=sample_no;
          end;{case}
        end; {for}

        AX:=2;Intr($33,mouse);  {hide cursor}
      AX:=0;Intr($33,mouse);                {reset all mouse drivers}

   END; {with mouse do}

   setcolor(white);
   outtextxy(100,280,'To redefine template press key - else PRESS SPACEBAR');
end;
(*************************************************************************)
procedure lms_template_start_stop(var templ:template;var start,finish:integer);
var tmp_res,x_stp,y_stp,sample_no,count:integer;
{declare vars for Leastsqr soln.}
x_data,y_data              :TNColumnVector;
```

```
Numpoints, Numterms        :integer;
Solution                   :TnRowVector;
YFit, Residuals            :TnColumnVector;
StdDeviation, Variance     :Float;
Fit                        :FitType;
Error                      :byte;
{declare vars for roots}
Degree, Numroots,
MaxIter                    :integer;
InitGuess                  :TNComplex;
Roots, yRoots, D_soln      :TNCompvector;
Iter                       :TNIntVector;
Tol                        :Float;

begin
repeat
  setcolor(white);
  WITH MOUSE DO begin
       AX:=0;Intr($33,mouse);                {reset all mouse drivers}
       AX:=7;CX:=23;DX:=521;Intr($33,mouse); {define horizontal limits}
       AX:=4;CX:=23;DX:=200;Intr($33,mouse); {define start}
       AX:=15;CX:=4;DX:=8;Intr($33,mouse);   {set mickey/pixel ratio}
       AX:=1;Intr($33,mouse);                {show cursor}

       For count := 1 to 2 do begin
         repeat
            AX:=3;Intr($33,mouse);    {monitor for button press}
         until (BX=1) or (BX=2);
         If BX=1 then begin
            AX:=4;CX:=CX+10;Intr($33,mouse);delay(300);
            moveto(CX-10,100);lineto(CX-10,250);
            sample_no:=round((CX-31)/2);
         end; {if}
         case count of
             1 : start :=sample_no;
             2 : finish:=sample_no;
         end;{case}
       end; {for}

       AX:=2;Intr($33,mouse); {hide cursor}

  END; {with mouse do}


  {Now generate LMS fit - 1st set up vars for Leastsqr soln.}
  for count:=1 to abs(start-finish)+10 do
  x_data[count]:=4*((count-1)+start)-248;{convert s_n to t-range in ms}

  Numpoints:=abs(start-finish)+1;
  Numterms:=4;                          {3rd-order Cheby. polynomial}
  Fit:=Poly;
```

```
   {now transfer SSA data to y_data}
   for count:=1 to abs(start-finish)+1 do
   y_data[count]:=templ[(count-1)+start];

   FillChar(Solution,Sizeof(Solution),0);

   Leastsquares(Numpoints,x_data,y_data,Numterms,Solution,YFit,
            Residuals,StdDeviation,Variance,Error,Fit);
   setcolor(white);
   outtextxy(60,280,'To redefine LMS template press key - else PRESS SPACEBAR');

   {display LMS fit}
   setcolor(lightgreen);
   for count:=1 to abs(start-finish)+1 do begin
      tmp_res:=round(Yfit[count]*(250/2048));
      x_stp:=2*((count-1)+start)+21;
      y_stp:=175-tmp_res;
      if count=1 then moveto (x_stp,y_stp);
      lineto(x_stp,y_stp);
   end;
   setcolor(white);
until readkey=' ';
   {solution stored in YFit - transfer to template array}
   for count:=1 to abs(start-finish)+1 do
   templ[(count-1)+start]:=round(Yfit[count]);
end;
(*************************************************************************)
procedure change_gain(var gain:integer;var done:boolean);
var key:integer;
begin
  repeat
     key:=ord(readkey);
  until (key=72) or (key=80) or (key=32);
  If key=72 then inc(gain) else
  If (key=80) and (gain>1) then dec(gain);
  done:=(key=32);
end;
(*************************************************************************)
procedure draw_template(templ:template;gain:integer;var temp_type:char);
var count,x1,y1,x_stp,y_stp:integer;

begin
     settextstyle(1,0,3);
     outtextxy(150,0,'Adaptive Filter - stage 1');
     settextstyle(1,0,1);
     setcolor(lightgreen);
     if temp_type='S' then begin
       outtextxy(20,25,'SSA Template, arrow keys change gain - spacebar selects cursor');
       setcolor(white);
       outtextxy(35,45,'Select template'+
       ' using the cursor - left button'+
```

```
      ', two points only')
     end
    else
    if temp_type='L' then begin
      outtextxy(20,25,'LMS Template, arrow keys change gain - spacebar selects cursor');
      setcolor(white);
      outtextxy(5,45,'Generate LMS template'+
      ', left cursor button, two points only')
    end else
    outtextxy(85,25,'Arrow keys change gain '+
    '- Press spacebar to continue');
    setcolor(white);
    settextstyle(0,0,1);

    draw_xax(20,175,20,25,5);
    moveto(145,155);lineto(145,195);
    outtextxy(125,200,'stim');
    moveto(295,150);setlinestyle(1,0,normwidth);lineto(295,200);
    outtextxy(285,200,'300');
    setlinestyle(0,0,normwidth);

        {display whole sweep}

    scale := 500/4096;
    x1:=21;y1:=175;
    Setcolor(yellow);

    For count:=1 to 250 do begin
        x_stp:=x1+(2*count);
        y_stp:=y1-round(gain*templ[count]*scale);
        if count=1 then moveto(x_stp,y_stp);
        lineto(x_stp,y_stp);
     end;{for count}
     outtextxy(x_stp+30,175,'Template');
end;
(*****************************************************************************)
procedure test_if_edited(var been_edited:boolean);
{Looks for a file_header on a: with .fh2 extension as the test}
begin
  repeat
     cleardevice;
     findfirst('c:\tmp\*.fh2',$3f,dirinfo);
     dir_error;
  until (doserror=0) or (doserror=18);
  been_edited:=(doserror=0);
end;
(*****************************************************************************)
procedure make_halfsine_template(var templ:template;var start,finish:integer;
chan,peak:integer);
var ct:integer;
rad_f:real;
```

```
begin
  rad_f:=2*pi*2.5;    {2.5 Hz sine-wave}
  chan:=0;
  start:=peak-25;finish:=peak+25;
  for ct:=1 to 250 do templ[ct]:=0;
(*  for ct:=100 to 150 do templ[ct-100+start]:=round(500*(sin(rad_f*(ct/250))));*)
{temp measure for testing, again}
  for ct:=111 to 141 do templ[ct-100+start]:=100;

end;
(*************************************************************************)
procedure load_and_filter_template(var templ:template;var alpha:real;
chan:integer);
var count :integer;
{note that this smoothing additional to the smoothing given on new SSA!!}
begin
{$R+}
    {transfer SSA data to buffer2}
    for count:=1 to 1500 do buffer2[count]:=
          round(store_block[count]/f_head.n_tgt1);
{$R-}
    {smooth SSA}
    filter_data(alpha);

    {copy SSA to template array}
    for count := 1 to 250 do
     templ[count]:=dat_out[count+(chan-1)*250];

   for count := 1 to 250 do templ[count]:=buffer2[count+(chan-1)*250];

end;
(*************************************************************************)
procedure select_template(var templ:template;var t_start,t_end,peak:integer;
var alpha:real;var chan:integer;var temp_type:char);
var
chr:char;
done:boolean;
max_point,count,gain:integer;
begin

    load_and_filter_template(templ,alpha,chan);

    {now find where the p3 peak is for setting up
    half-sine template - searches the whole template waveform}
    max_point:=0;
      for count:=1 to 250 do
           If templ[count] > max_point
         then begin peak:=count;max_point:=templ[count];
      end;
    If (temp_type='H') then begin
       make_halfsine_template(templ,t_start,t_end,chan,peak);
```

```
        peak:=(4*peak)-248; {convert to ms}
      end;

gain:=1;
REPEAT
    repeat
      cleardevice;
      draw_template(templ,gain,temp_type);
      outtextxy(45,70,'Channel = '+chans[chan]);
      change_gain(gain,done);
      setcolor(white);
    until done;

    if temp_type='S' then template_start_stop(t_start,t_end)
    else
    if temp_type='L' then lms_template_start_stop(templ,t_start,t_end)
    else outtextxy(mid_scr-120,320,'Press spacebar to continue');

  {now find where the p3 peak is - only for the SSA and LMS options
   searches the defined template within start and stop co-ords}
    If temp_type <> 'H' then begin
     max_point:=0;
     for count:=t_start to t_end do
         If templ[count] > max_point then begin
                 peak:=count;max_point:=templ[count];
         end;
         {convert peak to latency in ms}
     peak:=(4*peak)-248;
     outtextxy(100,300,'Peak = '+int_str(peak)+' ms');
     end
     else outtextxy(100,300,'Peak = '+int_str(peak)+' ms');
     chr:=upcase(readkey);
UNTIL chr=' ';
end;
(*************************************************************************)
procedure load_and_filt_sweep(var comp_arr:comp_array;alpha:real;chan:integer;
var file_end:boolean;yes_proc:boolean);
var sum,mean : longint;
count : integer;
begin
 {$I-}
     repeat
     blockread(tdat,buffer2[1],f_head.samples);
     io_err(tdat,file_end);
     until not ioerr;
 {$I+}

  If yes_proc=true then begin

   {hang on to unfiltered data for forming new lca}
     for count:= 1 to 1500 do temp_buf[count]:=buffer2[count];
```

```
      {now smooth raw Rare data prior 'search'}
    filter_data(alpha);

    For count := 1 to 250 do
    comp_arr[count] := dat_out[count+(chan-1)*250];

          {remove offsets}
    sum:=0;
    For count:=1 to 250 do sum:=sum+comp_arr[count];

    mean:=round(sum/250);
    For count:=1 to 250 do comp_arr[count]:=comp_arr[count]-mean;
  end; {If yes_proc..}

  {temp measure again}
    for count := 1 to 250 do comp_arr[count]:=0;
    For count := 80 to 129 do comp_arr[count]:=100;
    For count:= 150 to 199 do comp_arr[count]:=200;
     {end of temp}
end;
(*************************************************************************)
procedure display_template(templ:template;x1,y1,start,finish,srch,
srch_start:integer);
var count,x_stp,y_stp :integer;
begin
    setcolor(yellow);

    For count:=start to finish do begin
          x_stp:=x1+(2*(srch_start+(count-start)+srch));
          y_stp:=y1-round(templ[count]*scale);
          if count=start then moveto(x_stp,y_stp);
          lineto(x_stp,y_stp);
    end;{for count}

    setcolor(white);
end;
(*************************************************************************)

procedure display_sweep(comp_arr:comp_array;x1,y1:integer);
var count2,x_stp,y_stp,x_stp2,y_stp2:integer;
begin

    {draw axes}
    draw_xax(20,125,10,50,5);
    moveto(145,105);lineto(145,145);
    outtextxy(125,150,'stim');
    moveto(295,75);setlinestyle(1,0,normwidth);lineto(295,175);
    outtextxy(285,180,'300');
    setlinestyle(0,0,normwidth);

    For count2:=1 to 250 do begin
```

```
        x_stp:=x1+(2*count2);
        y_stp:=y1-round(comp_arr[count2]*scale);
        if count2=1 then moveto(x_stp,y_stp);
        lineto(x_stp,y_stp);
    end;{for count2}
end;
(*************************************************************************)
procedure correlate(x_arr:template;y_arr:comp_array;start,finish,srch_start,
srch_inc:integer;var rho:real;var Cxy:real);
var
        Sx,Sy,Sxx,Syy,Sxy       : real;
        Vx,Vy,denom             : real;
        count                   : integer;

{two data arrays - template and comp_array equivalent to x_arr
 and y_arr, calculates sum of x & y, sum of x*x & y*y, sum of x*y,
 variance of x & y, co-variance of xy (Cxy), correlation coefficient (rho)}

begin
        Sx:=0;Sy:=0;Sxx:=0;Syy:=0;Sxy:=0;

                {calculate all sums}

        For count:=start to finish do begin
          Sx:= Sx+x_arr[count];
          Sy:= Sy+y_arr[srch_start+(count-start)+srch_inc];
         Sxx:= Sxx+sqr(x_arr[count]);
         Syy:= Syy+sqr(y_arr[srch_start+(count-start)+srch_inc]);
         Sxy:= Sxy+(x_arr[count]*y_arr[srch_start+(count-start)+srch_inc]);
        end;{for count}

                {calculate variances and co_variance}

          Vx:= Sxx - (sqr(Sx)/(finish+1-start));
          Vy:= Syy - (sqr(Sy)/(finish+1-start));
         Cxy:= Sxy - ((Sx * Sy)/(finish+1-start));

        denom:= sqrt(Vx * Vy);

                {calculate corr coeff, rho}
        If denom <> 0 then rho:=cxy/denom;

                 {Z-transform Rho}
        Z_r:=0.5*ln((1+rho)/(1-rho));
 end;
(*************************************************************************)
procedure seek_max_correlation(comp_arr:comp_array;templ:template;var x1:
integer;y1,start_t,end_t,count:integer;var max_rho:real;var shuffle,jitter,
peak,chan:integer;p3_flg:boolean;pass:byte;var max_cov:real;method:char);

var search_inc,search_start,search_end,start_ofs,key:integer;
```

```
chr:char;
cov,rho:real;
resp:string;
begin

 settextstyle(0,0,1);

 start_ofs:=round((end_t-start_t)/2);
 search_start:=start_ofs;search_end:=240-start_ofs;
 {allow for width of template and search from start to end of data sweep}

max_rho:=0;max_cov:=0;
For search_inc:=0 to (search_end-search_start) do begin

    correlate(templ,comp_arr,start_t,end_t,search_start,search_inc,rho,cov);
    case method of
    'V': If cov > max_cov then begin
        max_cov:=cov;shuffle:=search_inc;max_rho:=rho;
        jitter:=shuffle-(start_t-search_start);
        end;
    'C': If rho > max_rho then begin
        max_rho:=rho;shuffle:=search_inc;max_cov:=cov;
        jitter:=shuffle-(start_t-search_start);
        end;
    end;

end; {search}

        {convert jitter to ms, referred to template P3 peak latency}
        jitter:=peak+(4*jitter);

REPEAT    {manual check}
    clearviewport;
    rectangle(0,0,639,249);

    case p3_flg of
      true:outtextxy(200,10,chans[chan]+' lead - Rare response '
      +int_str(count));
      false:begin
            case pass of
            1:resp:='rare';
            2:resp:='novel';
            end;
      outtextxy(200,10,chans[chan]+' lead - '+resp+' response '
      +int_str(count));
      end;
    end;

    display_sweep(comp_arr,x1,y1);
    display_template(templ,x1,y1,start_t,end_t,shuffle,search_start);
```

```
    correlate(templ,comp_arr,start_t,end_t,search_start,shuffle,rho,cov);
    jitter:=shuffle-(start_t-search_start);
    jitter:=peak+(4*jitter);
    outtextxy(175,220,'Rho = '+real_str(rho,1,3)+'  Cov = '+real_str(cov,1,3));
    outtextxy(207,230,'Peak = '+int_str(jitter)+', shift='+
    int_str(jitter-peak)+' ms');

    repeat                          {manual peak search}
      key:=ord(upcase(readkey));
    until (key=75) or (key=77) or (key=90);

    If key=75 then shuffle:=shuffle-1 else if key=77 then shuffle:=shuffle+1;
UNTIL key=90;

end;
(*************************************************************************)
procedure load_rej_rec(t_t:char);
var F:text;
ext:string;
temp:char;
ct:byte;
begin
    fillchar(rej_array,sizeof(rej_array),' ');

    If t_t ='r' then ext:='rrj'
    else ext:='nrj';

   assign(F,'c:\tmp\'+global_f_n+'.'+ext);
   reset(F);
   ct:=1;
  repeat
    read(F,temp);
    if temp <> ' ' then rej_array[ct]:=temp;
    inc(ct);
  until (temp=' ') or (ct=41);
  close(F);
end;
(*************************************************************************)
procedure create_coeff_file(alias,extn:string);
begin
{$I-}
    repeat
        ioerr:=false;
        assign(cc_file,'f:\patdat\'+alias+'.r'+extn);
        rewrite(cc_file);
        io_er(cc_file);
    until not ioerr;
{$I+}
end;
(*************************************************************************)
procedure create_jitter_file(alias,extn:string);
```

```
begin
{$I-}
    repeat
        ioerr:=false;
        assign(lcy_file,'f:\patdat\'+alias+'.l'+extn);
        rewrite(lcy_file);
        io_er(lcy_file);
    until not ioerr;
{$I+}
end;
(*************************************************************************)
procedure create_covar_file(alias,extn:string);
begin
{$I-}
    repeat
        ioerr:=false;
        assign(cv_file,'f:\patdat\'+alias+'.c'+extn);
        rewrite(cv_file);
        io_er(cv_file);
    until not ioerr;
{$I+}
end;
(*************************************************************************)
procedure create_lca_file; {To store new lca and updated header}
var file_end:boolean;
begin
{$I-}
    repeat
      ioerr:=false;
      assign(disk_file,'c:\tmp\'+global_f_n+'.lca');
      rewrite(disk_file,4);
      io_err(disk_file,file_end);
    until not ioerr;
    repeat        {create new file_header}
      ioerr:=false;
      assign(hdr_file,'c:\tmp\'+global_f_n+'.fh3');
      rewrite(hdr_file,1);
      io_err(hdr_file,file_end);
    until not ioerr;
{$I+}

end;
(*************************************************************************)
procedure adjust_lca(shift:integer);
{Take raw, unfiltered, data sweep, adjust latency then save to produce LCA
 - the procedure for latency adjustment will be a 'data wrap. Note that
the LCA is formed for each channel onm the basis of the data returned from Pz'}

var chan,count:integer;

begin
```

```
    shift:=shift div 4;

 for chan:=1 to 5 do begin
    {First deal with a 'positive' shift}
    If shift > 0 then begin

       for count:= 1 to 250-abs(shift) do
       buffer2[count+abs(shift)]:=temp_buf[count+((chan-1)*250)];

       for count:=1 to abs(shift) do
       buffer2[count]:=temp_buf[250-abs(shift)+count+((chan-1)*250)];

    end {now a 'negative' shift}
    else if shift < 0 then begin

       for count:= 1 to 250-abs(shift) do
       buffer2[count]:=temp_buf[count+abs(shift)+((chan-1)*250)];

       for count:=1 to abs(shift) do
       buffer2[250-count+abs(shift)]:=temp_buf[count+((chan-1)*250)];

    end;

    If shift = 0 then begin
     for count:=1 to 250 do begin
      buffer2[count]:=temp_buf[count+((chan-1)*250)];
     end;
    end;

    {build new average, the latency-shifted LCA}
    for count:= 1 to 250 do begin
     raw_av[count+((chan-1)*250)]:=
     raw_av[count+((chan-1)*250)]+buffer2[count];
    end;
 end;
end;
(*****************************************************************************)
procedure save_lca_file;
var
chan,count,mean:integer;
sum :longint;

begin
     {smooth LCA averaged data}

     for count:=1 to 1500 do
       filter_store[count]:=raw_av[count];
     smooth_data(filter_store,filter_store);
     for count:=1 to 1500 do
      raw_av[count]:=filter_store[count];
```

```
    For chan:= 1 to 5 do begin
     {remove offsets}
     sum:=0;mean:=0;
     For count:=1 to 64 do
      sum:=sum+raw_av[((chan-1)*250)+count];

     mean:=round(sum/64);
     For count:=1 to 250 do raw_av[((chan-1)*250)+count]:=
                        raw_av[((chan-1)*250)+count]-mean;
    end;

    {$I-}
    blockwrite(disk_file,raw_av[1],1500);
    close(disk_file);
    blockwrite(hdr_file,f_head,sizeof(f_head));{new header for lca}
    {$I+}

end;
(*****************************************************************************)
procedure save_corr_coeff(max_rho:real);
begin
{$I-}
  ioerr:=false;
  repeat
        writeln(cc_file,max_rho);
        io_er(cc_file);
  until not ioerr;
{$I+}
end;
(*****************************************************************************)
procedure save_jitter(jitter:integer);
begin
{$I-}
  ioerr:=false;
  repeat
        writeln(lcy_file,jitter);
        io_er(lcy_file);
  until not ioerr;
{$I+}
end;
(*****************************************************************************)
procedure save_covar(max_cov:real);
begin
{$I-}
  ioerr:=false;
  repeat
        writeln(cv_file,max_cov);
        io_er(cv_file);
  until not ioerr;
{$I+}
end;
```

```
(*************************************************************************)
procedure adaptive_filter(var chan:integer;p3_flg:boolean;pass:byte);
{This is now carried out on Pz only, all other channels are adjusted according to
latency corrections returned from Pz. It is possible to carry this process out
 on each channel if reuired}
var
temp_type,method,chr : char;
alias, extn,extn2,temp, f_n : string;
acc_tgt,tgt_ct,filter_setting,shuffle,jitter,x1,y1,
count,start_t,end_t,peak:integer;
alpha, max_rho, max_cov: real;
reject,yes_proc,file_end,all_seen,been_edited:boolean;

templ    : template;
comp_arr : comp_array;
                                    { alpha       cut_off
                                      0.6796        15
                                      0.8167        8
                                      0.8595        6
                                      0.9042        4
                                  0.9510        2}
begin

    alpha:=0.6796;     {select template at 15 Hz L_P}

    cleardevice;
    repeat
      color_box(mid_scr-200,150,mid_scr+200,250,lightblue);
      outtextxy(mid_scr-65,160,'TEMPLATE OPTIONS');
      outtextxy(mid_scr-150,190,'To manually select from SSA -  press S');
      outtextxy(mid_scr-150,210,'To use a LMS fit template   -  press L');
      outtextxy(mid_scr-150,230,'To use half-sine template   -  press H');
      chr:=upcase(readkey);
    until (chr='S') or (chr='H') or (chr='L');
    temp_type:=chr;

    select_template(templ,start_t,end_t,peak,alpha,chan,temp_type);
    cleardevice;
    outtextxy(100,110,'Enter the file alias for storage on f:\patdat\:');
    gotoxy(14,10);readln(alias);
    f_n:=alias+int_str(chan);{convert alias to specific channel}
    outtextxy(100,140,'Do you wish to search using correlation (C) or COVARIANCE (V)?');

    repeat method:=upcase(readkey); until (method='C') or (method='V');
FOR filter_setting := 0 to 0 do begin

     {1st test to see if edited & load rej_ct if yes}
     test_if_edited(been_edited);

     If p3_flg then begin {P3 file}
     tgt_ct:=f_head.n_tgt1;extn:='.trw';extn2:='r';
```

```
  if (been_edited) then load_rej_rec('r');
  end
  else                {P3a file}
  case pass of
    1:begin
        tgt_ct:=f_head.n_tgt1;extn:='.trw';extn2:='ar';
        if (been_edited) then load_rej_rec('r');
      end;
    2:begin
        tgt_ct:=f_head.n_tgt2;extn:='.nvr';extn2:='an';
        if (been_edited) then load_rej_rec('n');
      end;
  end;

     {open single sweep data file}
  assign(tdat,'c:\tmp\'+global_f_n+extn);
  reset(tdat,2);

  case filter_setting of
     0: begin alpha:=0.6796; extn:='2'; temp:='15';end;
     1: begin alpha:=0.8167; extn:='8'; temp:=extn; end;
     2: begin alpha:=0.8595; extn:='6'; temp:=extn;end;
     3: begin alpha:=0.9042; extn:='4'; temp:=extn;end;
    4: begin alpha:=0.9510; extn:='0'; temp:=extn;end;
  end;

  extn2:=extn2+extn;
  cleardevice;
  settextstyle(1,0,3);

  outtextxy(10,10,'Adaptive Filter, stage 2  -  single sweep correlation');
  if extn <> '0' then
  outtextxy(110,40,'Low-pass digital filter at '+temp+' Hz')
  else
  outtextxy(110,40,'Low-pass digital filter at 2 Hz');
  settextstyle(1,0,1);
  outtextxy(110,70,'File : '+f_n);

  setviewport(0,100,639,349,clipon);

  create_coeff_file(f_n,extn2);
  create_covar_file(f_n,extn2);
  create_jitter_file(f_n,extn2);
  create_lca_file;

  count:=1;
  all_seen:=false;file_end:=false;
  acc_tgt:=0;
REPEAT

  clearviewport;
```

```
    yes_proc:=(rej_array[count]='Y');
    load_and_filt_sweep(comp_arr,alpha,chan,file_end,yes_proc);
     {load single sweep and smooth}

    If ((been_edited) and (rej_array[count]='Y')) or (not(been_edited))
    then begin

       If not(file_end) then begin
         x1:=21;y1:=125;
         case pass of
            1:outtextxy(150,100,'Peak searching rare response number '+
          int_str(count));
          2:outtextxy(150,100,'Peak searching novel response number '+
          int_str(count));
         end;

          seek_max_correlation(comp_arr,templ,x1,y1,start_t,end_t,count,max_rho,shuffle,
                        jitter,peak,chan,p3_flg,pass,max_cov,method);
          outtextxy(175,220,'Rho = '+real_str(max_rho,1,3)+'  Cov ='+real_str(max_cov,1,3));
          outtextxy(207,230,'Peak = '+int_str(jitter)+', shift='+
          int_str(peak-jitter)+' ms');

         reject:=(jitter < 280) or (peak > 480);
         If not(reject) then begin
          save_corr_coeff(max_rho);
          save_covar(max_cov);
          save_jitter(jitter);
          adjust_lca(peak-jitter);
          inc(acc_tgt);
          sound(5000);delay(50);nosound;
         end;

       end;{If not(file_end...}
     end;
     inc(count);
     all_seen:=count=3{(count=41)};
   UNTIL all_seen or file_end;  {or (chr=' ');}

    save_jitter(peak);   {save SSA peak ltncy for reference}

    close(cc_file);
    close(lcy_file);
    close(cv_file);
    close(tdat);
    f_head.n_tgt1:=acc_tgt;{For the file-hdr associated with LCA}
    graphdefaults;
 END; {for filter_setting}
 graphdefaults;
end;
(*************************************************************************)
procedure load_f_head(extn:string;file_end:boolean);
```

```
begin
                        {read file_head}
    file_end:=false;
    repeat
      cleardevice;
      color_box(195,100,350,120,green);
      outtextxy(205,105,'Loading data file');
        ioerr:=false;
        findfirst('c:\tmp\*'+extn,$3f,dirinfo);
        assign(disk_file,'c:\tmp\'+dirinfo.name);
        reset(disk_file,1);
        blockread(disk_file,f_head,sizeof(f_head));
        io_err(disk_file,file_end);
    until not ioerr;
    close(disk_file);

              {strip file extension}
     delete(dirinfo.name,length(dirinfo.name)-3,4);
     global_f_n:=dirinfo.name;
end;
(*************************************************************************)
procedure load_t_aves(extn:string;file_end:boolean);
begin
{$I-}
        {read tgt ave}
    repeat
        ioerr:=false;
        assign(tave,'c:\tmp\'+global_f_n+extn);
        reset(tave,4);
        blockread(tave,store_block[1],f_head.samples);
        io_err(tave,file_end);
    until not ioerr;
    close(tave);
{$I+}
end;
(*************************************************************************)
procedure add_to_new_ave;
var ct:integer;
begin
  for ct:=1 to 1500 do store_block[ct]:=store_block[ct]+buffer2[ct];
end;
(*************************************************************************)
procedure smooth;{write data to filter_store,smooth,save back to store_block}
var ct,sam_ct:integer;
mean_val:real;
begin
    for ct:=1 to 1500 do filter_store[ct]:=store_block[ct];

    smooth_data(filter_store,filter_store);

    {remove offsets after filtering}
```

```
    For ct:=1 to f_head.channels do begin
      mean_val:=0;
      For sam_ct:=1 to 63 do   {pre_stim}
           mean_val:=mean_val+filter_store[sam_ct+((ct-1)*250)];

      mean_val:=mean_val/63;

      For sam_ct:=1 to 250 do
           filter_store[sam_ct+((ct-1)*250)]:=
           filter_store[sam_ct+((ct-1)*250)]-round(mean_val);
    end;{for ct}

    for ct:=1 to 1500 do store_block[ct]:=filter_store[ct];
end;
(*************************************************************************)
procedure create_rej_rec(t_t:char);
        {saves information relating to visual edits}
var
F:text;
ext:string;
begin
    case t_t of
     'r':ext:='rrj';
     'n':ext:='nrj';
    end; {case}
   assign(F,'c:\tmp\'+global_f_n+'.'+ext);
   rewrite(F);
   {now save table}
   writeln(F,rej_array);
   close(F);
end;
(*************************************************************************)
procedure create_new_ssa(p3_flg:boolean;extn:string;var been_edited:boolean);
{Build new stimulus synchronised avergae, after editing}
const ch_lbl:array[1..6] of string=('Fz','Cz','Pz','T3','T4','EOG');
var ct,x1,y1,x_stp,y_stp,max_ch,ch_show,ch_pt,rsp_ct,
uv_scl,new_av_ct,ch_left,swp_ct:integer;
sum:longint;
t_t,ch:char;
av_scale:real;
begin
  zero_storage_mem;
  fillchar(rej_array,sizeof(rej_array),' '); {set up record:default to false}

  assign(tdat,'c:\tmp\'+global_f_n+'.'+extn);
  reset(tdat,2);
  new_av_ct:=0;swp_ct:=1;

  If extn='trw' then begin t_t:='r';rsp_ct:=f_head.n_tgt1; end
  else begin t_t:='n';rsp_ct:=f_head.n_tgt2; end;
```

```
    {open rare/novel average file for display}
if extn='trw' then assign(tave,'c:\tmp\'+global_f_n+'.t10')
else if extn='nvr' then assign(tave,'c:\tmp\'+global_f_n+'.nvs');
reset(tave,4);
blockread(tave,lca[1],f_head.samples);
close(tave);

REPEAT
 repeat

 cleardevice;
 case t_t of
   'r':outtextxy(130,0,'Rare response '+int_str(swp_ct)+' of '+
   int_str(f_head.n_tgt1));
   'n':outtextxy(130,0,'Novel response '+int_str(swp_ct)+' of '+
   int_str(f_head.n_tgt2));
 end;
 setcolor(lightgray);
 outtextxy(350,0,'Average response * 4 gain');
 setcolor(white);
  blockread(tdat,buffer2[1],f_head.samples);
  ch_left:=f_head.channels;
  ch_pt:=0;
  x1:=40;y1:=70;

  color_box(40,315,300,349,green);color_box(410,315,590,349,red);
  outtextxy(50,330,'To ACCEPT into new SSA press Y'+
  '                  To REJECT press N');

  sum:=0;
  repeat
    if ch_left>1 then max_ch:=2 else max_ch:=1;

    for ch_show:=1 to max_ch do begin

    scale:=100/4096;{100 screen points for full-scale data}

      (* calculate eog offset then remove*)
     If ch_left=1 then begin
        for ct:=1 to 250 do sum:=sum+buffer2[ct+(ch_pt*250)];
        sum:=sum div 250;
        for ct:=1 to 250 do buffer2[ct+(ch_pt*250)]:=
                          buffer2[ct+(ch_pt*250)]-sum;
     end;

     If ch_pt <> 5 then setcolor(9+ch_pt) else setcolor(white);

       for ct:=1 to 250 do begin
        x_stp:=x1+ct;
        y_stp:=y1-round(buffer2[ct+(ch_pt*250)]*scale);
         if ct=1 then moveto(x_stp,y_stp);
```

```
      lineto(x_stp,y_stp);
     end;
   outtextxy(x1,y1-40,ch_lbl[ch_pt+1]);

   {superimpose averaged data}
   setcolor(lightgray);
   av_scale:=4*(100/4096);
   {For ave'd data assigns y_range of 400 points to full-scale data,
   although only room for 100 per channel - gain of 4!}

    for ct:=1 to 250 do begin
      x_stp:=x1+ct;
      y_stp:=y1-round((lca[ct+(ch_pt*250)]/rsp_ct)*av_scale);
       if ct=1 then moveto(x_stp,y_stp);
      lineto(x_stp,y_stp);
     end;
   setcolor(white);

   (*calculate eog uv_scl*)
   uv_scl:=round(1e6*(1/f_head.eog_gain)) div 5;
   (*now draw a eog scale to assist in rej/accept edit*)
   If ch_pt=5 then draw_yax(330,320,5,20,5);
   outtextxy(320,325,+int_str(uv_scl));
   settextstyle(0,1,1);
   outtextxy(325,230,'EOG uV/div');
   settextstyle(0,0,1);

     (*calculate eeg uv_scl*)
   uv_scl:=round(1e6*(1/f_head.eeg_gain)) div 5;
   (*now draw a eeg scale to assist in rej/accept edit*)
   If ch_pt=5 then draw_yax(330,120,5,20,5);
   outtextxy(325,125,+int_str(uv_scl));
   settextstyle(0,1,1);
   outtextxy(325,30,'EEG uV/div');
   settextstyle(0,0,1);

   inc(ch_pt);x1:=350;dec(ch_left);
  end; {for ch_show}
 x1:=40;y1:=y1+100;
 until ch_left=0;

repeat ch:=upcase(readkey); until (ch='N') or (ch='Y');

until (ch='N') or (ch='Y') or (swp_ct=rsp_ct+1);

If ch='Y' then begin
 add_to_new_ave;
 inc(new_av_ct);
 rej_array[swp_ct]:='Y';
end
else begin    {rejected}
```

```
    rej_array[swp_ct]:='N';
    if t_t='r' then
    f_head.r_times[swp_ct]:=0; {set this to 0, for calculating means etc}
   end;
   inc(swp_ct);
  UNTIL swp_ct=rsp_ct+1;

  cleardevice;
  If new_av_ct > 0 then begin
    color_box(195,100,370,120,green);
    outtextxy(205,108,'SAVING NEW SSA FILE');
    close(tdat);
    {first smooth data with 15 Hz bi-dir filter}
    smooth;
    {create new SSA file and save data}
    case t_t of
     'r':begin assign(tdat,'c:\tmp\'+global_f_n+'.ss2');
          f_head.n_tgt1:=new_av_ct; end;
     'n':begin assign(tdat,'c:\tmp\'+global_f_n+'.nv2');
          f_head.n_tgt2:=new_av_ct; end;
     end;
    rewrite(tdat,4);
    blockwrite(tdat,store_block[1],f_head.samples);
    close(tdat);
    {create new file header associated with this file}
    assign(disk_file,'c:\tmp\'+global_f_n+'.fh2');
    rewrite(disk_file,1);
    blockwrite(disk_file,f_head,sizeof(f_head));
    close(disk_file);
    create_rej_rec(t_t);
    been_edited:=true;
  end;

  cleardevice;
end;
(*****************************************************************************)
procedure p3_or_p3a(var p3_flg:boolean);
{Is this a "P3a" or "P3b" file ?}
 begin
  p3_flg:=false;
  findfirst('c:\tmp\*.nva',$3f,dirinfo);
  p3_flg:=(doserror=18); {this must be a p3 file, .nva file not there}
 end;
(*****************************************************************************)
procedure edit_p3_or_p3a;
var file_end,been_edited,p3_flg:boolean;
extn:string;
ct:byte;
ky:char;
Lst:text;
reg:registers;
```

```
time:longint;
dt:datetime;
begin
 {test to see if previously edited - offer option to re-edit
       use presence or absence of .fh2 file to 'flag'}
 repeat
   cleardevice;
   findfirst('c:\tmp\*.fh2',$3f,dirinfo);
   dir_error;
 until (doserror=0) or (doserror=18);
 been_edited:=(doserror=0);

 repeat
 cleardevice;
 color_box(mid_scr-150,100,mid_scr+150,200,lightblue);
 outtextxy(mid_scr-70,120,'MANUAL EDIT OPTION');
 If been_edited then
 outtextxy(mid_scr-145,150,
 'THIS FILE HAS PREVIOUSLY BEEN EDITED');
 outtextxy(mid_scr-135,180,'Do you wish to edit this file? Y/N');
 ky:=upcase(readkey);
 until (ky='Y') or (ky='N');

 If ky='Y' then begin
   been_edited:=true;
   p3_or_p3a(p3_flg);

   If p3_flg=true then begin  {P3 test}
      load_f_head('.fhd',file_end); extn:='trw';create_new_ssa(p3_flg,extn,been_edited);end
   else begin                 {P3a test}
      load_f_head('.fhd',file_end);extn:='trw';create_new_ssa(p3_flg,extn,been_edited);
      extn:='nvr';create_new_ssa(p3_flg,extn,been_edited);end {P3a test}
  end;{If..}

  If (been_edited) then begin
   p3_or_p3a(p3_flg);
   load_f_head('.fh2',file_end);
   assign(disk_file,'c:\tmp\'+global_f_n+'.fh2');
   reset(disk_file);
   getftime(disk_file,time);
   close(disk_file);
   unpacktime(time,dt);

   cleardevice;
   color_box(mid_scr-290,100,mid_scr+290,140,green);
   outtextxy(mid_scr-260,120,'Do you wish to PRINT the list(s) of'+
   ' accepted/rejected sweeps Y/N?');
   repeat ky:=upcase(readkey) until (ky='Y') or (ky='N');

   If ky='Y' then begin {print edited data record}
```

```
    cleardevice;
    closegraph;
    textcolor(white);
    assign(Lst,'LPT1');rewrite(Lst);
    writeln('   Subject name : '+f_head.pt_name);
    writeln('   Filename : ',global_f_n);
    writeln('   Date of recording : '+int_str(f_head.day)+'/'+
    int_str(f_head.month)+'/'+int_str(f_head.year));
    writeln('   Test type :'+f_head.t_type);
    writeln;
    writeln('   Total number of rare responses : '+int_str(f_head.n_tgt1));
    If not(p3_flg) then
    writeln('   Total number of novel responses : '+int_str(f_head.n_tgt2));
    writeln('   Total number of frequent responses : '+int_str(f_head.n_nontgt));
    load_rej_rec('r'); {load and print edited rare selection}
    writeln;
    textcolor(green+blink);
    with dt do begin
    writeln('   DATE LAST FILE EDIT : '+leadingzero(day)+'/'+leadingzero(month)+
    '/'+leadingzero(year)+'  at '+leadingzero(hour)+':'+leadingzero(min));
    end;
    textcolor(white);
    writeln('   Rare responses rejected: ');
    write('    ');
    for ct:= 1 to f_head.n_tgt1 do begin
       if rej_array[ct] = 'N' then begin write(int_str(ct));write(' ');end;
    end;

    if not p3_flg then begin {load and print edited novel selection}
     load_rej_rec('n');
     writeln;
     writeln('   Novel responses rejected: ');
     write('    ');
     for ct:= 1 to f_head.n_tgt2 do begin
       if rej_array[ct] = 'N' then begin write(int_str(ct));write(' ');end;
     end;
    end;
    intr(5,reg);        {print}
    write(lst,chr(10)); {form feed}
   end;
   set_graphics(vga,vgamed);
   settextstyle(0,0,1);
  end;

end;
(*****************************************************************************)
procedure woody_filter;
var chan:integer;
file_end,been_edited,p3_flg:boolean;
extn:string;
ky:char;
```

```
begin
      p3_or_p3a(p3_flg);
      test_if_edited(been_edited);

     repeat
       cleardevice;
       color_box(mid_scr-150,100,mid_scr+150,200,lightblue);
      outtextxy(mid_scr-70,120,'MANUAL EDIT OPTION');
      If been_edited then
       outtextxy(mid_scr-145,150,
       'THIS FILE HAS PREVIOUSLY BEEN EDITED');
      outtextxy(mid_scr-135,180,'Do you wish to edit this file? Y/N');
       ky:=upcase(readkey);
     until (ky='Y') or (ky='N');

     If ky='Y' then begin
      load_f_head('.fhd',file_end);
      cleardevice;
      color_box(mid_scr-140,100,mid_scr+140,200,lightblue);
      outtextxy(mid_scr-70,120,'Pre-filter stage');
      outtextxy(mid_scr-120,160,'Manual edit of RARE responses');
      outtextxy(mid_scr-80,180,'PRESS KEY TO CONTINUE');
      repeat until keypressed;
      extn:='trw';create_new_ssa(p3_flg,extn,been_edited);
     end;

      {now ready for lca on rare responses}
     If been_edited then begin
       extn:='.ss2'; load_f_head('.fh2',file_end);
       load_t_aves(extn,file_end);
       end
     else
     begin
       extn:='.t10';load_f_head('.fhd',file_end);
       load_t_aves(extn,file_end);
     end;

     {Get LCA data from Pz lead only, adjust all other this basis}
     chan:=3;
     adaptive_filter(chan,p3_flg,1);
     save_lca_file;

      if not p3_flg then {lca on novel}
      begin
       If ky='Y' then begin
        cleardevice;
        color_box(mid_scr-140,100,mid_scr+140,200,lightblue);
        outtextxy(mid_scr-70,120,'Pre-filter stage');
        outtextxy(mid_scr-120,160,'Manual edit of NOVEL responses');
        outtextxy(mid_scr-80,180,'PRESS KEY TO CONTINUE');
        repeat until keypressed;
```

```
        extn:='nvr';create_new_ssa(p3_flg,extn,been_edited);
       end;

       If been_edited then extn:='.nv2' else extn:='.nvs';
         load_t_aves(extn,file_end);
       chan:=3;
         adaptive_filter(chan,p3_flg,2);
      end; {If..}
end;
(*************************************************************************)
procedure choose(var ky:byte);
begin
  {select options for adaptive filter or producing edited SSA}

  cleardevice;
  color_box(50,50,590,250,red);
  color_box(210,60,430,85,blue);
  outtextxy(230,70,'ADAPTIVE FILTER OPTIONS');
  outtextxy(60,150,'1. EDIT SINGLE SWEEP DATA TO PRODUCE NEW SSA');
  settextstyle(0,0,2);outtextxy(430,145,'- KEY E');
  settextstyle(0,0,1);
  outtextxy(60,180,'2. WOODY FILTER');
  settextstyle(0,0,2);
  outtextxy(430,175,'- KEY W');settextstyle(0,0,1);
  color_box(210,220,430,240,blue);
  outtextxy(245,227,'TO STOP PRESS RETURN');

  repeat ky:=ord(readkey) until (ky=13) or (ky=101) or(ky=119);
  case ky of
   101:edit_P3_or_P3a;
   119:woody_filter;
  end;
end;
(*************************************************************************)
                                {main}
var ky:byte;
begin
    zero_storage_mem;
    set_graphics(vga,vgamed);
    settextstyle(0,0,1);
    repeat
     choose(ky);
    until ky=13;
    closegraph;
end.
```

A2.3 PROGRAM "ER.PAS"

```
{$A+,B-,D+,E+,F-,I+,L+,N+,O-,R-,S+,V+}
{$M 16384,0,655360}
Program ER;
                    {For the auditory oddball paradigm}
            {************* 12/89 MFG v 4.0 *************}
                          {latest revision 12/93}
      {manually set p, keep rejected rare count (in f_head.n_rej when r_time),
            save incorrectly identified rares slow wave measurement}

uses
Dos, Graph, Common, Crt, General, Plot, tp4d16, Rootsequ, Leastsqr;

type
  channel                          = 1..10;
  cur_num                          = 1..8;
var
  op_type,err_code,status,sweep_tgt,
  next_count,err,ch_left,
  ch_drawn,ch_pt,key,choice,i_s_i      : integer;
  ch                                        : channel;
  disk_err,ioerr,acq_flg,
  curs,fil_flg1,fil_flg2,fil_flg3,
  all_flg                          : boolean;
  rare_p                                 : single;
  scale,gain                             : real;
  dummy,answer                          : char;
  tgt_buf,ntgt_buf,tdat,ntdat,
  tave,ntave,disk_file,f_name      : file;
  buffer                                    : array[0..1500] of integer;
  buffer2                                   : array[1..1500] of integer;
  y_data_array                         : array[1..500] of real;
  store_block                      : array[1..3000] of longint;
  filter_store                           : data_array;
  file_name                        : string;
  dirinfo                                   : searchrec;

  f_head : record
       pt_name    : string[20];
         test_type  : string[10];
       year,month,
         day,dow    : word;
          channels   : byte;
          rate       : real;

            samples,
            fs_eeg,fs_eog, eog_gain,
          n_tgt1,n_tgt2,n_nontgt,
            n_rej                : integer;
          eeg_gain             : longint;
```

```
            proc_flg            : boolean;

               tgt1_mag,
               tgt2_mag,
               ntgt_mag   : array[channel,cur_num] of single;

               tgt1_ltncy,
               tgt2_ltncy,
               ntgt_ltncy : array[channel,cur_num] of single;

            r_times        : array[0..99] of single;
            comments            : string[200];
          end; {record}

(*************************************************************************)
procedure set_graphics(dvr,mde:integer);
begin
    Initgraph(dvr,mde,'d:\tp7\bgi');
end;
(*************************************************************************)
procedure menu;var
chr:char;

begin
        cleardevice;
        settextstyle(1,0,3);
         OUTTEXTXY(20,10,'DEPARTMENTS OF PSYCHIATRY & MEDICAL PHYSICS');
        outtextxy(55,100,'Auditory Evoked Response System ');
        outtextxy(55,150,'EEG analysis');
        outtextxy(55,200,'Eye-tracking');
        delay(1000);cleardevice;

{       rectangle(100,40,540,90);
        outtextxy(130,50,'To select                KEY');
        settextstyle(1,0,2);
        outtextxy(130,110,'P300 TEST                    1');
        outtextxy(130,150,'P50 TEST                    2');
        outtextxy(130,190,'EYETRACKING                    3');
        outtextxy(130,230,'EEG ANALYSIS                    4');
        outtextxy(50,300,'Data acquisition and processing - OPTIONS FOLLOW');
      Repeat
          chr:=readkey;
      until chr='1';}
      chr:='1';
end;
(*************************************************************************)
procedure choose;
var ky:char;
begin
        settextstyle(1,0,3);
        cleardevice;
```

```
        rectangle(240,5,400,45);
        outtextxy(264,12,'P300 TEST');
        rectangle(100,80,540,130);
        outtextxy(130,90,'To select                    KEY');
        settextstyle(1,0,2);
        outtextxy(120,150,'ACQUISITION                    A');
        outtextxy(120,190,'PROCESSING                    P');
        outtextxy(120,230,'PLOTTING                    L');
        outtextxy(180,300,'To FINISH press SPACEBAR');
        ky:=upcase(readkey);
        choice:=ord(ky);
      cleardevice;
        acq_flg:=false;
        f_head.comments:='';                {'zero' comments}
end;
(*************************************************************************)
procedure set_up;
var ky: char;
rare_str:string;
temp,range,sense: real;
err,count,cs:integer;
begin
  with f_head do begin
        samples:=250;                {per ch}
        rate:=250;                   {sampling rate per ch}
        eog_gain:=1000;              {eog amp}
        fs_eeg:=1;                   {1 volt}
        fs_eog:=1;
        proc_flg:=false;
        getdate(year,month,day,dow);
    end;

    fil_flg1:=false; fil_flg2:=false; fil_flg3:=false;

    setcolor(white);
    cleardevice;
    settextstyle(1,0,2);
    rectangle(240,10,400,50);
    outtextxy(268,20,'P300 TEST');
    settextstyle(0,0,1);
    setcolor(white);
    outtextxy(200,80,'Which test paradigm is required ?' );
    outtextxy(40,105,'For Reaction_Time');
    setcolor(lightred);
    outtextxy(180,105,' KEY  R');
    setcolor(white);
    outtextxy(320,105,'    For Target_Counting');
    setcolor(lightred);
    outtextxy(500,105,'   KEY T');

    with f_head do begin
```

```
repeat
     ky:=upcase(readkey);
until (ky='R') or (ky='T');
setcolor(lightgreen);
case ky of
    'R': begin
         test_type:='R_TIME';outtextxy(250,120,test_type+' selected');
         end;
    'T': begin
         test_type:='T_COUNT';outtextxy(250,120,test_type+' selected');
         end;
end; {case}

delay(500);

setcolor(white);
outtextxy(40,145,
'How many EEG channels do you wish to use? (1-5) =>');
repeat
    cs:=ord(readkey);
until (cs>48) and (cs<54);
channels:=cs-47;
setcolor(lightgreen);
outtextxy(450,145,int_str(channels-1)+' EEG  1 EOG selected');
setcolor(white);

outtextxy(40,171,'Enter rare stim probability [RETURN for default (0.1)] =>');
repeat
 err:=0;
 gotoxy(64,13);
 readln(rare_str);
 If rare_str<>'' then val(rare_str,rare_p,err)
                 else begin
                 rare_p:=0.1;outtextxy(500,171,'0.1');
                 end;
until (rare_p>0) and (rare_p<0.6) and(err=0);
rare_p:=rare_p+0.01;

samples:=samples*channels;                {total per sweep}
rate:=rate*channels;                    {rate for multi-ch}
trigger_point:=channels*60;

outtextxy(40,185,'Input the EEG amplifier range =>');
setcolor(lightred);
outtextxy(40,199,'(1,2,5,  10,20,50,  100,200,500)');
textcolor(lightgreen);
repeat
    gotoxy(39,14);readln(range);
until (range>0) and (range<501);

setcolor(white);
```

```
outtextxy(40,215,'Input the EEG channel sensitivity =>');
setcolor(lightred);
outtextxy(40,229,'For  uV - Key U   mV - Key M      V - Key V  =>');
    repeat
            ky:=upcase(readkey);
            choice:=ord(ky);
    until (choice=77) or (choice=85) or (choice=86);

case choice of
    77 : sense:=1e3;
    85 : sense:=1e6;
    86 : sense:=1;
    end; {case}

  setcolor(lightgreen);
    temp:=sense/range;
    eeg_gain:=trunc(temp);
    outtextxy(450,229,'EEG Gain = '+int_str(eeg_gain));

setcolor(white);
outtextxy(40,240,'Input the EOG amplifier range =>');
setcolor(lightred);
outtextxy(40,255,'(1,2,5,  10,20,50,  100,200,500)');
textcolor(lightgreen);
repeat
    gotoxy(39,18);readln(range);
until (range>0) and (range<501);

setcolor(white);
outtextxy(40,265,'Input the EOG channel sensitivity =>');
setcolor(lightred);
outtextxy(40,279,'For  uV - Key U   mV - Key M      V - Key V  =>');
    repeat
            ky:=upcase(readkey);
            choice:=ord(ky);
    until (choice=77) or (choice=85) or (choice=86);
  setcolor(lightgreen);
  temp:=sense/range;
  eog_gain:=trunc(temp);
  outtextxy(450,279,'EOG Gain = '+int_str(eog_gain));
  setcolor(white);

outtextxy(40,297,'Enter patient name (MAX 20 characters)=>');
gotoxy(47,22);
setcolor(lightgreen);
readln(pt_name);
setcolor(white);
outtextxy(40,311,'Enter filename for data storage (MAX 8 characters) =>');
gotoxy(60,23);
setcolor(lightgreen);
readln(file_name);
```

```
    setcolor(white);
    textcolor(white);

                        {zero cursor buffers}
    FillChar(tgt1_mag,sizeof(tgt1_mag),0);
    FillChar(tgt2_mag,sizeof(tgt2_mag),0);
    FillChar(ntgt_mag,sizeof(ntgt_mag),0);
    FillChar(tgt1_ltncy,sizeof(tgt1_ltncy),0);
    FillChar(tgt2_ltncy,sizeof(tgt2_ltncy),0);
    FillChar(ntgt_ltncy,sizeof(ntgt_ltncy),0);

                {zero r_t buffer}
    FillChar(r_times,sizeof(r_times),0);

    end;{with f_head}
    settextstyle(1,0,2);
end;
(*****************************************************************************)
procedure create_buffer;
{creates space on drive C for 40 tgt and 360 non_tgt sweeps, 6 channels}
var dummy:word;
    ct:integer;
begin
    cleardevice;
    outtextxy(200,100,'CREATING BUFFER SPACE');

    assign(tgt_buf,'c:\tgt.buf');
    rewrite(tgt_buf,2);          {rec size 2 bytes - 1 integer}
    For ct:=1 to 2 do blockwrite(tgt_buf,dummy,30000); {40 targets/6 ch max}

    close(tgt_buf);

    assign(ntgt_buf,'c:\n_tgt.buf');
    rewrite(ntgt_buf,2);
    For ct:=1 to 18 do blockwrite(ntgt_buf,dummy,30000); {360 ntgts/6 ch max}
    close(ntgt_buf);

end;
(*****************************************************************************)
procedure Draw_xax(x_1st,y_1st,n_xax,x_stp,x_tic:integer);
{start position(x,y), no of steps, size of steps, width of xtics}
      var
      x_step_count, x_inc,x_pos, y_pos : integer;
begin
      x_inc:=x_stp;
      moveto(x_1st,y_1st+x_tic);lineto(x_1st,y_1st-x_tic);  {draw 1st xtic}
      moveto(x_1st,y_1st);
            FOR x_step_count:=1 TO n_xax do      {draw x-axis}
            begin
                x_pos:=x_1st+x_inc;y_pos:=y_1st-x_tic;
              lineto(x_pos,y_1st);moveto(x_pos,y_pos);
```

```
            lineto(x_pos,y_pos+(2*x_tic));moveto(x_pos,y_1st);
            x_inc:=x_inc+x_stp;
          END; {for}
end;
(*************************************************************************)
procedure Draw_yax(x_1st,y_1st,n_yax,y_stp,y_tic:integer);
{start position(x,y), no of steps, size of steps, width of ytics}
      var
      y_inc,x_pos, y_pos, y_step_count : integer;

begin
      y_inc:=y_stp;
      moveto(x_1st-y_tic,y_1st);lineto(x_1st+y_tic,y_1st);  {draw 1st ytic}
      moveto(x_1st,y_1st);
            FOR y_step_count:=1 TO n_yax do          {draw y-axis}
              begin
                x_pos:=x_1st+y_tic;y_pos:=y_1st-y_inc;
                lineto(x_1st,y_pos);moveto(x_pos,y_pos);
                lineto(x_pos-(2*y_tic),y_pos);moveto(x_1st,y_pos);
                y_inc:=y_inc+y_stp;
              END; {for}
end;
(*************************************************************************)
procedure label_xax(x1st,y1st,n_lab,lab_inc,x_inc:integer;
                          lab_val:real;units:string);
var
  x_lab_count : integer;
begin
    FOR x_lab_count:=1 to n_lab do
      begin
      outtextxy(x1st,y1st,int_str(round(lab_val)));
      lab_val:=lab_val+lab_inc;
      x1st:=x1st+x_inc;
    end; {for}
    outtextxy(x1st-35,y1st+10,units)
end;
(*************************************************************************)
procedure label_yax(x1st,y1st,n_lab:integer;lab_inc:real;y_inc,lab_val:integer;
                          units:string);
var
  y_lab_count : integer;
begin
    FOR y_lab_count:=1 to n_lab do
      begin
        IF lab_val=0 THEN outtextxy(x1st,y1st,'') ELSE
          outtextxy(x1st,y1st,int_str(lab_val));
        lab_val:=round(lab_val+lab_inc);
        y1st:=y1st-y_inc;
    end; {for}
    outtextxy(x1st-35,y1st+20,units)
end;
```

```
(*************************************************************************)
procedure Zero_storage_mem;
{zeros storage memory block}
var
count : integer;
begin
        FillChar(store_block,sizeof(store_block),0);
        FillChar(filter_store,sizeof(filter_store),0);
end;
(*************************************************************************)
procedure buffer_to_store(s_loc:integer);
{create rare/ frequent average}
var
sam_ct,ch_ct,data,buf_ofs,ch_ofs,t_nt_ofs: integer;
begin

with f_head do begin
    For ch_ct:=1 to channels do
    begin
       buf_ofs:=ch_ct;
        ch_ofs:=(ch_ct-1)*((samples div channels)*2);

         For sam_ct := 0 to (samples  div channels)-1 do
        begin
            data:=buffer[buf_ofs];
            t_nt_ofs:=s_loc+sam_ct;
            store_block[(ch_ofs+t_nt_ofs)]:=
            store_block[(ch_ofs+t_nt_ofs)]+data;
              inc(buf_ofs,channels);
        end; {for sam_ct}
    end;{for ch_ct}

    {now transfer averaged data to filter_store}
    For ch_ct:=1 to channels do begin
      ch_ofs:=(ch_ct-1)*(samples div channels);
      for sam_ct:=0 to (samples div channels)-1 do begin
        t_nt_ofs:=s_loc+sam_ct;
        filter_store[ch_ofs+sam_ct+1]:=store_block[(ch_ofs*2)+t_nt_ofs];
      end;
    end;{for ch_}

end;{with}
end;
(*************************************************************************)
procedure buffer_to_buffer2;
{sort data according to ch - sampled s1c1,s1c2...snc1,snc2..}
var
sam_ct,ch_ct,buf_ofs,ch_ofs: integer;
begin
with f_head do begin
    For ch_ct:=1 to channels do
```

```
    begin
       buf_ofs:=ch_ct;
        ch_ofs:=(ch_ct-1)*(samples div channels);

         For sam_ct := 1 to (samples  div channels) do
        begin
            buffer2[ch_ofs+sam_ct]:=buffer[buf_ofs];
              inc(buf_ofs,channels);
        end; {for sam_ct}

    end;{for ch_ct}
    end;{with}
end;
(*************************************************************************)
procedure io_err(var f_nam:file);  {report runtime disk errs}
begin
    case ioresult of
        2:begin
                sound(1000);delay(200);nosound;
                   outtextxy(0,200,
                'Must enter a filename !! - enter then try again ');
                ioerr:=true;
                repeat until keypressed;dummy:=readkey;
                readln(file_name);
            end;
        101:begin
                sound(1000);delay(200);nosound;
                   outtextxy(0,200,
                'DISK FULL !! - Load new disk and ENTER');
                ioerr:=true;close(f_nam);erase(f_nam);
                repeat until keypressed;dummy:=readkey;
             end;
        105:begin
                sound(1000);delay(200);nosound;
                   outtextxy(0,200,
                'CANT OPEN FILE - ENTER and try again');
                ioerr:=true;repeat;until keypressed;dummy:=readkey;
            end;
       150:begin
              sound(1000);delay(200);nosound;
                 outtextxy(0,200,
              'DISK WRITE-PROTECTED - Correct then ENTER');
              ioerr:=true;repeat;until keypressed;dummy:=readkey;
          end;
    end;{caseof}
end;
(*************************************************************************)
procedure check_disk;
begin
   repeat
      findfirst('a:\*.*',$3f,dirinfo);
```

```
      dir_error
  until (doserror=0) or (doserror=18);

  If diskfree(1) < 1205000 then
  begin
      disk_err:=true;
       outtextxy(0,100,'NOT ENOUGH ROOM ON DISK - REPLACE then press key');
       dummy:=readkey;repeat until keypressed;
  end;
end;
(*************************************************************************)
procedure sort_data;
{read from drive c:, sort, write to drive a:}
var
count,count2,sam_ct : integer;
mean_val            : real;
avet                : text;{matlab}
begin
    cleardevice;
    settextstyle(1,0,3);
    outtextxy(10,100,'ENSURE AN EMPTY, FORMATTED DISK IS LOADED IN A :');
    outtextxy(160,140,'THEN PRESS KEY TO CONTINUE');
    repeat until keypressed;

{$I-}
   repeat       {check inserted,formatted and enough space}
      disk_err:=false;
       cleardevice;
      check_disk;
  until not disk_err;

                  {1st write away file_head}
    repeat
        cleardevice;
        outtextxy(80,100,'SORTING DATA AND WRITING TO DRIVE A :');
        ioerr:=false;
        assign(disk_file,'a:\'+file_name+'.fhd');
        rewrite(disk_file,1);
        io_err(disk_file);              {check for io errors}
        blockwrite(disk_file,f_head,sizeof(f_head));
    until not ioerr;

    close(disk_file);
                      { sort target data }

    assign(tave,'a:\'+file_name+'.tav');{create 'av' target file on a:}
    rewrite(tave,4);                    {4 byte record for long_int}
    assign(tdat,'a:\'+file_name+'.trw');{create file for raw tgt data on a:}
    rewrite(tdat,2);
    reset(tgt_buf,2);                   {open tgt buffer file on c:}
```

```
with f_head do begin
    count2:=samples div channels;  {250}
    For count:=1 to n_tgt1 do
    begin
        blockread(tgt_buf,buffer[1],samples);
        buffer_to_store(1);                {build up tgt 'average'}
        buffer_to_buffer2;        {sort tgt data according to channel}
        blockwrite(tdat,buffer2[1],samples);  {then write to a:}
    end;

    For count:=1 to channels do begin
      {1st remove offsets}
      mean_val:=0;
      For sam_ct:=1 to count2 do
          mean_val:=mean_val+store_block[sam_ct+((count-1)*2*count2)];

      mean_val:=mean_val/count2;

      For sam_ct:=1 to count2 do
          store_block[sam_ct+((count-1)*2*count2)]:=
          store_block[sam_ct+((count-1)*2*count2)]-round(mean_val);

      {write to tave from store_blk}
      blockwrite(tave,store_block[(count2*2)*(count-1)+1],count2);

    end;{for count}
    close(tave);
    close(tdat);

    {now smooth target then store on disk}
    assign(tave,'a:\'+file_name+'.t10'); {create smoothed rare av file on a:}
    rewrite(tave,4);

    smooth_data(filter_store,filter_store);
   {remove offsets after filtering}
    For count:=1 to channels do begin
      mean_val:=0;
      For sam_ct:=1 to 63 do   {pre_stim}
          mean_val:=mean_val+filter_store[sam_ct+((count-1)*count2)];

      mean_val:=mean_val/63;

      For sam_ct:=1 to count2 do
          filter_store[sam_ct+((count-1)*count2)]:=
          filter_store[sam_ct+((count-1)*count2)]-round(mean_val);
    end;{for count}

    blockwrite(tave,filter_store[1],1500);
    close(tave);

                        { sort non_tgt data }
```

```
    assign(ntave,'a:\'+file_name+'.nav');{create 'av' non_tgt file on a:}
    rewrite(ntave,4);                    {4 byte record for long_int}

    assign(ntdat,'a:\'+file_name+'.nrw');{create file for raw ntgt data on a:}
    rewrite(ntdat,2);

    reset(ntgt_buf,2);                   {open ntgt buffer on c:}

    For count:=1 to n_nontgt do
    begin
        blockread(ntgt_buf,buffer[1],samples);
        buffer_to_store(251);      {build up non-tgt 'average'}
      buffer_to_buffer2;         {sort ntgt data according to ch}
        blockwrite(ntdat,buffer2[1],samples);{then write to a:}
    end;

    For count := 1 to channels do begin

          {1st remove offsets}
      mean_val:=0;
      For sam_ct:=1 to count2 do
         mean_val:=mean_val+store_block[sam_ct+250+((count-1)*2*count2)];

      mean_val:=mean_val/count2;

      For sam_ct:=1 to count2 do
         store_block[sam_ct+250+((count-1)*2*count2)]:=
         store_block[sam_ct+250+((count-1)*2*count2)]-round(mean_val);

         {write to ntave from store_blk}
      blockwrite(ntave,store_block[((count-1)*(2*count2))+251],count2);

    end;{for count}

end; {with f_head}

    close(ntave);
    close(ntdat);
    {now smooth freq then store on disk}
    assign(ntave,'a:\'+file_name+'.n10');{create smoothed freq av file on a:}
    rewrite(ntave,4);

    smooth_data(filter_store,filter_store);
   {remove offsets after filtering}
    For count:=1 to f_head.channels do begin
      mean_val:=0;
      For sam_ct:=1 to 63 do   {pre_stim}
         mean_val:=mean_val+filter_store[sam_ct+((count-1)*count2)];

      mean_val:=mean_val/63;
```

```
      For sam_ct:=1 to count2 do
          filter_store[sam_ct+((count-1)*count2)]:=
          filter_store[sam_ct+((count-1)*count2)]-round(mean_val);
    end;{for count}

    blockwrite(ntave,filter_store[1],1500);
    close(ntave);

{$I+}
end;
(*****************************************************************************)
procedure buffer_to_disk(trig_type:integer);
begin
    case trig_type of
        $304: blockwrite(tgt_buf,buffer[1],f_head.samples);
        $308: blockwrite(ntgt_buf,buffer[1],f_head.samples);
    end;
end;
(*****************************************************************************)
function ave_dat(sweeps,ct:integer):real;
{averages each data point over n sweeps}
        begin
             ave_dat:=store_block[ct]*(scale/sweeps);
        end;
(*****************************************************************************)
procedure snap_show(x1,y1:integer);
var ct,x_stp,y_stp,max_ch,ch_show:integer;
begin
   scale:=100/4096;
   If ch_left>1 then max_ch:=2 else max_ch:=1;

   For ch_show:=1 to max_ch do
   begin
    setcolor(ch_pt+9);
    outtextxy(x1,y1-60,'C'+int_str(ch_pt));

    ct:=1;
    repeat
        x_stp:=x1+ct;
          y_stp:=(y1-round(buffer[ch_pt]*scale));
        If ct=1 then moveto(x1,y_stp);
        lineto(x_stp,y_stp);
          inc(ch_pt,6*f_head.channels);
          inc(ct,6);                              {draw every 6th data point}
    until ct=253;

    dec(ch_left,1);
    ch_pt:=(f_head.channels-ch_left)+1;
    x1:=350;
   end;
end;
```

```
(*************************************************************************)
procedure collect_data;
var rt_rej_ctr,temp_ct,r_ct,f_ct,trig_num,last_trig:integer;
Key:char;
no_rt_flg:boolean;
flg:string;
prob_r:real;

begin
with f_head do begin
        settextstyle(2,0,6);
        outtextxy(250,150,'Collecting data');

        n_tgt1:=0;n_nontgt:=0;n_rej:=0;f_ct:=0;r_ct:=0;rt_rej_ctr:=0;

        randomize;

  REPEAT

    trig_num:=random(1000);

    IF (trig_num > (rare_p*1000)) or (last_trig=$304)
    THEN  begin trigger_type:=$308;inc(f_ct); end     {freq}

    ELSE  begin trigger_type:=$304;inc(r_ct); end;    {rare}

    last_trig:=trigger_type;

    rej_flg:=false;r_t:=0;r_t_flg:=false;{'zero' flags}

    d16_ainsc(0,0,channels-1,1,0,1,samples,rate,buffer[0], err_code);

    REPEAT
        d16_dma_int_status(0, op_type, status, next_count, err_code);
        {wait until interrupts complete}
    UNTIL status=0;

    {now monitor for rejected rares and no-button-press rares}
    IF test_type='R_TIME' THEN
     begin
      If (trigger_type=$304) AND (r_t< trigger_point) and (not(rej_flg))
      then begin
        rej_flg:=true;inc(n_rej);inc(rt_rej_ctr);
        {count no_b_p rare (n_rej) and add to total rej ct (rt_rej_ctr)}
      end;
     end;
    IF not(rej_flg) THEN  {no rej - save data}
      begin
        buffer_to_disk(trigger_type);
         IF trigger_type=$304 THEN inc (n_tgt1) ELSE inc (n_nontgt);
        end
```

```
ELSE                    {rej_flg set}
 if (test_type='R_TIME') and (trigger_type <> $304)
 then inc (rt_rej_ctr)
          {n_rej=no_b_p rares, rt_rej_ctr=all rejects}
 else
 if (test_type='T_COUNT') then
  begin
    case trigger_type of
     $304: begin inc(n_rej);inc(rt_rej_ctr);end;
     {increment rare_rej ct (rt_rej_ct) & total rej ct}
     $308: inc(n_rej);
     {increment total reject count}
    end;{case}
  end;

IF (trigger_type=$304) AND (r_t>trigger_point) AND (test_type='R_TIME')
THEN r_times[n_tgt1]:=((r_t-trigger_point)*((1/rate)*1000))-30;
      {r_t in ms, adjusted for delay from mouse}

prob_r:=0;
if (r_ct>0) and (f_ct>0) then prob_r:=(r_ct/(r_ct+f_ct));

cleardevice;
outtextxy(70,0,'To PAUSE press KEY              To STOP press S');

IF test_type='T_COUNT' THEN begin
 outtextxy(60,463,''+int_str(n_tgt1)+' rare  '+int_str(n_nontgt)+
 ' freq  '+int_str(n_rej)+' rej  '+int_str(rt_rej_ctr)+' r_rej '
  +'  P_rare:='+real_str(prob_r,1,3));
end
ELSE begin  {R_TIME}
  outtextxy(20,463,''+int_str(n_tgt1)+' rare  '+int_str(n_nontgt)+
  ' freq  '+int_str(rt_rej_ctr)+' rej  '+int_str(n_rej)+' r_rej  '+
  'r_t='+real_str(r_times[n_tgt1],1,1)+'ms' +'  P_rare:='+
  real_str(prob_r,1,3));
end;

ch_pt:=1;ch_left:=channels;
snap_show(40,95);
If ch_left>0 then begin
 snap_show(40,240);
 snap_show(40,395);
end;{if}

If keypressed then begin {pause loop}
   setviewport(0,0,600,30,clipoff);
   clearviewport;
   outtextxy(180,0,'PAUSING - TO CONTINUE PRESS C');
   repeat
        key:=upcase(readkey)
   until (key='C') or (key='S');
```

```
    end;{if}

    {introduce random delay to cancel alpha activity}
    i_s_i:=random(125);
    delay(i_s_i);

    UNTIL (n_tgt1=sweep_tgt) or (n_nontgt=360) or (key='S');
    delay(1000);
    color_box(60,0,550,30,green);
    sound(1500);delay(200);nosound;sound(200);delay(400);nosound;
    outtextxy(100,5,'  TEST COMPLETE - PRESS KEY TO CONTINUE');
    repeat until keypressed; {pause to allow note of rare_rejects}

    cleardevice;
    setcolor(15);
    outtextxy(0,10,
    'Do you wish to enter any comments before saving data ?  Y  or N');
    repeat
        answer :=upcase(readkey)
    until (answer='Y') or (answer='N');

    If answer='Y' then begin
       outtextxy(0,30,'Input up to 146 characters');
       gotoxy(1,4);readln(comments);
    end;{if}
end;{with}
end;
(*****************************************************************************)
procedure demo_tones;
var
ans : char;
ct  : integer;

begin

    cleardevice;
    outtextxy(120,50,'To demonstrate RARE tone press key R');
    outtextxy(100,80,'To demonstrate FREQUENT tone press key F');
    outtextxy(0,110,
    'To demonstrate a run of 9 frequent with 1 rare tone key D');
    outtextxy(160,250,'TO START TEST PRESS SPACEBAR');

    repeat
       ans:=upcase(readkey);
       If ans='R' then begin
         port[$304]:=0;port[$300]:=0;end;

       If ans='F' then begin
         port[$308]:=0;port[$300]:=0;end;

        If ans='D' then begin
```

```
          For ct:= 1 to 10 do begin
               If ct=6 then begin
                  port[$304]:=0;port[$300]:=0;end
               else
               begin
                  port[$308]:=0;port[$300]:=0;
               end;
          delay(1100);
          end;{for}
        end;{if}

    until ans=' ';
end;
(*************************************************************************)
procedure set_gain;
begin
    color_box(0,10,350,35,9);
    setcolor(12);
    outtextxy(20,15,'Use UP/DOWN ARROW KEYS to change GAIN');
    setcolor(15);
    outtextxy(60,25,'Press SPACEBAR to continue');
    repeat
        key:=ord(readkey);
    until (key=72) or (key=80) or (key=32);

    If key=72 then gain:=gain+1
    else
    If (key=80) and (gain>1) then gain:=gain-1;
end;
(*************************************************************************)
procedure draw_data(x_1st,y_1st:integer;ext:string);
var
ave_tot,ct, x_stp, y_stp : integer;
y_sc:real;

begin
with f_head do begin

    If ch<channels then
    y_sc:=(((fs_eeg/2)/eeg_gain)*1e6)*(1/gain)
    else
    y_sc:=(((fs_eog/2)/eog_gain)*1e6)*(1/gain);

    cleardevice;
    setcolor(15);
    draw_xax(70,175,10,50,5);
    label_xax(50,185,11,100,50,-250,'ms');
    draw_yax(195,300,10,25,5);
    outtextxy(130,45,'+'+real_str(y_sc,1,2));
    outtextxy(130,295,'-'+real_str(y_sc,1,2));
    outtextxy(150,165,'uV  0');
```

```
    scale:=250/4096;

    outtextxy(50,0,'Gain = '+real_str(gain,0,0));

    If ext='.tav' then outtextxy(150,0,'B/W = 0.16 - 30 Hz')
    else if ext='.t10' then outtextxy(150,0,'B/W = 0.16 - 10 (b-d) Hz')
    else if ext='.t01' then outtextxy(150,0,'B/W = 1 - 10 (b-d) Hz')
    else if ext='.t02' then outtextxy(150,0,'B/W = 2 - 10 (b-d) Hz');

    outtextxy(400,0,'Channel '+int_str(ch));

    setcolor(10);
    outtextxy(400,10,'rare responses = '+int_str(n_tgt1));

    moveto(x_1st,y_1st);    {draw target data}
    For ct:=1 to (samples div channels) do begin
       x_stp:=(2*ct)+71;
       y_stp:=175-round(gain*(ave_dat(n_tgt1,ct+(500*(ch-1)))));
       IF ct=1 THEN moveto(x_stp,y_stp);
       lineto(x_stp,y_stp);
    end;{for}

    setcolor(lightblue);
    outtextxy(400,30,'rejects = '+int_str(n_rej));

    setcolor(14);
    outtextxy(400,20,'frequent responses = '+int_str(n_nontgt));

    moveto(x_1st,y_1st);
    For ct:=(samples div channels)+1 to 2*(samples div channels) do
    begin
        x_stp:=(2*ct)-500+71;
        y_stp:=175-round(gain*(ave_dat(n_nontgt,ct+(500*(ch-1)))));
        IF ct=251 THEN moveto(x_stp,y_stp);
        lineto(x_stp,y_stp);
    end;{for}
end;{with}
end;
(*************************************************************************)
procedure draw_all(x_1st,y_1st:integer);
{draws all 5 channels of rare response only, for P3 LMS fit}
const ch_cols:array[1..6] of integer=(12,13,9,10,7,15);
     ch_lbl:array[1..6] of string=('Fz','Cz','Pz','T3','T4','EOG');
var y_sc:real;
x_stp,y_stp,ch_ct,s_ct,eog_sc:integer;

begin
cleardevice;
with f_head do begin
  y_sc:=(((fs_eeg/2)/eeg_gain)*1e6)*(1/gain);
  setcolor(15);
```

```
  draw_xax(70,175,10,50,5);
  label_xax(50,185,11,100,50,-250,'ms');
  draw_yax(195,300,10,25,5);
  outtextxy(130,45,'+'+real_str(y_sc,1,2));
  outtextxy(130,295,'-'+real_str(y_sc,1,2));
  outtextxy(150,165,'uV  0');
  scale:=250/4096;
  eog_sc:=f_head.eeg_gain div f_head.eog_gain;

  For ch_ct:=1 to 6
   do begin
      setcolor(ch_cols[ch_ct]);
      moveto(x_1st,y_1st);
      For s_ct:=1 to (samples div channels) do begin
          x_stp:=(2*s_ct)+71;
          y_stp:=175-round(gain*(ave_dat(n_tgt1,s_ct+(500*(ch_ct-1)))));
          if ch_ct=6 then y_stp:=
          175-round(eog_sc*gain*(ave_dat(n_tgt1,s_ct+(500*(ch_ct-1)))));
          If s_ct=1 then moveto(x_stp,y_stp);
          lineto(x_stp,y_stp);
       end;
  outtextxy(420+((ch_ct-1)*30),10,ch_lbl[ch_ct]);
  end;
end;
end;
(*************************************************************************)
procedure peak_search(var sample_no :real;swp_ct:integer);
{looks 6 samples (24 ms) either side of selected point for a min or max t.p.}
var
t_p,s_n,count:integer;
mean,val,sum:real;
max:boolean;

begin
s_n:=round(sample_no);
sum:=0;
                {1st, get mean value of 13 data points}
For count:=s_n-6 to s_n+6 do begin
   sum:=sum+ave_dat(swp_ct,count);
end;{for}
mean:=sum/13;

                {See if its a max or min t.p. - approx method}
max:=(ave_dat(swp_ct,s_n) > mean);   {max t.p.}

                {Now get sample-number associated with t.p.}
val:=ave_dat(swp_ct,s_n-6);
IF max then begin
  For count:=s_n-6 to s_n+6 do
   If ave_dat(swp_ct,count) > val then begin
         val:=ave_dat(swp_ct,count);
```

```
        sample_no:=count;
    end
 end
ELSE
  For count:=s_n-6 to s_n+6 do
     If ave_dat(swp_ct,count) < val then begin
        val:=ave_dat(swp_ct,count);
        sample_no:=count;
      end;

end;
(*************************************************************************)
procedure pre_stim_base(var t_ofs,nt_ofs:real;chan:integer);
{evaluate pre_stim mean for reference}
var s_n:integer;
begin

t_ofs:=0;
for s_n:=1 to 61 do                {tgt}
   t_ofs:=t_ofs+ave_dat(f_head.n_tgt1,s_n+(500*(chan-1)));
t_ofs:=t_ofs/s_n;

nt_ofs:=0;                         {non_tgt}
for s_n:=1 to 61 do
   nt_ofs:=nt_ofs+ave_dat(f_head.n_nontgt,s_n+250+(500*(chan-1)));
nt_ofs:=nt_ofs/s_n;

end;
(*************************************************************************)
procedure cursor;
{uses int $33 for mouse/cursor operations}
var
c_x,ct,count:integer;
t_ofs,nt_ofs,sample_no:real;

begin
with f_head do begin

      proc_flg:=true;
      setviewport(0,330,639,349,clipon);
      clearviewport;
      graphdefaults;

       {scale is fed to function ave_dat}
      If ch < channels then scale:=((1e6/eeg_gain)/2)/2048
      else scale:=((1e6/eog_gain)/2)/2048;

      pre_stim_base(t_ofs,nt_ofs,ch);

      color_box(0,10,350,40,13);
      setcolor(15);
```

```
    outtextxy(15,15,'Use mouse to mark');
    setcolor(10);outtextxy(160,15,'RARE');setcolor(15);
    outtextxy(200,15,'features (8 max)');
    outtextxy(15,25,'Left button selects, right button to stop');
    setlinestyle(0,0,1);

    with mouse do
    begin
        AX:=0;
          Intr($33,mouse);              {reset all mouse drivers}

          AX:=7;CX:=73;DX:=571;  {define mouse horizontal limits}
        Intr($33,mouse);

        AX:=8;CX:=50;DX:=300;    {define vertical limits}
        Intr($33,mouse);

        AX:=4;CX:=73;DX:=50;     {start position}
          Intr($33,mouse);

        AX:=15;CX:=4;DX:=8;      {set m/p ratio}
        Intr($33,mouse);             {to move in 4ms steps}

        AX:=1;                        {show cursor}
          Intr($33,mouse);
     end;

count:=1;
REPEAT
      repeat
        with mouse do
        begin
            AX:=3;          {monitor mouse buttons}
          Intr($33,mouse);
        end;
      until ((mouse.BX)=1) or ((mouse.BX)=2);   {left/right buttons}

      IF (mouse.BX)=1 THEN
      begin
        with mouse do
        begin
            AX:=4;CX:=CX+10;    {jump cursor right by 10}
          Intr($33,mouse);delay(300);
        end;

        sample_no:=((mouse.CX-81)/2)+(500*(ch-1));
       {73 is mouse start_pos, added 10 in "jump"!}

       peak_search(sample_no,f_head.n_tgt1);

       c_x:=round(71+2*(sample_no-((ch-1)*500)));
```

```
        moveto(c_x,mouse.DX+10); {draw "feature" line}
        lineto(c_x,mouse.DX-10);

        tgt1_ltncy[ch,count]:=4*(sample_no-(500*(ch-1)))-248;

        tgt1_mag[ch,count]:=ave_dat(n_tgt1,round(sample_no))-nt_ofs;
                                        {subtract nt_ofs!!!}
        outtextxy(c_x,mouse.DX-20,'r'+int_str(count));

      If count<5 then
      begin
          ct:=0;

          outtextxy(ct,300+(count*10),'r'+int_str(count)+
            '='+real_str(tgt1_ltncy[ch,count],1,2)+' '+
            real_str(tgt1_mag[ch,count],1,2)+'uV');
      end

      else
      begin
          ct:=160;
          outtextxy(ct,260+(count*10),'r'+int_str(count)+
            '='+real_str(tgt1_ltncy[ch,count],1,2)+' '+
            real_str(tgt1_mag[ch,count],1,2)+'uV');
      end;

        inc(count);
     end;

UNTIL ((mouse.BX)=2) or (count=9);                {right button press}

setviewport(0,0,360,40,clipon);
clearviewport;

color_box(0,10,350,40,13);

outtextxy(5,15,'Use mouse to mark');
setcolor(14);outtextxy(150,15,'FREQUENT');setcolor(15);
outtextxy(220,15,'features (8 max)');
outtextxy(5,25,'Left button selects, right button to stop');

graphdefaults;

with mouse do          {reset}
begin
    AX:=0;
    Intr($33,mouse);
end;

with mouse do
begin
```

```
    AX:=7;CX:=73;DX:=571;          {define mouse horizontal limits}
    Intr($33,mouse);

    AX:=8;CX:=50;DX:=300;          {define vertical limits}
    Intr($33,mouse);

    AX:=4;CX:=73;DX:=50;  {start position}
    Intr($33,mouse);

    AX:=15;CX:=4;DX:=8;    {set m/p ratio}
    Intr($33,mouse);          {to move in 4ms steps}

    AX:=1;                  {show cursor}
    Intr($33,mouse);
end;

count:=1;
REPEAT
      repeat
        with mouse do
        begin
             AX:=3;          {monitor mouse buttons}
          Intr($33,mouse);
        end;
      until ((mouse.BX)=1) or ((mouse.BX)=2);   {left/right buttons}

      IF (mouse.BX)=1 THEN
      begin
        with mouse do
        begin
             AX:=4;CX:=CX+10;    {jump cursor right by 10}
          Intr($33,mouse);delay(300);
        end;

        sample_no:=((mouse.CX-81)/2)+(500*(ch-1))+250;
       {73 is mouse start_pos, added 10 in "jump"!}

       peak_search(sample_no,f_head.n_nontgt);

       c_x:=round(71+2*(sample_no-(((ch-1)*500)+250)));

        moveto(c_x,mouse.DX+10); {draw "feature" line}
        lineto(c_x,mouse.DX-10);

        ntgt_ltncy[ch,count]:=4*(sample_no-((500*(ch-1))+250))-248;

        ntgt_mag[ch,count]:=ave_dat(n_nontgt,round(sample_no))-nt_ofs;
                                        {subtract nt_ofs!!!}

        outtextxy(mouse.CX-10,mouse.DX-20,'f'+int_str(count));
```

```
        If count<5 then
        begin
            ct:=320;

              outtextxy(ct,300+(count*10),'f'+int_str(count)+
                '='+real_str(ntgt_ltncy[ch,count],1,2)+' '+
                real_str(ntgt_mag[ch,count],1,2)+'uV');
        end

        else
        begin
            ct:=470;
            outtextxy(ct,260+(count*10),'r'+int_str(count)+
                '='+real_str(ntgt_ltncy[ch,count],1,2)+' '+
                real_str(ntgt_mag[ch,count],1,2)+'uV');
        end;

          inc(count);
       end;

  UNTIL ((mouse.BX)=2) or (count=9);                {right button press}

        with mouse do
        begin
                AX:=2;                          {hide cursor}
            Intr($33,mouse);
        end;
   end;{with}
end;
(*****************************************************************************)
procedure lms_fit;

const ch_cols:array[1..5] of integer=(12,13,9,10,7);

var
x_stp,y_stp,max_val,ofs:integer;
s_ct,count,pk:integer;
t_ofs,nt_ofs:real;
point:array [1..2] of integer;
w_width:boolean;

{declare vars for Leastsqr solution}
x_data, y_data          : TNColumnVector;
Numpoints, Numterms     : integer;
Solution                : TNRowVector;
YFit, Residuals                 : TNColumnVector;
StdDeviation,Variance   : Float;
Fit                     : FitType;
Error                   : byte;

{declare vars for Roots}
```

```
Degree, Numroots,
MaxIter              : integer;
InitGuess            : TNComplex;
Roots, yRoots, D_soln  : TNCompvector;
Iter                 : TNIntVector;
Tol                  : Float;

begin

 REPEAT

  graphdefaults;
  draw_all(70,300);

  scale:=250/4096;

  color_box(0,0,390,40,13);
  setcolor(4);
  outtextxy(5,5,'Use to deal with multi-peak P3 complex only !!!');
  setcolor(15);
  outtextxy(10,15,'Use the mouse cursor to select LMS fit limits');
  outtextxy(55,25,'LEFT button selects - TWO points only');

  with mouse do begin
      AX:=0;
      Intr($33,mouse);            {reset all mouse drivers}

      AX:=7;CX:=73;DX:=571;       {define mouse horizontal limits}
      Intr($33,mouse);

      AX:=8;CX:=50;DX:=300;       {define vertical limits}
      Intr($33,mouse);

      AX:=4;CX:=73;DX:=50;  {start position}
      Intr($33,mouse);

      AX:=15;CX:=4;DX:=8;   {set m/p ratio}
      Intr($33,mouse);          {to move in 4ms steps}

      AX:=1;                    {show cursor}
      Intr($33,mouse);
  end;

  for count := 1 to 2 do begin
     repeat
       with mouse do begin
         AX:=3;Intr($33,mouse); {monitor for left button press}
       end;
     until mouse.BX=1;

     with mouse do begin
```

```
        AX:=4;CX:=CX+10; {jump right by 10}
        Intr($33,mouse);delay(300);
    end;

    point[count]:=round((mouse.CX-81)/2); {get sample number, related to ch1}

    moveto(mouse.CX-10,50);lineto(mouse.CX-10,300);{draw line at 'point'}
    outtextxy(mouse.CX,40+(10*count),int_str((4*(point[count])-248))+' ms');
  end;

  w_width:=(abs(point[1]-point[2]) < 101); {false when > 100}

  If not w_width then begin
    sound(300);delay(200);nosound;
    setviewport(0,0,390,40,clipon);
    clearviewport;
    color_box(0,0,390,40,13);
    setcolor(15);
    outtextxy(10,5,'Window width restricted to 100 points (396 ms)');
    outtextxy(150,15,'TRY AGAIN !!!!');
    setcolor(red);
    outtextxy(120,25,'PRESS KEY TO CONTINUE');
    setcolor(white);
    graphdefaults;
{    dummy:=readkey;}
    repeat until keypressed;
    dummy:=readkey;
  end;

UNTIL w_width;

with mouse do begin
    AX:=2;Intr($33,mouse);     {hide mouse cursor}
end;

setviewport(0,0,390,40,clipon);
clearviewport;

color_box(0,0,390,40,13);
setcolor(15);
outtextxy(60,10,'NOTE RESULTS - THEY ARE NOT SAVED !!!');
outtextxy(100,25,'Press any key to continue');

{Now get polynomial fit between 'points' and find peak, for each ch}

{1st - set up vars for Leastsqr}
for count:=1 to abs(point[1]-point[2]) do  {save time range in ms}
x_data[count]:=4*((count-1)+point[1])-248;

Numpoints:=abs(point[1]-point[2]);
Numterms:=4;                                {3rd-order Polynomial}
```

```
Fit:=Poly;                          {Chebyshev type}

For count := 1 to 5 do begin

  scale:=250/4096; {for screen}

              {transfer data values to y_data}
  for s_ct:=1 to abs(point[1]-point[2]) do
  y_data[s_ct]:=ave_dat(f_head.n_tgt1,((s_ct-1)+point[1])+((count-1)*500));

  FillChar(Solution,Sizeof(Solution),0);

  Leastsquares(Numpoints,x_data,y_data,Numterms,Solution,YFit,
              Residuals,StdDeviation,Variance,Error,Fit);

  max_val:=350;pk:=0;
  graphdefaults;  {Draw fit}
  for s_ct:=1 to abs(point[1]-point[2]) do begin
     x_stp:=2*((s_ct-1)+point[1])+71;
     y_stp:=175-round(gain*Yfit[s_ct]);
     If s_ct=1 then moveto(x_stp,y_stp);
     lineto(x_stp,y_stp);
     If y_stp < max_val then begin {get +ve peak}
        max_val:=y_stp;pk:=s_ct;
     end;
  end;
  pk:=4*(pk-1+point[1])-248;  {pk in ms}

  FillChar(D_soln,Sizeof(D_soln),0); {zero output arrays}
  FillChar(Roots,Sizeof(Roots),0);

  {Differentiate polynomial solution}
  For s_ct:=4 downto 2 do begin
     D_soln[s_ct-2].Re:=(s_ct-1)*Solution[s_ct];
     D_soln[s_ct-2].Im:=0;
  end;

  {set up vars for Root solution}
  Degree:=2;
  Numroots:=2;
  MaxIter:=100;
  InitGuess.Re:=pk;
  InitGuess.Im:=0;
  Tol:=1e-6;

  {Get roots of differentiated poly. by Laguerres method}
  Laguerre(Degree,D_soln,InitGuess,Tol,MaxIter,
              NumRoots,Roots,yRoots,Iter,Error);

  {get correct root for display}
  max_val:=32000;
```

```
  For s_ct:=0 to 2 do
     If abs(round(Roots[s_ct].Re) - pk) < max_val then begin
       max_val:=abs(round(Roots[s_ct].Re) - pk); ofs:= s_ct;
     end;

  {calculate y_value at this point}
  y_data[1]:=solution[4]*(Roots[ofs].Re*Roots[ofs].Re*Roots[ofs].Re)+
             solution[3]*(Roots[ofs].Re*Roots[ofs].Re)+
             solution[2]*Roots[ofs].Re+solution[1];

  scale:=(4096/250)*((1e6/f_head.eeg_gain)/2)/2048;
   {convert data at t.p. to scale in uV}

  y_data[1]:=y_data[1]*scale;

  scale:=((1e6/f_head.eeg_gain)/2)/2048;{for pre-stim baseline calc};
  pre_stim_base(t_ofs,nt_ofs,count);

  {Display result}
  color_box(0+(count-1)*128,310,120+(count-1)*128,345,ch_cols[count]);
  setcolor(black);
  outtextxy(25+(128*(count-1)),319,real_str(Roots[ofs].Re,1,2)+' ms');
  outtextxy(25+(128*(count-1)),331,real_str(y_data[1]-nt_ofs,1,2)+' uV');
  setcolor(white);
end;

repeat until keypressed;
dummy:=readkey;
end;
(*************************************************************************)
function sw_mean(s_n,sweeps:integer):real;
{get mean value of N3-700ms in rare}
var ct:integer;
sum:real;
begin
    sum:=0;
    for ct:=s_n to 237+((ch-1)*500) do
    begin
        sum:=sum+ave_dat(sweeps,ct);
    end;
    sw_mean:=sum/(238+((ch-1)*500)-s_n);
end;
(*************************************************************************)
procedure slow_wave;{allows calculation of mean SW value between N4 and 700 ms}
                    {referred to mean of pre-stim baseline, frequent response}

var s_n,c_x:integer;
   s_w_m,t_ofs,nt_ofs:real;
   out_of_range:boolean;
begin
```

```
repeat
  out_of_range:=false;
  setviewport(0,330,639,349,clipon);
  clearviewport;
  graphdefaults;

  If ch <f_head.channels then
  scale := ((1e6/f_head.eeg_gain)/2)/2048;

  pre_stim_base(t_ofs,nt_ofs,ch);
  color_box(0,10,350,40,lightred);
  setcolor(15);
  outtextxy(35,12,'USE LEFT MOUSE BUTTON TO SELECT N3');
  outtextxy(50,22,'Mean value between N3 and 700ms');
  outtextxy(70,32,'automatically calculated');
  setlinestyle(0,0,1);

  with mouse do
  begin
    AX:=0;
     Intr($33,mouse);          {reset all mouse drivers}

     AX:=7;CX:=73;DX:=571;     {define mouse horizontal limits}
    Intr($33,mouse);

    AX:=8;CX:=50;DX:=300;      {define vertical limits}
    Intr($33,mouse);

    AX:=4;CX:=73;DX:=50;       {start position}
     Intr($33,mouse);

    AX:=15;CX:=4;DX:=8;  {set m/p ratio}
    Intr($33,mouse); {to move in 4ms steps}

    AX:=1;                     {show cursor}
     Intr($33,mouse);
  end;

  repeat
    with mouse do begin
       AX:=3; {monitor mouse buttons}
       Intr($33,mouse);
    end;
  until mouse.BX=1;

  with mouse do begin
     AX:=4;CX:=CX+10;          {jump cursor right by 10}
     Intr($33,mouse);
  end;

  s_n:=((mouse.CX-81) div 2)+(500*(ch-1));
```

```
    out_of_range:=s_n-(500*(ch-1)) > 237;
    if out_of_range then begin
       sound(200);delay(300);nosound;
       color_box(0,10,350,40,red);
       setcolor(15);
       outtextxy(125,15,'OUT OF RANGE');
       outtextxy(100,30,'Select point < 700 ms');
       delay(1000);
    end;
  until not out_of_range;

    c_x:=71+2*(s_n-((ch-1)*500));
    moveto(c_x,mouse.DX+100);
    lineto(c_x,mouse.DX-100);
    s_w_m:=sw_mean(s_n,f_head.n_tgt1);

   with mouse do begin
       AX:=0;Intr($33,mouse); {reset}
       AX:=2;Intr($33,mouse); {hide cursor}
    end;
  color_box(150,310,490,345,lightblue);
  outtextxy(240,315,'N3 cursor at '+int_str(4*(s_n-(500*(ch-1)))-248)+' ms');
  outtextxy(195,325,'MEAN SLOW WAVE AMPLITUDE = '+real_str(s_w_m,1,1)+' uV');
  setcolor(red);
  outtextxy(225,335,'TO CONTINUE PRESS ANY KEY');
  setcolor(white);
  repeat until keypressed;
end;
(*****************************************************************************)
procedure save_cursor_data;
begin
    cleardevice;
    outtextxy(220,100,'Saving cursor data to disc');
{$I-}

(*temp f_head.eog_gain:=5000;*)

    repeat
        ioerr:=false;
        reset(disk_file,1);
        dir_error;
        blockwrite(disk_file,f_head,sizeof(f_head));
          io_err(disk_file);
    until not ioerr;
    close(disk_file);
{$I+}
end;
(*****************************************************************************)
procedure curs_opt;
{ allow selection of 'true' peak searching or least-squares-fit peak searcher}
var ky:char;
```

```
begin
    color_box(0,10,350,40,13);
    setviewport(0,10,350,40,clipon);
    outtextxy(15,12,'Cursor options : ');
    setcolor(11);
    outtextxy(150,2,'+ -  Peak search - key P');
    outtextxy(150,12,'P300 LMS fit     - key L');
    outtextxy(150,21,'Slow Wave mean   - key S');

    repeat
      ky:=upcase(readkey);
    until (ky='P') or (ky='L') or (ky='S');

    case ky of
      'P': cursor;
      'L': lms_fit;
      'S': slow_wave;
    end;
    clearviewport;
    graphdefaults;

end;
(*************************************************************************)
procedure display_channel;
var t_ofs,nt_ofs:real;
begin

     set_graphics(vga,vgamed);

repeat
     outtextxy(200,100,'Do you wish to inspect data ? Y or N');
     answer:=upcase(readkey);
until (answer='Y') or (answer='N');

If answer='Y' then
begin
    REPEAT
         gain:=1;
         repeat
              outtextxy(200,150,'Which channel for display 1 - '+
              int_str(f_head.channels));
              ch:=ord(readkey)-ord('0');
              cleardevice;
         until (ch > 0) and (ch < (f_head.channels));

         repeat
              draw_data(70,300,'.tav');
              set_gain;
         until key=32;

         setviewport(0,10,350,30,clipoff);
```

```
        clearviewport;

          repeat
            color_box(0,0,350,30,9);

            setcolor(12);
          outtextxy(50,5,'To process with CURSORS press C');
          setcolor(15);
          outtextxy(70,15,'Press SPACEBAR to CONTINUE');
          answer:=upcase(readkey);
          If answer='C' then
            begin
                clearviewport;
                graphdefaults;
                curs_opt;
            end;{if}
        until (answer='C') or (answer=' ');

        graphdefaults;
        cleardevice;
        outtextxy(200,100,'Display another channel ? Y or N');
        answer:=upcase(readkey);
    UNTIL answer='N';
end;{if}
end;
(*************************************************************************)
rocedure acquire;{collect data}

begin
    set_up;              {defaults & pt data}

    create_buffer;

    cleardevice;
    outtextxy(90,91,'How many target sweeps ? =>');
    gotoxy(52,8);
    readln(sweep_tgt);

    demo_tones;

    set_graphics(vga,vgahi);

    d16_init(0,816,3,1,err_code);
    delay(1000);

    Zero_storage_mem;

    reset(tgt_buf,2);            {open buffers ready for single sweep data}
    reset(ntgt_buf,2);

    collect_data;
```

```
    close(tgt_buf);
    close(ntgt_buf);

    sort_data;      {sort data from c: buffer - write to a:}

    cleardevice;

    display_channel;{look at individual channel data}

    If f_head.proc_flg then  save_cursor_data;
    acq_flg:=true;
end;
(*****************************************************************************)
procedure check_dir;
begin
   repeat
        cleardevice;
        findfirst('a:\*.*',$3f,dirinfo);
        dir_error;
   until (doserror=0) or (doserror=18);
end;
(*****************************************************************************)
procedure load_f_head(var f_name:string;answer:string);
begin
    repeat
      (*color_box(195,95,450,115,lightblue);
      outtextxy(200,100,'Enter filename:');
        ioerr:=false;
      gotoxy(44,8);
      readln(f_name);*)

      {do a blind file read}
{       f_name:='*';        }
      ioerr:=false;
      findfirst('a:\f_name.fhd',$3F,dirinfo);
      delete(dirinfo.name,length(dirinfo.name)-3,4);
      f_name:=dirinfo.name;
      If (answer='O') or (answer='S') or (answer='T') then
      assign(disk_file,'a:\'+f_name+'.fhd')
      else if (answer='E') then
      assign(disk_file,'a:\'+f_name+'.fh2')
      else if (answer='L') then
      assign(disk_file,'a:\'+f_name+'.fh3')
      else assign(disk_file,'a:\'+f_name+'.fhd');

        reset(disk_file,1);
      blockread(disk_file,f_head,sizeof(f_head));
        io_err(disk_file);
    until not ioerr;
    close(disk_file);
                {remove file extension}
```

```
    cleardevice;
    color_box(195,100,350,120,green);
    outtextxy(205,105,'Loading data file');

end;
(*****************************************************************************)
procedure load_tgt(f_name : string; ct:integer;extn:string);
var count:integer;
begin

    repeat
        ioerr:=false;
        assign(tave,'a:\'+f_name+extn);
        reset(tave,4);
        for count:=1 to f_head.channels do
        begin
            blockread(tave,store_block[(count-1)*(ct*2)+1],ct);
            io_err(tave);
       end;
    until not ioerr;
    close(tave);
end;
(*****************************************************************************)
procedure load_ntgt(f_name :string; ct:integer);
var count:integer;
extn:string;
begin
          {load filtered data if required}
    If (fil_flg1) or (fil_flg2) or (fil_flg3)
    then extn:='.n10' else extn:='.nav';
    repeat
        ioerr:=false;

        assign(ntave,'a:\'+f_name+extn);
        reset(ntave,4);
        for count:=1 to f_head.channels do
        begin
            blockread(ntave,store_block[(count-1)*(ct*2)+ct+1],ct);
            io_err(ntave);
       end;
    until not ioerr;
    close(ntave);
end;
(*****************************************************************************)
procedure load_data(var extn:string);
                {load averaged data arrays}
var
count2:integer;
chr:char;
f_name:string;
```

```
begin
{$I-}
    settextstyle(0,0,1);
    cleardevice;
    fil_flg1:=false; fil_flg2:=false; fil_flg3:=false;
    extn:='.tav';{default to unfiltered data}

    color_box(140,95,550,110,lightblue);
    outtextxy(150,100,'Which tgt file - unfiltered (U) or filtered (F) ?');
    repeat
        chr:=upcase(readkey);
    until (chr='U') or (chr='F');
    fil_flg1:=(chr='F');

    cleardevice;
    If fil_flg1 then begin
      color_box(140,95,550,180,lightblue);
      outtextxy(150,100,'Which filtered data file ?');
      outtextxy(150,120,'Smoothed+H_P=0.16 Hz (S)    Smoothed+H_P=1Hz (O)');
      outtextxy(150,140,'Smoothed+H_P=2Hz (T)        Edited SSA (E)');
      outtextxy(150,160,'Latency Corrected Average (L)');
      repeat
          answer:=upcase(readkey);
      until (answer='O') or (answer='S') or (answer='T') or
          (answer='E') or (answer='L');

      case answer of
      'O': begin
         extn:='.t01';
         fil_flg1:=false;
         fil_flg2:=true;
         end;
      'T': begin
          extn:='.t02';
          fil_flg1:=false;
          fil_flg3:=true;
        end;
      'E': extn:='.SS2';
      'L': extn:='.LCA';
      else
      extn:='.t10';
      end;
    end;

    repeat
        ioerr:=false;
        check_dir;
    until not ioerr;

    load_f_head(f_name,answer);
```

```
    count2:=f_head.samples div f_head.channels;
    load_tgt(f_name,count2,extn);
    load_ntgt(f_name,count2);
{$I+}
end;
(*************************************************************************)
procedure process;
const ch_lbl:array[1..6] of string=('Fz','Cz','Pz','T3','T4','EOG');
var x1,y1,x_stp,y_stp,ct,count,count2,max_ch,ch_show:integer;
t_ofs,nt_ofs:real;
ext,fle:string;
chr:char;

begin
    settextstyle(0,0,1);
    color_box(95,95,570,115,lightblue);
    outtextxy(100,100,
    'Ensure data disc is in drive a: then press key to continue');
    repeat until keypressed;

    f_head.proc_flg:=false;
    load_data(ext);
    settextstyle(0,0,1);
    cleardevice;

    outtextxy(0,10,'name: '+f_head.pt_name+'   date:'+
    int_str(f_head.day)+'/'+int_str(f_head.month));

    If f_head.proc_flg then
    begin
        repeat
            color_box(0,95,600,115,lightred);
              outtextxy(10,100,'This file has already been processed'+
              ' - do you wish to re-process Y or N');
            answer:=upcase(readkey);
        until (answer='Y') or (answer='N');
    end;

    If (answer='Y') or (not f_head.proc_flg) then begin

      f_head.proc_flg:=false;
      REPEAT
      gain:=1;
          repeat
                color_box(170,145,450,165,lightblue);
                outtextxy(175,150,'Which channel for processing 1 - '+
                int_str(f_head.channels));
                ch:=ord(readkey);
                cleardevice;
          until (ch > 48) and (ch < (f_head.channels+49));
          ch:=ch-48;
```

```
        repeat
             draw_data(70,300,ext);
             set_gain;
        until key=32;

        setviewport(0,10,350,40,clipoff);
        clearviewport;
        repeat

          color_box(0,0,350,30,9);
        setcolor(12);
        outtextxy(50,5,'To process with CURSORS press C');
        setcolor(15);
        outtextxy(70,15,'Press SPACEBAR to CONTINUE');
        answer:=upcase(readkey);
        If answer='C' then
        begin
             clearviewport;
             graphdefaults;
             curs_opt;
        end;{if}
      until (answer='C') or (answer=' ');

      graphdefaults;
        cleardevice;

      repeat
        outtextxy(175,100,'Process another channel ? Y or N');
        answer:=upcase(readkey);
      until (answer='N') or (answer='Y');

   UNTIL answer='N';

   If f_head.proc_flg then save_cursor_data;
end;{if answer}

cleardevice;
repeat
     outtextxy(100,100,'Do you wish to view raw target data ? Y or N');
     answer:=upcase(readkey);
until (answer='Y') or (answer= 'N');

If answer='Y' then  begin

  findfirst('a:\*.trw',$3f,dirinfo);
  assign(tdat,'a:\'+dirinfo.name);
  reset(tdat,2);

  count:=1;
  REPEAT
  repeat
```

```
        cleardevice;
        outtextxy(250,0,'Rare response '+int_str(count));
      outtextxy(120,340,'Press Z to view next sweep    SPACEBAR to stop');
        blockread(tdat,buffer2[1],f_head.samples);

      ch_left:=f_head.channels;
      ch_pt:=0;
      x1:=40;y1:=70;

      Repeat
       If ch_left>1 then max_ch:=2 else max_ch:=1;

         For ch_show:=1 to max_ch do begin

           If ch_left <> 1 then scale:=(1e6/f_head.eeg_gain)/4096
           else scale:=(1e6/f_head.eog_gain)/4096;
                    {show eog in same range as eeg}

            For ct:=1 to 250 do begin
               x_stp:=x1+ct;
                y_stp:=y1-round(buffer2[ct+(ch_pt*250)]*scale);
                If ct=1 then moveto(x_stp,y_stp);
               lineto(x_stp,y_stp);
            end;{for ct}

            outtextxy(x1,y1-40,ch_lbl[ch_pt+1]);
            inc(ch_pt);
            x1:=350;
            dec(ch_left);

         end;{for ch_show}

        x1:=40;y1:=y1+100;
       until ch_left=0;
       inc(count);
       chr:=readkey;
       until (chr='z') or (chr=' ') or (count=f_head.n_tgt1+1);
      UNTIL(chr=' ') or (count=(f_head.n_tgt1+1));

     close(tdat);
    end;{If answer}
end;
(*************************************************************************)
procedure plt_load;{load tgt/n-tgt data for plot}
var ext:string;
begin
    cleardevice;
    settextstyle(0,0,1);
    outtextxy(50,80,
    'Ensure data disk is loaded in drive a:  then press key to start');
    repeat until keypressed;
```

```
    load_data(ext);
    cleardevice;
    repeat
        outtextxy(100,80,'Do you wish to plot cursor data  Y or N ?');
        answer:=upcase(readkey);
    until (answer='Y') or (answer='N');
    cleardevice;
    If answer='Y' then curs:=true;
end;
(*************************************************************************)
procedure sum_to_ave;
var point,count,denom:integer;

begin
    with f_head do begin
        {convert stored tgt data to average}
     For point:= 1 to channels do begin
        for count:=1 to 250 do
          store_block[((point-1)*500)+count]:=
          store_block[((point-1)*500)+count] div n_tgt1;
     end;{for point}

          {convert stored non-tgt data to average}
     For point:= 1 to channels do begin
        for count:=1 to 250 do
          store_block[((point-1)*500)+250+count]:=
          store_block[((point-1)*500)+250+count] div n_nontgt;
     end;{for point}
    end;{with f_head}
end;
(*************************************************************************)
procedure borders;
begin
    plot_rect(0,0,359,279);
    plot_rect(0,250,359,279);
    plot_rect(0,0,180,39);
    plot_rect(0,39,180,60);
    plot_rect(180,0,359,60);
end;
(*************************************************************************)
procedure titles(var tic_spc:real);
var
line,lines:integer;
LLHC:position;
begin
                        {plot labels}
    with LLHC do begin
          x_coord:=20;y_coord:=267;
        LLHC_label('P300 TEST',horiz,5,7,LLHC);
        x_coord:=100;
        LLHC_label('Name : '+f_head.pt_name,horiz,3,4,LLHC);
```

```
        x_coord:=195;
        select_pen(2);
          LLHC_label(int_str(f_head.n_tgt1)+' rare responses',horiz,3,4,LLHC);
          select_pen(1);
        x_coord:=100;y_coord:=261;
          LLHC_label('File : '+dirinfo.name,horiz,3,4,LLHC);
          x_coord:=195;
        LLHC_label(int_str(f_head.n_nontgt)+' frequent responses',
          horiz,3,4,LLHC);
          x_coord:=280;
        LLHC_label('Vertical scale = '+
          real_str(tic_spc,1,1)+' uV/division',horiz,2,3,LLHC);
        x_coord:=20;y_coord:=255;
        LLHC_label('('+f_head.test_type+')',horiz,5,7,LLHC);
        x_coord:=100;
        LLHC_label('Date : '+int_str(f_head.day)+' '+int_str(f_head.month)+' '+
        int_str(f_head.year),horiz,3,4,LLHC);
          x_coord:=195;y_coord:=255;
          LLHC_label(int_str(f_head.n_rej)+' rejects',horiz,3,4,LLHC);
          x_coord:=280;
          LLHC_label('Horizontal scale = 100 ms/division',horiz,2,3,LLHC);
          x_coord:=2;y_coord:=56;

          If length(f_head.comments) > 80 then begin
                lines:=((length(f_head.comments)-1) div 80)+1;
                For line:=1 to lines-1 do
                  f_head.comments:=copy(f_head.comments,1,line*80+(line-1)*2)
                  +chr(10)+chr(13)+copy(f_head.comments,line*80+(line-1)*2+1,
                  length(f_head.comments)-line*80+(line-1)*2);
          end;{If length}

          LLHC_label(f_head.comments,horiz,2,3,LLHC);

    end;{with LLHC}
end;
(*************************************************************************)
pocedure filter_titles(var tic_spc:real);
var LLHC : position;
begin
    with LLHC do begin
          x_coord:=20;y_coord:=267;
        LLHC_label('P300 TEST',horiz,5,7,LLHC);
        x_coord:=100;
        LLHC_label('Name : '+f_head.pt_name,horiz,3,4,LLHC);
        x_coord:=195;select_pen(2);
          LLHC_label(int_str(f_head.n_tgt1)+' rare responses',horiz,3,4,LLHC);
        x_coord:=100;y_coord:=261; select_pen(1);
          LLHC_label('File : '+dirinfo.name,horiz,3,4,LLHC);
          x_coord:=195;

        If fil_flg1 then
```

```
        LLHC_label('Filters at 0.16-15 Hz(b-d)',horiz,3,4,LLHC)
        else if fil_flg2 then
        LLHC_label('Filters at 1-15 Hz(b-d)',horiz,3,4,LLHC)
        else if fil_flg3 then
        LLHC_label('Filters at 2-15 Hz(b-d)',horiz,3,4,LLHC);

        x_coord:=280;
      LLHC_label('Vertical scale = '+
        real_str(tic_spc,1,1)+' uV/division',horiz,2,3,LLHC);
      x_coord:=20;y_coord:=255;
      LLHC_label('('+f_head.test_type+')',horiz,5,7,LLHC);
      x_coord:=100;
      LLHC_label('Date : '+int_str(f_head.day)+' '+int_str(f_head.month)+' '+
      int_str(f_head.year),horiz,3,4,LLHC);
        x_coord:=195;y_coord:=255;
      If fil_flg2 then begin
        select_pen(2);
        LLHC_label('H-P filter @ 1 Hz',horiz,3,4,LLHC);
      end;
      If fil_flg3 then begin
        select_pen(2);
        LLHC_label('H-P filter @ 2 Hz',horiz,3,4,LLHC);
      end;
      select_pen(1);
        x_coord:=280;
        LLHC_label('Horizontal scale = 100 ms/division',horiz,2,3,LLHC);
  end;{with}
end;
(*************************************************************************)
procedure set_y_fields(n_to_v:real;var y_data:axis_data);
var point:integer;
min_v,max_v,abs_max : real;
begin

                    {set up y_axis vars}
  with y_data do begin
    data_type :=real_num;
    data_points:=250;
    axis_length:=70;
    tick_dir:=tick_across;

    abs_max:=0;
                    {find absolute max eeg data value}

    For ch:=1 to f_head.channels-1 do begin
      for point:=1 to 500 do
      y_data_array[point]:=store_block[((ch-1)*500)+point]*n_to_v;

        min_and_max(data_type,addr(y_data_array[1]),500,min_v,max_v);

      If abs(min_v) > abs_max then
```

```
        abs_max:=abs(min_v);

        If (max_v) > abs_max then
        abs_max:=(max_v);

        min_v:=-abs_max;
        max_v:=abs_max;

        scale_values(min_v,max_v,axis_length,axis_min,axis_max,tick_space);

        first_label  :=axis_min;
        label_inc    :=axis_max-axis_min;
        dec_places   :=1;
      end;{for}
  end;{with y_data}
end;
(*****************************************************************************)
Procedure set_x_fields(var x_data:axis_data);
begin
    with x_data do begin
      axis_length  :=100;
      tick_dir     :=tick_across;
      axis_min     :=-250;
      axis_max     :=750;
      tick_space   :=100;
      first_label  :=-250;
      label_inc    :=1000;
      dec_places   :=0;
    end;{with x_data}
end;
(*****************************************************************************)
procedure plot_cur_dat;
{plot cursos data}
var LLHC:position;
count:integer;
begin
   For ch:=1 to f_head.channels-1 do begin

   with LLHC do begin
       x_coord:=195+((ch-1)*35);
       y_coord:=56;
   end;{with}
   LLHC_label('Ch'+int_str(ch),horiz,2,3,LLHC);

    For count:=1 to 8 do begin                    {tgts}
      If f_head.tgt1_ltncy[ch,count] <> 0 then begin

        with LLHC do begin
         x_coord:=182+((ch-1)*35);
         y_coord:=52-((count-1)*3);
        end;
```

```
        LLHC_label('R'+int_str(count)+'='+
       real_str(f_head.tgt1_ltncy[ch,count],1,1)+' ms, '+
       real_str(f_head.tgt1_mag[ch,count],1,1)+' uV',horiz,1.5,2,LLHC);

      end;{If f_head}
     end;{for count}
   end;{for ch}

                        {non-tgt curs}
   For ch:=1 to f_head.channels-1 do begin
    For count:=1 to 8 do begin
     If f_head.ntgt_ltncy[ch,count] <> 0 then begin

       with LLHC do begin
        x_coord:=182+((ch-1)*35);
         y_coord:=27-((count-1)*3);
       end;

        LLHC_label('F'+int_str(count)+'='+
        real_str(f_head.ntgt_ltncy[ch,count],1,1)+' ms, '+
        real_str(f_head.ntgt_mag[ch,count],1,1)+' uV',horiz,1.5,2,LLHC);

      end;{If f_head}
     end;{for count}
   end;{for ch}
end;
(*****************************************************************************)
Procedure plot_r_times;
var LLHC:position;
rows,cols,rows_left,rows_printed,count,count2:integer;
begin
   with LLHC do begin
    x_coord:=75;
    y_coord:=35;
   end;

   LLHC_label('Reaction Times (ms)',horiz,2,3,LLHC);

   rows_printed:=0;
   rows_left:=f_head.n_tgt1;
   cols:=f_head.n_tgt1 div 8;
   If f_head.n_tgt1 mod 8 <> 0 then cols:=cols+1;

   For count:=1 to cols do begin
       LLHC.x_coord:=20+((count-1)*30);
       If rows_left > 8 then rows:=8 else rows:=rows_left;

       For count2:=1 to rows do begin
          LLHC.y_coord:=30-((count2-1)*4);
          LLHC_label('t'+int_str(rows_printed+1)+'='+
          real_str(f_head.r_times[rows_printed+1],1,1),horiz,2,3,LLHC);
```

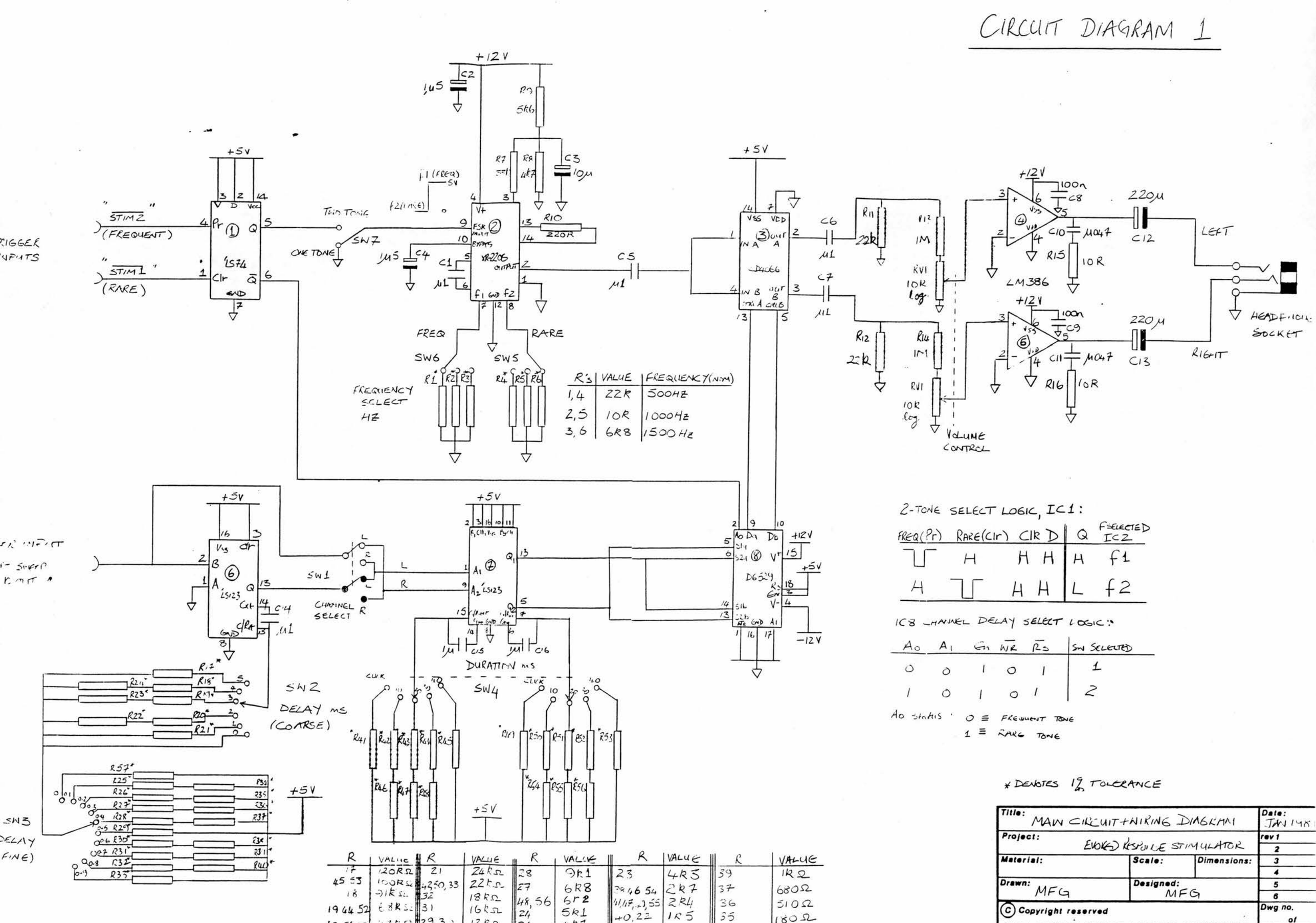
```
            inc(rows_printed);dec(rows_left);
        end;{for count2}
    end;{for count}
end;
(*************************************************************************)
procedure plot_dat;

const
y_cur_lnth=8;           {cursor size in mm}
ch_label : array[1..6] of string[3]=('Fz','Cz','Pz','T3','T4','EOG');
pen_1 : pen_no=1;
pen_2 : pen_no=2;
pen_3 : pen_no=3;
pen_4 : pen_no=4;
x_min : integer=-244;x_inc : integer=4;x_max : integer=752;

var
min_val,max_val,
abs_max,num_to_volts        : real;
x_data,y_data               : axis_data;
LLHC,cur_label              : position;
count,count2,point,
y_cur_indx                  : integer;

begin
    curs:=false;

    If not acq_flg then plt_load;

    sum_to_ave;

    set_x_fields(x_data);

    num_to_volts:=((f_head.fs_eeg/2)/f_head.eeg_gain*1e6)/2048;
      {converts eeg data to +- 50 uV range}

    set_y_fields(num_to_volts,y_data);

    outtextxy(200,80,'Plotting data');

    Initialise_plotter(Col6400,A3,landscape);

    select_pen(1);
    mm_scale;

    borders;

    If (fil_flg1) or (fil_flg2) or (fil_flg3)
    then filter_titles(y_data.tick_space)
    else titles(y_data.tick_space);
```

```
                    {plot eeg data first}
For ch:=1 to f_head.channels-1 do begin
  With LLHC do begin

   If ch < 4 then begin
     x_coord:=(ch-1)*120+10;y_coord:=160;
   end

   else begin y_coord:=70;x_coord:=(ch-4)*120+10;end;

  end;{with LLHC}

 draw_and_label_axes(x_data,y_data,LLHC,pen_1);

 for point:=1 to 500 do
 y_data_array[point]:=store_block[((ch-1)*500)+point]*num_to_volts;

 y_data.data_ptr:=addr(y_data_array[251]);      {non_tgt data}
 plot_y(x_data,y_data,x_min,x_inc,x_max,pen_1,no_mark);

 y_data.data_ptr:=addr(y_data_array[1]);        {target data}
 plot_y(x_data,y_data,x_min,x_inc,x_max,pen_2,no_mark);

 If (f_head.proc_flg) and (curs) then begin
    For count:=1 to 8 do begin  {tgt data}
     If f_head.tgt1_ltncy[ch,count] <> 0 then begin
      y_cur_indx:=round((f_head.tgt1_ltncy[ch,count]-x_min)/x_inc)+1;
      select_pen(1);
    pen_up;
      plot_abs(f_head.tgt1_ltncy[ch,count],
      y_data_array[y_cur_indx]+(y_cur_lnth*Y_units_per_mm/2));
    pen_down;
      plot_rel(0,-y_cur_lnth*Y_units_per_mm);
      pen_up;

      with cur_label do begin
            x_coord:=f_head.tgt1_ltncy[ch,count]-1.5*x_units_per_mm;
            y_coord:=y_data_array[y_cur_indx]+
            ((y_cur_lnth+1)*Y_units_per_mm/2);
      end;
      LLHC_label('R'+int_str(count),horiz,1.5,2,cur_label);

   end;{If}
    end;{For}

    For count:= 1 to 8 do begin   {Non-tgt data}
   If f_head.ntgt_ltncy[ch,count] <> 0 then begin
      y_cur_indx:=round((f_head.ntgt_ltncy[ch,count]-x_min)/x_inc)+1;
      select_pen(1);
    pen_up;
      plot_abs(f_head.ntgt_ltncy[ch,count],
```

```
        y_data_array[y_cur_indx+250]+(y_cur_lnth*Y_units_per_mm/2));
      pen_down;
        plot_rel(0,-y_cur_lnth*Y_units_per_mm);
        pen_up;

        with cur_label do begin
              x_coord:=f_head.ntgt_ltncy[ch,count]-1.5*x_units_per_mm;
              y_coord:=y_data_array[y_cur_indx+250]+
              ((y_cur_lnth+1)*Y_units_per_mm/2);
        end;

        LLHC_label('F'+int_str(count),horiz,1.5,2,cur_label);
     end;{If}
      end;{for}
  end;{If proc_flg and curs}

  mm_scale;
  With LLHC do begin
     x_coord:=x_coord+60;y_coord:=y_coord-5;
     select_pen(1);
     LLHC_label(Ch_label[ch],horiz,3,4,LLHC);
  end; {with}

end; {for ch}

with y_data do begin

num_to_volts:=((f_head.fs_eog/2)/f_head.eog_gain*1e6)/2048;
{converts data to +- 500 uV range}

ch:=f_head.channels;      {plot eog data}

     for point:=1 to 500 do
     y_data_array[point]:=store_block[((ch-1)*500)+point]*num_to_volts;

   axis_min:=-50;
   axis_max:=50;
   tick_space:=10;
   first_label  :=axis_min;
   label_inc    :=axis_max-axis_min;
end; {with y_data}

with LLHC do begin
     x_coord:=250;y_coord:=70;
end; {with}

draw_and_label_axes(x_data,y_data,LLHC,pen_1);

for point:=1 to 500 do
  y_data_array[point]:=store_block[((ch-1)*500)+point]*num_to_volts;
```

```
  y_data.data_ptr:=addr(y_data_array[251]);
  plot_y(x_data,y_data,x_min,x_inc,x_max,pen_1,no_mark);

  y_data.data_ptr:=addr(y_data_array[1]);
  plot_y(x_data,y_data,x_min,x_inc,x_max,pen_2,no_mark);    {!!pen_2}

  mm_scale;
  With LLHC do begin
       x_coord:=x_coord+60;y_coord:=y_coord-5;
       select_pen(1);
       LLHC_label(Ch_label[f_head.channels],horiz,3,4,LLHC);
  end; {with}

 If curs then plot_cur_dat;

 If f_head.test_type='R_TIME' then plot_r_times;

 quit_plotter;
end;
(*************************************************************************)
begin              {******* MAIN *******}
    set_graphics(vga,vgamed);
    menu;
    repeat
         choose;
         settextstyle(1,0,2);
         case choice of
             65 : acquire;
             80 : process;
             76 : plot_dat;
         end; {case}
    until choice=32;
    closegraph;
end.
```

CIRCUIT DIAGRAM 1



2-TONE SELECT LOGIC, IC1:

FREQ (Pr)	RARE (Clr)	CLK D	Q	F SELECTED IC2
⊓	H	H H	H	f1
H	⊓	H H	L	f2

IC8 CHANNEL DELAY SELECT LOGIC:

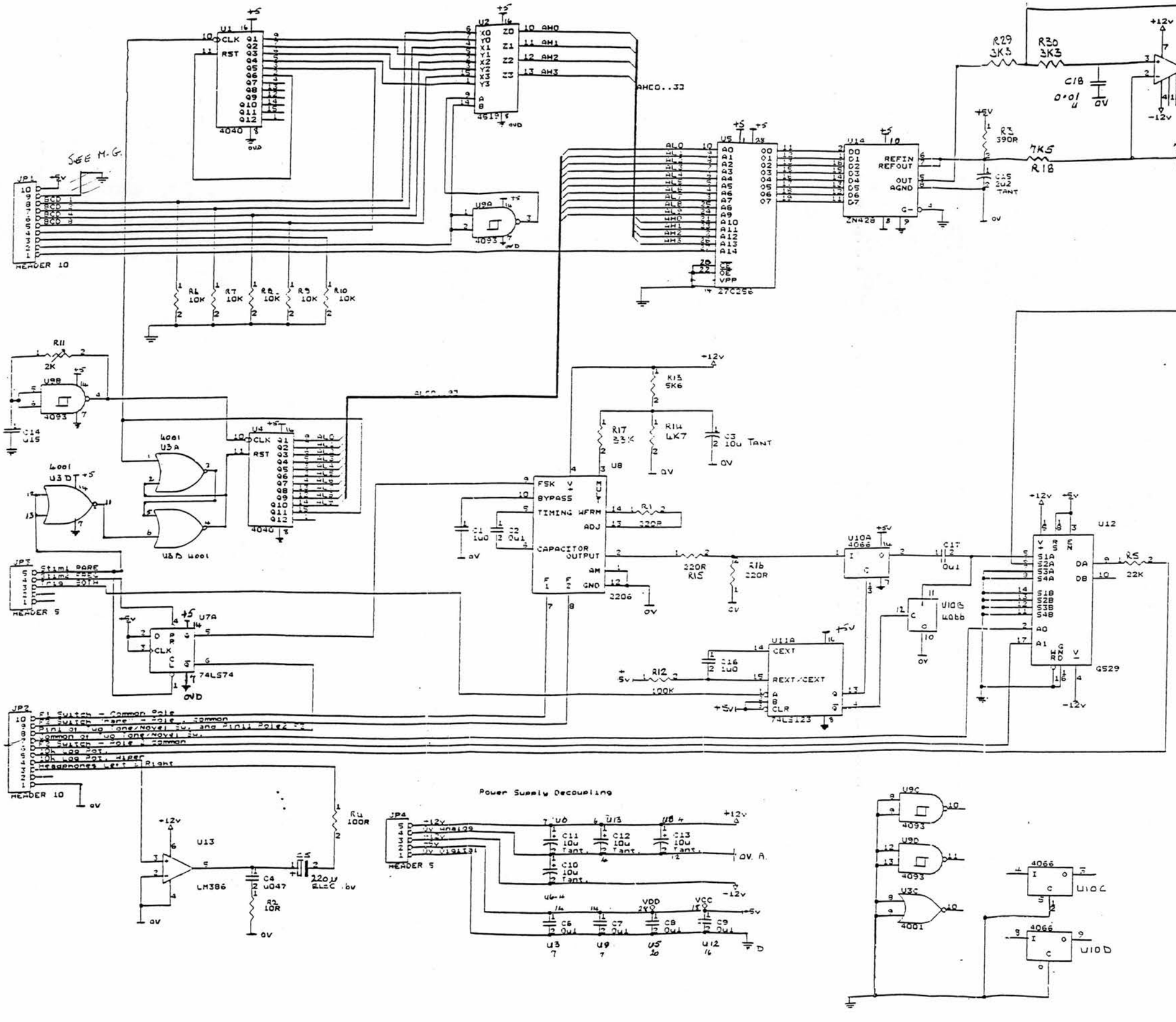
A_0	A_1	G_1	$\overline{WR}$	$\overline{R_3}$	SW SELECTED
0	0	1	0	1	1
1	0	1	0	1	2

A_0 STATUS: 0 ≡ FREQUENT TONE
1 ≡ RARE TONE

R	VALUE	R	VALUE	R	VALUE	R	VALUE	R	VALUE
17	120RΩ	21	24kΩ	28	9k1	23	4k5	59	1kΩ
45 53	100RΩ	42, 50, 33	22kΩ	27	6k8	24, 46, 54	2k7	37	680Ω
18	91kΩ	32	18kΩ	48, 56	6r2	41, 47, 51, 55	2k4	36	510Ω
19 44 52	68kΩ	31	16kΩ	21	5k1	+0.22	1k5	35	180Ω
43, 51, 20	47kΩ	29, 30	12kΩ	26,	4k7	25, 34	1k2	57	470Ω

* DENOTES 1% TOLERANCE

Title: MAIN CIRCUIT + WIRING DIAGRAM			Date: JAN 1985
Project: EVOKED RESPONSE STIMULATOR			rev 1
Material:	Scale:	Dimensions:	2
Drawn: MFG	Designed: MFG		3
			4
			5
			6
© Copyright reserved			Dwg no.
DEPT. of MEDICAL PHYSICS & MEDICAL ENGINEERING,			of
			File no.



CIRCUIT DIAGRAM 2

Glossary

A[i,j] matrix of dimensions i, j

ANOVA analysis of variance

$\|C\|$ Euclidean norm of vector c

cm centimetre

c_{xy} covariance

CMRR common-mode rejection ratio

CNS central nervous system

CRT cathode-ray tube

dF degrees of freedom

DFT discrete Fourier transform

ECG electrocardiograph

EEG electroencephalograph

EMG electromyograph

EOG electro-oculograph

EP evoked potential

ERP event-related potential

f frequency

F F-ratio

F^{-1} inverse Fourier transform

f_c cut-off frequency

FIR finite impulse response

f(t) time series, f

F[f(t)] Fourier transform of f(t)

F[f(t)]* complex conjugate of F[f(t)]

FFT Fast Fourier Transform

fMRI functional magnetic resonance imaging

GG Greenhouse-Geisser correction

$\underline{h}$ vector, h

H-P high-pass (filter)

IIR infinite impulse response

L orthonormal basis function

LCA, lca latency-corrected average

LMS, lms least-mean-squares

L-P low-pass (filter)

mmse minimum mean-square error

MRI magnetic resonance imaging

mse mean-square error

mV milli-Volt

N, n number

n(t) noise function, time domain

P, p probability

PC personal computer

P_Q power quotient

PS peak search method

PT peak track method

r correlation coefficient

rms root-mean-square

RT reaction-time

$\hat{s}$ estimate of s

$\bar{S}$ mean value of S

SD standard deviation

s(t) signal function, time domain

SNR signal-to-noise ratio

SPET single-photon emission tomography

SPL sound pressure level

SSA stimulus-synchronised average

t time, also 2-tailed t value from Students t-test

T period, seconds

VDU video display unit

V_n noise voltage

V Volts

V_s signal voltage

wss wide-sense stationary

w^T transposed vector, w

x(i) elements of matrix x

$X_m(t)$ ensemble average of m time domain waveforms

{y(n)} observed data sequence

z z-transfom

μV micro-Volt

α_R maximum likelihood estimator

γ weighting factor

$\delta(t)$ the Dirac delta function

Δ change in quantity

ε error

θ phase angle

$\xi(n)$ cost function, or mse

Σ sum

σ standard deviation

σ^2 variance

τ time constant

$\Phi(t)$ scaling function

Φ_{xx} auto-correlation

$R(t)$, r_{xy}, Φ_{xy} cross-correlation

Ψ orthogonal wavelet

ω angular frequency

ω_o resonant angular frequency

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Declaration

I declare that this thesis has been composed by me and that the work is my own

Publications

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Conference presentations

1. Oral

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2. Poster

Glabus, M.F., Souza, V, Walker, M.T., Sharp, C.W., Dunan, J.T., Muir, W.J., Blackwood, D.H.R. and Ebmeier, K.P. An investigation on the effect of high-pass filter cut-off, peak definition method, and electrode site on the amplitude and latency of the P300 in schizophrenia. Evoked Potentials

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Glabus, M.F., Ebmeier, K.P., O'Carroll, R.E., Mackenzie, D., Kydd, R.R., Blackwood, D.H.R., Rugg, M.D. and Goodwin, G.M. Cognitive brain potentials and regional cerebral blood flow equivalents during two- and three- sound auditory oddball tasks. The Fifth International Evoked Potentials Symposium, Milan, Italy, September 1994.

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Methodological considerations in measurement of the P300 component of the auditory oddball ERP in schizophrenia

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Summary Twenty-three schizophrenic patients and 26 age-matched control subjects were studied using the P300 recorded during the auditory oddball task, with counting. Our aim was to assess the most suitable method of measurement and analysis of P300 amplitude and latency for use in clinical studies of schizophrenia. The effect of high-pass filtering, peak definition method and recording electrode site were all investigated. We have developed a technique, based on a least-mean-squares approximation to data, which seems particularly well suited to dealing with multi-peak P300 complexes. We have also investigated the spectral composition of the P300 and have found some evidence to support a proposed 2-frequency model of the P300 complex.

Key words: Schizophrenia; Event-related potentials; P300; High-pass filter; Spectral analysis

Much attention has focused recently on how methodological issues may affect the clinical utility of the P300 (Goodin 1990; Pfefferbaum et al. 1990; Polich 1992). A recurring theme has been the need to achieve a widely accepted, standard data acquisition and processing technique to permit comparison of findings from different research groups. Detailed studies on the effect of electrode coupling (Denoth et al. 1986), choice of reference electrode (Denoth et al. 1986), peak definition method (Callaway et al. 1983; Polich 1991) and high-pass filters (Ebmeier et al. 1992) have all contributed to this growing debate.

A specific issue which continues to generate controversy, and which is of particular interest to our group, is the delayed P300 latency in schizophrenia. While there is almost universal agreement that reduced P300 amplitude is a feature of the disease (Baribeau-Braun et al. 1983; Barrett et al. 1986; Roth et al. 1986; McCarley et al. 1991; Ogura et al. 1991), conflicting results have been published regarding the latency of P300 in schizophrenia (Roth et al. 1986). The reported discrepancies may be due to the small number of subjects included in some of the studies (Ebmeier 1992), but another possibility could be the different methods adopted by researchers. For example, while we have consistently found that P300 latency is delayed in schizophrenia (Blackwood et al. 1987, 1991), Ebmeier et al. (1992) suggested that these results may have been influenced by the effect of the 1 Hz high-pass filter used during the recording of data. A differential effect of the high-pass filter was demonstrated, with a greater phase lead (positive time-shift) in P300 peak latency in control compared to schizophrenic data. A "2-frequency" model of the P300 was proposed, with a fundamental at 2.5 Hz representing the slow wave and a higher order harmonic at 7.5 Hz representing the P3a/P3b component. It was proposed that the observed differential effect was due to the ratio of the amplitudes of these two frequencies being different in schizophrenia and that spectral analysis could further test the proposed model. Transient evoked potentials have been successfully modelled on the basis of additive signal generators (Jervis et al. 1983), and the 2-frequency model postulated by Ebmeier et al. (1992) concurs with this.

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We have applied 2 different high-pass digital filters (1 Hz and 2 Hz) to a new set of data to investigate how the high-pass filter alters the appearance of the P300 complex in schizophrenics and controls. An understanding of this phenomenon is important, because the effect of the filter on a multi-peak P300 complex may have a major bearing on which peak is chosen as representing the P300. Polich (1991) deals specifically with the problem of the multi-peak P300 complex, arguing that a series of observations across central and parietal leads should be made to define P300 latency using his "$P3_{max}$" criterion. We have also examined data from both groups in the frequency domain to see if the proposed 2-frequency model offers an additional means of separating control from schizophrenic data.

Our previously adopted method of P300 peak identification was to select the maximum peak in the window 280–450 msec. A multi-peak complex was dealt with using the slope-intersection method described by Goodin et al. (1978). Our latest approach to this problem involved the assessment of two different software algorithms in an attempt to provide an objective measurement technique on all leads. P300 peak latency measurements were made independently, using both algorithms, on data filtered at 3 high-pass settings then, using the method described by Ebmeier et al. (1992), peaks identified at 0.16 Hz filter setting were tracked after subsequent high-pass filtering. This method (tracking peaks) allows a proper evaluation of the effect of the filters. However, peak tracking will not necessarily produce the same result for P300 latency as for the case where $P3_{max}$ is selected. We will present some examples to show how independent examination of data filtered at different high-pass settings may lead to a different peak being selected for P300, and how one of the techniques we have developed deals with this anomaly. The aim of the study, therefore, was three-fold: to identify a method best suited to define the P300 in clinical studies, with particular emphasis on peak definition method, electrode site and high-pass filter setting; to attempt a replication of the study of Ebmeier et al. (1992), showing the effect of the high-pass filters on control and schizophrenic P300 data; and to determine whether there are any spectral differences in schizophrenic and control data, if indicated by the filtering experiment.

Methods I

Recording and stimulus parameters

Twenty-six controls and 23 age-matched schizophrenics, meeting RDC and DSM III-R, were studied. Data were recorded from 3 scalp locations (Fz, Cz, Pz) using silver-silver chloride electrodes, positioned according to the international 10–20 system. EOG was recorded from a single electrode positioned supraorbitally from the left eye. A left ear reference (A1) was used and the right ear (A2) was used as the amplifier ground. Skin/electrode impedances were kept below 3 kΩ. Scalp signals were amplified at a gain of 10^4 within a bandwidth of 0.16–30 Hz (−3 dB). An auditory oddball P300 paradigm was employed, where rare tones at 1500 Hz ($P = 0.1$) and frequent tones at 1000 Hz ($P = 0.9$) were played to the subjects in random sequence through headphones. Inter-stimulus interval was 1.1 sec, tone duration was 40 msec, at 70 dB SPL. Subjects were asked to count the number of rare tones presented, normally 40, and count accuracy was within $\pm 10\%$ for both control and patient groups. Data sampling rate was set at 250 Hz, and 250 samples were collected from each channel — 62 pre-stimulus (248 msec) and 188 post-stimulus (752 msec). All data acquisition and stimulus presentation procedures were performed under the control of a Borland Turbo Pascal™ program running on an IBM PS/2 utilising a Metrabyte™ DAS-16 Data Acquisition Card.

An on-line artefact rejection procedure rejected data from any channel exceeding ± 45 μV. Raw target and non-target responses were stored on floppy disk for later processing, off-line. Two consecutive recordings were made from each subject.

Data processing

The stimulus synchronised average (SSA) was formed from the raw target responses for each of the 3 channels for every subject. Data were then digitally filtered and processed using two peak-searching algorithms. All amplitude measurements were referred to the mean pre-stimulus value of the frequent response.

Digital filters

Infinite impulse response (IIR) digital filters having the equivalent response to Butterworth, single-pole, analogue filters with slope −6 dB/octave, were synthesised using the PC-MATLAB (™The Mathworks Inc.). Data were first smoothed using a bidirectional (zero phase shift) low-pass filter, with −6 dB point at 15 Hz. Two different high-pass filters, −3 dB frequencies at 1 and 2 Hz, were then applied separately to the data. The aim was to induce a phase lead (positive time-shift) on the data and assess whether there was a differential effect on the subject groups. While 0.16 and 1 Hz are filter settings which have been used in practice, data were also filtered at 2 Hz to assist in the evaluation, and hence the address the implication of spectral differences between groups.

Peak definition algorithms

Two peak definition algorithms were developed and applied to the data separately:

(a) Peak search (PS). This algorithm searches 6 samples on either side (± 24 msec) of a visually selected data point. The algorithm looks for a maximum or minimum turning-point and then classifies the peak as positive or negative. The maximum (positive or negative) data value in this range, in μV, is then returned as is the latency, in msec, associated with the peak.

(b) Least-mean-squares (LMS). A data window is interactively defined using a mouse pointer to select two data points — normally near the N2 and N3 components of the ERP. A least-mean-squares approximation to the windowed data is then generated using a third-degree polynomial:

$$y = c_4x^3 + c_3x^2 + c_2x + c_1 \quad \text{(i)}$$

This polynomial solution is then differentiated and the solution to the resultant equation

$$dy/dx = 3c_4x^2 + 2c_3x + c_2 = 0 \quad \text{(ii)}$$

is solved using Laguerres method (both procedures are available as part of the Borland Turbo Pascal™ Numerical Methods Toolbox). The two roots of this equation are equivalent to the turning-points, or peaks, of the data fit described by Eqn. (i).

Methods II

Filtering and peak definition procedure

After constructing the SSA for each channel and then smoothing, the data were digitally filtered at the two high-pass settings (1 and 2 Hz), producing two further sets of data for each subject. The peak definition algorithms were then applied to the data in two different ways: (i) each data set from each patient was measured independently using both PS and LMS algorithms; (ii) using only the PS algorithm, P300 peaks identified at the 0.16 Hz high-pass filter setting were peak tracked (PT) by examining the data filtered at 1 Hz and 2 Hz at the same time. This was the method adopted by Ebmeier et al. (1992) to assess the effect of the filters.

Data from each study group were separated into two separate sub-groups — one group which showed the peak-change phenomenon and the other which showed the more stable, single peak behaviour, when applying the high-pass filters.

Fig. 1 shows an example of a single lead from two different subjects which exhibit both single peak and peak-changing behaviour when the filters are applied, and how the 3 methods deal with selecting the P300 peak.

The left-hand series of captions (1a, c, e) illustrate how the 3 methods deal with data which are unambiguous. In each case the peak search, peak track and LMS fit have selected the same peak, with a minimal error introduced by the LMS fit. The right-hand side shows a typical example of data which undergoes the peak-change phenomenon after the application of the high-pass filter. In Fig. 1b, the P3b component is dominant and has been selected by the peak-searching algorithm. The application of the high-pass digital filters induces a differential phase shift in the signals and the lower frequency component of the complex moves to the left, causing P3a to increase in magnitude compared to the P3b component. The peak-search algorithm will now select the P3a component as representing the P300. In every case where there was a peak change, the error induced was always toward an earlier peak. For the proper assessment of the filter effect, the peak tracking technique was used. Fig. 1d shows how the peak identified at 0.16 Hz high-pass filter setting is tracked at the 2 higher frequency filter settings. Comparing Fig. 1b and 1d demonstrates how it is possible to make large errors in latency measurement unless the correct peak is tracked. Six of the 26 controls and 13 of the 23 schizophrenics manifested the peak-change phenomenon when the high-pass filters were applied. If peaks were not tracked in the manner described, large errors would have accumulated in the latency measurements, the mean filter effect appearing greater in the schizophrenic group.

Methods III

Spectral analysis

The averaged and smoothed data for each lead from each subject were processed using a Fast Fourier Transform (FFT) algorithm available in the PC-MATLAB. Initially, any offset was removed and then the data were windowed with a Hanning window. The data were then normalised and a 512-point FFT algorithm was then applied. The FFT bin separation was 1 Hz but zero-padding from 250 to 512 points allowed interpolation of intermediate values at approximately 0.5 Hz resolution. The spectra from each lead within each group were then summed and averaged to give mean group spectra, which were then plotted. The averaged spectra were scaled to preserve the total mean power relationship between groups. Mean spectrum data were split into 2 frequency bands which on examination appeared to show differences in spectral composition, and which separated the two frequencies postulated in the 2-frequency model: 0.48–4.8 Hz and 5.28–9.6 Hz. The power in these two bands was summed separately and then expressed as a ratio, P_Q:

$$P_Q = \frac{\sum_{h=5.28}^{9.6} P_h}{\sum_{l=0.48}^{4.8} P_l}$$

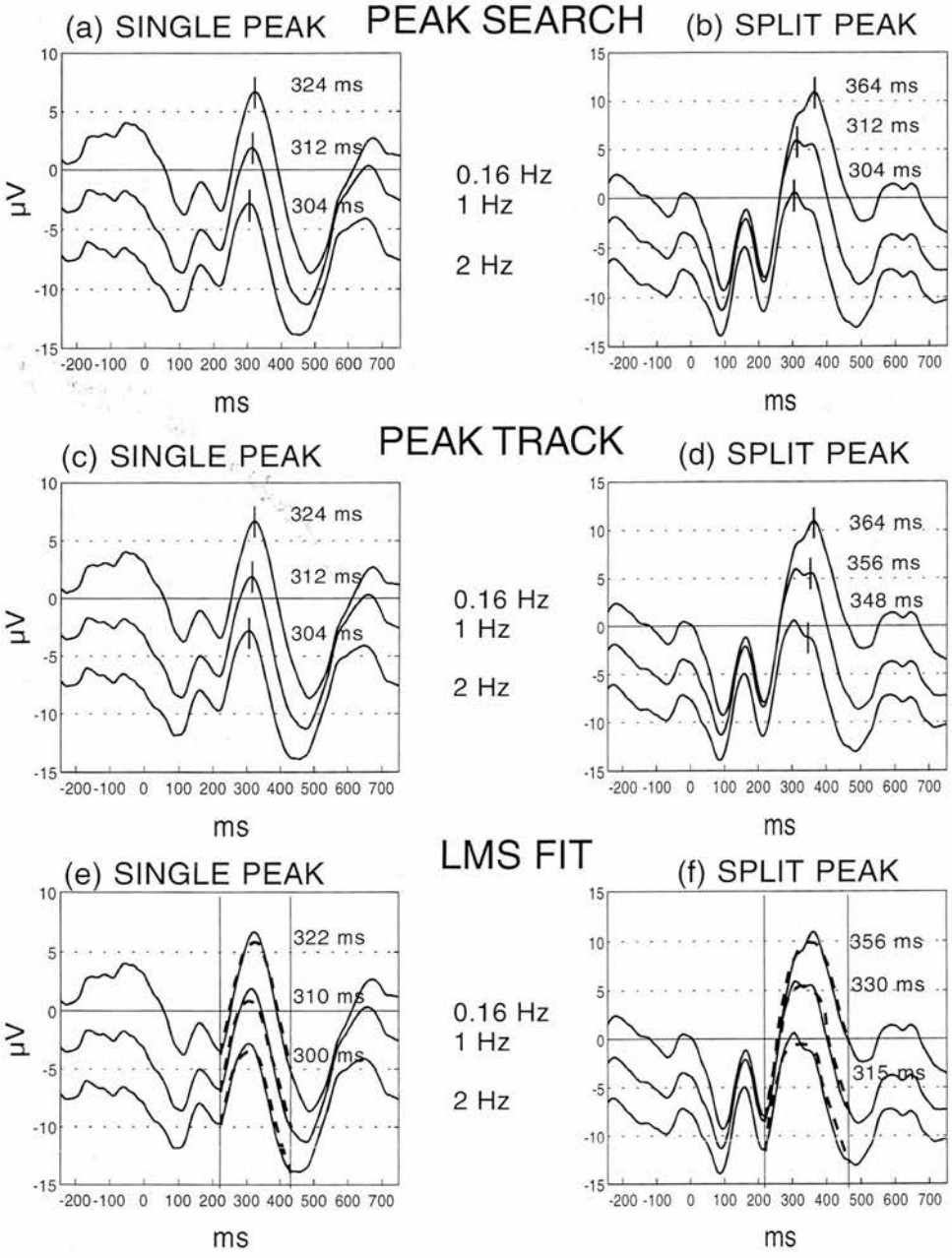

Fig. 1. Three different methods of peak definition applied to two different types of P300 complex – single peak and split peak. Each box shows the signal before and after applying a digital high-pass filter at 1 Hz and at 2 Hz.

Results

Three main, repeated measures analysis of variance (ANOVA) tests were carried out — one on the amplitude data, the other two on latency data. Degrees of freedom (*df*) were adjusted using the Greenhouse-Geisser correction where appropriate. Each ANOVA used 3 leads, 3 filter settings and 2 methods for within-subjects factors. For the latency ANOVAs, one used PS and LMS as the methods, the other used PS and PT as the methods. No amplitude measurements were made with the peak-track method as this was used solely to assess the effect of high-pass filtering on latency.

Latency measurements

Table I shows the mean P300 latency for both groups at each lead at the 3 different filter settings, measured by the 3 methods. The results of independent *t* tests between each group of data are also given.

Table II shows the results from the first main repeated measures ANOVA and indicates a significant group, filter and lead effect. The method of peak definition, PS or LMS, was not significant. The indi-

cated group effect was for a significantly delayed P300 latency in schizophrenia (Table I).

Filter effect. The biggest effect on latency was due to the filters, but there was no second-order interaction with group, indicating that the filters affected both sets of data to the same degree. The effect of the filter was, as expected, an introduction of a time-lead to the P300 latency as the filter setting increased (Table I).

Lead effect. The significant lead effect and group × lead interaction was further investigated by 3 secondary repeated measures ANOVAs, one for each lead. The most significant group effect was found at the Fz lead ($F_{1,47} = 10$, $P = 0.003$) compared to Cz ($F_{1,47} = 3.3$, $P = 0.075$) or Pz ($F_{1,47} = 4.8$, $P = 0.034$). Referring to Table I, it can be seen that, by all methods at all filter settings, the Fz lead gives the greatest significance level (largest t value) compared to Cz and Pz leads.

Filter-lead interaction. The significant filter × lead interaction was investigated by 3 secondary repeated

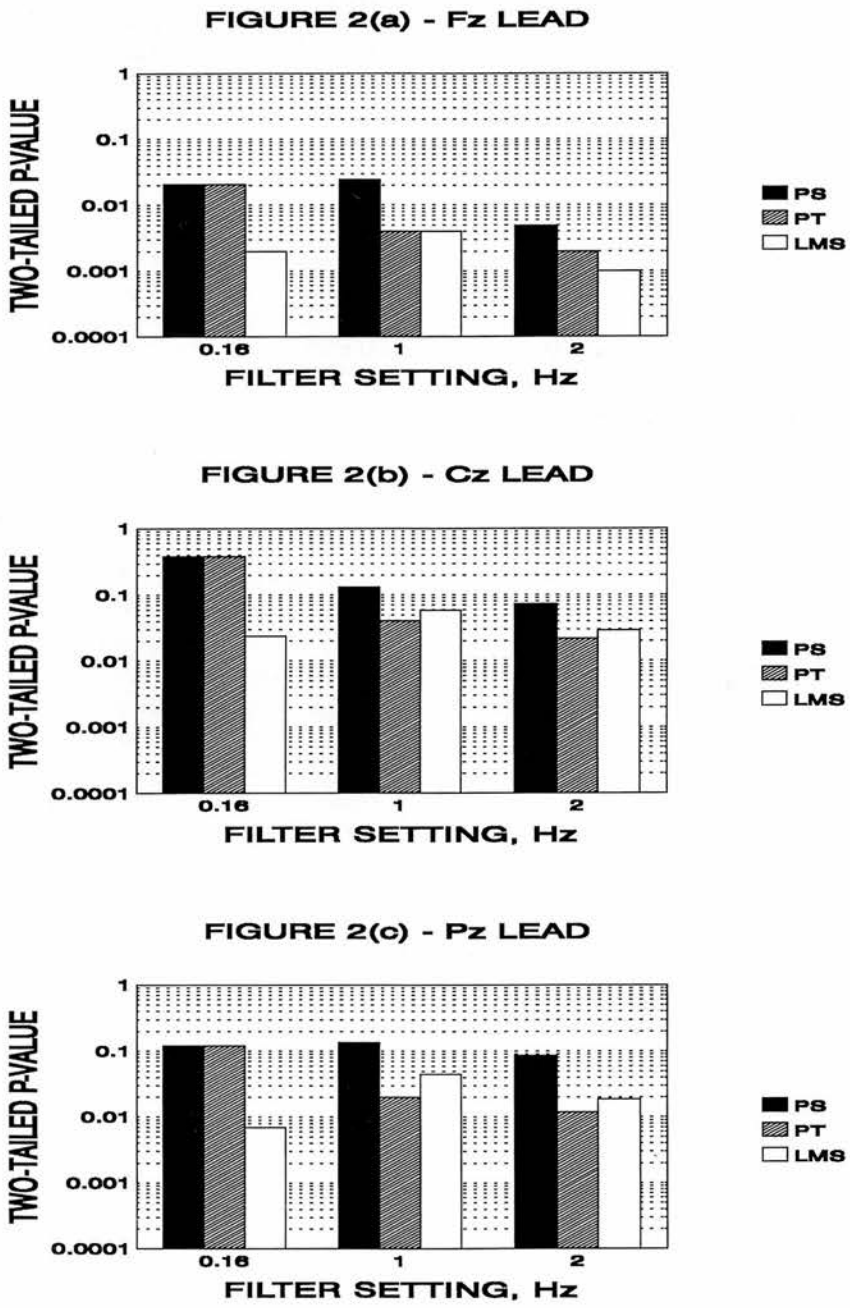

Fig. 2. P value from t tests on P300 latency of control and schizophrenic groups as a function of high-pass filter setting. The trend for decreasing P value with filter setting is significant by the peak tracking method, for all 3 leads. At 0.16 Hz, the peak-search and peak-track methods will identify the same peak – peak tracking only occurs after the introduction of 1 and 2 Hz high-pass filters.

TABLE I

Mean P300 latency and t tests.

Filter and method	Lead	Ctrl (msec ± S.D.)	Scz (msec ± S.D.)	t *	Two-tailed P *
0.16 Hz, PS	Fz	337 (±28)	371 (±61)	2.44	0.021
	Cz	341 (±25)	352 (±52)	0.88	0.385
	Pz	353 (±22)	372 (±54)	1.59	0.122
0.16 Hz, LMS	Fz	338 (±23)	378 (±51)	3.48	0.002
	Cz	341 (±27)	367 (±45)	2.37	0.024
	Pz	355 (±26)	386 (±46)	2.86	0.007
1 Hz, PS	Fz	326 (±28)	353 (±50)	2.35	0.025
	Cz	324 (±27)	343 (±54)	1.54	0.133
	Pz	329 (±23)	347 (±52)	1.53	0.135
1 Hz, LMS	Fz	320 (±22)	356 (±51)	3.11	0.004
	Cz	320 (±24)	340 (±45)	1.96	0.059
	Pz	325 (±24)	347 (±46)	2.09	0.045
1 Hz, PT	Fz	329 (±28)	373 (±63)	3.09	0.004
	Cz	330 (±23)	355 (±52)	2.13	0.041
	Pz	337 (±25)	368 (±55)	2.45	0.02
2 Hz, PS	Fz	316 (±22)	348 (±49)	3.00	0.005
	Cz	316 (±30)	338 (±57)	1.84	0.073
	Pz	316 (±26)	337 (±52)	1.76	0.087
2 Hz, LMS	Fz	311 (±21)	349 (±55)	3.25	0.001
	Cz	309 (±23)	334 (±52)	2.28	0.029
	Pz	309 (±27)	338 (±52)	2.46	0.019
2 Hz, PT	Fz	320 (±23)	369 (±62)	3.53	0.002
	Cz	323 (±25)	352 (±52)	2.42	0.022
	Pz	329 (±27)	363 (±57)	2.66	0.012

* Separate variance estimate.
Methods: PS = peak search; PT = peak track; LMS = least-mean-squares fit; controls, n = 26; schizophrenics, n = 23.

measures ANOVAs, one for each filter setting. The most significant lead effect was found at the 0.16 Hz filter setting ($F_{1.5,\ 72.7} = 11.7$, $P = 0.000$) compared to 1 Hz ($F_{1.7,\ 78.2} = 5.3$, $P = 0.01$) or 2 Hz ($F_{1.7,\ 82.6} = 3.8$, $P = 0.03$). Reference to Table I confirms that the greatest difference in latencies across the 3 leads occurs at the 0.16 Hz filter setting in both groups, by either method (PS or LMS).

TABLE II

ANOVA of P300 latency. 3 leads with 3 filter settings and 2 methods (PS and LMS fit).

Effects	F value	Hypothesis * (error df)	P value
Group	6.2	1, 47	0.016
Filter	190	1.4, 65.3	0.000
Method	0.03	1, 47	0.87
Lead	5.9	1.5, 72.5	0.008
Group × filter	0.41	1.4, 65.3	0.6
Group × method	5.9	1, 47	0.042
Group × lead	4.8	1.5, 72.5	0.018
Filter × method	8.9	1.4, 68.2	0.001
Filter × lead	13.3	2.9, 135	0.000
Method × lead	0.53	1.9, 91.5	0.59
Group × filter × method	1.5	1.4, 68.2	0.235
Group × filter × lead	0.76	2.9, 135	0.51
Group × method × lead	0.27	1.9, 91.5	0.76
Filter × method × lead	0.41	2.9, 136.1	0.74
Group × filter × method × lead	0.66	2.9, 136.1	0.57

* Degrees of freedom adjusted for multiple comparisons using the Greenhouse-Geisser correction.

Peak definition. No significant main effect was found between PS and LMS peak definition methods. With a view to assessing the effect of the filters, another repeated measures ANOVA was carried out using PT and PS as the two methods. Similar results to those in Table II were found, but this time there was a highly significant method effect ($F_{1,\ 47} = 20.3$, $P = 0.000$). Two further repeated measures ANOVAs were carried out, one for each method. Both indicated a significant group effect, with PT showing the greatest significance ($F_{1,\ 47} = 8.2$, $P = 0.006$) compared to PS ($F_{1,\ 47} = 4.3$, $P = 0.043$). There was also a significant group × filter effect for the PT method ($F_{1.2,\ 63.1} = 6.8$, $P = 0.006$), replicating previously reported results (Ebmeier et al. 1992). There was no group × filter interaction for the PS method.

The results of the two main latency ANOVAs are particularly well illustrated by Fig. 2, which shows the effect of the filters and peak definition methods at the 3 electrode sites.

Amplitude measurement

Table III gives the mean P300 amplitude and independent t test results for 3 leads at 3 filter setting by

TABLE III

Mean P300 amplitude and t tests.

Filter and method	Lead	Ctrl (μV ± S.D.)	Scz (μV ± S.D.)	t *	Two-tailed P *
0.16 Hz, PS	Fz	8.3 (±3.9)	6.8 (±4.7)	1.2	0.241
	Cz	11.2 (±4.0)	7.7 (±3.9)	3.03	0.004
	Pz	12.8 (±5.6)	8.0 (±3.7)	3.63	0.001
0.16 Hz, LMS	Fz	7.1 (±3.8)	6.1 (±4.5)	0.84	0.404
	Cz	10.0 (±3.9)	7.1 (±3.8)	2.55	0.014
	Pz	11.7 (±5.5)	7.7 (±3.7)	2.99	0.005
1 Hz, PS	Fz	7.5 (±4.2)	6.0 (±4.5)	1.2	0.237
	Cz	10.0 (±3.9)	6.7 (±3.7)	3.0	0.004
	Pz	11.5 (±4.9)	7.2 (±3.3)	3.62	0.002
1 Hz, LMS	Fz	6.1 (±4.0)	4.9 (±3.7)	1.09	0.283
	Cz	8.8 (±4.0)	5.8 (±3.2)	2.96	0.005
	Pz	10.4 (±5.0)	6.3 (±3.2)	3.44	0.001
2 Hz, PS	Fz	6.5 (±3.8)	4.9 (±3.7)	1.56	0.126
	Cz	8.1 (±3.5)	5.1 (±3.0)	3.21	0.002
	Pz	8.9 (±3.8)	5.5 (±2.5)	3.87	0.000
2 Hz, LMS	Fz	5.2 (±3.2)	4.2 (±3.0)	1.05	0.298
	Cz	7.1 (±3.4)	4.5 (±2.7)	3.06	0.004
	Pz	8.1 (±3.9)	4.9 (±2.4)	3.57	0.001

* Separate variance estimate.
Methods: PS = peak search; LMS = least-mean-squares fit; controls, n = 26; schizophrenics, n = 23.

PS and LMS methods. Table IV shows the result of the main repeated measures ANOVA on the amplitude data. Significant group, filter, method and lead effects are indicated. The group effect was manifested by a significant reduction in amplitude in the schizophrenic group compared to controls at all filter settings by either method at the Cz and Pz leads (Table III).

TABLE IV

ANOVA of P300 amplitude. 3 leads with 3 filter settings and 2 methods (PS and LMS fit).

Effects	F value	Hypothesis * (error df)	P value
Group	7.2	1, 47	0.01
Filter	105	1.3, 61.1	0.000
Method	79	1, 47	0.000
Lead	25	1.1, 53.8	0.000
Group × filter	2	1.3, 61.1	0.15
Group × method	25	1, 47	0.047
Group × lead	7.5	1.1, 53.8	0.006
Filter × method	0.8	1.2, 55.5	0.4
Filter × lead	22.6	2.1, 98.7	0.000
Method × lead	4.3	1.3, 61.5	0.032
Group × filter × method	0.75	1.2, 55.5	0.42
Group × filter × lead	3.9	2.1, 98.8	0.023
Group × method × lead	0.13	1.3, 61.5	0.8
Filter × method × lead	0.37	2.3, 108.8	0.72
Group × filter × method × lead	2.1	2.3, 108.8	0.15

* Degrees of freedom adjusted for multiple comparisons using the Greenhouse-Geisser correction.

Filter effect. The effect of the high-pass filters was to reduce the P300 amplitude in both groups. There was no significant group × filter interaction.

Lead effect. The significance of the lead effect becomes obvious when referring to Table III, which shows that the greatest t value is associated with the Pz lead by both methods at all filter settings, while the Fz lead never gives a significant difference between groups — the group × lead interaction is therefore expected.

Filter-lead interaction. The filter × lead interaction was further investigated by a repeated measures ANOVA carried out for each filter setting. The most significant lead effect was found at the 0.16 Hz setting ($F_{1.2,\ 55.3} = 29$, $P = 0.000$). Reference to Table III shows that the biggest range in amplitude across leads is found at this filter setting, by either method for both groups.

Peak definition. A repeated measures ANOVA was carried out for each of the peak definition methods — PS and LMS. The most significant result was returned for the PS method ($F_{1,\ 47} = 7.9$, $P = 0.007$) compared to the LMS method ($F_{1,\ 47} = 6.3$, $P = 0.015$). While this result indicates that it may be better to use the PS method to discriminate groups by amplitude measurement, the LMS method was indicated as best for discriminating groups by latency. It would be prudent to adopt the same method for latency and amplitude measurements, however, as the LMS method is best at dealing with data with additional or misleading peaks.

Group-filter-lead interaction. Repeated measures ANOVAs were carried out for each lead, and the

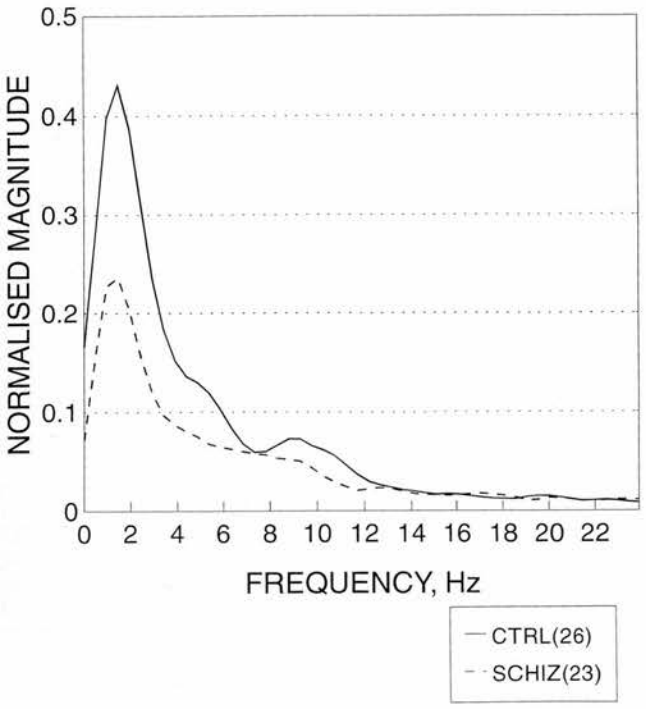

Fig. 3. Averaged spectra for control and schizophrenic groups at the Pz lead. The total power for control and schizophrenic groups is preserved and spectra are scaled accordingly.

greatest filter effect was found at the Pz lead ($F_{1.3, 59.5} = 116$, $P = 0.000$). It has been shown that the groups are best separated at the Pz lead and the filters appear to further enhance this separation. It is feasible that the gradual reduction in slow wave amplitude is more apparent at this site, and accounts for this third-order interaction.

Spectral analysis

The mean P_Q for control and schizophrenic groups, calculated for the 3 leads, gave values as predicted by the 2-frequency model (Ebmeier et al. 1992) — P_Q was greater in the schizophrenic group. The significance of these differences were tested using a Mann-Whitney U test because the data were not normally distributed. The results for the Fz and Cz leads were not significant. However, the P_Q ($\pm$S.D.) values returned for the Pz lead were 0.28 (0.14) for controls and 0.46 (0.45) for schizophrenics, and just missed the 5% significance level with a 2-tailed $P = 0.06$. Fig. 3 shows the mean spectra for the Pz lead.

Discussion

We have attempted to resolve some of the reported inconsistencies relating to the use of P300 latency as a marker in schizophrenia. The appearance of the P300 complex in the time domain reflects underlying physiological processes, which in schizophrenia are probably less coherent and more diffuse than in normal subjects. While the proposed topography is for a more frontal P3a generator and central/parietal P3b generator (Regan 1989), multi-peak complexes occur more frequently in schizophrenia, particularly in the parietal region. The underlying mechanisms for this are unclear but may be due to different processing strategies. It is also conceivable that the appearance of double-peaked parietal complexes in schizophrenia is due to a reduction in the P3b component, leading to an unmasking of the parietal contribution of the P3a.

The sometimes bizarre appearance of the P300 complex in schizophrenia makes it difficult to acquire meaningful measurements — it is not always possible to identify the P300 as a simple wave form consisting of a slow wave with P3a and P3b components superimposed on it. In such circumstances, a $P3_{max}$ measurement is less valid because it is not possible to quantify these additional peaks in the same way as the P3a and P3b components. It is possible that these additional peaks may yet yield important information which will assist in understanding the underlying neuropathological processes. Some of the anomalies associated with multi-peak complexes could also be clarified by producing a latency-corrected average with an adaptive filter (Woody 1967), but at present we are more interested in assessing whether a more global measurement has use as an indicator or trait marker for schizophrenia. Our findings in Tables I and III support the use of P300 latency, as well as amplitude, as a biological covariate of the disease.

Peak definition method

The least-mean-squares method of peak definition appears to give the most consistent result across all leads at all filter settings. By this method, the groups always showed a significant separation of means. The success of this technique is probably related to the way it smoothes out many of the additional peaks and resolves a single peak. An important conclusion may be drawn from this result with reference to previous results reported by our group and other groups.

At 0.16 Hz, and 1 Hz in particular (the high-pass filter setting previously used in Edinburgh), there is no significant difference between the means of controls and schizophrenics at the Cz and Pz leads when measured by peak searching. These results become highly significant when the LMS method is used, however. The method of peak definition previously used was slope intersection, where the intersection of ascending and descending tangents define the peak latency. This technique is an approximation to the more exact method of least-mean-squares fit. This could explain why significant differences have been reported between the latencies of schizophrenics and controls by

our group (Blackwood et al. 1987, 1991) and not by others who have used peak-search methods.

Filter setting

Previous criticism of the high-pass filter setting used when recording the P300 now appears invalid. We have shown that it is possible to separate controls and schizophrenics on the basis of P300 amplitude and latency at 2 filter settings presently and previously used (0.16 Hz and 1 Hz), while also demonstrating that even a 2 Hz high-pass filter would be acceptable, regardless of whether peaks are tracked, as all 3 methods give a significant group separation for latency.

Electrode site

We have managed to show a significant separation of control from schizophrenic P300 data at the 3 central leads using the least-mean-squares measurement technique. While any of the 3 leads would be suitable to use for latency discrimination, Fz gave the largest group difference. The Pz lead appears to give the best resolution for amplitude discrimination. It is well understood that the amplitude maximum of P3b is centro-parietally located, and the Pz lead is probably best sited to maximise the amplitude measurement.

High-pass filter effect and spectral analysis

A significant group × filter interaction occurred only when the peak-tracking technique was used. Peak tracking is a slightly artificial method of making the latency measurement, as data are not normally filtered at a range of settings, but it is the only way to sensibly evaluate the effect of the high-pass filter on single peaks. The value of adopting this approach is revealed when comparing peak-track and peak-search methods, as shown in Fig. 2. These figures illustrate the increase in group separation when the homologous peaks are identified. The action of the filter coupled with the effect of peak changes would tend to reduce the effect size between groups when using the peak-search method, and this is shown particularly well at the Pz lead (Fig. 2c). The *P* value remains almost constant with filtering when peak searching is used, a consequence of the high number of peak changes in this lead in the schizophrenic group. The effect of the high-pass filter on single peaks, when evaluated more correctly with peak tracking, was to introduce a greater phase lead in controls than in schizophrenics (Fig. 4). The degree of time lead introduced is much greater in the control group, at all leads. This confirms the result previously reported by Ebmeier et al. (1992).

This significant time domain effect implies differences in spectral composition. The model predicts that a time domain difference can be accounted for by spectral power shifts between the fundamental frequency and higher order harmonic. Spectral analysis

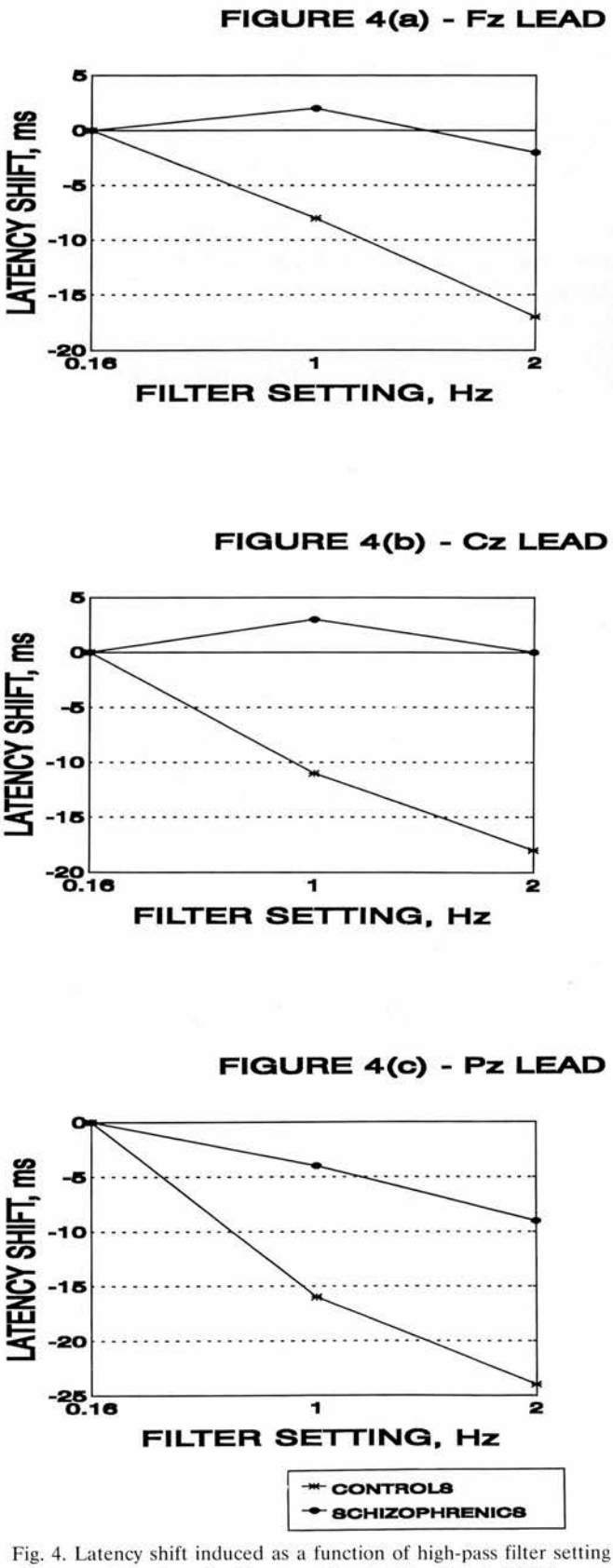

Fig. 4. Latency shift induced as a function of high-pass filter setting for the peak-track method in control and schizophrenic P300 latency data. A highly significant group × filter effect was found using this method. It can be seen that the filters introduce a much greater time lead in the control data at all leads.

indicated a trend for this result from the Pz lead only, where the biggest change in control latency occurs. This is probably due to the fact that the slow wave generator is parietally sited. Fig. 3 shows that the total power in the averaged schizophrenic spectra is less than in the averaged control spectra (a reflection of reduced amplitude in the time domain) and that there is a trend for the relative distribution of power away from the fundamental towards the higher order harmonic in the schizophrenic group.

Taking account of the fact that scalloping and spectral leakage, due to windowing data, will reduce spectral resolution (Harris 1978; Jervis et al. 1989), this result shows that the FFT technique is still sensitive enough to allow the viability of the 2-frequency model to be tested. Further, while the model is rather rigid in that two single frequencies are specified, the actual frequencies involved may vary from subject to subject, and some spread of power on averaging spectra is anticipated.

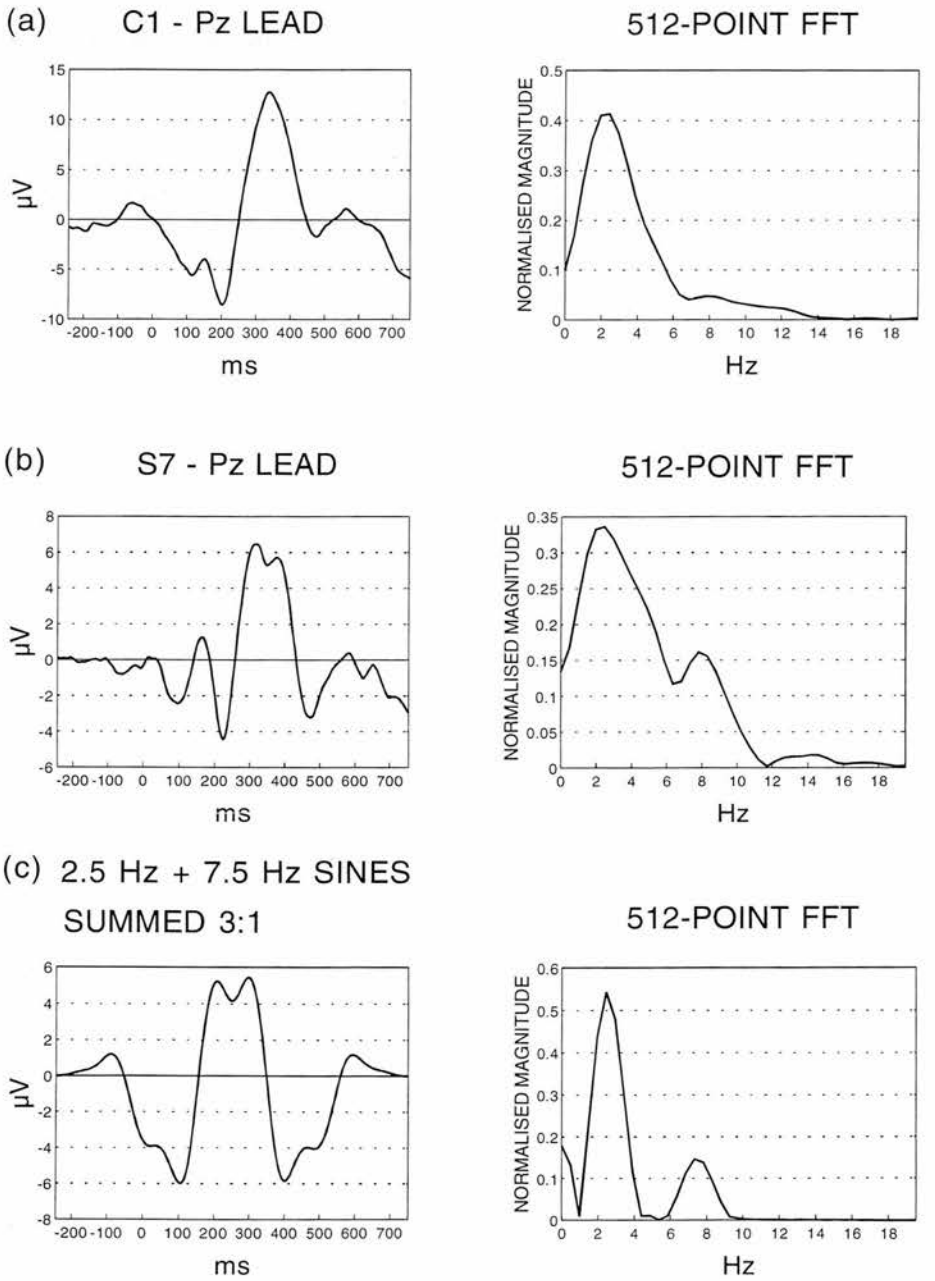

Fig. 5. Time and frequency domain representations of an averaged P300 complex from 2 different subjects – 1 control (a) and 1 schizophrenic (b) – and synthesised P300 complex (c). The shift in power from the 0–5 Hz to 5–10 Hz frequency band reflects the reduction in slow wave amplitude/increase in amplitude of the P3a and P3b components in the schizophrenic subject. Note the similarity between the spectra of (b) and (c). (c) was synthesised by summing two sine waves at 2.5 and 7.5 Hz in the ratio 3:1, then windowed with a Hanning window.

It would be judicious to consider other explanations as to why the result is most significant at the Pz lead. It could be argued that alpha activity generators are sited parietally, and the spectral differences found are due to contamination from these sources. Such activity would be expected to peak in the 8–11 Hz band. Reference to Fig. 3 shows that the main spectral differences are spread across a lower frequency band, between 2 and 8 Hz. The ability of the spectral analysis technique to discern between alpha activity and shifts in power of the slow wave to P3a/P3b complex is demonstrated in Fig. 5.

In each set of traces we have a time domain averaged recording of a P300 complex and its decomposition in the frequency domain. The top traces show a dominant P300 complex with low magnitude N100, P200, N200 components. Most of the power is concentrated below the 5 Hz band. In the middle pair of traces, the P300 slow wave component is much reduced and the P3a and P3b components are now clearly resolved. The amplitude of the exogenous components has increased, and this is reflected by a shift of some power from the middle to the top of the 0–5 Hz band. A large peak has also appeared in the middle of the 5–10 Hz band. The lower pair of traces were derived by synthesising a P300 complex. Two sine waves of frequencies 2.5 and 7.5 Hz were summed in a ratio of 3:1. The data were then multiplied by a Hanning window. The time domain features of the complex bear some resemblance to the P300 complex in the middle trace. The effect of spectral leakage and windowing distort the result in the frequency domain, but two clear peaks, corresponding to the constituent frequencies, are well resolved.

It is difficult to speculate whether there is a significant P3a/P3b complex in the top example, or its contribution in the frequency domain, but the absence of a significant power contribution in the 5–10 Hz band is probably due to the absence of a P3a/P3b complex. The appearance of the P300 complex in the centre set of figures quite clearly allows this distinction to be made by comparison with the synthesised data – the source of the peak in the middle of the 0–5 Hz band can be derived by extrapolation, with our knowledge from the synthesised data.

This series of figures demonstrate the spectral differences due to a shift in power between the fundamental and a higher order harmonic of the P300 complex. It is conceivable that because we have observed a trend for a similar shift in power to occur in our data, spectral differences observed are due to different power ratios as hypothesised in the 2-frequency model.

The utility of this information is difficult to determine at present. However, Van Dijk et al. (1992) have demonstrated the use of spectral analysis of P300 in quantifying the contribution of alpha activity during the generation of the evoked response (this was achieved with a very small data window, demonstrating the power of the FFT). A reduced slow wave amplitude in schizophrenics has been reported (Barrett et al. 1986) and frequency domain analysis may allow the degree of reduction to be quantified, giving an acceptable 2-frequency model. If sufficient numbers can be studied in future, it may be that further evidence for the 2-frequency model of P300 will emerge, which could be used to enhance the prospects of deriving a precise set of markers from the P300 in schizophrenia.

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