PHYSIOLOGICAL AND PSYCHOLOGICAL ASSESSMENT OF SCHIZOPHRENIA AND AFFECTIVE DISORDERS

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ABSTRACT

The study examined data on the physiological and psychological changes which occur in schizophrenia and the affective disorders. The main physiological variable studied was the P3, a component of Event Related Potentials (ERPs), which has been hypothesized to reflect a manifestation of information processing involving the matching of incoming stimuli with the subject's cognitive set. Information processing deficits have also been implicated in schizophrenia and in the affective disorders.

The specific aims were:

a) to compare the P3 components of the ERPs in clinical groups (schizophrenia, bipolar depression and unipolar depression) and non-patient groups (normal controls and relatives of schizophrenic patients)

b) to identify dysfunctional cognitive styles which correlate with abnormalities in P3 latency and amplitude

c) to consider whether the cognitive and physiological abnormalities correlate with structural change measured by Magnetic Resonance Imaging (MRI) in the schizophrenic patients

d) to consider whether another physiological variable (Eye Tracking Dysfunction, ETD) which is also involved in information processing differentiates the groups and correlates with cognitive function and structural change.

Three studies were conducted. In the first study, physiological responses (P3 and ETD) and psychological performance related to the formation and use of cognitive sets were identified in 24 schizophrenic, 10 bipolar manic, 10 bipolar depressed, 10 unipolar depressed and 24 control subjects. P3 latencies were found to be significantly different in the schizophrenic and bipolar groups compared with the control subjects. Deficits in cognitive function in these patient groups correlated significantly with increased P3 latencies, indicating that schizophrenic and bipolar subjects experience dysfunctions in cognitive set which are reflected in their physiological funtioning. Two sub-groups were identified in the schizophrenic population: one group showed a strong correlation between P3 latency and tests which are sensitive to frontal lobe function, and the other group showed a significant correlation between P3 latency and performance in verbal recall.

In the second test, MRI measures of structural change were correlated with physiological and cognitive scores, to validate the specific deficits identified in the schizophrenic population. Thirty schizophrenic patients and thirty control subjects were assessed. The data indicated that the schizophrenic subjects who showed

physiological abnormalities had frontal lobe or hippocampal impairment or both. A decline in IQ with illness was found in the sub-group which showed most frontal lobe impairment. The same psychological tests were applied to schizophrenic patients' relatives (n=30). Relatives with prolonged P3 latencies showed deficits in frontal lobe and hippocampal function which were similar to those found in the patients.

The third study compared the P3 amplitude and latency of visual ERPs to emotive stimuli in 15 depressed, 15 recovered depressed and 15 control subjects. The physiological data were correlated with ratings of severity of depression, depressogenic attitudes and personality variables. Significant differences were found between the depressed and control subjects in the physiological and psychological data. A significant relationship between the physiological and psychological measures was established. The study supported cognitive theories of depression by showing a negative set in information processing.

The results from the three studies supported the hypothesis that P3 abnormalities reflect dysfunctions in cognitive set.

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INTRODUCTION

The definition of mental disorder is essentially descriptive, and is concerned with the amount of dysfunction which is manifested by an individual. The patient's subjective experiences and objective signs of dysfunction are classified as symptoms and signs from which a diagnosis of the disorder is made. This pragmatic approach is partially the result of lack of knowledge about the aetiologies of what Kraepelin termed the "functional" psychoses.

Diagnosis, with regard to schizophrenia and affective disorders, rests on the presence of a required number of symptoms to a certain degree of severity. These operational definitions which are stipulated in standard classificatory systems are widely used in research and clinical applications, and serve to identify discrete disease entities. However, diagnosis by symptoms highlights the lack of understanding of underlying deficits in these disorders and raises contentious issues.

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There is a lack of knowledge about the underlying cause of the symptoms. While the essence of these disorders is the manifestation of characteristic cognitive and emotional dysfunctions, there is a need to gain a more complete understanding of the range of functional abnormalities which occur in these disorders. More information about

specific cognitive impairments and physiological abnormalities is needed to indicate the locus of deficit in information processing terms. There is also a need to look beyond the functional impairments to establish whether structural changes play any part in the aetiology of these disorders.

Diagnosis by symptoms often leads to a confusing overlapping of what were initially proposed to be discrete disorders. It has generally been found that there is no one symptom which is seen in every patient within these discrete categories, and many symptoms are not specific to one disorder. The contentious issue of whether schizophrenia and bipolar affective disorder are discrete disease entities or lie on a continuum of psychotic pathology may be addressed by studying points of rarity or similarity within these groups. Within the affective disorders, similar controversy surrounds the definition of bipolar and unipolar disorders. There is a need to gather more information about these groups of patients to assess their similarities and differences in terms of the types of dysfunction with which they present. This may be helpful in considering whether there are clear-cut boundaries between these groups of patients, although resolution of these issues ultimately depends on establishing aetiologies.

To meet these needs, directly observable data are required to describe the disorders in terms of physiological and anatomical abnormalities. Until the advent of EEG recordings and brain scanning techniques, studies of clinical populations were restricted to

measuring performance variables, and the functional and structural abnormalities of the brain were largely hidden within the "black box" and could only be inferred.

Event related potential (ERP) studies permit comparisons of brain waveform activity in response to specific stimuli. These electrophysiological responses are epiphenomena of information processing. Measurement of event related potentials provides information about the activity of the brain between the input stimulus and the output response.

Studies of cognitive impairment in clinical groups generally hypothesize that there are deficits at specific stages in information processing. However, previous studies have relied on the measurement of the effect of manipulation of input stimuli on output performance, without giving any directly measurable information on the intermediate stages of information processing. In these studies, different underlying deficits may be obscured if all subjects manifest the same performance rates. These studies may also be affected by experimental or subject bias.

Event related potential recordings may enable the observastion of successive stages in information processing. They provide a bias-free method of recording responses within the subject. The use of event related potential recordings with tests of cognitive function may give an indication of the locus of physiological dysfunction within the sequence of information processing which underlies cognitive dysfunctions.

Computer Tomography and Magnetic Resonance Imaging scanning techniques have allowed the comparison of precise measurements of brain structures in living psychopathological subjects. Post-mortem studies were ineffective in examining changes in brain structures throughout the course of illness. Scanning techniques allow measurements to be taken at any stage during the course of illness and compared with healthy controls.

The sheer number of individuals who suffer from schizophrenia and affective disorders makes these disorders an important area of study. While schizophrenia and bipolar affective disorder each occur in approximately 1% of the population, the prevalence of major depressive disorder has been estimated to be as high as 26% of females and 12% of males. However, in terms of in-patient admissions for the Royal Edinburgh Hospital in 1988, schizophrenia accounted for 15.6%, affective psychosis for 20.8% and non-psychotic affective disorder for 4.4% of admissions.

The main objective of the study was to identify physiological and psychological dysfunctions in schizophrenia and affective disorders, and to define the relationship between these abnormalities. The study hypothesized that dysfunctions in information processing are reflected in physiological responses as manifested by the P3 component of ERPs and in cognitive impairments.

The specific aims of the study were:

a) To compare the physiological responses of schizophrenic, bipolar affective disorder, unipolar affective disorder and normal control subjects. Previous studies have reported that schizophrenia and bipolar affective patients manifest abnormally prolonged P3 latencies relative to unipolar depressed patients and normal controls. It has also been reported that patient groups show differences in P3 amplitude and in signal:noise ratio in smooth pursuit eye tracking when compared to normal controls. This study aimed to replicate these findings and to identify a group of healthy controls who manifested abnormalities in P3 latency in the absence of clinical symptoms. Abnormality of P3 latency was defined as the mean plus two standard deviations of the P3 latency of a group of normal control subjects.

b) To construct an operational definition of the information processing function of P3. The study aimed to review the antecedent conditions which have been found to produce a P3 response, and from this to form a hypothesis of the information processing function of P3. This hypothesis would then be used to predict dysfunctions in information processing when abnormalities in P3 are found. If dysfunctions in information processing are reflected both by impairments in cognitive functions and by P3 abnormalities, the prediction would be that level of cognitive impairment will correlate with physiological abnormalities. The evidence which suggests that P3 is generated within specific cortical areas will be reviewed and tested by correlating P3 responses with cognitive functions associated with these areas.

c) To identify dysfunctional cognitive styles in normal controls who show abnormalities in P3 the hypothesis was that the relationship between the physiological and psychological variables would hold true in a non-clinical group, and therefore, could not be attributed to global deficits in psychopathological subjects.

d) To consider whether physiological and cognitive abnormalities correlate with structural change in the schizophrenic subjects. Prolonged P3 latency has been shown to be a robust, stable characteristic, and the study aimed to show that the cognitive dysfunctions associated with it are enduring deficits and not transient, mood-related changes. This would suggest that both variables may be related to permanent structural changes in the brain. The hypothesis was that prolonged P3 latency is associated with localized cognitive impairments and with specific structural changes in the brain.

The structure of the thesis is briefly described below. Chapter 2 gives a short description of ERPs and the P3 component in particular. Antecedant conditions of the P3 and its hypothesized information processing functions are reviewed. The overall conclusion is that P3 is evoked by unexpected stimuli, and a definition of what the subject perceives as expected or unexpected is necessary. Models of information processing are discussed and the hypothesis that P3 reflects a dysfunction in the implementation of associative networks is proposed. Deficits in cognition which are predicted to result from such a dysfunction are suggested to be impairments in association and conceptualization.

Chapter 3 describes the symptoms which are required for a diagnosis of schizophrenia. Findings of cognitive impairments in schizophrenic patients in association and conceptualization are reviewed. Chapter 4 adopts the same format as the preceding Chapter and addresses the same issues for affective disorder patients.

Chapter 5 describes the rationale and method for Study I. This study aimed to compare and correlate the physiological variables of P3 and signal : noise ratio (smooth pursuit eye movement ; SPEM) and the cognitive performance on tests of association and conceptualization in 24 schizophrenic, 20 bipolar affective disorder, 10 uniplar affective disorder and 24 control subjects. Chapter 6 presents the results of the first study and discusses these results. As was expected, the schizophrenic and bipolar affective disorder patients showed significantly prolonged P3 latencies when compared with the unipolar affective disorder group and control subjects. The schizophrenic and bipolar manic subjects showed impairments in association and conceptualization which correlated significantly with the degree of abnormality of this physiological variable. The P3 responses of the unipolar depressed group and the control group were similar. Cognitive impairments were found in the unipolar depressed group but were suggested to be due to lack of concentration and motivation, and were not significantly correlated with P3 latency.

Chapter 7 describes the rationale and method for Study II. P3 and schizophrenia have been associated with the frontal lobes and temporal lobes, and this study aimed to compare the performance on

neuropsychology tests sensitive to frontal lobe and temporal lobe function of 30 schizophrenic, 30 normal control subjects and 30 healthy subjects who were relatives of schizophrenic patients. MRI measurements of brain structures were compared between the schizophrenic and control subjects, and correlated with P3 latency and performance on the neuropsychology tests. Chapter 8 describes the results of Study II and discusses these results. Impairments of performance on tests of frontal lobe function and temporal lobe function and decline in IQ were found in the schizophrenic group and the relatives with abnormal P3. In the MRI data, evidence of increased ventricular brain ratio and abnormalities in temporal lobe structures was found.

The rationale and method for Study III are presented in Chapter 9. This study aimed to compare the P3 component of visual event related potentials to emotive stimuli in unipolar depressed, recovered unipolar depressed and control subjects. Beck's cognitive theories of depression propose that depressed subjects have a predominantly negative content of thought and predict that depressed subjects expect negative events more than positive events or neutral events. Physiological vulnerability markers in recovered depressed subjects were also predicted. Chapter 10 describes the results of Study III and discusses them. The depressed group was found to show significantly different P3 amplitudes to negative stimuli relative to neutral stimuli compared with the other two groups. Measures of severity of depression, dysfunctional attitudes and personality variables correlated with the physiological abnormality.

Chapter 11 draws conclusions from the findings of the three studies and discusses the implications these have for the understanding of underlying deficits in schizophrenia and affective disorders, and for the distinctions between these disorders. The evidence supporting a schizophreniform disorder is also discussed. Limitations of the study and implications for future research are discussed.

Chapter 2

P3 AND INFORMATION PROCESSING

2.1 Description of Event Related Potentials.

Event related potentials (ERPS) are electroencephalographic (EEG) responses to specific stimuli.

Richard Caton, who first recorded the electrical activity of the brains of animals in 1875, noted that the voltages recorded from the brain's surface could be influenced by external sensory stimulation. The first sensory ERPs were recorded in man by Lord Adrian in Cambridge, who measured the EEG in response to a series of bright flash stimuli using electrodes situated over the frontal lobe.

i Measurement

The EEG signal is a potential difference between two small silver electrodes. The electrodes may be placed over two active brain sites for bipolar recordings, or over one active site and an indifferent area for unipolar recordings. The EEG signal is then amplified and different frequency ranges can be selected for analysis.

The continuous EEG is monitored throughout the course of an experimental session, and can be displayed on an oscilloscope screen. At a precisely defined time, a stimulus is presented. This exactly defined point of time is used to segment the EEG so that the electrical activity which is produced pre- and post-stimulus can be averaged and stored.

The brain activity which is elicited by a known stimulus is often of much lower amplitude than the background EEG and therefore difficult to discern. Stimulus related activity can often only be detected by employing the techniques of averaging.

Methods of separating out the small potentials from the larger oscillations of the spontaneous background EEG were developed in the 1940's by George D. Dawson. He devised the technique of giving a large number of similar stimuli to the subject, and adding the responses together by photographic superimposition. Consequently, the consistent features of the response are reinforced, while the random variation or noise in the background is minimized. Later developments of this technique involve the use of an electronic averager, whereby the addition is done by breaking each sample into approximately 1000 intervals, and consigning the value of the voltage of each interval to a particular storage element. For example if the duration of each sample is 1 second, and the voltage in this interval is sampled every

millisecond, 1000 addresses are used to store the data. Averaging is triggered at the same time as each stimulus is presented. An event related potential which follows the stimulus with a constant latency accumulates in the memory, whereas the summated background EEG activity, because it is randomly related in time to the stimulus will fluctuate around zero. When the desired number of stimuli have been presented, the averaged voltage in each address is displayed. The signal : noise ratio increases by a factor of $\sqrt{N}$. The resulting waveform produced by averaging the responses to stimuli presentations, therefore, shows the stimulus related activity in the EEG, and is referred to as an ERP.

The ERP following a stimulus in any sensory modality is composed of a series of waves which in some circumstances may persist for several seconds or more and the sweep time used must be adjusted accordingly. Furthermore, it is important to record the pre-stimulus activity as a baseline to measure the post stimulus voltage fluctuations.

The choice of the site for positioning the electrodes depends on the modality and type of the stimuli employed, and the purpose for which the data are being collected e.g. to examine laterality differences. Electrode placements are defined by the International 10-20 system.

Eye movement potentials are one of the major sources of artefacts in ERP recordings. Limb movements may also affect ERP recordings, due to a slowly increasing negative potential which occurs maximally in the cental regions during the second or so prior to the movement. The electrocardiogram may produce artefact at some electrode sites and electromyelogram from scalp muscles can interfere with recordings over a wide scalp distribution.

The level of subject's arousal may also have an effect on ERP recordings. However, as Regan (1972) pointed out, when attempting to determine ERP correlates of attention, there is a difficulty in defining attention, and a further difficulty in manipulating this attention. It should not be assumed that all responses to identical stimuli will themselves be identical. The effects of habituation, fatigue or drowsiness are known to alter the characteristics of some ERPs. Habituation of ERPs has been found to be less to auditory stimuli than to visual stimuli (Regan op.cit.).

ii Components

Cortical potentials are classified according to their latencies into the fast or middle-latency potentials (8 - 80 msec), slow potentials (50 - 400 msec), and very slow potentials or contingent negative variation (CNV).

The slow cortical potentials were first described by Davis in 1939. By 1963 Davis and Yoshie, using averaging techniques, obtained clear recordings.

iii Endogenous and Exogenous Potentials.

A typical response to an auditory binaural click stimulus, recorded at the vertex consists of a small positive peak (P1) at 50 - 70 msec, a larger negative peak (N1) at about 100 - 150 msec, and a positive peak (P2) at 175 - 200 msec. The N1/P2 complex is readily identifiable in adults, and provides a good measure of assessing the audiometric threshold.

These peaks in the ERP are described as exogenous components, that is they are evoked by events extrinsic to the nervous system, and their variance is accounted for primarily by the physical characteristics of the stimulus e.g. intensity, modality and interstimulus interval, and not by the performance of the subject to the stimulus. If the subject is required to respond to the stimulus in some way, then some components of the ERP will reflect this cognitive processing. These ERP components are termed endogenous components or association cortex potentials. Their variance is particularly determined by the specific tasks and instructions

assigned to eliciting events and they appear to be most closely related to the psychological parameters involved in stimulus evaluation. Donchin (1988) claimed that endogenous components are insensitive to the physical attributes of stimuli but sensitive to the variation in the information processing activities imposed on the subject by the assigned tasks. The N2, P3 and N4 responses recorded during a two tone discrimination task are thus endogenous potentials. N2 occurs as a small negative peak followed by a slower positive peak (P3) at around 300 msec, and sustained negative response peaking at N4.

iv Relationship between Event Related Potentials (ERPs) and Information Processing.

Psychophysiological research is concerned with the relationships between physiological activity and psychological processes. Having described these relationships, it is proposed that inferences can be made about psychological process from physiological activity. It is assumed that the physiological and psychological measures both reflect the same process, namely information processing.

Previous attempts to understand how the mental processes relate to physiological events have involved the use of models of neuropsychological function. It is necessary to formulate a model

which is valid in terms of the physiological operations of the brain and in terms of behaviour at the psychological level.

The earliest waves of the ERP (up to 100 msec) seem to reflect the activation of cells in the cortical projection area of the sense involved. These would be equivalent to feature detector cells proposed by Treisman and Paterson (1984) which respond to specific, physical characteristics of the stimulus such as shape, orientation and size. The intermediate waves (100 - 200 msec) and the long latency components are recorded over wide areas of the scalp, and are relatively small over the sensory projection area. The longer latency components appear to be associated with high - level pre-conscious stimulus analysis. Evidence for this will be provided in the next section. The wide distribution of the later ERP components suggests that there is loss of anatomical specificity when signals travel beyond the sensory projection area into the systems concerned with complex pattern recognition and conscious perception.

The relationship between the physiological and psychological parameters provides the foundation for the search for psychological correlates of ERP components. If the assumption that the physiological and psychological variables both reflect information processing functions is correct, this should be shown in the correlations between

the two. It should also be possible to make predictions about one of the parameters by manipulating the other.

The ERP components have become associated with specific cognitive processes. N1 has been associated with general level of arousal. N1 and P2 are thought to be manifestations of the activation of a feature analysis system. Decision making or stimulus recognition may be reflected by the negativity in N2. Banquet, Renault and Lesevre (1981) reported that a task effect is seen for N2, with increasing amplitude and latency for the condition which was generally a positive or expected response, suggesting that the subject builds up templates for expected responses in memory. An increase in latency and a decrease in amplitude of the N2 component has been found with difficult as opposed to easy distinctions, suggesting that there is some delay in making a difficult decision (Ford, Roth and Kopell 1976, Naatanen, Hukkahen and Jarvilehto 1980, Ritter, Simpson, Vaughan and Friedman 1979, Towey, Rist, Hakerem, Ruchkin and Sutton 1980). P2 latency has been claimed to reflect some preliminary analyses of the sensory input after the stimulus has been registered (Gomer et al 1976) P3 is associated with psychological processing, being evoked only by stimuli that are important to the subject in some way, and depends on the unexpectedness of the relevant event (Sutton 1965, 1967). N4 has been associated with semantic improbability (Kutas and Hillyard 1980) and with semantic priming effects (Rugg 1985).

2.2 Findings relating P3 to Information Processing

The P3 component of the ERP was first reported by Sutton in two papers in 'Science' (1965,1967). For the first time it became possible to identify ERP components whose variance was specifically related to cognitive function. Sutton showed that P3 amplitude was inversely related to the probability of the stimulus occuring. Since then a large number of papers have been published showing that a varied range of psychological parameters and experimental conditions evoke and/or affect the P3 response.

Donchin and Coles (1988) stated that, to understand the endogenous components of the ERP, it is necessary to use data about the component's antecedent conditions to form hypotheses about the information processing function of the underlying brain activity. The next section reviews the antecedent conditions of P3 which have so far been reported.

i Antecedent Conditions

P3 has been found to occur in different modalities, and has also been reported to occur when no stimulus has been presented. Haider et al (1964) demonstrated that the later components of event related potentials were elicited by the 'missed' signals in a vigilance task.

Sutton's original finding that there is an inverse relationship between stimulus probability and P3 amplitude is well established, and has been replicated many times including the study of Tueting, Sutton and Zubin (1970), Friedman Hakerem, Sutton and Freis (1973) and Donchin, Kuboy, Kutas, Johnson and Herning (1973). Findings include both the objective (Regan 1972) and subjective (Squires et al 1973, Sutton et al 1965, Donchin, Ritter and McCallum 1978) probability of the stimulus to the subject. Objective probability refers to the rareness of the stimulus. Regan (1972) showed that the amplitude of the P3 increases as the frequency of the rare stimulus decreases. Subjective probability refers to the subject's own internally generated expectations. P3 potentials have been found to be elicited by events that confirm or disconfirm the subject's predictions or expectations (Donchin, Ritter and McCallum op.cit., Hillyard et al 1971, Squires et al 1975 and Parasuraman and Davies 1975) and even by the absence of a stimulus which acts to resolve some expectation (Regan op.cit). The more unexpected (informative) the event, the larger is the resulting P3 amplitude (Donchin, Ritter and McCallum op.cit., Ruchkin and Sutton 1983).

In addition to these findings that P3 is elicited by events that are important to the subject's internal expectations, it has also been found that P3 is elicited by events that are relevant to the experimental condition. Task relevant stimuli have been found to evoke

larger responses than task irrelevant stimuli (Regan op.cit.). Roth, Ford and Kopell (1978) and Couchesne, Courchesne and Hillyard (1978) reported that P3 latency for targets was 15 msec shorter than P3 latency for non-targets. In a letter-matching task, Posner, Klein, Summers and Buggie (1973) found that P3 latency was 50 msec earlier for matches than for mis-matches. Kerkhof (1981) concluded that stimulus evaluation time is longer and more variable for negative than for positive decisions. However, P3 is not elicited by all attended, task relevant and unexpected stimuli. It has been found that certain requirements of detection confidence have to be met. P3 latency has been found to increase with level of difficulty in detection and with decision latency (Ritter, Simpson and Vaughan 1972, Squires et al (op.cit).

Kerkhof (op.cit) claimed that observed latency variations in P3 could be interpreted as changes in the detectability of stimulus events, and found that latency correlated negatively with confidence. The P3 latency was shorter for high confidence signal - present trials. Davies and Parasuraman (1977) recorded ERPs to responses varying in confidence level, and found that ERPs averaged to correct decisions had longer latency P3's for doubtful responses than for confident responses, and these responses also had longer decision latencies. As Hillyard (op.cit) summarized, there is an indication that the P3 wave is enhanced only when stimulus information is being actively

processed, and is uniquely associated with the occurence of a signal and its correct detection.

P3 has also been shown to occur in response to an unattended stimulus in the orienting reflex index ; that is when the subject is alerted to the presentation of an unattended and unexpected stimulus (Ritter et al 1968, Roth 1973, Courchesne 1978, Courchesne, Hillyard and Galambos 1975 and Schandry and Hoeffing 1979).

P3 has been associated with memory. Increases and decreases in P3 amplitude have been found as a function of learning. In a pattern recognition test, Poon, Thompson, Williams and Marsh (1974) found a larger P3 during initial learning than after overlearning. They concluded that while P3 responses have been shown to occur with matches or template matching, there is an absence of or reduction in P3 during routinized or automatic processing of a frequently occuring stimulus.

This finding from studying P3 and memory, indicates that, while P3 has been shown to occur with the matching of a stimulus with a template held in memory, i.e. during learning or as seen earlier in experimentally induced conditions when identifying targets (signals), P3 does not occur when these stimuli become overlearned, and processing becomes automatic. Therefore, P3 seems to be associated

with the 'informativeness' of the stimulus on some dimension, rather than the simple matching of stimulus with template. It is proposed that this dimension is expectancy, and evidence for this from studies of P3 and memory will be presented.

Sternberg (1969) reported that in tests involving comparison of the stimulus with a memory set, P3 amplitude decreased and P3 latency increased as set size increased. The increase in latency may reflect the increasing time taken to process information as the amount of information increases, and ties P3 activity to cognitive function. Functions relating P3 latency to set size are highly linear and almost identical in slope, and as such appear to be indicative of a serial search in memory. In memory search tasks, the P3 latency has been found to be longer for negative responses as compared with positive responses (Ford, Roth, Mohs, Hopkin and Kopell 1979, Ford, Mohs, Pfefferbaum and Kopell 1980, Brookhuis, Mulder, Gloerich, von Dellen, von der Meere and Ellerman 1981). However, Gomer, Spicuzza and O'Donnell (1976) and Adam and Collins (1978) reported equal latencies for the two conditions. A number of studies have associated P3 with memory and expectancy. The stucture of information held in long term memory is proposed to determine partially a subject's expectations. Boddy (1981) measured ERPs to words in a sentence, and reported that P3 occured with incongruous words. He interpreted this as an attempt to make sense of a meaningless sentence. Boddy defined incongruity as

words which were not related in Chomsky's deep structural semantic networks in long term memory. He also found that P3 responses were evoked by the first and last words in a sentence. Karis, Fabiani and Donchin (1984) showed that a P3 response was evoked by isolates; that is by words that are incongruous with their context, in terms of relationships between words held in semantic networks in long term memory. This response was found to be a good predictor of whether words would be subsequently recalled. However, the P3 response was not found to be predictive of recall when the subject was using strategies to aid recall. Verleger (1988) also referred to semantic networks between stimuli and emphasized that it is the frequency of categories which is decisive in evoking P3 rather than the frequencies of single stimuli. However, Verleger stated that any stimuli can be assigned to categories e.g. targets and non-targets. Polich and Donchin (1988) found that P3 latency was shorter for common compared to uncommon words, and non-words. They accounted for this by claiming that this reflects a longer search in memory for uncommon words and an exhaustive or self - limited search for non-words.

P3 amplitude and latency appear to be affected by experimental manipulations. Claims that P3 amplitude are inversely proportional to the subjective probability of the eliciting events seem to be well supported, and it may be that P3 amplitude reflects the amount of processing required by the stimulus. P3 latency appears to depend upon

the processing time required for the stimulus (Donchin and Coles 1988).

The claim that P3 is not a unitary phenomenon but refers to a collective group of components has been made by Squires, Squires and Hillyard (1975), Barber (1980) and Rosler, Clausen and Sojka (1986), among others. The presence of P3a, P3b and PSW (Positive Slow Wave) have been replicated in several studies, and they appear to be distinguishable by their latency, topography and different susceptibility to experimental manipulations. It is possible that the different sub-components of P3 are manifestations of different cognitive functions. Tueting 1978) claimed that they may represent a complex of brain activity that is differentially related to such factors as subjective probability or expectancy, task relevance and decision confidence. Rosler et al (op.cit) devised the double - priming paradigm ; that is the use of two priming stimuli before the test stimulus. This enables manipulation of the events which have been shown to elicit P3 : that is probabilities of single events, event categories and event sequences. They recorded P3 response using the double -priming technique and confirmed that it was composed of P3a, P3b and PSW components. They claimed that P3a was reliably influenced by the pattern of the evoking stimulus. With the more complex symbols, the latency was about 10 msec shorter than with the less complex symbols. They suggested that the latency of this component may be

related to stimulus encoding time. They reported that the amplitude of the P3b component was increased when the stimulus was different to what the subject was primed to receive, while when the stimulus was consistent with the previous priming stimulus the amplitude was negligibly small. They showed that PSW occured when the experimental task imposed on memory retrieval mechanisms.

Summary

The main findings regarding ERPs are:

1. Exogenous components have been shown to be associated with the physical characteristics of the stimulus, and are thought to be evoked by events which are extrinsic to the nervous system.

2. Endogenous components e.g. the P3 occur when the subject has to respond to the stimulus and it is hypothesized that they reflect cognitive processing.

3. P3 has been shown to be associated with the subjective and objective probability of the stimulus.

i: Hypotheses relating to proposed information processing function of P3

A number of hypotheses have been proposed which describe the information processing function of the P3 component of the ERP. It has been suggested that P3 is a physiological sign of the delivery of task relevant information and stimulus salience, of the resolution of prior uncertainty, and of a reactive change in state of arousal. While these hypotheses serve to describe some of the attributes of stimuli that have been shown to evoke P3, other hypotheses have used these functions to infer that P3 manifests some cognitive function based upon stimulus salience. Brookhuis et al (op.cit) that P3 latency is a reflection of stimulus evaluation time in perceptual and cognitive processing, and is associated with response selection and organization. However, the P3 peak has been found to precede motor reaction by an average of only 30 msec (Giedke, Thier and Bolz 1981) and in some cases motor reaction has been found to occur before completion of the P3 component (Donchin et al 1978, Tueting 1978). Therefore, it appears that stimulus evaluation must start before the P3 peak.

Hillyard et al (1971) hypothesized that P3 occurs when there is a match between the stimulus and a template of the signal held in memory. He reported that the amplitude of P3 increased with the closeness of the template match, and claimed that P3 is involved in perceptual decision making tasks. A mis-match is thought to occur when the presented stimulus does not meet the criterion of the template (Naatanen and Gaillard 1983, Naatanen, Simpson and Loveless 1982, Pritchard 1981). However, as has already been discussed, P3 does not always occur when there is a match between a stimulus and its template in memory. Donald (1983) proposed an alternative hypothesis which stated that if memory can correctly predict the input, a match is registered and the P3 amplitude is reduced ; if not a mismatch is registered and the P3 is enhanced. On similar lines, Karis, Fabiani and Donchin (op.cit) suggested that P3 is sensitive to the strength of a decaying memory representation, proposing that if the representation is active in working memory, no P3 will be evoked, but if the trace has faded a P3 will occur and the representation will be reactivated. They further reported that isolates result in larger P3 amplitudes than items belonging to a category which also emphasizes the association between P3 and items which are not currently represented in context (working memory) for the subject.

Donchin's context-updating hypothesis which is described below, shares similar features with Donald's template-matching hypothesis, in that both agreed that P3 occurs when the subject fails to match the stimulus with an available template. However, Donchin used the concept of working memory to describe these available templates, that is information about the subject's immediate environment.

Donchin (1981) has proposed that P3 occurs when the subject needs to revise his model of the environment in response to the stimulus, that is when there is a discrepancy between received and expected information. P3, therefore, reflects a 'context updating' process where current representations in working memory are revised to incorporate the most recent discrepant information. The amount of processing is proportional to P3 amplitude. P3 latency depends upon the time necessary for stimulus evaluation, and they concluded that P3 itself reflects the process which maintains an accurate environmental model by continuously revising this model according to the nervous system. The model is primed, so that aspects
that are central to the present task are the most active, and they form the working memory. When less central aspects of the model must be activated to allow processing of novel or rare events, other segments of the model are brought into working memory. This hypothesis takes into account various factors which have been associated with P3 : probability, salience, information - content, categorizability and

task relevance of the stimulus. Donchin stated that P3 is related to the encoding of the stimulus and the beginning of associative organizational processes in categorizing the stimulus.

Verleger (1988) has agreed that subjects maintain a set of expectancies that affect the evaluation of each stimulus. He claimed that stimulus evaluation may lead to revision of expectancies and that P3 reflects the revision of expectancies. However, he does not concur that working - memory is necessarily the exclusive domain of these revisions and he has claimed that P3 occurs with awaited and not unexpected stimuli. This has formulated his context closure hypothesis. He has stated that P3 is evoked when expectancies are fulfilled. Although this hypothesis meets some of the antecedent conditions of P3, for example it could be argued that context closure operates when the subject's hypothesis about his environment is confirmed or disconfirmed, it would not explain the presence of P3 with the orienting reflex.

Other hypotheses develop along similar lines to that of Donchin's context updating hypothesis, although they do not use the concept of working memory to provide the framework for expected and unexpected information. However, they share the construct of some sort of primed network which determines what the subject is expecting to receive, be it in the form of semantic networks, other associative networks such

as cognitive sets and schemata or working memory, and state that P3 occurs when the stimulus which is being processed is discordant with what the subject is 'primed' to receive.

Boddy (op.cit) claimed that ERPs reflect the coding of the brain's registration of connotative meaning, by activation of Chomsky's deep structures of semantic meaning. ERPs reflect semantic discrimination by revealing activation in the logogen network. Logogens are units of information which are hierarchically related on the basis of semantic attributes. The interacting activation between the elements of the semantic network cause some events to be expected. P3 is hypothesized to reflect the activation of an unexpected logogen. Bentin, McCarthy and Wood (1985) showed that ERPs differentiate semantically primed and unprimed words on a lexical decision task. Rugg (op.cit) reported semantic priming effects evident in the ERPs 300 msec and later after the presentation of the stimulus. Polich and Donchin (1988) claimed that P3 is contingent upon the classification and categorization of incoming stimulus events in semantic memory, with its latency being proportional to the time required for stimulus categorization, while P3 amplitude is sensitive to processing capacity demands. They stated that spreading activation in semantic networks can account for word frequency patterns obtained, with shorter P3 latencies for common

words than uncommon and non-words, in that uncommon words will be sited at a greater distance than common words in semantic networks, and will, therefore, take more time to be reached and activated.

The remaining hypotheses develop the proposal that P3 occurs when the stimulus does not fit in with what is 'expected', that is what is in working memory or currently activated in a semantic or associative network, and that P3 reflects the updating of working memory or the activation of an inactive part of the network. These hypotheses claim that P3 reflects some associational or categorizing process. Halgren et al (1987) studied P3 and N4 responses during encoding, storage and retrieval of complex cognitive information. He concluded that properties of P3/N4 modulation may act to organize partially specified elements into a network. Pritchard (1981) and Ruchkin and Sutton (1983) have suggested that P3 reflects the completion of an evaluation and categorization of the stimulus.

As previously mentioned, the essence of most of these hypotheses is that it is a difference between the received stimulus and what the subject is expecting to receive that evokes a P3 response. The theories fail to define a common basis for determining what makes a stimulus unexpected in the light of how information is processed.

Therefore, the next section will consider how information is encoded and stored in memory, and how the individual can make use of this structure in information to derive predictions about future events.

2.3 Information Processing Theory

The use of information processing analogies to represent human cognitive processes forms the basis for much of the current work on cognitive functions, the aim being to understand the stages that occur between stimulus input and response output.

The intermediate stages between the observable input and output parameters are thought to consist of : receiving the information, operating upon it according to certain rules, storing the results in memory, altering the contents of certain areas of memory to which new information is relevant, and reporting the results of these operations in a specified form (Wyer 1974).

i Models of Information Processing

Although there are many variations in information processing models, there are fundamental similarities concerning the essential stages which are incorporated in most models. The principal stages and levels of processing correspond to : the registration of information in immediate sensory memory in the icon (the internal representation of the external stimulus) ; feature encoded short term memory by automatic and controlled processing (Schneider and Shiffrin 1977) ; long term memory organized in terms of feature ensembles or associative networks in which associated nodes form assemblies or concepts and combined concepts form schemata ; and retrieval of information from short term memory or long term memory by serial search processes. The flow of information is bidirectional. The schema accepts information as it becomes available at sensory surface, and it is changed by that information. It may also facilitate the processing of certain information.

Information processing theory attempts to interpret perception of an event as representations of the event in the nervous system. Perceptual encoding is thought to occur at several different levels of the nervous system from the peripheral sensory receptors to result in representations of the information being accessible at the highest levels in conceptual thought. This section will consider the theories

that have been proposed to describe the encoding and representation of information in memory. It will be proposed that P3 is a function of the implementation of the organization of information in memory.

Various models have been put forward to describe the structure and organization of memory. These models use different descriptions of how information is encoded in memory, but this section aims to emphasize the similar and complementary aspects of these models.

It is generally accepted that what is stored in memory is not replicas of experience, but representations in terms of integrations of concepts and attributes. This becomes evident when attempting to recall a message ; much of the information concerning the physical properties of the input is lost while the meaning of the message is retained, suggesting that the encoded representation is in the form of attributes of concepts. Memory traces established at the peripheral sensory levels decay, or are interfered with more rapidly than traces established at the central conceptual levels (Wickelgren 1977). It is this encoding of information into concepts that is of concern to semantic memory models.

All information processing models attempt to describe the state of information preserved by an individual. As such, these models entail the analysis of stored information into constituents (nodes) and the

expression of relations between these nodes. Meaningful conceptual memory is proposed to be structured in hierarchically arranged networks, where concepts or categories are the major units of structural representation. Each concept occupies a separate node. Subordinate to each concept is a list of constituent attributes and examples or members of that concept or category, which are also contained in individual nodes. The meaning of a concept is derived from the combination of the sets of attributes. It is assumed that the various attributes of a concept and the pieces of information that are possessed about that concept are stored close to each other rather than being randomly distributed throughout semantic memory. The links between the nodes determine their relationship to each other, forming propositions or logical reasoning. For example, the way in which a subsidiary node is linked to a concept node establishes whether it is an attribute of, or an example of, or even phonetically or semantically similar to a concept. Other ways in which nodes may be linked are by syntactical structuring.

The main approach to modelling the stucture of memory has been to define these networks and to describe the contents of the nodes and the relationships between them. The theories of semantic memory networks differ to some extent but they are united in their emphasis on the importance of word concepts to the structure of semantic

memory. Some models incorporate information about events in the framework of conceptual memory networks and some models have also included information about emotion in the networks (Bower 1981).

Examples of network theories include Quillian's (1969) model of semantic memory, which hierarchically arranges the nodes and states the relations between them. Categories, their properties and examples are linked, and information about concepts are stored at the highest level of generality to save storage space and to avoid multiple entries.

Anderson and Bower's (1973) Human Associative Memory model couches the structural aspects of memory in terms of a mixture of ideas drawn from linguistics and from association theory, labelling direct associations between memory elements in terms of linguistic properties. Sentences are encoded in the form of propositions and mapped onto a network of labelled associations.

Rumelhart, Lindsay and Norman's semantic memory model (1972) distinguishes between concepts and events within a network of relationships. Wickelgren (op.cit) claimed that long term conceptual memory is associative, and that events may be stored by networks of nodes connected by means of associations, in which associative strengths are increased by the activation of two nodes close together

in time. However, he also stated that events may be stored in a non-associative way by encoding and storing events in locations in the order in which they occur. Bower's model of associative memory which proposes that emotions are stored in nodes within conceptual networks will be discussed in more detail in chapter 4.

The evidence for encoding information into and retrieval of information from semantic networks comes mainly from psychology studies rather than from physiological evidence, which will be discussed later. Reder and Anderson (1980) have found interference effects from subsequent or prior learning of similar material. They showed that, when asking subjects to learn many associations to a common stimulus, the ability to recall or recognize any of the associations decreased. Therefore, the information from previous and later trials caused interference, indicating that information is stored in an associative manner. In tests of free recall, Jenkins, Russell, Bousfield Dease and Tulving (1972) showed that subjects tended to cluster items that were highly associated to each other or form the items into common category labels. Temporal, spatial and semantic properties of items were used to categorize them. Reaction time and free recall for similar concepts increased as compared with those for different concepts.

Therefore, the evidence suggests that information stored in memory is categorized, resulting in greater organization in storage and more accurate and efficient retrieval. There is also evidence which suggests that information is stored in hierarchical networks in memory. A series of reaction time studies showed that access was faster to more closely related items within categories, that is items related by simple propositions, than to items related by more complex propositions. It has already been proposed that associated nodes are located near each other, which is how categories are structured in memory. Collins and Loftus (1975) also define how activation spreads between associated nodes, strengthening pathways between associated nodes and lowering thresholds between them. The Spreading Activation Theory claims that the activation of a concept occurs when the corresponding node in semantic memory is activated, and the activation then spreads from that concept to neighbouring ones. The exact spread of activation is determined by the strength of the initial activation, the proximity to the point of activation and the amount of time that has passed since the onset of activation. The greater the semantic relatedness of an instance and a category, the faster the decision that the instance is a member of that category. The amount of activation arriving at any node is a function of the number of links that the activation has traversed. Therefore, the amount of activation given to a connected concept is a function of distance ; the closer

the concept is in memory to the input concept, the more it will be activated.

Priming is the term which describes the process where a prior stimulus activates (primes) the semantic network to facilitate reception of associated stimuli. It is thought that priming may occur when activation of a high level concept node causes decreased threshold levels for its subordinate nodes, thereby making perceptions of its associations easier. Also, activation of certain nodes which are involved in a particular concept or category may result in decreased thresholds for other nodes which are also constituents of the category. Because the amount of information stored in memory is so large, a successful model of memory requires mechanisms that allow efficient access by focusing on some subset in memory. Activation is maximal at the closest set of concepts to the initial concept, and this set becomes available for selection or decision processes.

Context effects, demonstrating how prior knowledge primes the semantic network to facilitate reception of associated stimuli, have been found by Posner (1969), Cohen (1969) and Tversky (1969). McKoon and Ratcliff (1979) demonstrated that both semantic and episodic associates prime a lexical decision response.

Spreading activation theory accounts for such facilitation by stating that activation spreads from the prime (prior stimulus) to the target, so that when the target is presented, its activation level has already been raised. Therefore, a faster and more accurate response can be made to the target because less additional activation is needed to reach a response criterion.

Meyer and Schvaneveldt (1971) were among the first to consider spreading activation as the mechanism responsible for priming in lexical decision. They found that responses to pairs of associated words in the memory structure were faster showing that proximity allowed faster accessing of information. They claimed that retrieving information from a particular memory location produces a passive spread of activation to other nearby locations facilitating faster retrievals from them. Reaction time varied with semantic similarity.

Automatic semantic priming may not occur for all semantically related items under any and all circumstances. It may be that the process occurs when the subject is 'set up' to perform in such a way. Priming may occur automatically, attributed to spreading activation and strategically due to the development of the subject's expectations that primes will be followed by associated words as targets (Ratcliff and McKoon 1988). The data suggests that both senses of an

ambiguous word are primed directly after the word is presented, but that later in processing only the appropriate sense is primed. Spreading activation explains this by postulating initial activation followed by decay due to the processing of other material. The sense appropriate to the context is maintained because it receives activation from other compatible sources. Priming has been shown to extend beyond the sensory modality within which information is presented (Graf et al 1985). It operates on both semantic and perceptual processes.

ii Physiological Evidence of Associative Networks.

The use of an effective priming mechanism implies that the underlying semantic representations are intact. Physiological support for the existence of semantic networks is controversial but the parallel between interactive semantic networks and the complex network of neurons in which activation of some neurons leads to the activation of other neurons suggests that both networks are a kind of associational structure. Certain processes which have been shown to occur in physiological recordings of neurons are habituation, lateral inhibition and disinhibition. These are also features in information processing models of spreading activation associative networks.

Wickelgren's (1977) theory of cortical association proposes that the pattern-synthesizing cell in the infero-temporal cortex may be associated with lower level feature detector cells by lowering conduction thresholds for these pathways. The cell or cell cluster in the infero-temporal cortex would then represent the stimulus pattern and it could be supposed that the cell would act like an association node in a memory network. The nodes may be connected to other areas of the brain, for example the speech motor cortex so that the stimulus can be named. The associating mechanisms would allow cross- modal associations.

Gray (1982) interprets the function of the hippocampus and septo-hippocampal system in information processing as integrating received and stored information. He emphasizes the input to these areas from the sensory association cortex, prefrontal cortex and amygdala. He states that the septo-hippocampal system acts to compare actual with expected information in the environment. The system receives actual sensory data via its sensory association area inputs and matches these with expected predictions based on previous experience generated in the cingulate and prefrontal cortex. When actual and expected coincide, the system functions passively, permitting continued elaboration of the motor plan, and passing on information that a match

has taken place for storage elsewhere. If actual and expected no longer agree, the septo- hippocampal system takes active control of behaviour.

The hippocampus is also thought to be involved in the orienting reflex index. This requires the comparison of a new, novel stimulus with the system of old.previously encountered stimuli, as such a comparison alone can show whether a given stimulus is in fact novel and whether it must give rise to an orienting reflex index, or whether it is old and its appearance requires no special mobilization. This type of mechanism can permit a process of habituation so that a repeatedly presented stimulus loses its novelty and special mobilization is no longer necessary.

It is hypothesized that the hippocampus and caudate nucleus are amongst the brain regions responsible for this function of comparing stimuli, reacting to the appearance of novel stimuli and blocking activity with the development of habituation to repeated stimuli.

iii Cognition as a component of information processing.

Models of semantic networks have been proposed which consist of associated nodes with facilitation effects operating between them. These provide the constructs with which to describe the formation and use of concepts and schemata in cognition.

Information in semantic memory seems to be organized around concepts rather than attributes of concepts. Concepts may be concrete or abstract ; concrete being directly activated by one or more sets of lower level constituent attributes while very abstract concepts may be only directly activated from sensory input by means of prior activation or propositional representatives. The concepts can be activated in a bottom-up fashion by activation of their attributes. Concepts can also be activated in top-down fashion by activation of the proposition in which the concepts are incorporated.

Concept learning occurs through observation and inference of common elements. Perceptual features and perception of functioning attributes play a role in determining concepts. Inferential concept learning depends on the use of propositions already in semantic memory.New propositions are acquired in semantic memory by the

recognition of familiar nodes in new ways. Many abstract concepts show an apparent absence of structure, and the core of the concept is those aspects which deal with its relation to other concepts.

Schemata are larger, well-integrated chunks of knowledge, compounded of combinations of concepts. They are organized structures of stereotypic knowledge which extract the common elements from a range of situations and events. Rumelhart (1980) says :

"There are schemata representing our knowledge about all concepts ; those underlying objects, situations, events, sequences of events, actions and sequences of actions. A schema contains, as part of its specification, the network of interrelations that is believed to hold normally among the constituents of the concept in question." Meanings are encoded in terms of the typical situations that provide concrete examples for the schema. Schemata may incorporate new information and are sometimes changed by it, and are thus flexible with respect to the current environment. However, they are also well-structured in that they consist of series of associations built up through experience and inference which enable the individual to impose structure on his environment.

The categories that are formed guide subsequent thinking and behaviour, and shemata influence several psychological processes including perception, learning and retrieval. For example, in

perception, they serve to reduce processing demands. Schemata help to determine what is perceived through prior expectations and context effects. Schemata permit the use of information about the regularities of events and situations to form accurate inferences about the world and can facilitate the comprehension of complex passages and stimulus events. By forming and using concepts and schemata the individual categorizes and structures the information he stores in memory.

Therefore, it has been proposed that the structure of memory comprises the construction of associative networks from which the subject develops the schemata with which he interprets his environment. These schemata are based on regularities perceived in previous experience, and encoded into memory in associative network. In this format, the subject can call upon the information stored in memory to make inferences based on propositions which are also stored between units of information. It has also been proposed that spreading activation, between associated nodes within the network, causes some information to be expected, while inactive nodes are unexpected. As such, the subject is able to make sense of his environment in that he can make predictions about future events based on the knowledge he has stored in memory. Schemata may incorporate new information and are sometimes changed by it, and are thus flexible with respect to the current environment. However, they are also well-structured in that

they consist of series of associations built up through experience and inference which enable the individual to impose structure on his environment.

iv The Role of Expectation or Bias in Information Processing

Most models of normal functioning accept that perception is dependent upon interaction between the stimulus presented and stored memories of regularities from previous input which result in expectancies or response biases and serve to reduce information processing demands.

However, the same or identical physical objects have been shown to be perceived differently at different times by the same subject. Prior associations between relevant and irrelevant sources of information have usually facilitated performance in the priming paradigm (Posner 1978) and inhibited performance in the Stroop paradigm (Dyer 1973, Jensen and Rohwer 1966). Facilitation and inhibition effects are stronger the closer the association between relevant and irrelevant information (Fox, Shor and Steinman 1971). When the stimulus configuration is compatible with habitual associations or with current predictions or with both, the evidence provided from associations and predictions reduces the evidence required from the target or reported dimension to choose a response with an acceptable level of accuracy.

When the stimulus configuration conflicts with associations and predictions, the evidence they provide is misleading and increases the evidence required from the target or reported dimension. Evidence accumulates over time, and conflicting configurations increase reaction time.

Subjects apply their knowledge about a given situation to form differential expectancies or subjective probabilities for the various events that might occur. There information processing triggered by the occurence of an event is affected by the expectancy associated with that event.

Squires et al (1976) described the three factors which they claim determine a subject's expectations in an ERP experimental situation. They are :

1. The a - priori probability of an event which is pre-set and observable

2. The subject's own internally generated expectation which is not observable.

It is hypothesized that the subject, because of his psychological state and because of the experimentally induced set, has a bias to expect that a specific pattern will continue rather than break up.

3. The rate with which previously perceived events of the same type fade in memory will cause some events to be more unexpected than others.

2.4 Information Processing and Psychophysiology

i P3 as a Manifestation of Information Processing

The evidence which has been presented to support the hypothesis that neurophysiological recordings are manifestations of information processing functions and even that information processing constructs have anatomical bases is controversial. As Donchin and Coles (1988) pointed out, it is possible that the neuronal ensembles whose activity is recorded by ERPs do not constitute distinct and unique neuroanatomical entities. However, Donchin and Coles claimed that because the neuronal activities have the geometry and temporal characteristics so that they contribute to the P3, they are elicited to perform some specifiable information processing task. Thet stated

that the function of the brain is to process information, and the biochemical interactions it performs must accomplish tasks that can be described in information processing terms.

Because of the temporal coincidence between the stimulus presentation and the P3 response, it is assumed that there exists a causality relationship between the triggering event and the specific wave pattern that follows it. Rosler (1983) stated that the primary causality relationship is between the triggering stimulus and some internal processing activity which follows the stimulus input. The implication is made that endogenous ERPs are a manifestation of the internal information processing stages. Donchin et al (1986) stated :

"We assume that the consistency displayed by an ERP component in its relation to experimental manipulations is due to the fact that the activity it manifests is generated by the invocation of a distinct component of the information processing system".

To formulate a hypothesis about the information processing function of P3, it is necessary to : "abstract from the directly observed variables and the particular experimental settings, one common 'denominator'" (Rosler 1983), that is, it is necessary to examine the antecedents of the P3 response to search for some common

attribute. As Rosler continued : "one must add some assumptions about the information processing activities performed by the brain ; in short one must formulate more or less explicitly a cognitive theory".

The common properties derived from examining the antecedent conditions of the P3 in an earlier section were shown to be the probability and task relevance of the stimulus and the confidence with which the stimulus was perceived by the subject. As discussed earlier, probability can be objective, that is determined by the frequency with which the stimulus occurs, and subjective, that is determined by the the subject's own internally generated expectations and biases, and the rate with which events fade in memory (Squires 1976). Squires found a correlation of -0.88 between the sum of all three sub-functions of expectancy and P3 amplitude.

Task relevance is determined by the meaningfulness of the stimulus for the subject. Whether or not the stimulus is meaningful to the subject may depend upon such factors as the psychological state of the subject and task instructions. Task relevance operates only to the extent that the stimulus becomes important to the subject and requires processing to extract information from it.

Confidence in being able to detect the stimulus correctly has also been shown to be associated with P3. This merely indicates that it is important that the presented stimulus intensity is adequate to ensure accurate and easy perception of the stimulus so that P3, as a manifestation of an information processing function, does not become confounded with the effect on P3 of difficulty in discerning the stimulus. Stimulus recognition is not proposed to be the information processing function of P3, but to be the function of earlier components. Difficulty in identifying the stimulus prolongs and decreases the P3 indicating that the stimulus is difficult to process and therefore, takes more time. Therefore, examination of P3's antecedent conditions focuses attention on the importance of expectancy in eliciting a P3 response. This leads to the general hypothesis of this study, which is that when there is a mismatch between the received information and what the subject is expecting to receive as determined by the associative networks activated, a P3 response in the EEG will be produced. This hypothesis is in accordance with Donchin's theory of context updating where models of immediate environment held in working memory are revised in response to unexpected incoming stimuli. However, this hypothesis is not exclusive to information processing in working memory. The significance of associative networks built up in long term memory as a result of experience and inference is thought to be paramount in determining a subject's expectations and biases. Spreading activation between

related nodes in associative networks enable an individual to use the structure of information in memory to determine what is expected and what is not expected. If the stimulus is already activated in the subject's associative network, it will be congruent with his current category or schemata, and, therefore, expected. The stimulus association with the presently activated schemata will be further strengthened, and no or little P3 response will be evoked. However, if the stimulus activates a node which is situated in a different network or schema, this will not fit in with the previous shema. If the node is in a different network, then the nodes in the new network will be activated, by spreading activation causing the subject to become aware of a new set of expectations. In this case a P3 response is evoked. It may even be appropriate to form a pathway between the new network and the previously activated network, in case the relationship between the two is relevant. This will be the case if the two networks are subsequently associated on future occasions, and the pathway will be strengthened. It is hypothesized that P3 is the manifestation of the process of activating an inactivate network by spreading activation. This concurs with Desmedt's statement that P3 begins when stimulus categorization ends, if the stimuli are categorized as expected and unexpected. This categorization is determined by the state of activation of the node which represents the stimulus in long term memory. P3 response is maximal when the stimulus has been categorized as unexpected, that is when its node is inactive,

and it is hypothesized that P3 serves to activate the associates of the new stimulus. Therefore, P3 reflects the spread of activation between nodes in associative networks. Activation of new associative networks creates new sets of expectations so that the subject then becomes geared up (primed) to receive a different set of stimuli. Therefore, it is hypothesized that P3 is a physiological manifestation of the information processing function of priming.

Shimamura et al (1987) reported that Alzheimer's Disease patients exhibited impaired priming as opposed to Korsakoff's patients who maintained intact priming, although both groups were impaired in recall and recognition. Blackwood et al (1985) reported that prolonged P3 latency and decreased P3 amplitude occur in Alzheimer's Disease but not in Korsakoff's Syndrome. Blackwood et al reported that the Alzheimer's Disease patients exhibited repetitive speech and difficulties in word finding and naming, which correlated with P3 latency. Shimamura et al proposed that the deficit in priming may reflect an impairment in the ability to activate representations that store lexical memory, and that this deficit might account for problems in word finding and semantic memory that are prominent cognitive functions of Alzheimer's Disease. They suggested that impaired priming may be the result of damage to cortical representations in the neocortex that store lexical memory.

ii The Neuroanatomy of P3

Several studies have been published which suggest possible origins or generators of the scalp recorded P3. The medial temporal lobe has been proposed as the site where P3 is generated. Intracranially recorded ERPs from the medial temporal lobes have been shown to have similar task correlates and latency range to the scalp recorded P3, and both are shown to be evoked by rare stimuli (Smith, Stapleton and Halgren 1987). Halgren et al (1980) demonstrated P3 like fluctuations in ERP recordings from the hippocampal formation and amygdala to infrequent events. These temporal lobe P3 recordings have been shown to be consistent with studies which have reported increased latency of the scalp P3 as categorization difficulty increases (Hillyard and Kutas, 1983). However, Stapleton (1987) showed that with unilateral temporal lobectomy, there was a lack of any real difference obtained in P3 recordings.

Knight (1984) suggested that the prefrontal cortex contributed to the generation and modulation of P3. He showed that two different types of P3 response were evoked by different stimuli : a non-specific parietally distributed P3 to target stimuli, and an earlier latency, frontally distributed N2/P3 complex to novel stimuli. Knight showed that in patients with prefrontal disease, the second type of P3 was eliminated and they responded to novel stimuli as the former P3

response. However, in patients who had undergone surgical removal of diseased areas, he found no evidence of a lateralized decrease in P3 response over the absent cortex. He concluded that the prefrontal region was not the primary generator but modulates generators that are located elsewhere.

McCarthy (1985) has demonstrated during a two tone discrimination task, two distinct intracranial ERP patterns which overlap in time with P3. One pattern was recorded from the region of the hippocampus and the second was consistent with a source within the frontal lobe. The lack of large cortical potentials and the broad central-parietal distribution of scalp recorded P3 suggests that P3 originates from a diffuse cortical source and that there may be multiple generators. The medial temporal lobes and prefrontal cortex may be two of these sources, or they may act to modulate generators elsewhere. These possibilities indicate that it may be informative to consider the relationship between P3 and frontal lobe and temporal lobe function. In this study, the relationship between P3 and cognitive functions which are associated with the frontal and temporal lobes will be examined.

2.5 Hypotheses derived from the literature review.

If abnormalities in P3 reflect dysfunctions in the mechanism which revises current expectations to incoming stimuli, that is a priming mechanism, it is hypothesized that a decrease in amplitude in the P3 will suggest that this priming mechanism is not fully operational and that perhaps activation between associated nodes is not occuring. An increase in P3 latency may reflect a delay in the operation of the mechanism.

With normal P3 responses, subjects are hypothesized to process incoming stimuli in a manner which enables them to form hypotheses about future events from the information that they have in memory based on past experience, and to form expectations. The subjects are then primed to receive associated stimuli. Therefore, associative processes will be enhanced, leading to integration of associated features, fluency of thought, concept formation and abstract thought. It is predicted that subjects who show abnormalities in P3 may have dysfunctional associative networks and show more bizarre associations, impoverished thought content, restriction of relatedness and integration, concrete thinking, impairment in the ability to form and use concepts, perseveration, lack of fluency, increased latency in information processing, and slow response latency. They will show

memory and learning impairments with dysfunctions in the ability to associate new information with stored information and to integrate the two.

Chapter Three

SCHIZOPHRENIA

3.1 General Description

i Definition

The diagnosis of schizophrenia is made on the basis of the presence of characteristic symptoms, which include : delusions, hallucinations, disturbances in affect, disturbances in the form of thought and disorders of movement. The aetiology of schizophrenia is not understood and so its definition rests upon clinical symptomatology and outcome. It is probably a group of conditions which have a course of illness which includes a tendency towards onset in early adult life, recurrence of psychotic (active) episodes, and deterioration in social and occupational functioning from premorbid levels which persists between the psychotic episodes.

The major classificatory systems are International Classification of Disease (ICD-9) of the World Health Organization and the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-

III-R). The latter attempts a fuller glossary of definition of terms and suggests clearer criteria for diagnosis than the former. Research Diagnostic Criteria (Spitzer et al, 1977) and the symptoms elicited by the standardized interview, the Schedule for Affective Disorders and Schizophrenia (SADS, Spitzer and Endicott, 1978) differ only slightly from the DSM-III-R criteria.

The definition of schizophrenia includes the following:

1) Disturbances of content of thought which include delusions e.g. delusions of being controlled or influenced. Delusions may be multiple, fragmented or bizarre e.g. persecutory delusions and delusions of reference. Delusions of thought broadcasting, thought insertion and thought withdrawal are particularly associated with schizophrenia but somatic, grandiose, religious and nihilistic delusions are also commonly experienced.

2) Disturbances in the form of thought, usually referred to as formal thought disorder. Speech may be difficult to follow due to lack of logical or meaningful connections between words, phrases or sentences, excessive use of incomplete sentences, excessive irrelevancies or abrupt changes in subject matter, distorted grammar or syntax, idiosyncratic word usage and use of empty, repetitious, stereotyped or obscure phrases. Loosening of the associations (derailment) occurs

when the patient moves from one topic to the next without there being a readily understandable relationship between the ideas, or shifts idiosyncratically from one frame of reference to another. Illogical thinking is characteristic of schizophrenia, where facts are obscured, distorted or excluded, internal contradictions are included and one premise does not follow from another. Poverty of content of speech is evident, where speech is adequate in amount, but conveys little information because of vagueness, talking past the point, empty repetitions or use of stereotyped or obscure phrases. The schizophrenic patient may include neologisms in his speech, or standard words to which he has given new idiosyncratic meanings. These words may be invented to designate an experience which is outside all normal experience.

3) Disturbances in perception which include hallucinations. Auditory hallucinations are the most common e.g. where a voice keeps up a running commentary on the patient's behaviours or thoughts, or where two or more voices converse with each other. Tactile and somatic hallucinations are also common. The patient may experience sensations of bodily change, hypersensitivity to sound, sight and smell, and illusions.

4) Disturbances of affect which include flattening or blunting of the mood and inappropriate and incongruous mood. Affect is described as flat when the patient is observed to express little or no emotion to emotional stimuli or situations. Patients may report that they feel less or even no emotion. Inappropriate affect may be seen when the patient responds in a seemingly inappropriate way to an emotional situation.

5) Disturbances in volition affecting the self-initiated, goal-directed activities of the patient, so that he has inadequate interest, drive or ability to follow a course of action to its logical conclusion. The patient may suffer impaired interpersonal functioning and relationship to the outside world which may result in social withdrawal and emotional detachment.

6) Movement disorders which are common in schizophrenia and usually take the form of involuntary, twitching movements of the face and the upper limbs. In catatonic states, schizophrenia may present almost entirely as a movement disorder but this is very rare.

The typical course of schizophrenia is described by DSM-III-R as comprising three phases : the prodromal phase; the active phase and the residual phase. The active phase is usually preceded by a prodromal phase in which there is a clear deterioration from a

previous level of functioning. This deterioration takes the form of social withdrawal, impairment in role functioning, peculiar behaviour, neglect of personal hygiene and grooming, blunted or inappropriate affect, disturbances in communication, bizarre ideation, unusual perceptual experiences,and lack of initiative, interest or energy.

During the active phase, the psychotic symptoms are prominent. These have been described above as those which set the criterion by which schizophrenia is diagnosed.

A residual phase usually follows the active phase. This is similar to the prodromal phase, except that affective blunting or flattening and impairment in role functioning is more common. Some psychotic symptoms may persist.

A full return to the level of premorbid functioning is unusual, and the most common course consists of acute episodes of psychotic symptoms with residual impairment between episodes. Residual impairment may increase between episodes during the initial years of the disorder, but there is some evidence that in many cases the residual symptoms become attenuated in the later phases.

ii Sub-types

The following sub-types have been identified by RDC and DSM-III-R according to the patient's clinical syndrome, and it is stated that diagnosis of a patient's type should be based on the predominant clinical picture which accompanied the most recent evaluation of the patient.

The catatonic type is differentiated by marked psychomotor disturbance. This may be seen as stupor where there is a marked decrease in reactivity to the environment and/or reduction in spontaneous movements and activity; negativism when there is apparently motiveless resistance to all instructions or attempts to be moved; rigidity where the patient maintains a rigid posture against efforts to be moved; excitement where there is excited motor activity which is apparently purposeless and not influenced by external stimuli; and posturing where there is voluntary assumption of inappropriate or bizarre postures.

The disorganized (hebephrenic) type requires marked formal thought disorder,shallow or silly affect, or fragmentary delusions or hallucinations whose content is not organized into a coherent theme. It is characterized by incoherence, marked loosening of the associations, grossly disorganized behaviour and flat or inappropriate

affect. This type is associated with extreme social impairment, poor premorbid personality, an early and insidious onset and a chronic course without significant remissions.

The paranoid type is preoccupied with one or more systematized delusions or with frequent auditory hallucinations related to a single theme. The symptoms which are characteristic of the disorganized and catatonic types, such as incoherence, flat or grossly inappropriate affect, catatonic behaviour or grossly disorganized behaviour are absent. Impairment in functioning may be minimal if the delusional material is not acted upon. The onset tends to be later in life than for the other types, and the distinguishing characteristics may be more stable over time. Some evidence suggests that the prognosis for the paranoid type, particularly with regard to occupational functioning and capacity for independent living may be considerably better than for the other types of schizophrenia.

The undifferentiated type includes those patients whose prominent psychotic symptoms i.e. delusions, hallucinations, incoherence or grossly disorganized behaviour, cannot be classified in any of the previously described categories. Alternatively they are patients who meet the criteria for more than one category.

The residual type consists of patients who have had a period of illness in the past that met the criteria for active schizophrenia, but whose clinical picture is currently without prominent psychotic symptoms, although residual symptoms persist. Emotional blunting, social withdrawal, eccentric behaviour, illogical thinking and mild loosening of associations are common. If delusions and hallucinations are present, they are not prominent.

ICD-9 also includes simple type, acute schizophrenic episode, latent schizophrenia, and schizoaffective type. "Simple schizophrenia" is characterized as a psychosis in which there is insidious development of oddities in conduct, inability to meet the demands of society, and decline in total performance. Delusions and hallucinations are not in evidence and the condition is less obviously psychotic than are the hebephrenic, catatonic and paranoid types.

"Acute schizophrenic" episode is described as a disorder in which there is a dream- like state with slight clouding of consciousness and perplexity. External things, people and events may become charged with personal significance for the patient. There may also be emotional turmoil. In many cases, remission occurs within weeks or months even without treatment.

"Latent schizophrenia" describes a condition of eccentric or inconsequent behaviour and anomalies of affect that give the impression of schizophrenia. However, no definite schizophrenic anomalies have been manifest. "Schizoaffective type" is a psychosis in which pronounced manic or depressive features are intermingled with schizophrenic features, and which tends towards remission without permanent defect, but which is prone to recur.

ICD-10 proposes to introduce classification for postschizophrenic depression, schizophrenic spectrum disorders, persistent delusional disorders, acute and transient psychotic disorders and other non-organic psychotic disorders. The ICD system provides a broader classification of schizophrenia, and includes patients who would not be diagnosed as schizophrenic but as personality disorder or schizo-affective disorder patients with RDC and DSM-III-R.

RDC and DSM-III-R classify patients as acute, subacute, subchronic and chronic. Acute schizophrenia requires sudden onset, short course (less than 3 months), and full recovery from any previous episode. Subacute schizophrenia has a course which is closer to that of acute schizophrenia than that of chronic schizophrenia, requiring shorter durations of active episodes and full recovery between episodes. Subchronic schizophrenia has a course which is closer to that of chronic schizophrenia than acute schizophrenia, in that significant

signs of schizophrenia should be evident more or less consistently for longer durations and the patient does not fully recover between episodes. Chronic schizophrenia requires that significant signs of schizophrenia should be present more or less continuously for at least the last two years.

Much support has been given to the classification of characteristic symptoms of schizophrenia into postive and negative symptoms (Wing 1978, Andreasen 1982). Positive symptoms include delusions, hallucinations and thought disorder. Patients with positive symptoms have been generally found to have a good prognosis and show a good response to phenothiazines. As such they are associated with acute schizophrenia rather than chronic schizophrenia. Negative symptoms include extreme social withdrawal, poverty of thought, poor judgement and planning, apathy and flattening of affect. It has been found that they experience cerebral atrophy, poor prognosis and a poor response to treatment and therefore, are associated with chronic schizophrenia. On a battery of psychometric tests, Green and Walker (1985) found that positive symptoms related to deficits on tests that involve short-term verbal memory, while negative symptoms are associated with poorer performance on tests that measure visual-motor and visual-spatial skills. Negative symptoms are associated with reduced intellectual abilities, and cognitive developmental deficits in tests of conceptualization (Kay et al 1986). Patients with

negative symptoms were found to be deficient in elementary conceptual and representational modes of thought. Kay et al also found that while negative symptoms were associated with failures in cognitive maturation, positive symptoms were associated with conceptual disorganization. Positive symptoms were associated with paranoid types of schizophrenia, while residual schizophrenia is more associated with negative symptoms. Both positive and negative symptoms may be evident in hebephrenic schizophrenia. Crow (1980) devised a system of classifying schizophrenic patients into Type I and Type II patients which is primarily based on the presence of positive and negative symptoms. Type I patients manifest predominantly positive symptoms while Type II patients charactistically display negative symptoms.

Schneider (1959, 1971) introduced the concept of 'first rank' symptoms when proposing a list of symptoms to differentiate schizophrenic patients from manic-depressed patients. Although the differentiation is not so clear-cut as Schneider proposed, first rank symptoms are still recognised as positive symptoms which are characteristic of schizophrenia, and have been incorporated into the main classifications such as DSM-III-R and PSE.
These systems of classifying schizophrenia reflect the need for researchers to define accurately a condition which can be recognized by its symptoms. The strict definition of symptoms has led to good reliability between different clinicans in the diagnosis of

schizophrenia, but the validity of these clinical categories remains largely untestable. The best approach in schizophrenia research at present is to define patients by several operational criteria avoiding too many theoretical assumptions.

iii Epidemiological Findings

Helgason (1964) reported a 0.9% morbidity risk of schizophrenia in his study of the population of one island in Iceland from which there was a very high rate of ascertainment of over 99%. He identified 36 cases of schizophrenia from a population of 5,395. McCreadie (1982) reported a prevalence rate of 2% based on finding 133 cases in a Scottish survey. Of the other similar studies which have been conducted, there are few instances where rates have been sufficiently different from the average to be considered as possibly abnormal. First contact with psychiatric services in S.E. London was recorded as 14 per 100,000 (Wing and Fryers 1976), while 15.5 per 100,000 was estimated for first admissions with schizophrenia to Scottish mental hospitals. These rates have been shown to pertain world-wide. The incidence of schizophrenia is approximately equal in both sexes, with a slight excess in males. The onset of schizophrenia occurs some five to ten years earlier in males (HMSO 1986). Only about 2% of male cases

begin after the age of 35, compared with 17% in females. Flor-Henry (1985) has noted that the stricter the diagnostic criteria applied, the greater the excess of males found.

In-patient admission records for the Royal Edinburgh Hospital in 1988, analyzed by diagnosis and sex, revealed 377 admissions with a diagnosis of schizophrenia (131 females and 246 males). This accounts for 15.6% of all admissions for that year.

iv Biology of Schizophrenia

a) Specific Areas of the Brain Implicated in Schizophrenia.

Much research has been conducted into the importance of the frontal lobes and temporal lobes in schizophrenia, since Kraepelin (1919) argued that the deficits in higher cognitive function found in schizophrenia such as poor judgement, inability to plan, loss of the 'critical faculty' and loss of creativity were the result of frontal lobe damage, whereas the peculiar speech disorders and auditory-verbal hallucinations which are evident in schizophrenia were due to presumed irritative damage to the temporal lobe. Jacobi and Winkler's (1927) pneumoencephalogram findings linking hallucinations with temporal lobe damage, and intellectual deficits with frontal lobe damage were seen as confirming Kraepelin's theories.

Hughlings-Jackson (1931) also proposed that schizophrenia must involve the highest levels of brain function, that is the frontal and temporal lobes. He hypothesized that damage to the frontal and temporal lobes released sensory and perceptual systems from inhibition and produced dreaming while awake which took the form of hallucinations and illusions. Hughlings-Jackson also accounted for positive and negative symptoms as a result of brain damage. He proposed that negative symptoms were a direct result of the loss of function of the damaged area, and positive symptoms to be the result of distribution in intact brain areas which were normally inhibited by the damaged area.

Converging evidence from clinical, neurophysiological, brain-imaging and neuropsychological sources suggest that there is frontal lobe and temporal lobe dysfunction in schizophrenia. This section will consider this evidence.

1) Clinical evidence.

Levin (1984) claimed that negative symptoms seen in schizophrenia, such as flat affect, alogia, mutism, apathy, anhedonia, social withdrawal, distractibility and impairments in volition, planning and goal-directed behaviour, are clinical manifestations of frontal lobe damage. Zec and Weinberger (1986) also pointed out that deficits in

maintaining and shifting set are shared by schizophrenic and frontal lobe patients. Seidman (1983) considered negative symptoms to be attributable to frontal lobe dysfunction, and positive symptoms to be attributable to dysfunctions in limbic regions while Levin (1984) attributed positive symptoms to the temporal parietal area. However, Andreasen (1986) stated that abnormalities of the temporo-limbic regions are manifested as auditory hallucinations, disorganized speech and thinking, affective and emotional blunting and possibly memory impairment. All of these have been established as schizophrenic characteristics,although some have been described as positive symptoms and others as negative symptoms.

2) Neurophysiological evidence.

Studies using computer-determined EEG topography or brain electrical activity mapping have reported increased slow frequency activity in frontal regions in schizophrenic patients. Buchsbaum (1979) reported increased frontal delta activity in schizophrenic patients compared with controls. Other studies have found inconsistent results, but the study of Morihisa and McAnulty (1985) may help to clarify the picture. They reported greater frontal EEG abnormalities in those patients with marked frontal atrophy as determined by a CT scan. This finding suggests that there may be a relationship between regionally specific functional and structural abnormalities.

Interest in the involvement of the temporal lobes in schizophrenia originated from the introduction of EEG recordings followed by clinical reports that patients with temporal lobe epilepsy were more prone to psychopathology and especially psychosis than patients with lesions in other brain regions. Slater, Beard and Glitheroe (1963) reported the presence of chronic, paranoid, hallucinatory states and the presence of delusions and Scheiderian first rank symptoms in patients with temporal lobe epilepsy. They found that the medial temporal areas were the most likely source of seizures. This has subsequently been confirmed by many studies.

3) Evidence from brain-imaging.

While studies of temporal lobe epilepsy highlighted the possible role of the temporal lobes in schizophrenia, the developments in scanning and imaging techniques have also drawn attention to possible structural changes in the frontal lobes in schizophrenic subjects. In the first reported CT study, Johnstone et al (1976) compared 18 chronically institutionalized schizophrenic patients with age matched normal controls, and found lateral ventricular enlargement in the schizophrenic group with little overlap between the groups. Weinberger et al (1979) performed CT scans on 58 chronic schizophrenics under the age of 50, and found that 40% fell outside a control range for lateral ventricle size, and 53% were beyond 2 standard deviations of the mean.

Reveley et al (1985) found that about 20% of schizophrenic patients manifested ventricular enlargement and/or cortical atrophy. They claimed that these abnormalities were associated with cognitive impairment and poor outcome and antedate the onset of the illness. Tanaka et al (1981) found enlargement of the third ventricle in a proportion of schizophrenic subjects in a CT study. Reviews of CT scan findings in schizophrenic patients by Reveley (1985) and Shelton and Weinberger (1986) summarizing the results of a very large number of studies concluded that schizophrenic patients showed the following abnormalities: lateral ventricular enlargement; sulcal widening; widening of the third ventricle; atrophy of the cerebellum; decreased brain frontal tissue density and possibly reversed cerebral asymmetries. Reveley (op.cit) followed up 30 schizophrenic patients and rescanned them after 4 to 7 years. He found that the structural changes were not progressive : for example, he found little change in ventricular size over the time period he studied. CT studies have also shown abnormalities in the temporal region in schizophrenic subjects (Hill 1957, Abenson 1970).

MRI studies have confirmed ventricular enlargement (Johnstone 1976) and atrophy (Weinberger et al 1981, Andreasen et al 1982, Nasrallah et al 1982, Reveley et al 1982), in schizophrenic patients including young, unmedicated patients (Schulz 1983). Andreasen (1986) in a study of 38 chronic schizophrenic patients and 49 controls,

reported that the schizophrenic subjects had smaller frontal lobes, cerebrums and craniums. However, Johnstone (1986) found no difference between schizophrenic and control subjects in an MRI study and Andreasen herself later concluded that faulty technique may have led to erroneous conclusions. Demyer et al (1988) found that schizophrenic patients had smaller right hemispheres and smaller frontal areas than control subjects.When education was taken into account, they found that only the left frontal area was smaller in the schizophrenic subjects. They also found that there was a great deal of overlap between the schizophrenic and control subjects. Larger brain areas were associated with better cognitive test performance and fewer neurological signs. Benes (1986) reviewed imaging studies, and concluded that there may be a group of schizophrenic patients with smaller frontal lobes. While the evidence from MRI studies concerning differences in the frontal lobes in schizophrenic patients and control subjects remains rather inconclusive, decreases in the volume of medial temporal lobe structures have been shown by de Lisi (1988), Suddah et al (1989) and Johnstone (1986). There is also post mortem evidence that there is a group of schizophrenic patients with significantly smaller limbic and temporal lobe structures, such as the hippocampus and amygdala (Bogerts 1983).

The evidence to support frontal lobe dysfunction in schizophrenia is perhaps most compelling in cerebral blood flow studies. Ingvar and Franzen (1974) measured regional cerebral blood flow (rCBF) in elderly and medicated patients. They found an abnormal hypofrontal distribution of rCBF consisting of low blood flow frontally and high blood flow postcentrally compared with control subjects. Since rCBF is a function of regional cerebral metabolism, the hypofrontal pattern suggests that these patients have depressed frontal cortical activity. They reported that the greatest degree of hypofrontality correlated with negative symptoms.

Gur et al (1985) investigated rCBF in unmedicated schizophrenic subjects They found a higher resting left hemisphere flow in schizophrenic subjects than in control subjects. Although no hypofrontality was noted, it was found that the more severely affected patients showed decreased anterior left hemisphere activity during spatial tasks, a pattern which was rarely found in controls.

Weinberger et al (1986) examined rCBF during a specific frontal mediated behaviour; performance of the Wisconsin Card Sorting test. They studied young, unmedicated patients and normal controls and found that the rCBF measured in the dorsolateral prefrontal cortex was

increased in controls but not in schizophrenics while performing this test. They claimed that the results provide direct evidence for a link between pathophysiology and cognitive function.

4) Neuropsychological evidence

Several studies have been carried out to measure the performances of schizophrenic patients on batteries of neuropsychology tests which are sensitive to frontal lobe and temporal lobe dysfunction. Specific disorders of cognitive function which have been associated with injury to the prefrontal cortex include concrete thinking, impaired attention, difficulty in abstracting or categorizing, a decrease in spontaneity in speech, a decrease in voluntary motor behaviour, repetitious or perseverative behaviour and difficulties in shifting response set (Foster 1980). Damage to the limbic system which includes the septal nuclei, mammillary bodies, amygdala and hippocampus has been shown to result in dysfunctions in the reception of information. The structures in the system are defined as registers of information, and damage to these structures produces loss of the ability to learn new information and retain it in long term memory (Scoville and Milner 1953). Moses and Hamish (1988) reviewing the use of the Luria- Nebraska battery in schizophrenic patients, concluded

that, with chronic patients with poor premorbid functioning, increased ventricular brain ratio and frontal lobe related cognitive deficits were seen concurrently.

Keilp et al (1988) studied 28 chronic schizophrenic patients ranging from 19 to 44 years of age. They were administered CT scans and batteries of cognitive tests. Enlargement of the anterior portion of the lateral ventricles; the frontal horns, was found to be related to deficits in general intellectual level, conceptual thinking, immediate verbal memory and psychomotor speed. They concluded that widespread impairment of schizophrenics' cognitive functioning may be related to structural abnormality within the frontal lobes. However, Obiols et al (1987) found no correlation between ventricular enlargement and neuropsychological impairment, although they did show increased ventricular size and impaired performance on neuropsychology tests compared with controls. The difference in findings may be due to Keilp et al using the measurement of the anterior portion of the lateral ventricles while Obiols appeared to use the body of the lateral ventricles. Keilp stated that, as a link between the frontal lobes and schizophrenia has been found, enlargement of the bodies of the lateral venticles may only be weakly related to impairment of cognitive processes mediated by the frontal lobes. Underutilized measurements of

structural abnormality in frontal areas, such as the frontal horn, may prove to be more strongly related to the particular cognitive deficits observed among schizophrenic patients.

Kolb and Wishaw (1983) reported that schizophrenic patients were impaired in all tests of verbal and non-verbal memory which are sensitive to temporal lobe function. These include : recall of logical stories (Wechsler Memory Scale) and the Rey-Osterreith Figure. Deadwyler (1987) and Gray (1982) have proposed that the function of the hippocampus in memory is to integrate new received information with old stored information, and therefore, to be able to match received with expected information. The role of the hippocampus in associative learning has already been suggested. Associative learning has been shown to be impaired in schizophrenic subjects who show impaired ability to adapt or monitor their behaviour according to external stimuli. It has been suggested that these cognitive deficits are due to hippocampal damage.

Gruzelier et al (1988) administered a battery of neuropsychological tests which are sensitive to hippocampal function, parietal/frontal function,frontohippocampal function and frontal function to 36 schizophrenic patients and 29 normal controls. Patients with affective psychoses were also included in this study. Deficits in the test of left sided tempero- hippocampal function (Milner 1971 in

Gruzelier 1988) were more frequent and more severe in the schizophrenic group than in controls. Impairments of frontal functions were also found in the schizophrenic group. The schizophrenic patients performed less well than controls on spatial and non-spatial conditional associate learning tests indicating impairments in fronto-hippocampal function.

b) Schizophrenia as a Neuro-Developmental Model

Weinberger (1987) proposed that schizophrenic symptoms develop as a result of a lesion from early in life that interacts during development with normal brain maturational events. Following the evidence which has already been discussed on brain areas implicated in schizophrenia, Weinberger claimed that non-specific histopathology exists in the limbic system, diencephalon and pre-frontal cortex. He specified that the appearance of diagnostic symptoms is linked to the normal maturation of the brain areas which are affected by the early developmental pathology, particularly the dorsolateral prefrontal cortex. Weinberger referred to the findings that structural changes observed in CT scans do not correlate with duration of illness (Reveley 1985) and stated that these findings indicate that the underlying pathologic process in schizophrenia is not active and progressive. He emphasized that schizophrenia usually becomes

clinically evident in late adolescence, and cited a study by Achte et al (1969) which examined the prevalence of psychosis in 3552 brain-injured veterans of the Finnish wars, and found that schizophrenia-like symptoms were five times more likely to develop if the subject was injured before 20 years of age than after 35 years of age. Weinberger claimed that this supports his hypothesis that the psychosis results from an interaction between the lesion and age-related (maturational) aspects of brain physiology.

Weinberger stated that the dorsolateral prefrontal cortex is the last structure to reach functional maturity, which occurs in early adulthood. In humans, it is the last brain area to begin myelination and may continue myelination throughout life. The myelogenic cycle for the dorsolateral prefrontal cortex is thought to occur primarily during the second and third decades. Weinberger claimed that this explains why the lesions he hypothesized to exist in the dorsolateral prefrontal cortex have little effect on the behaviour of children. It is only when the dorsolateral prefrontal cortex becomes functionally mature in early adulthood that the effect of these lesions are evident as clinical symptoms. This theory is attractive but difficult to assess because the dorsolateral prefrontal cortex is such an ill-defined area.

c) Laterality

Further to the findings that schizophrenia is associated with frontal lobe and temporal lobe damage, evidence on laterality has predominantly suggested that schizophrenia may be specific to left hemisphere lesions. Evidence from clinical, neurophysiological, brain imaging and cognitive sources will be presented in this section.

1) Clinical evidence

On the basis of examination of patients awaiting temporal lobe surgery, Flor-Henry (1969) noted that those with a lesion situated in the dominant side in the temporal lobe were more likely to present with schizophrenic-like symptoms, compared with patients with a temporal lobe lesion in the non-dominant hemisphere who were more likely to present with manic-depressive symptoms.

2) Neurophysiological evidence

Most of the findings from physiological studies support the hypothesis that schizophrenia is associated with left hemisphere deficits. Gruzelier (1973) reported an absence of skin conductance response in the left hand of schizophrenic subjects, and on the basis

of the established finding that no skin conductance response is found in the hand which is ipsilateral to the brain lesion, confirmed that these schizophrenic patients were suffering from left-sided lesions.

Gruzelier (1979) carried out a series of dichotic listening studies which indicated that schizophrenic patients had an impairment of left hemisphere auditory functions.

In reviewing EEG studies which looked at laterality differences, some inconsistencies in the reported results were found. Abrams and Taylor (1979) claimed that left sided disorders were more common, while Small (1979) reported that right sided disorders were most frequently found. Flor-Henry (1979) found abnormal power distribution in the left temporal region in unmedicated schizophrenic subjects. Visual ERP abnormalities indicating dysfunction of the left temporal lobe have been reported in schizophrenic patients (Buchsbaum et al 1979, Connolly et al 1983). Connolly tested unmedicated schizophrenic patients. Roemer et al (1978) reported lower left hemisphere stability in schizophrenic patients compared with controls which he interpreted as left hemisphere desynchronization in schizophrenic patients. Shagass et al (1983) found left hemisphere ERP abnormalities in schizophrenic patients which indicated left temporal lobe and left occipital lobe dysfunction. Inconsistencies found in laterality differences may be due in part to the state or type of the patients

being studied and also to differences in methodology employed by different research teams. Certain experimental conditions may highlight dysfunctions more than others. Etevenon (1983) compared schizophrenic subjects who had been diagnosed as paranoid with control subjects and replicated findings of EEG differences in the left hemisphere only of the two groups. Stevens and Livermore (1982) compared residual type schizophrenic patients with control subjects and reported that differences were found mainly in the left hemisphere in paranoid schizophrenia and in the right hemisphere in catatonia. EEG abnormalities in the right hemisphere have been reported by Gjessing et al (1967). Helmchen (1968) and Shenton et al (1989).

3) Evidence from brain-imaging

CT studies and MRI studies have found larger left-sided cerebral ventricles, smaller left frontal lobes, decreased left hemisphere density, and higher grey : white density in the right hemisphere in studies comparing schizophrenic patients with control subjects.

4) Neuropsychological evidence

Various studies have used neuropsychological test batteries to compare performance of schizophrenic and other subjects on tests which are sensitive to left and right hemisphere function. In all the tests

it was generally found that chronic schizophrenic patients showed more impairment than acute schizophrenic patients. Flor-Henry and Yeudal (1979) reported right-hemisphere dysfunctions in schizophrenic subjects as well as affective disorder patients, but the schizophrenic patients also suffered from left hemisphere frontal and temporal dysfunctions. Abrams and Taylor (1979) also reported that schizophrenic and affective disorder patients had bilateral hemisphere dysfunction with far more left hemisphere (temporal and parietal) deficits in the schizophrenic patients. Golden et al (1981) found that neuropsychological impairment on the Luria-Nebraska battery was associated with CT scan density deficits in the left frontal lobe in schizophrenic patients. Silverstein et al (1983) found left frontal lobe dysfunction in some schizophrenic subjects. Gruzelier's (1988) study reported more frequent and severe left temporohippocampal deficits in schizophrenic subjects. Results from neuropsychological testing suggest that bilateral deficits are present in schizophrenic subjects with more common and more severe left hemisphere deficits.

3.2 Schizophrenia as a Dysfunction in Information Processing

This section will review findings on information integration, storage and retrieval in schizophrenia, with respect to associative networks in long term memory. The first part of this section will discuss whether the deficits found in informastion processing in schizophrenic patients is due to abnormalities in the structure of associative networks or to dysfunctions in the implementation of associative networks.

i Evidence which suggest deficits in associative networks.

In tasks which demand access to information stored in memory, either in encoding and storing information or in retrieving information, it is evident that schizophrenic patients experience deficiencies in organizing information within associative networks. Neufeld and Broga (1981)that schizophrenic patients were impaired in their ability to make use of semantic dimensions for organizing sets of items, which resulted in an impairment of recall. They also found that schizophrenic patients were unable to relate multiple meanings of items to identify similarities between these items, although they were found to know these meanings.

Kay (1982) also reported that schizophrenic patients fail to organize information in an appropriate way and experience a dysfunction in using conceptual structures. He found that schizophrenic patients rely on salient affective and physical cues at the expense of contextual attributes. Kay measured the reliance of schizophrenic and control subjects on three dimensions for encoding : conceptual, affective and physical. He found that the schizophrenic subjects were weaker on the conceptual dimension and stronger on the affective dimension than the control subjects.

ii Do the deficits reflect abnormalities in the structure or use of associative networks?

Kay (op.cit) claimed that deficiency in processing of cues essential for conceptual operations seems to underlie the conceptual dysfunction in schizophrenia. Schizophrenic subjects do not typically organize information into a cohesive conceptual framework. The cues that are initially registered form memory traces and are not easily retrieved because of their low semantic relevance. For schizophrenic subjects, the criterion for relatedness and forming concepts is unduly influenced by physically salient properties, and the conceptual dysfunction which occurs in schizophrenia is in connection with defective semantic encoding. Therefore, Kay proposed that the

disorganization occurs at the stage of encoding,q and that the storage of information in associative networks is abnormally based on salient physical cues.

However, Neufeld and Broga (op.cit) claimed that the associative networks in schizophrenic patients are intact and normal but the implementation of these networks is dysfunctional. Schizophrenic subjects experience deficits in implementating these networks to establish structure on the stimulus. These two hypotheses and supporting evidence are shown in Table 3a. Both hypotheses explain the same observeable deficits. The evidence suggests that Broga and Neufeld are correct, as it has been shown that schizophrenic patients have access to intact networks when provided with enriched cues, and that schizophrenic performance improves when given instruction on how to process information. The findings of several studies have indicated that the semantic dimensions are intact in schizophrenic patients. Hamlin and Folsom (1977) presented triads of proverbs of similar meaning to schizophrenic patients. They found that, in the presence of enriched cues, the patients had greater access to relatively intact dimensions of meaning.

This inability to structure information from their environment may explain why schizophrenic patients find it difficult to discern relevant and irrelevant information. Magaro (1984) found that

TABLE 3a

Hypotheses put forward to account for deficits in information processing in schizophrenia.

Deficit

Schizophrenic patients show dysfunctions in organizing information which would enable them to use semantic conceptual processes.

Hypotheses:

1. Schizophrenic patients suffer from an impairment in the ability to make use of the organization in memory (Magaro, 1984, Hemsley, 1987) but the information which they have stored in memory is intact (Neufeld and Broga, 1981).

2. Schizophrenic patients store information abnormally in memory (Kay, 1982).

Evidence

- deficit in organizing sets of items leads to impaired recall but if items are already sorted into conceptual categories performance approximates controls (Larsen and Fromholt, 1976)
- enriched cues increase proverb interpretation (Hamlin and Foisom, 1977)
- encoding of affective and semantic strategies increases recall (Kon et al., 1976)
- dysfunctions in priming (Bullen and Hemsley, 1987)

schizophrenic subjects could selectively attend to relevant stimuli, but their impairment lay in organizing stimuli extensively relative to others. Hemsley (1987) agreed that schizophrenic patients are deficient in being able to utilize the structure of information in memory, to establish stored memories of regularities, and, therefore, are deficient in forming expectations. He stated that schizophrenic patients fail to establish response biases which reduce information processing demands. This results in a slowness in differentiating meaningless and meaningful information, and a lesser ability to make use of the redundancy and patterning of sensory information.

Koh et al (1976) showed that induced encoding of affective and semantic strategies can ameliorate deficits found in recall of schizophrenic patients, and concluded that the deficits :

"are not attributable to some permanent structural impairment".

Larsen and Fromholt (1976) showed that sorting words into categories improved recall.

The final and perhaps most conclusive evidence for the failure of schizophrenic patients to implement semantic networks in long term memory comes from a study by Bullen and Hemsley (1987). They measured recognition thresholds in a study which was designed to

facilitate or inhibit perception of target words. They tested 12 schizophrenic patients, 9 depressive patients and 12 normal controls and found that the priming effect was much weaker in the schizophrenic subjects than in the depressed patients and normal controls.

The rest of this section will discuss impairments in cognitive function which have been found in schizophrenia, and which may be explained by a dysfunction in the implementation of associative networks. These are presented in Table 3b.

iii Loosening of the associations

One of the processes which seems to occur in schizophrenic thought, as is evident from speech samples is a loosening of the associations, and it is hypothesized that this is due to dysfunction in implementing semantic networks. When loosening of the associations occurs, thought and speech processes become disconnected and fragmented and the patient jumps from one idea to a totally unrelated and irrelevant idea. The associations may drift aimlessly instead of being focused on a central theme or concept, which makes speech and thought vague, diffuse and unfocussed. Thoughts veer widely from the central theme until they seem wholly unrelated to what seemed to initiate them.

As Bleuler (1911) stated, associative processes are used by normal subjects as connections between ideas which enable them to organize and interrelate many single thoughts and exclude irrelevant thoughts. However, in schizophrenia, the most important determinant of associations, the concept of purpose is lacking. Therefore, thoughts are not related nor directed by any unifying concept of purpose of goal. In the absence of a central determining idea, the sequence of thought becomes determined by incidental associations such as sound, alliteration or non-essential details. However, schizophrenic patients lose themselves in irrelevant side associations and logical thought does not occur. Kraepelin noted that schizophrenic patients lose the faculty of logical ordering of their trains of thought, and suggested that this was due to attention to causal external impressions. Several studies have found using the Kent-Rosanoff Word Association list, that schizophrenic subjects have associations that are less common than normal controls (Sommer, Dewar and Osmond 1960) and that are more idiosyncratic than normals Shakow and Jellinek 1965) and less related to stimuli than normals (Moran 1953).

Rattan and Chapman (1973) described the intrusion of inappropriate associates as a classic feature of schizophrenic verbal behaviour. The inappropriate intrusion is a verbal response that has an associative link with other words that are in the patient's consciousness at the time. Broen (1968) stated that the intrusions are

responses which are associated in some way with the context. Schizophrenic subjects share many of the same response tendencies as normal subjects, but seem to have an abnormal equivalence of the alternate response tendencies. Strauss (1975) claimed that the associative intrusion was due to exaggerated strong meaning - response bias. The patient failed to attend to or process appropriate contextual cues or mediating response alternatives but selects the strongest, most common associate. In this way many schizophrenic cognitive symptoms are best understood as excessive tendencies to yield to normal biases in using strong though often incorrect associates as the basis for choosing responses in difficult situations. Normal associates have a strong influence on the vocabulary and concept formation of schizophrenic patients.

iv Dysfunctions in the formation and use of concepts.

The hypothesis that schizophrenic patients fail to implement the associative networks in long term memory is considered when looking at the types of deficits in the formation and use of concepts which have been found in schizophrenia. Hamlin and Folsom (1977) found that the formation and use of concepts in schizophrenic patients was immature in that they gave concrete responses when abstract responses would be more appropriate. Lothrop (1961) reported that schizophrenic patients have apparent difficulty in generalizing, in seeing abstact

relationships between things and in shifting from one conceptual frame of reference to another. On the Benjamin proverbs test, Watson (1973) found that chronic schizophrenic patients were more deficient than acute schizophrenic patients. He concluded that schizophrenic patients suffer from a reduced ability to form abstractions and that those that they do form are inappropriate. Forrest and Affleck (1975) reported that schizophrenic subjects and their relatives find difficulty in comprehending and explaining abstact ideas in the Benjamin proverbs test.

Hemsley (1977) claimed that schizophrenic patients used approximation in their cognitive style more than normal controls, where a number of stimuli receive the same response rather than each receiving a different response. Stimuli may be treated as equivalent on the basis of superficial similarities. Schizophrenic patients used less psychological constructs. Therefore, schizophrenic subjects have a simplified categorizing system, using wider categories and employing fewer of them, but using them more frequently. Longer term patients were found to have more stereotyped responses than acute patients.

Studies using the Object Sorting test have suggested that the use of categories by schizophrenic patients is abnormal. Chaika (1982) reported that they used strange concepts and ideas to classify the objects. Schizophrenic subjects also have been shown to make errors

of conceptual overinclusion. Payne (1959) stated that acute schizophrenic patients showed an extreme degree of stimulus generalization in concept formation, and chronic schizophrenic patients had a tendency to place objects into categories with which they were related but did not belong. He stated that schizophrenic patients were susceptible to intrusions from an abnormally broad range of associations.

Cutting et al (1987) compared 42 schizophrenic subjects with 44 neurotic subjects on tests of categorical thinking in an attempt to discover the nature of overinclusive thinking. Subjects were administered a test of verbal and non-verbal conceptual loosening, a verbal fluency test examining out-of- category verbal items, a colour sorting test and a hue matching test examining out-of-category matching. They found that the schizophrenic subjects were worse on the non-verbal than on the verbal categories with more conceptual loosening and a tendency toward overcategorization. They claimed that the schizophrenic subjects adopted a piecemeal strategy, suggesting that they lacked the ability to form a Gestalt of the task.

McConaghy (1961) studied recovered schizophrenic subjects and reported that they manifested allusive thinking even after recovery. Allusive thinking is the inclusion of objects into classes to which they do not strictly belong and failure to focus precisely on deep

concepts. Allusive thinkers use broader concepts of the meanings of words, and include relatively peripheral concepts and ideas. They use words in a less sharply focused sense to show the intrusion of concepts which are only partially relevant, and they choose more remote or unusually associated words as attributes of concepts. Hemsley and Richardson (1980) employed a task based on an experimental paradigm devised by Treisman (1984). This required subjects to shadow one of two simultaneously binaurally presented passages using contextual variables. This test requires category state thresholds to be altered according to the preceding context. Schizophrenic subjects were found to be impaired relative to control and depressed subjects.

Schizophrenic subjects have also been found to be impaired on the Wisconsin Card Sorting test, which measures the ability to form and use categories, and the ability to shift set. It has been found that schizophrenic subjects make more errors on this task than normal controls and have difficulty in identifying the correct categories with which to sort a set of cards. It has also been found that they perseverate, finding it difficult to switch from one category or means of sorting the cards to another. Goldberg and Weinberger (1988) found that even when schizophrenic patients received concrete and explicit instructions on how to do the Wisconsin Card Sorting test, they still did poorly unless receiving card-by-card instructions.

Bannister and Fransella (1966) showed that schizophrenic patients used looser psychological constructs, and that the constructs that they used were less consistent than those of normal controls. They administered the Repertory Grid test of thought disorder, derived from Kelly's Personal Construct Theory, to schizophrenic patients and normal controls. The subject is required to assign constructs such as: kind, stupid, selfish, sincere, mean and honest to photographs of different individuals on a test-retest basis. The purpose of the test is to measure the subject's tightness of construct system and consistency. They interpreted the results as showing that the schizophrenic patients had had such poor validation from their construct systems in the past despite any reversals and changes they tried, that their construct systems became very loose.

v Abnormalities in speech

Abnormalities in speech in schizophrenic patients have generally reflected lack of organization which is proposed to be due to a dysfunction in the implementation of associative networks. Rochester et al (1973) have described speech organization as hierarchical with dependency relationships between nodes. However, these hierarchical networks are proposed to be dysfunctional in schizophrenic patients. Rochester has described schizophrenic speech as "islets of coherence" within overall disorganization, describing the lack of structure or

use of propositions in organizing speech. Propositions can be described as creating the hierarchies between units of information being the rules which determine how they are related to each other. The schizophrenic subjects relied on non-propositional cues such as phonetic similarities, word play and affective factors rather than propositional relationships in linking multiple statements.

vi Memory impairments

Studies on memory impairments in schizophrenic patients also have implications for the structure of information in long term memory and the implementation of semantic networks. Koh and Klayton (1974) proposed that recall deficit in schizophrenic subjects is due to impaired mnemonic organization. They stated that patients showed limited storage capacities of the primary and secondary memories, vulnerability to intrusion, slow response time, inefficiency in utilizing stimulus contiguity for organization, and consequential recall deficits. Koh, Klayton and Berry (1973) suggested that the recall memory of young,non-psychotic schizophrenics is probably impaired because of their difficulty in organizing input materials into higher units to economize the limited capacity of short term memory. Lawson, McGhie and Chapman (1964) and Truscott (1970) found that schizophrenic patients have difficulty remembering passages with higher contextual constraints. They interpreted this finding as

Table 3b

Cognitive processes impaired by dysfunctions in implementing associative networks.

Dysfunctions in implementing network of associations lead to deficits in structuring information (Neufeld and Broga, 1981)

A. Loosening of the associations

- concept of purpose lacking (Bleuler, 1911)
- no logical ordering of thoughts (Kraepelin, 1919)
- less common associates (Sommer e al., 1960)
- idiosyncratic responses (Shakow and Jellinek, 1965)
- intrusions (Ratton and Chapman, 1973)
- strong meaning - response bias (Strauss, 1975)

B. Formation and use of concepts

- concrete (Hamlin and Folsom, 1977)
- difficulty in abstraction (Lothrop, 1961, Watson, 1973, Forrest and Affleck, 1975)
- wider and fewer categories (Hamsley, 1977)
- strange concepts (Chaika, 1982)
- overinclusion (Payne, 1959, Cutting, 1987, McConaghy, 1961)
- dysfunction in category state thresholds (Hemsley and Richardson, 1980)
- dysfunction in ability to form and use categories (Goldberg and Weinberger, 1988)
- looser psychological constructs (Bannister and Fransella, 1966)

C. Speech

- dysfunctional hierarchical networks (Rochester, 1973)

D. Memory

- impaired mnemonic organisation (Koh and Klayton, 1974)
- lack of organization leads to impaired recall (Koh et al., 1973, Lawson et al., 1964, Truscott, 1970)

evidence of the relative inability of schizophrenic patients to perceive the organization inherent in the passages. They found that the recall deficit decreased with lower contextual passages, suggesting the significance of an organizational factor in the schizophrenic patients' recall deficit.

In summary the evidence shows that schizophrenic patients manifest impairments in association, conceptualization, speech and memory. All of these can be accounted for by a dysfunction in the implementation of associative networks resulting in a deficit in organizing information.

vii Intellectual Deterioration

Kolb and Wishaw (1983) reported that IQ scores obtained by using the Wechsler Adult Intelligence Scale (WAIS) showed that schizophrenic subjects have a mean Full Scale IQ score which is 15 points below that of control subjects. The major deficit lies with the Performance scores obtained for the two groups; the schizophrenic group scored 19 points on average below the control group. For the Verbal scores, the schizophrenic group mean score was 6 points below that of the control group. The schizophrenic group performed more poorly than the control subjects on all the Performance sub-tests which comprise : digit symbol (a timed test which requires the subject to substitute symbols

for digits); picture completion (where the subject has to name the essential feature which is missing in a picure); block design (where the subject has to replicate a design using the pattern on the blocks); picture arrangement (in which the subject sorts a series of pictures into a sequence which makes a logical story); and object assembly (in which the subject has to assemble a set of parts to build up a complete figure). In the Verbal sub-tests, the schizophrenic subjects performed better on the Vocabulary and Information sub-tests than any of the other sub-tests. This seems to indicate that the schizophrenic subjects experienced some decline in IQ at some time, as shown by their differential performances on the sub-tests. Performance on the Vocabulary and Information sub-tests as well as reading skills are usually relatively unimpaired by organic brain damage, as has been found in Alzheimer's Disease (O'Carroll 1987), while performance on other sub-tests is impaired. The amount of deficit between performance on the Vocabulary and Information tests and the remaining tests gives an indication of how much intellectual deterioration has been sustained.

Martin et al (1977) proposed two possibilities to account for a decline in IQ in schizophrenic patients. Firstly, IQ loss may be a product of the schizophrenic symptoms and will be remedied as the symptoms remit. Secondly, IQ deficit is not due to the symptoms of the illness but IQ deficit precedes and facilitates the development of

schizophrenia while individuals with high IQ scores are protected from the illness. If this is the case, the IQ deficit will not be remedied with symptom remission. Martin reported that her findings supported the second hypothesis. She found a slight disruption of IQ in the morbid stage of schizophrenia, but within average limits. She also found that IQ did not increase significantly after treatment. Martin proposed that sub-types of schizophrenic patients may differ in intellectual functioning. It has been found that more chronic patients than acute patients obtained lower IQ scores in childhood and failed to show significant gains in IQ after treatment (Schwartzman and Douglas 1962, Haywood and Moelis 1963). However, in these studies it has been found that remitting schizophrenics do show significant IQ gains while non-remitting schizophrenics show significant reductions in IQ. It may have been that the subjects studied by Martin were predominantly chronic patients.

Watson et al (1987) divided a group of schizophrenic patients into high and low scoring IQ groups. The low IQ group had a mean IQ of 77 and the high IQ group had a mean score of 114 points. Both groups were administered the Army General Classification test, and were retested at follow-up. Watson reported that the arithmetic scores of the high IQ group decreased significantly at the second test whereas they showed no differences in the vocabulary and spatial aptitude scores. He found no significant mean changes in the low scoring group, and

concluded that intellectual decline is limited to certain skills and to a subset of subjects. These findings seem to be contradictory to those of Martin. High IQ does not appear to be a protective factor in schizophrenia. Martin proposed that chronic schizophrenic patients were generally those with low IQ who showed a decline in IQ after illness. However, Watson showed that his low IQ group showed no change in IQ. Watson does not clarify whether the groups can be differentiated into acute and chronic. It may be that the low scoring group experienced a decline in IQ at the onset of their illness, as suggested by Martin's hypothesis, which becomes stable and is not influenced by their psychological state. Moreover, it is thought that this group is more likely to contain chronic patients. Watson's high-scoring group is believed to have contained mainly acute achizophrenic patients who manifested a decline in IQ scores with the appearance of their psychotic symptoms. It is thought that when in remission these patients may experience an increase in IQ scores to their premorbid level of functioning.

Hamlin (1969) administered intelligence tests to 48 chronic schizophrenic patients followed by retests eight and fourteen years later. The results showed that there was no progressive loss in IQ with illness. Hamlin tested both paranoid and non-paranoid schizophrenic patients, using verbal and non-verbal sub-tests. He stated that schizophrenic patients may lose their intellectual

abilities early in their illness, but once they have become chronic, their mean IQ scores remain stable. Severity of psychotic symptoms in acute illness seems to have a demonstrable relationship to IQ test scores. When the symptoms improve, the test scores increase. Intellectual deterioration does not occur in all functions, with some intellectual functions remaining intact.

3.3 Schizophrenia and Psychophysiological Variables

i P3 latencies and amplitudes

The early ERPs, P1 and N1, have been shown to be reduced in amplitude for acute schizophrenic subjects but not for chronic or paranoid subjects (Shagass 1980), while the later ERP components are usually of lower amplitude and this is found especially in chronic schizophrenic patients (Shagass op.cit). The early ERPs have been shown to be more stable in chronic and floridly psychotic patients than in acute and latent patients and normal controls. The later ERP components have been found to be less stable in the chronic patients than in normal controls.

Auditory ERPs have been seen to have lower than normal amplitudes on average for all components, especially the N1 in schizophrenic patients. The latencies of the early ERPs have been found to be shorter than those for normal controls, while the latencies for the later components and especially the P3, are shown to be longer for the schizophrenic population. A consistently reported observation in schizophrenic subjects is a decrease in amplitude of P3 with auditory stimuli (Roth et al 1972, Levit et al 1973, Verleger and Cohen 1978, Roth et al 1980, Steinhauer and Zubin 1982, Baribeau-Brown et al 1983 and Pfefferbaum et al 1984). Visual ERPs have been shown to be less stable over the whole waveshape for schizophrenic patients than for normal controls, and a pronounced decrease in amplitude for the P3 is evident in the schizophrenic group (Pass et al 1980, Brecher and Begleiter 1983).

Muir, St. Clair and Blackwood (in press) measured auditory ERP recordings of 96 schizophrenic patients and 213 normal controls, presenting high and low pitched stimuli in a ratio of 1:9. They defined N1 as the maximum negativity between 70 and 120 msec, P2 as the maximum positivity between 140 and 230 msec, P3 as the maximum positivity between 260 and 500 msec, and N2 as the maximum negativity before P3. The latencies they recorded for the two groups were not significantly different for N1 and P2. However, the latencies for N2

and P3 were highly significantly different for the schizoprenic subjects and the control subjects. The P3 latency was significantly prolonged and more variable in the schizophrenic subjects.
The mean P3 latency and standard deviation for the schizophrenic group was 338 and 35 msec while for the control group the mean P3 latency and standard deviation was 301 and 23 msec.

The amplitudes for the two groups were found to be significantly different for P2 and N2 and highly significantly different for P3. P3 amplitude was significantly reduced in the schizophrenic group. The mean P3 amplitude and standard deviation for the schizophrenic group was 6.4 and 3.3 mv and for the control group 9.8 and 2.9 mv. St Clair reported finding that 39.4% of schizophrenic patients showed an abnormally prolonged P3 latency compared with 3.8% of controls.

Blackwood et al (1987) tested a group of schizophrenic patients and a group of control subjects. Most of the patients were tested on three occasions; when they were medication free, one week after the start of treatment and 4 weeks after the start of treatment. The purposes of the study were to determine whether there are changes in ERPs related to clinical state and whether drug treatment affects ERPs. They proposed that any changes in ERPs with improvement of clinical state may reflect the disappearance of attentional difficulties which may occur in acute psychosis. These changes could

be separated from the more permanent changes which occur in schizophrenia, by comparing treated schizophrenic patients with control subjects.

They found that the two groups showed very significant differences for N2 and P3 latencies, and for P3 amplitudes. When comparing the ERP latencies and amplitudes of the schizophrenic group for the three treatment conditions they found no significant differences in the P3 latencies or P3 amplitudes on any occasion. The only significant differences found were for N1 amplitude and P2 amplitude.

They concluded that P3 latency in schizophrenic subjects is not related to the duration or stage of illness nor to the use of drugs. They stated that the constancy of the P3 latency and amplitude changes following treatment and partial remission of psychiatric symptoms suggests that these measures in schizophrenia reflect an underlying disorder of auditory information processing and are not merely the result of attentional deficits accompanying an acute psychiatric illness.

P3 changes have been associated with age in control subjects (Goodin et al 1978, Brown et al 1983, Pfefferbaum et al 1984, Picton et al 1984, Polich 1985, St Clair et al 1985). It is suggested that a

significant increase of P3 latency with age does not occur until the age of 60. However, P3 latency has not been shown to increase with age in schizophrenic patients (Blackwood et al 1987).

ii Eye Tracking Dysfunction (ETD)

The majority of schizophrenic patients have abnormal smooth pursuit eye tracking (Holzman et al 1973,1974). This finding has been replicated many times using a variety of recording and scoring techniques (Shagass et al 1974, Kuechenmeister et al 1977, Cegalis and Sweeney 1979, May 1979, Klein et al 1976, Mialet and Pichot 1981). These studies have established that pursuit impairments in schizophrenia are not due to age or neuroleptic drug artefacts. Impairment in eye tracking in schizophrenic patients has been found to be limited to smooth pursuit and fixation eye movements, and to consist of an interruption of these eye movements by small saccades. Impairment of pursuit in schizophrenic patients seems to occur with slow eye movements and not with fast eye movements. The saccadic movements themselves have been found to be normal (Levin 1982).

Holzman, Proctor and Hughes (1973) and Holzman et al (1974) found disruptions of smooth pursuit eye tracking in as many as 86% of schizophrenic patients. St Clair (MD thesis) studied 213 control subjects and 96 schizophrenic patients. He reported that the

schizophrenic group had a mean signal:noise ratio of 4.24 (s.d. 1.16) and the control group had a mean signal:noise ratio of 4.95 (s.d. 0.92). He found that abnormal eye tracking occurred in 12.3% of the schizophrenic patients and only 4% of the control subjects.

iii Are Physiological Variables Associated with Structural Change?

The main findings from the physiological studies are of an increase in abnormalities in both the P3 latency and ETD in schizophrenic patients. These abnormalities may occur alone or in combination, and they are correlated. St Clair (op.cit) reported that 7% of schizophrenic patients experienced both P3 abnormalities and ETD while only 0.7% of control subjects experienced both. The correlation between P3 latency and ETD was positive, with r=0.53 for control subjects and r=0.47 for schizophrenic subjects. The findings strongly suggest that anomalies in P3 and ETD reflect some common underlying process which is linked to schizophrenia. These psychophysiological abnormalities appear to be present at the onset of symptoms, since in a group of schizophrenic subjects studied, there is no difference in P3 latency between first onset and chronic schizophrenia (St Clair) and eye movement impairments have been shown to be stable in schizophrenic subjects (Levin 1982). It is proposed that the structural changes in the frontal and temporal lobes (as described

earlier) determine the clinical manifestations of the illness, the accompanying ERP and ETD findings and impairments in information processing.

4.5 Hypotheses derived from the literature review

i. <u>There will be differences in the P3 latencies, amplitudes and ETD measurements of schizophrenic subjects compared with controls.</u>

It is hypothesized that the physiological parameters will replicate previous findings, that is the schizophrenic subjects will show longer latency P3 and smaller amplitude P3 components of auditory ERPs than control subjects, and that the signal : noise ratio measured in an eye tracking task will be smaller in the schizophrenic group than in the control group.

ii <u>There will be differences in scores on cognitive tests between schizophrenic and control subjects.</u>

It is hypothesized that schizophrenic subjects experience deficits in information processing due to an impaired ability to implement associative networks in long term memory. Therefore, it is thought

that the schizophrenic patients as compared with control subjects will manifest impairments in cognitive tests which measure the use of associative networks such as in the formation and use of concepts, verbal recall to categorized and unrelated information, retrieval and storage of associates, perseveration and the ability to shift set.

iii Some scores on the cognitive tests will correlate with P3 latencies and amplitudes.

It is proposed that P3 abnormalities also reflect dysfunctions in the implementation of associative networks in long term memory.

iv Differences will be found between schizophrenic and control subjects in MRI measures of temporal lobe structures of the brain.

Previous CT and MRI studies have found differences between schizophrenic and control subjects in temporal lobe structures, and it is predicted that this study will replicate these findings. This will support the hypothesis that temporal lobe damage is implicated in schizophrenia.

v There will be a relationship between MRI, physiological and psychological scores in the schizophrenic subjects.

It is proposed that frontal lobe damage and temporal lobe damage in schizophrenia will be implicated in physiological abnormalities and cognitive dysfunctions. The correlations between performance on psychological tests and physiological parameters will provide support for the claim that the physiological parameters reflect some underlying dysfunctional process which impairs information processing. It is also thought that the results of this study will provide further support for the view that ERPs are physiological manifestations of information processing and provide a direct, bias-free method of studying the stages involved in information processing.

Chapter 4

AFFECTIVE DISORDERS

4.1 General Description

i Definition

As with schizophrenia, the aetiology of affective disorders is not understood, and their definitions depend on the presence of certain characteristic symptoms and outcomes. The essential feature of an affective disorder is a severe and prolonged disturbance of mood which may be depression and anxiety when the patient is diagnosed as being in a depresssed state, or elation and excitement when the patient is diagnosed as being manic or hypomanic.

a) Mania

DSM-III-R describes the typical characteristics of a patient in a manic state as follows. The patient's predominant mood is elevated, expansive or irritable. This mood disturbance and accompanying cognitive abnormalities are sufficiently severe to cause marked

impairment in occupational functioning or in social activities or relationships with others, or to require hospitalization to prevent harm to self or others. RDC also require that the mood disturbance is so severe, as to make meaningful conversation impossible. The elevated mood may be recognized by those who know the patient well as excessive. The expansive quality of the mood disturbance is characterized by unceasing and unselective enthusiasm for interacting with people, and seeking involvement with other aspects of the environment.

Associated symptoms include inflated self-esteem, grandiosity, and decreased need for sleep, pressure of speech, flight of ideas, distractibility, increased involvement in goal-directed activity, psychomotor agitation and excessive involvement in pleasurable activities which have a high potential for painful consequences that the patient often does not recognize. Inflated self-esteem may range from uncritical self-confidence to marked grandiosity, which may be delusional. The patient may feel that he is very important and have special powers, plans, talents and abilities. The patient needs less sleep than usual, and yet feels full of energy. When the sleep disturbance is severe, the patient may go for days without any sleep, and not feel tired. The patient may talk more than usual, or feel a pressure to keep on talking. Manic speech is typically loud, rapid and difficult to interpret. It may be full of jokes, puns, plays on

words and irrelevancies. Clanging may occur,where word choice is governed by similarities in sound rather than conceptual relationships. Loosening of the associations and incoherence may occur which is evident in his speech and in disturbance of thought. The patient may experience flight of ideas which is evident in a flow of accelerated speech, with abrupt changes from topic to topic. Changes in topic are usually based on understandable associations, distracting stimuli or plays on words. If the symptom is severe, speech may be disorganized and incoherent.

The patient may be distractible, that is he may have trouble concentrating on what is going on, because his attention jumps to unimportant items, evidenced by rapid changes in speech or activity as a result of responding to various irrelevant external stimuli. The manic patient may exhibit an increase in goal-directed activity, which often involves excessive planning of and participation in multiple activities. This can include social, work, sexual and physical activities. The patient's social interactions usually become intrusive, domineering and demanding, although he does not recognize this. His activities often have a disorganized, flamboyant or bizarre quality. The patient may indulge in foolish activities which have a high risk component. If the patient's mood is that of irritability rather than elation, he may manifest aggressive and even violent behaviour.

The manic patient often does not realize that he is ill, and will resist efforts to treat him. He often exhibits lability of mood, with rapid shifts to anger or depression. Occasionally, the depressive and manic symptoms occur simultaneously, or they may alternate rapidly within the space of a few days.

Delusions or hallucinations may be present during the episode of prominent mood symptoms. Their content is usually consistent with the predominant mood. Manic episodes usually begin suddenly, with a rapid escalation of symptoms over a few days and recovery may be complete.

b) Depression

The essential feature of a major depressive episode, as described in classificatory systems is depressed mood or loss of interest and pleasure in all activities. Associated symptoms include appetite disturbance, weight disturbance, sleep disturbance, psychomotor agitation or psychomotor retardation, a decrease in energy and being easily fatigued and tired, feelings of worthlessness and guilt, difficulty in thinking and concentrating and making decisions, and recurrent thoughts of death or suicidal ideation and attempts. RDC diagnosis requires that the symptoms are severe enough to cause the patient to seek or be referred for help, to take medication, or to show appreciable impairment with family, at home, at work or socially.

Disturbances in appetite may be seen as decreased or increased appetite, and this results in a corresponding consistent and prolonged loss or gain in weight. The depressed patient may show a decrease or increase in sleep. Lack of sleep may occur as a result of being unable to fall asleep initially, restlessness and waking during the night, and waking very early in the morning and being unable to get back to sleep. Alternatively, the patient may find that he is sleeping for much longer than usual. The patient may experience psychomotor agitation, where he is unable to sit still, or psychomotor retardation where he is slowed down. The depressed patient may express feelings of worthlessness and guilt, and may also experience slowed thinking.

Other features of depression may be seen as tearfulness, anxiety, irritability, brooding, obsessive ruminations, excessive concern with physical health, panic attacks and phobias. If delusions and hallucinations are present they are usually mood-congruent. A common delusion is of being punished because of a moral transgression or some personal inadequacy. The depressed patient may experience nihilistic delusions of the world or personal destruction, somatic delusions of serious illness, or delusions of poverty. Hallucinations are usually transient and not elaborate, and may involve voices that berate the patient for his shortcomings or sins.

The onset of a major depressive episode is variable; the symptoms usually develop over days to weeks, although in some cases, it may be sudden as when associated with stress. In some cases, there are prodromal symptoms such as generalized anxiety, panic attacks, phobias or mild depressive symptoms.

The duration of the major depressive episode is variable. Untreated, the episode typically lasts six months or longer. Usually, there is a complete remission of symptoms, and general functioning returns to the premorbid level. Some patients have episodes separated by many years of normal functioning; others have clusters of episodes; and others have increasingly frequent episodes as they grow older. However, in a large proportion of cases (20% - 35%), some symptoms of the episode persist, and this is termed chronic Major Depressive Disorder.

ii Sub-types

The major affective disorders are subclassified by the DSM-III-R as bipolar and unipolar disorders. The essential feature of bipolar disorders are the presence of one or more episodes of mania or hypomania which usually occur with a history of major depressive

episodes. The essential feature of unipolar depressive disorder is one or more periods of depression which occur without a history of either mania or hypomania.

Bipolar illnesses are usually sub-classified according to the predominant mood of the current episode. Thus a bipolar affective disorder patient who is unwell may be described as in a manic state, or a depressed state, or a mixed state. If the mood disturbance consists of both pronounced elation and depression at the same time, the patient is classified as exhibiting a mixed state, in accordance with ICD-9 classification.

iii Epidemiological Findings

Helgason (1964) reported from his study of 5,395 probands in Iceland, that the risk of developing an affective disorder was 5.39% for males and 9.19% for females. DSM-III-R states that the prevalence of bipolar affective disorder has been estimated as 0.4% to 1.2% of the adult population. Studies of the prevalence of Major Depressive

Disorder in the USA and Europe have reported a wide range of values for the proportion of the adult population; being from 9% to 26% for females, and from 5% to 12% for males.

In bipolar disorder, the sex incidence is equal or shows a slight excess of females. The peak age of onset is 25 to 29 years with no sex difference. Onset is rare before puberty or after the age of 60. In unipolar disorder, the peak age of onset is 40 to 44, the rate for females, being twice that of males.

The number of in-patient admissions to the Royal Edinburgh Hospital for 1988 with a diagnosis of affective psychoses was 504 comprising 324 admissions for female patients and 180 admissions for male patients. This accounted for 20.8% of all admissions for that year, and accounted for more admissions than any other diagnosis. Admissions with a diagnosis of depressive disorder (neurotic/ non-psychotic) consisted of 106 cases or 4.4% of all admissions; with 74 admissions for female patients and 32 for male patients.

iv Controversies

a) Are unipolar and bipolar affective disorders distinct disease entities?

Initially Kraepelin (1919) combined unipolar and bipolar affective disorders in his category of manic-depressive illness, and it was not until Leonhard (1957) separated unipolar and bipolar affective disorders that they came to be treated as separate illnesses in terms of research. However,it remains the case that in some patients the distinction between unipolar and bipolar illness is obscure. Between 10% - 20% of patients whose first three episodes of illness are all depressive and are, therefore, classified at that stage as unipolar, subsequently develop manic episodes and consequently become diagnosed as bipolar (Kendell 1987). Akiskal (1983) reported that associated features which are present in those patients who switch from a unipolar to bipolar diagnosis, include : onset before age 25, especially acute onset, psychotic depression, postpartum episodes, hypersomnic retarded clinical picture, pharmacologic hypomania and a family pedigree with a large number of members affected in consecutive generations. Cases where hypomanic episodes occur as a result of ECT or antidepressant drugs are fairly frequent and Akiskal (op.cit) stated that there is a population of 'pseudo-unipolar' depressed patients characterized by bipolar family history, early onset, high rates of recurrence, pharmacologic hypomania and response to lithium. As Kendell (op.cit) pointed out, the existence of this group of patients serves to further obscure the distinction between unipolar and bipolar affective disorder.

Leonhard's (1957) distinction between unipolar and bipolar disorders has been supported by several findings, including studies of familial distribution, natural history and response to treatment. The rate of illness found amongst first degree relatives differs significantly for bipolar and unipolar probands, the risk of affective illness being greater in relatives of bipolars (Perris 1966). Perris studied 138 bipolars and 139 unipolars. In the bipolar probands, bipolar heredity occured in 16% of the cases, and unipolar heredity occured in 0.8% of the cases. In the unipolar probands, a bipolar heredity was estimated to occur in 0.5% of the cases, and a unipolar heredity in 10.6% of cases. Twin studies have revealed a greater concordance between bipolar monozygotic pairs than between unipolar monozygotic pairs (Allen 1976, Bertelsen et al 1977). Perris (op.cit) and Angst (1966) demonstrated that bipolar disorders tended to start at an earlier age than unipolars, to recur more frequently, and to have a poorer overall social adjustment. Treatment studies have revealed further differences. Antidepressants seem to reduce the risk of relapse in unipolar but not in bipolar illness.

b) Are schizophrenia and bipolar affective disorder distinct disease entities?

As Kendell (op.cit) stated, the aetiologies of schizophrenia and the affective disorders are not yet fully understood. Both illnesses are described and defined by their clinical syndromes, and none of these syndromes has been shown to be separated by a point of rarity, but to merge into one another. The two illnesses respond to different treatments and have different long term prognoses,although there is a good deal of overlap between the two illnesses for both these factors. Generally, schizophrenia responds to neuroleptics and bipolar affective disorder to lithium. Schizophrenic illnesses result far more frequently in permanent personality changes, and chronic invalidism than bipolar affective disorder, which generally shows full remission between episodes. Increased morbidity risk of schizophrenia has been found in the relatives of schizophrenic probands, and an increased morbidity risk of affective disorder is found in the relatives of affective probands (Tsuang, Winokur and Crow 1980). Cloninger (1985) used self-report ratings of 500 schizophrenic and affective disorder outpatients and 1,248 first degree relatives and derived a discriminant function which distinguished between the symptoms of schizophrenia and affective disorders.

However, patients who manifest both schizophrenic and affective symptoms are fairly frequently seen. Kendell (op.cit) stated that patients who exhibit this mixed symptomatology are as common as those with purely schizophrenic or purely affective symptoms. Kendell also

pointed out that it is widely recognized that some patients with affective disorders eventually relapse into a state of chronic invalidism, and that many schizophrenic illnesses have been found to respond to ECT and some to lithium, while mania and some depressions have been shown to respond to neuroleptic drugs. Enlargement of lateral ventricles and association of high Expressed Emotion in precipitating relapse have been found in both schizophrenia and bipolar affective disorders. Epidemiologically, Hare (1968)reports that the two groups are similar in sex ratio, age-incidence, risk of suicide and seasonal variations in onset and birth. Crow (1986)has proposed that schizophrenic and bipolar affective psychoses lie on a continuum which has a genetic basis, and that they form separate points on this continuum.

c) Is there a vulnerability marker for major depressive disorder?

Beck et al (1979) proposed that the depression-prone individual is characterized by stable trait-like depressogenic schemata which are activated by certain types of events. Abramson et al (1978) suggested that depressed and depression-prone individuals are characterized by a trait-like internal stable and global attributional style for negative events.

Beck's theory of depression invokes three sets of cognitive concepts to explain the psychological aspects of depression; they are the "cognitions, schemata and errors in logic" (Beck 1983). Cognitions are "labile, reflect current events or memories and in depressed people are generally negative in content" (Beck 1983). Errors in logic "involve systematic negative distortions in the interpretation of information, a matter of thinking style". Schemata "are more stable, general underlying beliefs and assumptions about the nature of the world, and how one relates to it". In depressed patients, the schemata which they use to form assumptions are predominantly negative. Beck (1984) claimed that the depressed person's dysfunctional schemata lie dormant until activated, either by some external stressor or by an internal physiological change. These schemata are thought to be formed by early experiences. Once activated, the schemata distort the depressed person's information processing, leading to unduly negative inferences and perceptions. Schemata can refer to a single belief or to an organized structure such as 'negative self-schemata' and 'negative world-schemata, and sometimes to an organizing process that is responsible for interpreting incoming perceptual information in a negative way.

Eaves and Rush (1984) studied automatic thoughts, attitudes and attributional biases in a group of 11 endogenous depressed patients, 13 non-endogenous depressed patients and 17 non-depressed control

subjects using the Dysfunctional Attitudes Scale (Weissman and Beck, 1978) and the Attributional Style Questionnaire (Seligman et al 1979). They reported that measures of dysfunctional attitudes and depressive attributional biases continued to persist in both the endogenous and non-endogenous groups after treatment, and proposed that these may be trait markers of individuals who are predisposed to depression. They suggested that dysfunctional depressive beliefs and a lasting tendency to attribute negative outcomes to internal,global stable causes were identified as possible long-term cognitive characteristics. However, the follow-up of subjects in remission was only 2 - 3 weeks, and it has been suggested that the patients may have been still manifesting some residual features of their depressive episode (Fennell and Campbell 1984).

Hollon, Kendell and Lumry (1986) studied groups of subjects which included 12 recovered bipolar subjects and 13 recovered unipolar subjects, using the Automatic Thoughts Questionnaire (Hollon and Kendell, 1980) and the Dysfunctional Attitude Scale, and reported that while the scores of subjects were elevated when depressed, they found no evidence that depressotypic cognitive processes were even slightly elevated intermorbidly in remitted patients. Wilkinson and Blackburn (1981) compared the responses of a group of recovered depressed subjects with a group of depressed patients, a group of recovered 'other' subjects and a group of normal controls on the Hopelessness

Scale, the Cognitive Style Test, and the Cognitive Response Test. They found that the depressed patients obtained high mean scores on all the cognitive measures, but after recovery depressed patients did not show any cognitive distortions. However, Blackburn pointed out that Beck defined the idiosyncratic schemata which become active during depressive episodes as being relatively inactive during the non-depressive periods, and she suggested that these depressotypic schemata may only be activated in vulnerable individuals under stress.

Fennell and Campbell (1984) measured the responses of currently depressed, never depressed and recovered depressed subjects on the Cognitions Questionnaire. This questionnaire provides a total score for depressive distortions to negative, positive and neutral hypothetical events. They found a strong positive association between degree of depression and level of cognitive distortion. They proposed that there may be two possible markers of residual cognitive vulnerability, these being generalization from negative events, and the actual responses to the question about the experience of depression itself. They also reported finding a sub-group, who showed a specific vulnerability, that is a tendency to interpret normal dysphoria as the onset of a new episode. Chodoff (1972) stated that the only consistent evidence regarding the premorbid personality of unipolar depressed patients was that they tended to show a greater degree of non-specific neuroticism than controls.

Blackburn, Eunson and Jones (1986) proposed that recovered depressed subjects would show a greater similarity with currently depressed subjects in their view of the self than in their views of the world or the future. They stated that there is some indication that a relatively negative view of the self is more stable than the other components.

4.2. Affective disorders as dysfunctions in information processing

Dysfunctions which occur in the content, organization and retrieval of information in memory in affective disorders will be discussed, within the context of dysfunctions in the structure and implementation of associative networks in memory. These proposed dysfunctions will be described and their effect on performance in information processing will be discussed.

i Dysfunctions in the content and use of associative networks in unipolar and bipolar affective disorders.

Findings which show impairment in structuring information indicate that in affective disorder patients, some dysfunction in the structure and/or function of associative networks may be in operation. The findings and the proposals of other authors suggest that although the

deficits which occur in mania and depression are similar, the underlying dysfunctions may be different. Evidence will be presented to show that the performance of the manic patients is comparable to that of the schizophrenic patients in cognitive tests, and it is proposed that similar impairments in the implementation of associative networks exist in mania and schizophrenia. However, in depression, it is proposed that while these associative networks may not be implemented as effectively as in controls these networks are abnormally negative in content.

Bower's (1981) model of semantic memory incorporates the effects of mood or emotion into semantic networks, and offers an account of the construction and activation of pervasive negative networks which result in deficits in information processing.Bower proposed that each distinct emotion has a specific node or unit in memory that collects together many other aspects of the emotion connected to it by associative links. Among these are propositions describing events during which that emotion was aroused, its associated autonomic reactions, standard role and expressive behaviours.

Emotion nodes can be activated by physiological or symbolic verbal means. Activation of an emotion node spreads activation throughout the memory structures to which it is connected, creating sub-threshold excitation at those event nodes. Therefore, a weak cue that partially

describes an event may combine with activation from an emotion unit to raise the total activation of a relevant memory above a threshold of consciousness. The essence of this model is that, within the network of associations which constitute long term memory, an emotion or mood such as depression, will be linked with representations of those events and concepts which have been previously associated with or activated during that mood. The strength of the linkages will be determined by the extent to which the mood, concepts and clusters of propositions representing events, have been previously associated. The node representing a personal episode from the past receives activation through linkages both from the emotion node due to variation in mood, and from propositions or concepts related to the event. Summation of activation from these two sources will exceed the threshold for 'accessibility' more often for positive memories when in a good mood, and for negative memories when in a depressed mood. Memories acquired in one state are accessible mainly in that state but dissociated for recall in an alternate state. The model suggests that concepts themselves, by repeated association with or activation during particular mood states, can become associatively linked with particular emotion nodes.

The current emotional state of the individual should influence associative processes, the interpretation of ambiguous situations and the salience of congruent emotional material. The prevailing mood acts

as a constant source of activation so that the asociations receiving the highest activation lie on an intersection between mood and stimulus. The current mood activates and primes mood-congruent categories into readiness, and these are used in expectation-driven or top-down processing to classify and assimilate indeterminate experiences.

Network theory suggests that the concepts, interpretations and memories that become accessible in depression are those that have previously been activated or encoded in that state, or associated with it. Depressogenic experiences, such as loss and failure, if common, may cause these concepts in memory to become associated with negative self-evaluation, which becomes associated with depression. Subsequent activation of the depression node by the presence of the state of depression will spread activation to concepts and event representations throughout the network to an extent that depends upon their prior association with that mood state. Negative concepts and events will have been more often associated with depressed mood in the past, and therefore they become relatively more activated when that mood state is reactivated. This activation will lead to concepts and representations of events related to the negative view of the self and the world exceeding the threshold at which they affect conscious

experience. The view of the future may be determined by the relative availability of the cognitive representations of different types of experience from the present and the past.

Evidence for Bower's model comes from a series of studies which examined the effect of mood on recall. Lloyd and Lishman (1975) presented a group of clinically depressed patients with a series of neutral cue words, and asked the subject to recall either a pleasant or unpleasant event associated with the word. In the more depressed patients, the latency to retrieval was significantly shorter for unpleasant memories. This effect was found to be reversed in the less depressed patients. The percentage of pleasant and unpleasant memories recalled was also significantly correlated with severity of depression.

Teasdale et al (1980) measured the availability of pleasant and unpleasant memories, in a test which required the subject to recall memories without specifying the hedonic tone of the memory to be produced. He reported that depressed mood reduced the availability of positive memories and increased the availability of negative memories. Fogarty and Hemsley (1983) found similar results when they presented a group of clinically depressed patients with a word cue and asked them to produce a memory in response. Depressed subjects showed an increased probability of recalling negative memories. Retesting

established that the effect was correlated with the depth of depression. In mild depression, it is the accessibility of happy memories that declines, whereas in more depressed subjects there appears to be an increase in the availability of sad memories

Weingartner (1977) reported that in bipolar patients, episodic events generated from semantic memory can be recalled more completely in a similar mood state, than in a different mood state. The association learned while a patient was manic or depressed was more effectively reproduced during a period of similar mood.

Kovacs and Beck (1978) claimed that the negative schemata which are activated in depression gradually replace more appropriate ways of organizing and evaluating information. Hyperactivity of the depressive schemata are thought to occur in depression and consequently to interfere with the operation of other cognitive structures. Their intensity noticeably affects the patient's interpretations and information processing.

The rest of this section will review the findings on cognitive functioning in affective disorder patients which are relevant to the hypotheses that manic patients manifest a dysfunction in the implementation of associative networks, and that depressed patients process information on the basis of predominantly negative schemata.

While the control of the associative networks used by schizophrenic and manic patients are intact, it is hypothesized thast these patients experience dysfunctions in implementing these networks. Similarities in the cognitive functioning of schizophrenic and manic patients will be discussed. The depressed patients are hypothesized to be able to implement associative networks fairly effectively but the content of these networks is hypothesized to be abnormally negative. These hypotheses and reviews of cognitive impairments are presented in Tables 4a and 4b.

ii Associative Loosening

Findings generally show that manic patients show abnormalities which are similar to schizophrenic patients, while the associations of depressed subjects are abnormally negative.

Associative loosening has been stated to occur as frequently in mania as in schizophrenia (Andreasen 1979). She reported that manifestations which occur with nearly equal frequency in schizophrenia and mania include tangentiality, derailment, incoherence, illogicality and loss of goal. Rochester (1973) stated that flight of ideas and loosening of associations occured in manic patients and in schizophrenic patients. Manic patients have been reported to produce loose and causal associations which is evident in

TABLE 4a

Dysfunctions in information processing.

Hypothesis:

Manic patients will show impairments in the implementation of associative networks which are similar to those seen in schizophrenic patients.

Impairments in cognitive functioning which are indicative of dysfunctions in the implementation of associative networks:

A) Loosening of the associations:

- flight of ideas (Rochester, 1973, Andreason, 1979)
- idiosyncratic associates (Weingartner et al, 1970, Henry et al 1971)

B) Formation and use of concepts:

- concrete (Wolfe, 1987).
- difficulties in abstraction (Savard et al, 1980, Harrow, 1986).
- overinclusive (Harrow, 1986, Payne, Hewlett, 1960, Hawks, Payne, 1971).
- perserveration (Moice and McNicol, 1986)
- looser psychological constructs - (Fransella and Bannister, 1977, Mellsop, 1971, Breakey and Goodell, 1982, Ashworth et al, 1982)

C) Speech

- no logical order (Hofman et al, 1986)
- dysfunction in hierarchies (Rocherster, 1973, Hofman et al, 1986)

D) Memory

- deficit in encoding and organizing information (Henry, 1971)
- lack of structuring - deficit in recall (Harvey, 1982)

TABLE 4b

Dysfunctions in information processing

Hypothesis:

Depressed patients can implement associative networks but the content of these networks will be abnormally negative.

Impairments in cognitive functioning which are indicative of dysfunctions in the structure and use of associative networks:

A Loosening of the associations

- negative content (Henry et al 1971)

B Formation and use of concepts

- difficulties in abstraction (Savard et al, 1980, Silberman et al 1983)

- no difficulties in abstraction (Beck, 1963).

- impairments due to pervasive interconnected negative thoughts, Wenzlaff et al (1988)

- overinclusive (Payne and Hirst, 1957)
  not overinclusive (Payne and Hewlett, 1960)

- perseveration of disconfirmed (negative) hypothesis (Silberman et al, 1983).

- more rigid psychological constructs (Ashworth et al, 1982)

C Speech

- retardation, lower rates of verbal behaviour (Libet and Lewinsohn, 1973)

  more negators, more expressions of feeling (Hinchliffe et al, 1971).

D Memory

- deficit in transfer of information from short term memory to long term memory (Harvey, 1971)

- deficit in actively structuring information (Silberman et al 1983, Weingartner and Silberman 1982).

their speech and thought. Weingartner et al (1970) studied patterns of verbal associates that are elicited to common word events. While the patients were manic, they produced more idiosyncratic responses to single word stimuli. Willner (1984) reported that the associations generated from semantic memory can be regenerated more completely in a similar mood state. Therefore, the production of associations is partially state dependent. However, it may be the case that mood state induces specific encodings and interpretations of events, and differences in mood may be related to discrete strategies for searching for stored trace events. During periods of mood disturbance, patients learn poorly and remember events with greater difficulty, and therefore, their reproduction of associations is less complete. However, the fact that the associations learned while the patient was manic are reproduced more effectively when the patient is manic than when he is not manic, suggests that a simple relationship between disturbance in mood and deficits in performance cannot adequately account for the findings.

Henry, Weingartner and Murphy (1971) compared the word association patterns of patients when they were manic and when they were not manic. They found that word association patterns were altered in direct proportion to the severity of manic symptoms. An increase in

severity of mania was associated with a decrease in high frequency associations in five out of seven patients, and with an increase in idiosyncratic associations in all seven.

Depressed subjects have also been shown to generate more idiosyncratic responses in word association tests when ill (Henry et al op.cit). In a study of 11 unipolar psychotically depressed subjects, Henry reported that differences in degree of depression affects the frequency of responses to word association stimuli, and that the patients gave more idiosyncratic responses when they were ill.

The most pronounced feature of the depressed patient, however, is his construction and use of schemata and inherent associations with a pervasive negative theme.

iii Dysfunctions in the formation and use of concepts.

Impairments found in the formation and use of concepts in manic patients are generally similar to those found in schizophrenics in the implementation of associative networks, while depressed subjects impairments suggest that the dysfunction is abnormally negative content of these networks.

Manic patients have been found to use more immature, concrete modes of thinking and to show deficits in tests of abstract thinking. Wolfe et al (1987) reported that bipolar subjects were more impaired than unipolar subjects on demanding cognitive tests such as concept formation and problem solving. Savard et al (1980) tested 11 unipolar patients and 15 bipolar patients on the Categories sub-test of the Halstead-Reitan battery. This test is a measure of abstract reasoning and necessitates both differentiation and integration of concepts. The subject is required to discover a correct organizing principle to differentiate stimuli. The bipolar patients were found to make significantly more errors than the unipolar patients and the normal controls, although the unipolar patients also made more errors than the control group. Most of the bipolar patients, 87%, scored in the abnormal range, while 64% of the unipolar patients and 36% of the controls scored in the abnormal range. When in remission, it was found that the older bipolar subjects continued to remain in the abnormal range, while the younger bipolar subjects and all the the unipolar subjects scored mainly in the normal range. The variability of error scores in the older bipolar group was smaller than that among the younger patients, and the authors concluded that the degree of cognitive deficit as reflected in this test was much more consistent in the older group of bipolar patients.

Harrow et al (1986) tested a group of manic patients and a group of schizophrenic patients using the Gorhams Proverbs Test to measure bizarre thinking. They found that the manic patients showed impairment on this test and concluded that a large number of manic patients showed relatively severe bizarre and idiosyncratic thinking. When the patients were reassessed at follow-up one year later, 44.5% of the manic patients still showed signs of abnormal thinking.

Harrow et al (1982) tested a group of 113 manic, schizophrenic and non-psychotic patients during the acute state of illness on the Proverbs Interpretation test. They found that hospitalized manic patients manifest as much impairment as hospitalized schizophrenic patients. They stated that the manic patients showed more negative thought pathology on the overall level of bizarre idiosyncratic thinking as measured by the proverbs interpretation test than the schizophrenic patients ($p<.05$). Both psychotic groups showed more impairment than the control group. The impairments in the psychotic groups declined after the acute phase.

Silberman, Weingartner and Post (1983) reported that depressed patients showed deficits in proverb interpretations and that the degree of deficit was correlated with severity of illness. They

concluded that depressed subjects show a deficit in logical reasoning from reported impairments in tests for logic and strategy in abstract reasoning (Levene 1966).

However, Beck (1963) stated that unipolar depressed patients have not been found to be impaired in proverb interpretation that their impairments have been limited to specific areas which involve the distortion of personal conceptualizations because of idiosyncratic schemata. Wenzlaff, Wegner and Roper (1988) stated that the enhanced accessibility of interconnected negative thoughts can undermine more appropriate thoughts.

Silberman, Weingartner and Post (op.cit) concluded that the abstract reasoning deficits of depressed patients consisted of two types of error : an inability to narrow down the set of possible solutions (poor focusing) and perseveration on disconfirmed hypotheses. They found that poor focusing,that is the selection of hypotheses from inappropriately large sets, increased significantly with level of depression.

Manic patients, when ill,and bipolar depressed,when recovered, have been shown to produce more abnormal sortings on the Object-Classification test. The object sorting test is a measure of the ability to form categories and to use overinclusion in forming these categories.

Harrow et al (1986) tested 34 manic patients, 30 schizophrenic patients and 30 non-psychotic patients on the Goldstein- Scheerer Object Sorting Test, as a measure of bizarre, idiosyncratic thinking. Manic patients were found to be impaired on this test while ill and at follow-up Duhm and Plaum (1986) compared groups of 13 endogenous depressed patients, 16 manic patients and 51 schizophrenic subjects on a modified version of the Goldstein-Scheerer Object Sorting Test. They found that the manic patients reacted faster than the depressed patients, and the depressed patients sorted fewer objects. They found no differences in the performances of psychotic patients. Payne and Hewlett (1960) reported that manic patients obtained a higher score for incorrect categories than did normal controls, although they found that the schizophrenic patients were equally impaired on the object sorting test during the acute phase of illness. Hawks and Payne (1972) found that scores of overinclusion correlated significantly with hostility, motor activity. talkativeness, motor speed, verbal responsiveness and thought disorder.

Studies of overinclusion in unipolar depressed subjects have shown inconsistent results. Payne and Hirst (1957) found that endogenous depressed patients performed more overinclusively than normal controls on the Epstein Overinclusion Test. However, in an extensive experiment which involved 13 measures of overinclusion, Payne and Hewlett (1960) found that 20 endogenous depressed subjects did not differ from 20 normal controls.

Bipolar patients have also been found to manifest increased perseveration and inability to shift set. Silberman, Weingartner and Post (1983) showed that depressed patients perseverate on disconfirmed hypotheses in a test of abstract reasoning. Morice and McNickol (1986) referred to the use of repeated words and parts of words by manic and schizophrenic patients.

Affective disorder patients have been found to manifest abnormalities in repertory grid tests (Fransella and Bannister 1977) derived from Kelly's Personal Construct Theory (1955).Mellsop et al (1971) compared the performance of 12 manic patients and 24 schizophrenic patients with thought process disorder using the Bannister-Fransella Grid Test of thought disorder. They reported that the two groups were significantly differentiated for the intensity score but not for the consistency score. However, Breakey and Goodell (1972) found no differences in scores of intensity and consistency in

schizophrenic and manic patients. They found that schizophrenic patients and control subjects had significantly different scores for consistency only from the control subjects. They concluded that thought disorder as measured by the Bannister-Fransella grid test occurs with approximately the same frequency in manic and schizophrenic subjects.

Ashworth, Blackburn and MacPherson (1982) used repertory grid techniques to measure 'cognitive simplicity', 'monolithic' and 'articulated' structure, 'integration of self and others' and 'self-esteem' in a study of 20 depressed, 10 manic, 10 schizophrenic, 10 physically ill and 10 recovered depressed patients. They found that the manic patients had relatively complex (or confused) grids with unarticulated structure, a small distance between self and other and high self-esteem while there was a tendency for the depressed patients to be characterized by grids which showed relative cognitive simplicity and monolithic but inarticulated structure. A monolithic system is a single, large cluster of constructs which is prototypical of 'cognitive simplicity', and compares with a segmented structure of several small clusters.

Dilation indicates that the person, in order to reorganize his perceptual field on a more comprehensive level, considers an array of new elements. Circumspection refers to the employment of additional

constructs. Kelly (1955) postulates that, in mania, this takes on a frantic form, with the patient jumping from one element or construct to another, rapidly and illogically. It is proposed that the uncontrolled dilation and circumspection of the manic patient may result in a fragmented and segmented construct system. Constriction is where the subject minimizes apparent contradictions among his cognitive subsystems by decreasing the aspects of the environment to which he attends. Pre-emptive thinking involves limiting the number of constructs applied to each aspect of the environment and dealing with events in an unvarying, stereotyped, negative way. Repertory grid measures in depressed subjects reflected constriction and pre-emption.

Ashworth et al (op.cit) reported that the depressed group occupied one extreme position on all the measures while the manic patients occupied the other extreme on most of them. The depressed group was found to be more cognitively simple than the normal controls but not significantly so. However, other studies found no difference between depressed subjects and controls (Fransella and Bannister 1977, Sperlinger 1971, Space and Cromwell 1980). Manics were found to have confused performance and a high degree of cognitive complexity by Adams and Webber (1979).

iv Abnormalities in speech

Findings of abnormalities in speech reflect an underlying dysfunction in the implementation of associative networks and negative content of associative networks in mania and depression respectively.

Abnormalities in the speech of manic patients have been noted in numerous studies, most of which draw parallels between the speech of manic patients and schizophrenic patients. Andreasen (1979) stated that schizophrenic and affective disorder patients, and especially manic patients, reveal communication disorders at similar frequencies and severities.

Hoffman, Stopek and Andreasen (1986) stated that thought disorder, as evidenced in abnormalities in language, occurs among manic patients at least to the same degree as among schizophrenic patients. With both types of language, listeners are unable to organize the speech into a single, coherent whole. Pressure of speech, flight of ideas, loose associations, distractibility and inability to adhere to a line of thought are characteristic of formal thought disorder, and are characteristic of manic and schizophrenic speech. On the other hand, depressive subjects are characterized by slowness and inhibition of thought and often complain that they cannot follow up ideas.

Rochester (1973) stated that manic speech often yielded large, well-formed hierarchical sub-structures along with breaks in coherence, while schizophrenic speech generally yielded smaller discourse trees regardless of whether deviance occured or not. Schizophrenic patients rely heavily on non-propositional cues such as phonetic similarities, wordplay, and affective factors rather than the propositional relationships between statements. Manic speech at times reflects phonetic relationships as in clang associations, but in general manic patients have free access to propositional and phonetic linkages. Hoffman et al (1986) stated that the incoherence of manic speech is due to shifts from one coherent discourse structure to another, while the ability of schizophrenic speakers to construct any discourse structure is deficient.

High frequencies of incompetent references and reference failures were reported in manic and schizophrenic speech by Docharty, Schnur and Harvey (1988). Harvey (1983) found that frequency of incompetent references differentiated thought disturbed manic and schizophrenic patients from non-thought disturbed manic and schizophrenic patients. Ragin and Oltmanns (1987) reported that thought disorder was significantly associated with decreased communicability and that communicability increased with remission in all groups.

Chaika and Alexander (1986) studied the discourse of 22 schizophrenic and manic patients, and 25 normal controls. They reported that the schizophrenic and manic patients showed defects in narration, ranging from serious neologizing disruptions in syntax and narrative technique.

Andreasen (1979) stated that pressure of speech, clanging, distractive speech and circumstantiality are commoner in mania, while poverty of speech and poverty of content of speech are commoner in schizophrenia. Earle-Boyer et al (1986) associated positive and negative thought disorder in 8 manic and 14 schizophrenic acute admission patients with language disorders. They concurred with Harvey et al (1984), finding that stability of negative thought disorder was greater for mania. They found that in manic patients, pressure of speech, derailment, tangentiality and incoherence were consistently associated with global positive thought disorder while in schizophrenic subjects illogicality and poverty of speech and negative thought disorder were stable across episodes. Docherty, Schnur and Harvey (1988) reported that the frequency of incompetent references and the severity of negative thought disorder were stable independent traits of schizophrenic patients; high levels of reference failures at index predicted psychosis at follow-up.

Fraser et al (1986) found that the following variables were included in those which discriminated schizophrenic and manic patients from normal controls ; % semantically deviant sentences; % well-formed major sentences; % syntactically and semantically deviant sentences; number of sentences with indeterminate clause structure; % syntactically deviant sentences; % analysable sentences; number of errors of grammatical insertion; mean length of utterance of analysable sentences; % indeterminate clause structure; % sentences with embedding; mean number of embedded clauses per complex sentence; and number of truncated sentences. They stated that each group was not individually characterisable, but there appeared to be a continuum of linguistic degeneration across the psychotic spectrum from controls who produced fluent, complex and error-free utterances to schizophrenic and manic patients who produced dysfluent, simple and error-ridden speech.

Hinchliffe, Lancashire and Roberts (1971) reported that depressed subjects showed higher numbers of personal references, higher numbers of negators and higher numbers of expressions of feeling in their speech than controls. Libet and Lewinsohn (1973) stated that depressed subjects exhibited significantly lower rates of verbal behaviour, emitted fewer positive reactions, and had longer action latencies. Depressed subjects gave more negative reactions and fewer positive reactions.

v. Memory impairments

Evidence of memory impairments suggests that in bipolar disorders the deficit may involve a dysfunction in organization while in unipolar disorders other factors such as a deficit in the transfer of information from short term memory to long term memory and more controlled processing may be more important.

In tests of short term memory, the evidence suggests that affective disorder patients are not impaired to any great extent. Henry, Weingartner and Murphy (1971) administered a serial learning test to groups of bipolar and unipolar depressed patients. They reported that the patients' performance on the first trial of the serial learning test did not change significantly with mania or depression, although performance on later trials was impaired. They found that it was only performance on later trials that seemed to be associated with mania and depression. During affective disorder episodes, both the bipolar and unipolar patients exhibited a significant drop in performance on the later trials, and the unipolar patients showed greater impairment than the bipolar depressed patients. The manic patients were noted to be particularly susceptible to intrusions. They concluded that mania is associated with impairment of the longer-term learning functions of recent memory; that is in the encoding and organizing of information, transferring information to different storage systems and retaining

information in storage and retrieving information, and that depression interferes with the transfer of information from short term memory to long term memory. Memory impairments are the most frequent complaint of affective disorder patients.

Harvey et al (1982) reported measurements of the degree of structure in encoding in long term memory, indexed by the level of organization present in recalled speech of 20 manic patients, 20 schizophrenic patients and 10 normal controls. The manic patients performed significantly worse than the control subjects, producing less well integrated stories and recalling less information. The manic patients were able to use organization which was already present in a story they heard, but they were unable to impose organization themselves in random conditions. The schizophrenic and the manic patients did not differ on many of the discourse organization and memory dependent variables, except that the schizophrenic patients were unable to benefit from the structuring of information as the manic patients did. Recall depends partially upon the individual's ability to organize words according to some associational structure. If the associational pattern of manic patients is different from that of normal controls, the manic patients will encode information differently. Also, if the associated networks are unstable, the

encoded and stored information may be relatively irretrievable. Henry, Weingartner and Murphy (1971) stated that this would account for the increased intrusions in manics' responses.

Depressed patients have been found to show similar deficits in organizing information in long term memory as manic patients. Silberman et al (1983) stated that an inability to organize effectively may be an important component of memory impairment in depression. He claimed that support for the role of organization is provided by the finding that the performance of depressed patients was aided by instructions to focus. Weingartner and Silberman (1982) found that depressed patients were worst at learning unrelated words, but were not impaired in learning highly organized material. Weingartner (1981) examined the responses of unipolar subjects when using three types of strategy in recall. He found that, relative to controls, depressed patients were unable to take advantage of the more elaborate strategy which used semantic processing to enhance recall. They showed a deficit in the recall of random words which needed more elaborate processing, but not in the recall of highly structured information which required less elaborate processing, and they showed a relative inability to impose structure on lists of words when the form of presentation required an active restructuring. Russel and Beckhuis (1976) stated that depressed subjects imposed less order (clustering) on recalled material.

The unipolar patients showed similar impairments to the bipolar patients, but other factors have been proposed to affect memory in unipolar patients. Brand and Jolles (1987) reported that unipolar subjects showed impaired memory scanning compared with controls. They were also slower than controls in non-scanning processing stages. They seemed to adopt a less efficient search strategy, and showed more controlled processing as opposed to automatic detection. They found that bipolar subjects were not slower than controls in memory scanning, but they made more errors.

A number of studies have compared the severity of impairments in memory in bipolar and unipolar patients. Bipolar affective disorder patients have been found to show memory impairments in several studies. Henry, Weingartner and Murphy (op.cit) reported that the unipolar patients were more impaired than the bipolar patients, and that depression was associated with significant impairment on the free recall test for the unipolar group only. However, on comparison, the bipolar group was not as severely depressed as the unipolar group.

Wolfe et al (1987) compared the performance of 20 unipolar, 12 depressed bipolar, 10 Huntingdon's Disease and 20 control subjects on tests of recall, recognition and verbal fluency. Bipolar subjects were found to be more impaired than unipolar subjects on all three tests.

Rosen and Fox (1986) reported that depressed, bipolar and schizophrenic patients were impaired in their ability to recall three words after two intervening tests compared with control subjects. They concluded that functional psychiatric patients manifest a measurable abnormality in recall and recent memory.

Henry et al (1973) concluded that learning and memory disruption occurs during both the manic and depressed phases, and the extent to which such cognitive changes take place is a function of the intensity of the disturbance of mood. The evidence which differentiates the severity of memory impairments in bipolar and unipolar subjects is inconclusive, but the hypothesis that the memory impairments manifested by the two disorders are due to different underlying deficits is supported.

4.2 vi Intellectual Deteriation

Miller (1975) reviewed a series of studies on cognitive deficit in affective disorder patients, and concluded that there is some evidence that bipolar affective disorder is associated with intellectual deterioration that is at least as great as that in schizophrenic patients. Mason (1956) studied a group of bipolar subjects whose premorbid IQ was below that of the normal controls, and

found that the bipolar subjects experienced greater intellectual deterioration than the schizophrenic group. Rapaport (1945), and Wittman (1933) found significant intellectual deterioration in bipolar subjects using the Babcock-Levy test.

There is some inconsistency in the findings as to whether IQ decreases in unipolar subjects. Payne (1961) reported that neurotic depressed patients showed above average IQ scores during depressed episodes, and Granick (1963) found that 50 psychotic depressed patients' IQ's did not differ from those of 50 normal controls, matched for age, sex,race, education and religion, using the WAIS Information and Similarities sub-tests and the Thorndike-Gallup vocabulary test. Friedman (1964) compared 55 depressed patients with 65 normal controls, matched for age, sex, education, vocabulary and race on a battery of 33 cognitive, perceptual and psychomotor tests. The patients obtained lower scores on only 4% of the 82 test scores derived. Actual ability and performance during severe depression is not consistent wwith the patient's unrealistically low self-image.

Experimental studies of intellectual speed using decision time, in the Nufferno Speed Test (Furneaux 1956) found slowness in responding in endogenous depressed patients. Payne and Hewlett (1960) also reported that endogenous depressed patients showed intellectual slowness. Fisher (1949) found that recovered depressed subjects had

higher mean digit-symbol scores than subjects who were currently ill. Beck (1962) found no relationship between digit-symbol scores and depression.

Three studies suggested that the intellectual deterioration associated with bipolar affective disorder and endogenous depression is reversible with improvement in clinical status, suggesting that depression does not result in permanent or progressive deterioration in IQ. Davidson (1939) reported increases in Stanford-Binet IQ scores for all bipolar subjects after treatment. Those who did not respond to treatment showed reduced IQ scores. Callaghan (1952) and Fisher (1949) reported increases in IQ scores in depressed subjects after clinical improvement.

Blackburn (1975) found that retardation in intellectual speed could only be found in bipolar subjects. Intellectual speed measured in the Nufferno Speed tests under unstressed but not stressed conditions, differentiated ill and recovered bipolar subjects, but not ill and recovered unipolar subjects. Motor speed measured by the Gibson Spiral Maze test differentiated bipolar and unipolar subjects and ill and recovered bipolar subjects, but not ill and recovered unipolar subjects.

4.3 Affective disorders and psychophysiological variables

i P3 latencies and amplitudes

Muir, St Clair and Blackwood (in press) compared 88 patients with bipolar disorder, 48 with unipolar disorder, 96 with schizophrenia and 32 in-patient controls with non-psychotic psychiatric disorders with 213 normal controls. Fourteen bipolar subjects were rated as severely depressed and 24 as manic. 22 unipolar subjects were rated as severely depressed. The bipolar patients had longer P3 latencies; (336 s.d. 33) than the unipolar patients (302 s.d.20) and the control groups (310 s.d.28) and (301 s.d.23) respectively ($p<.001$). There was no difference between P3 latencies for schizophrenic and bipolar patients. Bipolar patients had reduced P3 amplitudes (6.6 s.d. 2.7) compared with the control groups (9.5 s.d. 3.5) and (9.8 s.d. 2.9 $p>.05$) but not compared with the unipolar subjects (8.2 s.d. 3.3). The schizophrenic subjects had smaller P3 amplitudes (6.4 s.d. 3.3) than the unipolar subjects, ($p<.05$). No significant differences were found between bipolar depressed and manic subjects.

The amplitude of ERPs in depression has been found to be related to clinical state (Friedman and Meares 1979, Blackwood et al 1987). Blackwood et al (1987) reported that P3 amplitude was reduced in 16

acutely depressed patients diagnosed as major depressive disorder, but became normal after treatment, compared with 59 control subjects. P3 amplitude increased from 6.7 (s.d. 0.97) to 8.3 (s.d. 0.72) four weeks after treatment started, which was a significant improvement at $p<.05$. No difference was found in the P3 latencies for the depressed group with a mean latency of 301.4 (s.d. 4.6) and the control group with a mean latency of 300.2 (s.d.2.9). No difference was found in P3 latency for the depressed group four weeks after treatment started ; 301 (s.d. 8.4).

4.3.ii Eye Tracking Dysfunction

In a number of investigations, ETD has been reliably found in about 40% of bipolar subjects and about 8% of the normal population (Shagass, Armadeo and Overton 1974, Holzman et al 1973). Lipton, Levin and Holzman (1980) found no differences in ETD between schizophrenic and bipolar subjects. However, Holzman et al (1984) found that ETD only occured in 10% of the parents of bipolar patients, which was similar to the rate in the control population. Levy et al (1985) emphasized the inconsistency in findings regarding the prevalence of abnormal smooth pursuit eye movements in patients with major affective disorders. They found ETD in 88% of lithium treated affective disorder patients whose smooth pursuit eye tracking was normal prior to receiving lithium. They also found that over half of lithium treated

affective disorder patients in remission also showed ETD. The authors concluded that ETD cannot be considered to be a biological trait associated with the major affective disorders.

Iacono et al (1982) studied 25 unipolar and 24 bipolar patients in remission with a history of recurrent affective disorder and 24 schizophrenic patients in remission, using a variety of smooth pursuit and saccadic eye tracking tests. The results indicated that the performance of the two affective disorder groups was not significantly different from a control group on any of the tasks. ETD was found for patients on lithium. The schizophrenic subjects produced more tracking errors than both affective disorder groups, but significantly more only with respect to the unipolar subjects.

4.4 Hypotheses derived from the literature review.

i <u>There will be differences in the physiological variables in bipolar, unipolar and control subjects.</u>

It is hypothesized that the physiological parameters will replicate previous findings, and that the bipolar subjects will show longer latency P3 and smaller amplitude P3 components of auditory ERPs than control subjects, and that unipolar depressed subjects will show smaller amplitude P3 components than control subjects. It is also

predicted that bipolar subjects will show smaller signal:noise ratio (SPEM) than control subjects. Finally, it is predicted that there will be differences in the P3 responses of depressed and control subjects to emotive stimuli.

ii <u>There will be differences in scores on cognitive tests between bipolar, unipolar and control subjects.</u>

It is hypothesized thast the affective disorder patients will show impairment in the cognitive tests relative to control subjects, and that these impairments will be consistent with previous findings. It is predicted that the bipolar subjects will show impairments in cognitive tests which measure the use of associative networks such as in the formation and use of concepts, verbal recall to categorized and unrelated information, retrieval and storage of associates, perseveration and the ability to shift set. It is predicted that unipolar subjects will show deficits related to lack of concentration and motivation, and to automatic processing, and will also show abnormally negative content in the associative networks which they use.

iii Some scores on the cognitive tests will correlate with P3 latencies and amplitudes.

It is proposed that P3 abnormalities also reflect dysfunctions in the implementation of associative networks.

Chapter 5

STUDY 1 METHOD

5.1 Rationale and aims

The aims of the first study were to examine the physiological and psychological responses of schizophrenic, bipolar and unipolar affective disorder patients in comparison with a group of control subjects, and to consider the relationships between the physiological and psychological responses within the different groups.

i Physiological responses

The first study aimed to show that the auditory ERPs and the smooth pursuit eye tracking of the schizophrenic, bipolar and unipolar affective disorder groups were consistent with those reported in previous studies, and were different in some respect to those of a group of normal control subjects. Recording these physiological variables in the groups under study had three purposes. Firstly, replication of findings from previous studies in schizophrenic patients would establish the reliability and validity of the methodology used in recording physiological dysfunction as the

findings regarding this group are established and well supported. Secondly, this would, by analogy, establish the validity of the findings in bipolar and unipolar groups and if the results support previous findings, would serve to establish the reliability of findings in those groups. The third purpose of recording the ERPs and ETD was to correlate physiological measures with psychological tests of specific aspects of information processing, so as to articulate a more coherent model of information processing dysfunction in schizophrenia and the affective disorders.

ii Psychological tests.

A battery of psychological tests was compiled to assess how impairments in cognitive functioning of the patient groups compared with the control group. Each test was selected on the basis of its sensitivity to measure specific functions, namely associative processes, conceptualization and memory.

The study aimed to test whether the schizophrenic and bipolar manic patients would be impaired in all these functions compared with control subjects. Schizophrenic and bipolar manic patients were also

compared to test whether the extent of dysfunction found on the different tests was the same for the two groups. Previous studies have shown conflicting results.

The study also aimed to show that the depressed subjects would manifest impairments on the cognitive tests, which would be consistent with previous findings, that is particularly in the memory tests and tests of psychomotor speed. The study aimed to compare bipolar and unipolar depressed patients to identify any differences in extent of impairment.

iii Relationship between physiological variables and cognitive performance

Performance on the psychological tests was correlated with P3 measurements of latency and amplitude, and the computed signal : noise ratio taken from samples of smooth pursuit eye tracking. The study aimed to demonstrate that P3 abnormalities would be associated with dysfunctions in the cognitive functions of association, conceptualization and memory, and that there would be a positive relationship between severity of P3 abnormality and extent of cognitive impairment. The study also aimed to test whether impairment on the psychological tests would be associated with abnormalities on the other physiological variable, ETD.

5.2 Design

Two sessions were generally required to collect the physiological and psychological data. In the first session, the subjects' auditory ERPs and smooth pursuit eye tracking were measured, and they were interviewed for the purpose of scoring the Brief Psychiatric Rating Scale (Overall and Gorham, 1962), The Hamilton Rating Scale for Depression (Hamilton, 1960) and the Modified Manic State Rating Scale (Blackburn et al, 1977). If the subject were willing and the ward schedule allowed it, the psychological tests were administered during the same session. However, these tests were administered to most patients in a separate session later during the day. In a few cases, patients became tired, inattentive or uncooperative before the testing session had been completed, and testing had to be carried over for one or more days. For some of the control subjects, arrangements had to be made for them to attend the Royal Edinburgh Hospital on two separate occasions when their other committments prevented them from completing all the tests in one session. As assessment of clinical state was irrelevant for the control subjects, it was thought that an interval of a few days between the physiological and psychological tests would not result in any significant change in mental state for these subjects.

The bipolar manic and bipolar depressed groups consisted of different subjects, as there was no guarentee that any subject would experience both a manic and a depressive episode during the study period.

5.3 Subjects

Twenty-four schizophrenic, twenty bipolar affective disorder, ten unipolar affective disorder and twenty-four control subjects took part in the first study. The schizophrenic patients consisted of both in-patients and out-patients who were being treated at the Royal Edinburgh Hospital. The affective disorder patients were all in-patients who were being treated in the acute admissions wards of the Royal Edinburgh Hospital. The control subjects consisted of volunteer members from the hospital staff and the local community.

i Criteria for selection

The patients were interviewed using the SADS interview and diagnosed according to RDC and DSM-III-R criteria by a psychiatrist.

Ten bipolar subjects who were suffering manic episodes and ten bipolar subjects who were suffering depressive episodes were admitted to the study. The bipolar manic subjects were required to score over 15 on the Modified Manic State Rating Scale (MMSRS). The bipolar depressed subjects were required to score 10 or more on the Hamilton Rating Scale for Depression (HRSD) to be classified as moderately depressed, and to score 17 or over to be classified as severely depressed. The unipolar affective disorder patients were required to score 17 or over on the HRSD to enter the study. The control subjects had no history of psychiatric illness.

ii Description of subjects

The schizophrenic subjects comprised 17 males and 7 females, with a mean age of 29.8 years (standard deviation 10.3). The control subjects had the same sex ratio and were closely matched for age; with a mean age of 29.2 (s.d. 10.0). The bipolar manic subjects consisted of 8 males and 2 females with a mean age of 32.9 years (s.d. 11.0). The depressed groups were significantly older than the other three groups. The bipolar depressed group of 6 males and 4 females had a mean age of 43.0 (s.d. 13.5) and the unipolar group had a mean age of 43.5 years (s.d. 9.2). This group consisted of 9 females and 1 male. The age and sex characteristics of the unipolar group reflect the later onset of the illness, and the predominance of females with this

disorder.(Table 5a) The sex ratios and the age distributions of the groups were significantly different. However, there was no significant difference in the age distribution for males and females.

Severity of illness was measured using the appropriate rating scales for each group of patients. The BPRS and the HRSD were administered to the schizophrenic group. Scores from the BPRS yielded 4 subscores which measured : thought disorder, anxiety/depression, withdrawal and hostility. The MMSRS only was administered to the bipolar manic group and the HRSD only to the two depressed groups. The mean scores for the groups on the different rating scales are shown in Table 5b. One way analysis of variance of scores on the HRSD showed that the depressed groups were significantly more depressed than the schizophrenic group.

All the patients were taking drugs at the time of testing. Appendix A1 lists age of first onset of illness, length of time in hospital for the current episode and current medication.

AGE, MEANS (STANDARD DEVIATIONS) AND SEX RATIOS OF SUBJECTS

	1 Schizophrenic 24	2 Bipolar Manic 10	3 Bipolar Depressed 10	4 Unipolar Depressed 10	5 Controls 24	P
M/F	18/6	8/2	6/4	1/9	18/6	.002 (+)
Age	29.8 (10.3)	32.9 (11.0)	43.0 (13.5)	43.5 (9.2)	29.2 (10.0)	.003 (++)

(+) X^2 = 16.59 df = 4

(++) ANOVA F = 4.447 df = 4,72

5.4 Measures and rating scales used.

The measures used for diagnostic, state severity rating, physiological and psychological purposes were established and validated tests which have been extensively used in research and clinical practice. This enables comparisons to be made with other studies, and replication of this study.

i Diagnostic

The need for standard diagnostic criteria to identify discrete homogeneous groups of patients on the basis of the presence and severity of defined signs and symptoms is evident in a research project which aims to compare groups of patients. This enables researchers to report their findings about groups of patients whose diagnoses are based upon specific criteria which can be replicated by other researchers.

a) Research Diagnostic Criteria (RDC)

The RDC (Spitzer et al 1977) were developed to meet the problem at the time of low reliability of psychiatric diagnostic procedures in clinical work and research. The RDC are a set of specific diagnostic criteria for a selected group of functional psychiatric disorders. They were developed specifically as part of a collaborative project on the psychobiology of depressive disorders sponsored by the Clinical

SEVERITY OF SYMPTOMS TABLE 5b

(a) Schizophrenic Patients' Scores on BPRS Sub-scores

	Thought Disorder	Anxiety/ Depression	Hostility	Withdrawal
Mean	3.3	1.3	4.0	1.0
Std. dev.	3.1	1.4	3.2	1.7
Range	0 - 12	0 - 4	0 - 13	0 - 6

(b) Scores by group on Affective Disorder Scales (Hamilton Rating Scale for Depression and Modified Manic State Rating Scale

	1 Schizophrenic	2 Bipolar Manic	3 Bipolar Depressed	4 Unipolar Depressed
Hamilton RSD	(Median 4.0)			
Mean	5.3		18.4	18.8
Std. dev.	6.1		6.0	2.6
Range	0 - 26		10 - 28	17 - 23
M.M.S.R.S.				
Mean		33.2		
Std. dev.		10.4		
Range		19 - 46		

Research branch of the National Institute of Mental Health (NIMH). Its development occured through the modification and elaboration of some of the diagnostic criteria developed at the Washington University School of Medicine in St. Louis, known as the Feighner Criteria. These were diagnostic conditions for which there was evidence of validity in terms of clear clinical descriptions, consistency over time and increased familial incidence.

Examination of the patient is based on a focused, clinical interview or a structured interview guide and rating scales which are designed specifically for eliciting information relevant to these categories, such as the SADS. Information from the patient's notes can also be used for the diagnosis.

Reliability of the RDC was tested in three separate studies. In the first and second studies, joint interviews were conducted, where one rater interviewed and the second rater observed. Both raters made independent ratings. In the first study, an early draft of the RDC was used, where 68 newly admitted in-patients at the New York State Psychiatric Institute were interviewed by research assistants. No formal structured interview was used. Kappa coefficients of agreement were obtained for schizophrenia 0.80, for manic disorder 0.82, and for Major Depressive Disorder 0.88. In the second study, the first edition of the RDC was used at four centres in a pilot study of the

psychobiology of the depressive disorders at NIMH, Washington University School of Medicine, University of Iowa Medical School and at Harvard Medical School. The SADS was used to interview 150 newly admitted in-patients with criteria for a depressive or manic syndrome. Kappa coefficients of agreement were 0.98 for manic disorder and 0.90 for Major Depressive Disorder. In the third study, a test-retest design was used, in which two raters interviewed the patient at different times using the second edition of the RDC at the same four facilities as in the second study. Kappa coefficients of agreement were obtained for 60 patients for schizophrenia 0.65, for manic disorder 0.82 and for Major Depressive Disorder 0.90.

However, two studies have challenged the validity of the RDC with regard to the diagnosis of primary major depressive disorder (Nelson 1978, Feinberg 1979). Nelson reported a problem of false positive diagnoses using the criteria exactly. Feinberg noted that using the RDC resulted in false positive and false negative errors with 30% of the patients classified incorrectly. He stated that the Kappa coefficient of agreement between clinical diagnosis and RDC was only .41. However, of the 6 patients incorrectly classified as not depressed, 3 were bipolar 'with unequivocal episodes of hypomania meeting RDC criteria'. With regard to the false positives, the majority had atypical dysphoric presentations.

The reliability of using the RDC in conjunction with information gained from a structured interview such as the SADS has been shown to be high (Spitzer et al 1978). The SADS interview can be used for diagnosing current episodes of illness as well as previous episodes, and for making multiple diagnoses of functional psychiatric illness. If the researcher is interested in obtaining a lifetime prevalence of diagnoses, then the lifetime version of the SADS may be used. Built into the SADS and RDC is a system that gives the researcher an option of examining the data by choosing patients on the basis of degrees of certainty of diagnosis. For example, there are specific criteria for probable versus definite diagnoses, and the researcher can therefore use the option of including only definite cases.

Endicott, Cohen, Nee, Fleiss and Sarantakod (1981) reported that the HRSD has shown a strong correlation with the items the SADS used as criteria for Major Depressive Disorder.

The high reliability of the RDC categories obtained when using the SADS (Spitzer et al 1978) on a test-retest basis are superior to that of the Feighner Criteria used in the St. Louis study. In this study, each patient was independently interviewed by two psychiatrists again on a test-retest basis. The Kappa coefficients of agreement obtained were for depression 0.55, for mania 0.82 and for schizophrenia 0.58. By omitting the patients with 'undiagnosed psychiatric condition', the

coefficients increased to 0.70 for depression, 0.93 for mania and 0.66 for schizophrenia. These are comparable with the RDC coefficients obtained even with the undiagnosed patients included, of depression 0.90, mania 0.82 and schizophrenia 0.65.

b) Diagnostic and Statistical Manual III (DSM-III)

The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM III-R) is the revision of the third edition of a standard diagnostic classificatory system which was introduced in 1952 and re-edited in 1968 and 1980. It aims to define the 'clinically significant behavioural or psychological syndrome or pattern that occurs in a person and that is associated with present distress or disability or with an increased risk of suffering death,pain, disability or an important loss of freedom', which conceptualizes each of the mental disorders. DSM-III-R does not assume that each mental disorder is a discrete entity with boundaries or discontinuity between it and other psychiatric disorders.

The aim of DSM-III-R is to provide specific diagnostic criteria as guides for making diagnoses to enhance interjudge diagnostic reliability. The first edition, DSM-I, appeared in 1952 and was the first manual of mental disorders to contain a glossary of descriptions

of the diagnostic categories. DSM-II was based on the mental disorders section of the eighth revision of the International Classification of Diseases. DSM-III was produced to provide a new classificatory glossary that would, as much as possible reflect the most current state of knowledge regarding mental disorders, yet maintain compatibility with ICD-9. There was concern that ICD-9 classification and glossary would not be sufficiently detailed for clinical and research use. The introduction of ICD-9-CM was to answer these criticisms, by including several sub-categories.

DSM-III-R was revised from 1983 to meet the following objectives among others : to improve reliability of the diagnostic categories, to enhance the acceptability of DSM-III-R to clinicians and researchers of different theoretical orientations, to achieve consistency with data from research studies bearing on the validity of diagnostic categories, and to enhance suitability for dementing subjects in research studies.

Changes were only implemented if there was supporting evidence from empirical studies, there was a consensus among experts that the revision would significantly improve the validity of the category, and that the revision would meet with some degree of diagnostic

reliability. The greatest weight was given to the presence of empirical support from well conducted research studies or failing that, to clinical experience.

DSM-III-R is descriptive, in that the definitions of the disorders are generally limited to descriptions of the clinical features of the disorders. The approach is atheoretical except with regard to disorders where causes are well established and included in the definition. The characteristic features consist of easily identifiable behavioural signs or symptoms, such as disorientation, mood disturbance or psychomotor agitation, which require a minimal amount of inference on the part of the observer. For most of the categories, the diagnostic criteria are based on clinical judgement and have not yet been fully validated by data about such important correlates as clinical course, outcome, family history, and treatment response.

ii Severity rating scales

a) Brief Psychiatric Rating Scale (BPRS)

The BPRS,(Overall and Gorham 1962) was developed to provide a rapid assessment technique which is particularly suited to the evaluation of patient change. It yields a comprehensive description of major symptom characteristics.

Sixteen symptom constructs which form the BPRS resulted from factor analyses of several larger sets of items from Lorr's Multidimensional Scale for Rating Psychiatric Patients (1953) and Inpatient Multidimensional Psychiatric Scale (1960). Originally there were fourteen symptom constructs, and Unusual Thought Content and Blunted Affect were added later. The other constructs are : somatic concern, anxiety, emotional withdrawal, conceptual disorganization, guilt feeling, tension, mannerisms and posturing, grandiosity, depressive mood, hostility, suspiciousness, hallucinatory behaviour, motor retardation, and uncooperativeness. These sixteen category point rating scales assess patient symptomatology in relatively discrete symptom areas.

In administration of the BPRS, it is advised that a uniform procedure is adopted in research projects, and that a standard interview procedure is used to eliminate differences in interview procedures. Ratings are based on observation and verbal report. Observations are made of tension, emotional withdrawal, mannerisms and posturing, motor retardation and uncooperative- ness. Verbal report is used to rate conceptual disorganization, as evidenced in confusion, irrelevance, inconsistency, disconnectedness, disjointedness, blocking, confabulation, autism and unusual chains of association: unusual thought content; anxiety; guilt feelings; grandiosity;

depressive mood; hostility; somatic concern; hallucinatory behaviour; suspiciousness; and blunted affect. Total pathology score is the sum of ratings on the sixteen scales.

Inter-rater reliability coefficients measured by product-moment correlation between ratings by different individuals are shown, based on a study of paired independent ratings on 83 newly admitted schizophrenic patients : somatic concern 0.81; anxiety 0.86; emotional withdrawal 0.62; conceptual disorganization 0.80; guilt feelings 0.87; tension 0.56; mannerisms and posturing 0.84; grandiosity 0.84; depressive mood 0.76; hostility 0.86; suspiciousness 0.84; hallucinatory behaviour 0.87; motor retardation 0.72; uncooperativeness 0.68; unusual thought content 0.83 and blunted affect 0.67.

b) Hamilton Rating Scale for Depression (HRSD)

The HRSD (Hamilton 1960) is based on a factor analytic study based on 272 depressed in-patients. It was revised in 1967. Its main purpose is to provide a simple way of assessing the severity of a patient's depression quantitatively and for showing changes in the condition.

The HRSD is an observer rating scale. It has become the standard instrument for psychiatrists' ratings. It is meant to be completed after a clinical interview and to take account of information from all sources concerning the patient's behaviour during the previous week.

The full scale consists of 21 items, but the 17-item version is more commonly used, as it excludes items which are diagnostically relevant to sub-types of depression. The scores are added to give a total score measuring severity of depression. Each of the seventeen items is scored on a 3 (0 to 2) or a 5 (0 to 4) point scale for its intensity or frequency.

The reliability has been found to range from 0.81 (Prusoff et al 1972) to 0.90 (Hamilton 1972) between raters at the same interview. The validity of the scale as assessed by its correlation with other instruments for measuring depression ranges from 0.79 (Brown and Zung 1972) to 0.82 (Williams et al 1972). The scale is short enough to allow easy completion yet thorough.

c) The Modified Manic State Rating Scale (MMSRS)

The MMSRS (Blackburn et al 1977) is a version of the Manic State Rating Scale which was developed by Beigel and Murphy (1971). The MMSRS was developed to meet the relative lack of specific rating

scales of mania compared with those measuring depressive illness, and to provide information on such issues as the diversity of manifestations of mania, the relative rate of remission of different symptoms, or the relationship of mania to depressive illness and other psychiatric states. An observer rated scale was necessary due to the patient's inability to rate himself because of lack of insight.

The Manic State Rating Scale was found to produce difficulties in lack of agreement on the elicitation and definitions of symptoms, and from confusion between related but separately scored items. It also omitted certain important aspects of manic behaviour such as sleep disturbance. The MMSRS resulted from omitting an unimportant item (dress), condensing related items in some cases, and adding important omitted symptoms or signs. This resulted in a rating scale consisting of 28 items. Each item can be scored from 0 (absent) to 5 (Continuous and gross). Information for scoring each item is obtained by interviewing the patient using a standard interview, by asking ward staff for information and through observing the patient. Reliability and validity measures were provided by the authors who conducted a study on sixteen manic in-patients, who fulfilled Feighner's Criteria for a manic illness. Ratings of the patients using the MMSRS were administered every two weeks, as were analogue ratings of mania by doctors and nursing staff. Each patient was rated independently by three raters, after an interview by one of the raters using the PSE

(Wing et al 1974). The overall correlations between each pair of raters was 0.85, 0.79, and 0.81. All the individual items except 'looks depressed' significantly correlated with the total score. Validity, as estimated by comparing the MMSRS ratings with the analogue ratings of the medical staff was computed as r=0.654 to 0.801 for all ratings.

iii Physiological measures

a) Event Related Potentials (ERPs)

Auditory ERPs were recorded using a Nicolet Ca1000 clinical signal averaging computer. The paradigm for eliciting and recording the auditory P3 wave followed that of Goodin et al (1978).

Bipolar recordings were made between silver/silver chloride electrodes at the vertex (Cz) position, and an indifferent ear clip electrode at the left ear-lobe. A ground electrode was positioned at the right ear-lobe. In all cases impedances were measured and were less than 2k .

All recordings were made within a sound-attenuated screened room. Auditory stimuli were delivered through headphones at a level of 70 db and with an interstimulus interval of 1.1 sec. Subjects were instructed to count silently randomly presented tones of 1.5 kHz which occured in a regular series of lower pitched 1.0 kHz tones. The overall rate of high-pitched to low-pitched tones was 1 : 9.

The EEG signal was amplified by 10,000 and passed through analogue filters which were set from 1 to 30 Hz (3 db down). The signal was then digitized at a rate of 1 kHz over a time epoch of 750 msec. A total of 75 msec of EEG was captured prior to the delivery of the auditory stimulus to serve as a baseline for subsequent measurements. A total of 400 epochs were recorded and the data for high and low pitched tones averaged separately. An artefact- reject circuit excluded all trials where the voltage exceeded + 45 mV. Two recordings were made with each subject.

Investigators who were blind to the subjects' diagnoses independently measured latencies and baseline-to-peak amplitudes of the individual components of the recorded waveforms. These were designated as N1, P2, N2 and P3. P3 was the only component which was used in the analyses of this study. P3 was defined as the maximum positivity between 260 and 500 msec. The baseline amplitude was determined from the prestimulus record, and amplitudes were measured

with respect to this from the pen-recorded tracings. Latencies were measured from the stimulus to the point of maximum amplitude using the cursor provided by the computer on the visual display unit and by inspection of the pen-recorded trace. The mean of the two separate recordings was taken for the final results.

b) Eye Tracking Dysfunction (ETD)

Smooth pursuit eye tracking was recorded through two silver/silver chloride electrodes placed at the left and right lateral canthus. A ground electrode was positioned at the left earlobe. In all cases impedances were measured and were less than 2 k . The EOG was amplified by 10,000, and the amplifier band width was 0.016 to 30 Hz. The signal was recorded for later analysis on a FM instrumentation tape recorder. The target was a round spot subtending 0.5 of visual arc which was displayed on a monitor screen and which moved sinusoidally at frequencies ranging from 0.2 to 1.0 Hz subtending a maximum angular amplitude of 30 . The recorded signal was later digitized at a rate of 50 samples a second to a total of 1024 samples for a sample of eye tracking recorded at a frequency of 0.4 Hz. The reconstructed signal was displayed on a monitor and ten seconds of blink free signal selected for Fourier transform. Spectral power density in the range 0.3 to 0.5 Hz (signal) was compared to power density in the range 0.8 to 8.0 Hz (noise). The natural logarithm of

the signal : noise ratio was used as the measure of smooth pursuit eye movement; a low ratio indicating increased saccadic movements and greater abnormality.

iv Cognitive tests

a) Association

1) The Word Association Test.

The word association test used was adapted from that developed at the Johnson O'Connor Research Foundation (1977). The test consists of a serially administered list of target words. These words are read one at a time to the subject and the subject's response to each word is recorded. The subject is required to report the first word which comes into his mind upon hearing the target word.

The norms for frequency of response of different associations were standardized using an American sample. It was considered necessary to collect responses from a British sample with which to compare the responses of the subjects in this study, as it was assumed that cultural differences would affect the responses given by the different populations.

The original list of target words consisted of eighty words. Seventy-three words were selected from this list which had a frequency of not less than one in one hundred thousand in the English language (Toglia and Battig 1978). Responses to these seventy-three words were collected from a sample of 106 control volunteers from hospital staff, University students and members of the local community. 53 males and 53 females who were matched for age participated in the test. The age distributions for each group were : 17 - 30 24; 31 - 40 15; 41 - 50 8 and 51 - 65 6, as it was felt that this would most likely reflect the age distribution of patients who would be participating in the studies. The distribution of occupations fell into the following categories : students 14; 'unskilled' occupations 16; 'skilled'/clerical occupations 38; 'professional' occupations 24; housewives 5; retired 6; and unemployed 3. Although more of the schizophrenic patients were unemployed, it was thought that this was due to their illness, as before they had manifested schizophrenic symptoms they had held various occupations or had been students. The occupations of the other patient groups were reflected fairly well by the distribution of occupations in the sample.

The responses to the target words from the large sample were listed in order of frequency. A final list of target words was selected for which the most frequent response accounted for over 33% of the total response given. This left a list of thirty-six words for

which there was one highly associated response. For this list of thirty-six words, the responses given by the sample were ranked, so that the most frequent response was ranked as one. The test was scored by adding the number of frequent responses given; that is the number of times the subject gave a response to the target word which was one of the top three responses given by the sample (ranked one down to three). A second score was yielded by adding the rank values for the response to each target word given by the subject. If the subject gave a response which had not been given by the sample he scored nine for that response, which was a greater value than any of the rank scores.

2) The Paired-Associates Tests

A second test was used to examine the access of schizophrenic and manic patients to normal stucture of associations, and their ability to utilize this stucture. This was a test of paired-associates and was administered in two parts. In the first part, the examiner read two words and asked the subject if the words made a pair. Paired-associates were used for half the pairs, and were taken from Jenkins-Palermo (1970) word association norms. Randomly interspersed with the paired-associates were pairs of unrelated words picked at random from Toglia and Battig (1978) word lists. This test was scored according to the number of correct responses made by the subject. This part was used to test whether the subject had access to normal associations.

In the second part of the test, a different set of paired-associates were used. One of the pair was presented to the subject, and he was asked to name the partner. The score was the number of correct responses, according to the Jenkins-Palermo word association norms. The second part of the test was to measure to what extent the subject was able to use the knowledge he had about associations (as measured in part one) to produce his own associations. The main purpose of this test was to examine any deficit in part two compared with part one in schizophrenic and manic subjects as compared with control subjects and other patient groups.

b) Conceptualization

1) The Wisconsin Card Sorting Test (WCST)

The WCST (Berg 1948, Grant and Berg 1948) is an abstract reasoning, problem solving test that involves achieving abstract sets, maintaining these sets and then changing them. The subject is presented with four stimulus cards bearing designs that differ in colour, number or shape. The task is to sort the remaining sixty cards that vary along these dimensions. The subject must deduce the correct principle for sorting the cards from the examiner's responses to the subject's placements. After a run of 10 correct placements, the examiner shifts the principle which is indicated to the subject

through the 'right' and 'wrong' statements of the examiner to his placements. The test begins with colour as the basis for sorting, shifts to number and then to shape. The test is scored according to the number of errors that the subject makes. Errors may be perseverative, which occur when the subject continues to sort according to a previously successful principle or when the subject persists in sorting on the basis of an initial erroneous guess. Robinson et al (1980) reported that patients with right frontal lesions made five times as many perseverative errors as control subjects. Lezak (1985) stated that the perseverative error score is useful in documenting problems in forming concepts, profiting from correction and conceptual flexibility. 'Other' errors are also scored. Milner and Petrides (1984) claimed that difficulty in using environmental stimuli to regulate action causes inpairment on the WCST and is associated with lesions in the superior frontal cortex. In the WCST, impairments seen after such a lesion seem to stem from the patient's inability to overcome previously established response tendencies, resulting in the generation of fewer hypotheses and frequently in a high incidence of errors involving perseveration. They stated that these deficits may be seen after frontal lobe removal from either hemisphere, but are more reliably associated with left sided lesions, which supports the findings of Drewe (1974). Lezak (op.cit) reported that frontal lobe damage is associated with difficulty sorting according to a category, suggesting an impaired ability to

form concepts,and/or difficulty in shifting when the category changes. Milner (1963, 1964) reported that frontal lobe patients achieved fewer sorting categories and made more perseverative errors than other brain tumour patients.

2) The Witkins Embedded Figures Test (WEFT)

The WEFT is similar to the Hidden Figures Test (Thurstone 1944). The WEFT consists of twelve complex figures with a selection of five simple shapes beside each complex figure. One of these five shapes is 'embedded' or hidden within the complex figure, and the subject has to identify which shape is hidden within the complex figure. In Thurstone's study of normal perception, successful performance on this test was strongly associated with 'the ability to form a perceptual closure against some distraction' and 'the ability to hold a closure against distraction'. The test is a measure of figure-ground perception, and measures the ability to identify the essential or discriminating features of the salient shapes. Talland (1965) reported that impairment on this test may be caused by problems in perceptual shifting, and focusing as the test requires the subject to shift his attention away from the discrete figure to the inclusive design, necessitating a change of perceptual set in the process. Beard (1965) noted that perceptual flexibility also appeared to contribute significantly to the performance of teenagers. Teuber (1951) reported

that patients who had surgery involving the frontal cortex had a significantly impaired performance on this test. Liddle (1987) stated that poor-figure ground perception may reflect temporal lobe dysfunction.

3) The Stroop Test

The Stroop Test (Stroop 1935) measures the ease with which the patient can shift his perceptual set to conform to changing demands. Talland (1965) used the Stroop Test to measure perceptual interference.

For this study, the Stroop Test was administered by micro-computer. The subject was required to sit in front of a VDU and the micro-computer keyboard. He had to respond to the stimuli which were presented on the VDU by pressing an appropriate key on the keyboard. The stimuli which were presented were a series of words which consisted of the name of a colour; red, yellow, green or blue, printed in different coloured ink, for example the word red printed in yellow.

The test consisted of two conditions. In the first condition, the subject was required to ignore the colour that the word was printed in and to respond by giving the word itself. Four keys on the keyboard corresponded to red, yellow, green and blue, and the subject was

required to press the correct key to correspond with the word stimulus. His response time and the accuracy of his response was stored automatically by the micro-computer. Fifteen words were presented to the subject per trial. At the end of the trial, his average response time and the number of correct responses he made were recorded. For the second condition, the subject was required to ignore the word and to respond by giving the colour that the word was printed in. The procedure was otherwise the same as that for the first condition. Two trials for each condition were administered after a practice run for each condition.

Nehamkis and Lewinsohn (1972) administered the Stroop Test in its original card form to left and right hemisphere lesioned patients. The left hemisphere patients took approximately twice as long as the control subjects to read the cards, but the interference effect in the most distracting condition (naming the colour and ignoring the word) was no greater for left than for right hemisphere patients. Lezak (op.cit) stated that performance on the Stroop Test is a measure of frontal lobe dysfunction. Previous reference to the Stroop Test effect with respect to the interference effect was made in Chapter 2.

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4) The Similarities Test

The Similarities sub-test of the Wechsler Adult Intelligence Scale (Wechsler 1955) is a test of verbal concept formation. This test consists of thirteen pairs of items e.g. wood and alcohol, which requires the subject to state a way in which the two items are alike. The test involves the subject identifying a common property, or common category for the two items.

All the WAIS subtests were standardized on a sample of 1700 American adults. The raw score obtained on each subtest is converted into a scaled score which can be compared with scores obtained by the subject's age group within the original sample, which was selected as representative of the American population on the basis of the 1950 U.S. Census. The application of scaled scores enable the evaluation of an individual's ability in the relevant subtest against a norm represented by the ability of adults at the height of their mental capacity. The reliability coefficients for the Similarities subtest at ages 18 - 19, 25 - 34, and 45 - 54 are 0.87, 0.85 and 0.85 respectively (Wechsler 1955).

The Similarities subtest, as a measure of abstract concept formation, is sensitive to the effects of brain damage, and as such is classified as one of the 'non-hold' subtests. A low score on the

Similarities subtest is likely to reflect concrete thinking. This concrete thinking may be associated with brain damage especially if the subject is found to score significantly higher on one or more of the other subtests.

When scoring the test, the subject can be awarded two points for answers that are abstract generalizations, but only one point for specific concrete likenesses, and no points for a wrong answer. The raw score is the sum of points obtained for the thirteen pairs. The Similarities subtest is reported to be a good test of general intellectual ability (Lezak op.cit), as it is the least affected by the subject's academic background. Hirschenfang (1960) stated that the Similarities subtest tends to be more sensitive to the effects of brain injury regardless of localization than the other verbal subtests. However, McFie (1975) and Newcombe (1969) reported that this subtest is associated with left temporal and frontal involvement. Lezak (op.cit) stated that the Similarities subtest is one of the best predictors of left hemisphere damage in the WAIS battery. However, Sheer (1956) reported that low Similarities scores have been associated with bilateral frontal lesions.

c) Memory

1) The Digit Span Test

The Digit Span Test is a another verbal subtest of the WAIS. It is a measure of concentration and short term memory. The test involves two tasks. In the first task, the subject is required to repeat a sequence of digits, starting with three digits and increasing by one on the successful completion of each sequence. His digit span forwards is the number of digits which he can accurately repeat. The maximum number in the subtest is nine. The second task requires the subject to repeat the sequences backwards. Digit span backwards is tested by the same procedure as digit span forwards, but the maximum number of digits in the sequence is eight. The digit span raw score is the the sum of digit span forwards and digit span backwards. Most control subjects obtain a difference score between digit span forwards and digit span backwards of one. Gross differences have been associated with brain damage (Costa 1975, Lezak 1979, Weinberg et al 1972).

Digit span forwards measures the efficiency of attention. It has been found to be more vulnerable to left hemisphere involvement than to right (Newcombe 1969, Weinberg et al 1972). Lezak (1985) reported that it is a relatively stable ability that is likely to be resistant to the effects of many dementing diseases.

Digit span backwards calls upon working memory, which must operate simultaneously with the reversing procedure. Again this is sensitive to left hemisphere damage (Newcombe 1969, Weinberg et al 1972). However, digit span backwards has been shown to be vulnerable to diffuse damage that occurs with dementing processes (Lezak 1985).

2) Verbal Recall

Verbal recall tests were devised to compare the rate of recall of different patient groups with control subjects in different conditions. Seven lists of word were compiled which varied in degree of relatedness and degree of emotive content (Toglia and Battig 1978). Two lists of words were related by length of word; one list contained short words and the other list contained long words. Two lists were highly related and consisted of members of two categories; animals and education-related words. Within each of these four lists was one isolate. Two lists were highly emotive; one contained positive words and the other contained negative words. The last list contained neutral words which were unrelated on all dimensions. The dimensions used for selecting words were included in the Toglia and Battig word lists. Ratings for 'pleasantness' and 'unpleasantness' were used to assign words to positive and negative lists respectively. Short words were of three letters or less and long words were of nine letters or more. Animals had a high rating on 'concreteness' while education

words had a low rating. All the words occured with a frequency of not less than one in one hundred thousand in the English language, and all had high ratings on 'familiarity'. Each list consisted of twelve words. Lezak (1985) reported that there was no significant age difference in rate of recall for this number of words up to the age of sixty. It was felt that the use of twelve words would prevent a ceiling effect. The position of the word in the list was kept constant so that primary and recency effects could be taken into account. The order of presentation of the different lists changed between subjects so no list was susceptible to practice effects or fatigue effects.

One of the purposes of using the verbal recall tests was to determine whether the patient groups would manifest impairments, compared with the control subjects. Dease (1959, 1960) and Jenkins et al (1958) found that when associative connections exist between words presented in a list, the mean recall score is increased. Dease (1959) reported that inter-item associative strength was positively correlated at 0.88 with the number of words recalled per list, and correlated negatively at 0.48 with the number of extra-list intrusions in recall. This test was used to examine whether associative connections would benefit the schizophrenic and manic patients in recall to the same extent as control subjects.

d) Premorbid IQ

The National Adult Reading Test (NART) (Nelson 1978) was developed to assess impairment in intellectual functioning in dementia. Until its development the method of estimating deterioration in functioning was to compare 'hold' and 'non-hold' tests. However, this was rather unsatisfactory due to the wide range in abilities which can occur in many individuals.

Nelson and McKenna (1975) showed that word reading ability and general intelligence were highly correlated (r=0.75) in a group of 98 normal adults using the WAIS FSIQ and the Schonell Graded Word Reading Test (GWRT) score. A regression equation was extracted from the normative data to enable a WAIS FSIQ to be predicted from the score on the GWRT. Testing a group of dementing patients showed that word reading ability was well maintained.

Nelson found that the GWRT did not contain enough difficult items to produce a reliable estimate of the higher IQ levels. On the basis of this, the NART was constructed and standardized. The NART aims to provide an estimate of premorbid IQ levels by providing a sensitive measure of previous familiarity with words. All the words contained in

the NART are irregular and therefore, their pronunciation cannot be inferred from phonetic knowledge but only from familiarity. The NART consists of fifty words printed in order of increasing difficulty.

The words were selected from an initial list of one hundred and forty irregular words used in a pilot study with twenty-five non-dementing patients with extra-cerebral disorders, and ten relatives of out-patients. The NART was standardized using one hundred and twenty in-patients with extra-cerebral disorders. Seven WAIS subtests and the GWRT were also administered. The reliability of the NART was assessed by a split-half coefficient (Cronbach alpha) which gave a reliability technique of 0.93.

Nelson and O'Connell (1978) administered the NART and the GWRT to forty patients with bilateral cortical atrophy. The atrophy group had a lower mean WAIS score than the one hundred and twenty patients used in the standardization study. The two groups scored closer in the NART than in the GWRT, suggesting that the NART is even more resistant to the effects of dementing processes.

The NART is a relatively quick test to administer, and does not demand prolonged concentration or motivation. Nelson reported that it is suitable for depressed patients and other psychiatric patients. Although the data are not available of NART scores with different

psychiatric illnesses, Nelson stated that 'there is no reason to suppose that word reading ability would be impaired by psychiatric disorders'. Scores on the NART were correlated with years of education for all patient groups used in this study.

e) Handedness

The Edinburgh Handedness Inventory was used to assess lateral dominance. Lateral dominance is the preferred use and superior ability of one side of the body. Information about laterality can be used as a non-invasive way to infer cerebral dominance in patients. Richardson (1978) showed that manual preference is strictly unidirectional.

Laterality assessment procedures possess good reliability coefficients ranging from 0.78 to 0.88 for hand dominance. McMeekan and Lishman (1975) reported a test-retest reliability of 0.97 on seventy-three subjects retested after fourteen weeks using the Edinburgh Handedness Inventory. Sherman et al (1976) reported a reliability coefficient of 0.97 for a handedness questionnaire, and a correlation of 0.96 between this questionnaire and a handedness performance measure, providing validatory evidence.

In one-tenth of the population, left hemisphere dominance is absent (Zanghill 1960, Palmer 1964). The ambidextrous, left-handed populations are heterogeneous for lateral specialisation (Benton 1962). Some 60% have predominant language functions in the left hemisphere and about 40% have the opposite organization.

5.5 Procedure

ERP recordings and smooth pursuit eye tracking recordings were obtained from the subjects in the first instance. Patients were then interviewed by a psychiatrist for the purpose of completing the symptom severity rating scales. This took about one hour. The battery of psychology tests was administered subsequently. This took approximately one and a half hours.

For the ERP recordings, subjects were seated in a comfortable reclining armchair in a darkened sound-attenuated room. The electrodes were attached and the impedances checked. Ear-phones were placed on the subject. The subject was told that he would hear low pitched tones interspersed occasionally with high pitched tones, and that he was required to count the high pitched tones. He was told that he would be asked at the end of the trial how many high tones he had heard. The subject was instucted to relax and to keep as still as possible during

the test. The arm chair was set in a reclining position, and the light was dimmed. The sequence of tones was initiated and it continued until 400 tones had been presented. The subject's average responses to the high and low pitched tones as stored in the two channels were plotted out. The memory channels were cleared and the impedance was rechecked. A second trial was then carried out using the same procedure. After completion of the second trial, the ear-phones and electrodes were removed.

The subject then moved into the adjoining room for the eye tracking recording. He was seated facing a VDU, and electrodes were attached. He was instructed to follow the moving target which would appear on the VDU keeping his head still and following the target with his eyes only. He was told to follow the target as smoothly and accurately as possible and to try not to blink. The light was dimmed, and the trial was initiated by presenting a target moving at the speed of 0.2 cycles/sec. The subject's eye movements were recorded for 10 - 15 sweeps approximately, and then the speed of the target was reset to 0.4 cycles/sec, and his eye movements were recorded at this speed in the same way. The same procedure was followed for recording samples of eye movements at 0.6, 0.8, 1.0 and 0.4 (repeated) cycles/sec. The electrodes were then removed.

The cognitive tests were administered in a comfortable sitting-room which was adjacent to the two physiology recording rooms. The order in which the tests were administered was random so that performance on any specific tests would not be affected by factors such as fatigue, decline in motivation, or decline in anxiety. The subject and the tester were seated in armchairs and a table was used to place cards etc upon. All the tests except the Stroop Test required verbal responses. The tester recorded all the subject's responses. The Stroop Test was administered using a micro-computer, which was in the same room. The procedure for administering the Stroop Test has already been described in section 5.4.iv. The tester initiated the Stroop Test, and changed the condition during the test by using a prewritten program which was stored on floppy disc.

5.6 Hypotheses

The hypotheses of the study were that

i The P3 latencies of the schizophrenic and bipolar groups would be significantly prolonged compared with control subjects.

ii There would be no differences between the P3 latencies of the schizophrenic and bipolar groups.

iii There would be no differences between the P3 latencies of the unipolar depressed and control groups.

iv The P3 amplitudes of the schizophrenic, bipolar manic, bipolar depressed and unipolar depressed groups would be significantly reduced compared with the control subjects.

v ETD would be greater in the schizophrenic group than in the control group.

vi The schizophrenic and bipolar manic group would show impairments in tests of association, conceptulization and recall of related items compared with control groups.

vii The cognitive performance of the bipolar depressed group would be more similar to the bipolar manic group than to the unipolar depressed group.

viii The unipolar depressed group would show a similar performance to control subjects on tests of association and conceptualization, but would be impaired on memory and reaction time tests.

ix P3 latency would correlate with measures of association, conceptualization and memory in schizophrenic and bipolar subjects.

x P3 amplitude would correlate with state and state dependent measures of cognitive functioning in all patient groups.

5.7 Statistical Analyses

Two way analyses of variance with groups and sex as factors were used to compare differences in P3 latency. P3 amplitude, ETD, premorbid IQ, present IQ and difference in IQ. Scores on cognitive tests were compared between groups using one way analyses of covariance using age and IQ as covariates. Kruskal-Wallis analyses of variance were used when non-parametric tests were indicated. Inter-test correlations for all the groups were analysed using Pearson Product Moment corelations or Spearman non-parametric correlations. Correlations between physiological measures and scores on the cognitive tests were analysed using Pearson Product Moment Correlations, or Non-Parametric Correlations when the data required this. Factor analysis was carried out to combine the correlations between the cognitive tests, producing 2 factors. Factor scores were compared between the groups using one way analyses of variance.

Chapter 6

STUDY I RESULTS AND DISCUSSION

6.1 Results

i Description of subjects on physiological variables

The means and standard deviations for the physiological variables by group are presented in Table 6A. Two way analyses of variance (Group by Sex) were used, as the sex ratios were significantly different for the groups (see Table 5A). Tables of the analyses of variance are presented in Appendix A3. Scheffe's range tests were used to show which differences between groups reached significance.

TABLE 6A
DESCRIPTION OF SUBJECTS ON PHYSIOLOGICAL VARIABLES, MEANS (STANDARD DEVIATIONS)

	1 Schizophrenic 24	2 Bipolar Manic 10	3 Bipolar Depressed 10	4 Unipolar Depressed 10	5 Controls 24	p
P3 latency (msec)	346.1 (43.5)	353.9 (47.8)	359.9 (41.7)	319.4 (25.4)	300.5 (25.1)	.000 1=2=3>4=5
P3 amplitude	32.1 (18.2)	55.6 (25.7)	55.1 (20.5)	71.1 (28.3)	52.1 (16.5)	.0001 1=5<4
Signal: Noise Ratio (SPEM)	443.5 (121.2)	399.3 (151.7)	389.3 (131.6)	417.7 (147.7)	494.8 (115.1)	.18

As was expected, P3 latency was significantly longer for the schizophrenic and bipolar groups than for the control and unipolar groups ($F=7.04$, $df=4,72$). However, P3 amplitude was significantly higher for the unipolar depressed group than for the schizophrenic and control group ($F=8.82$, $df=4,72$). P3 amplitiude of the unipolar depressed and bipolar groups were not significantly different. Signal : noise ratio was not significantly different between the groups.

No sex differences and no interaction effects (Group by Sex) were found for P3 latency, P3 amplitude or signal : noise ratio.

ii Description of subjects on IQ scores

Means and standard deviations of the IQ scores for the groups are presented in Table 6B. Two way analyses of variance (Group by Sex), followed by Scheffe's range tests, showed that levels of premorbid IQ, present IQ and difference between premorbid IQ and present IQ were significantly different between the groups. Tables of the analyses of variance are shown in Appendix A3.

TABLE 6B

DESCRIPTION OF SUBJECTS ON IQ SCORES, MEANS (STANDARD DEVIATION)

	1 Schizophrenic 24	2 Bipolar Manic 10	3 Bipolar Depressed 10	4 Unipolar Depressed 10	5 Controls 24	p
Premorbid IQ (NART)	108.2 (12.7)	109.2 (15.2)	116.7 (9.5)	109.6 (9.2)	121.2 (5.2)	.001 >1<5
Current IQ (WAIS)	101.3 (16.3)	98.4 (20.2)	102.5 (9.9)	98.8 (9.7)	122.3 (11.8)	.0001 1=2=3 =4<5
(N)IQ Diff (NART V IQ)	9.2 (9.6)	12.6 (10.6)	14.2 (9.0)	12.0 (7.1)	3.3 (4.2)	

NART = National Adult Reading Test

WAIS = Wechsler Adult Intelligence Score

The schizophrenic subjects had a lower premorbid IQ level than the control subjects ($F=5.45$, $df=4,77$). The schizophrenic and all the affective disorder groups had lower present IQ scores than the control group ($F=9.14$, $df=4,77$). The bipolar depressed group showed a significantly greater decline in IQ than the control group ($F=4.28$, $df=4,77$).

No sex differences and no interaction effects (Group by Sex) were found for any of the IQ scales.

Having determined that there were no sex differences for age, physiological variables and IQ scores, subjects were not classified by sex for the remaining analyses. This would have resulted in groups consisting of a small number of subjects in some cases. However, the differences in age and IQ which were found between the groups were controlled for in further analyses. Level of premorbid IQ was used as the controlling variable. Premorbid IQ minus present IQ gives an estimate of how much intellectual deterioration has occured since onset of illness. This study aimed to examine the extent of this deterioration in the patient groups as compared with the control group and to consider the effect this deterioration has on cognitive functioning. The performance of the patient groups was compared with the control group on cognitive tests with respect to their premorbid level of IQ. Controlling for present IQ levels would obscure the deterioration in cognitive skills which the study aimed to examine. It

was expected that the schizophrenic subjects would possess some abilities which had remained at their premorbid level of functioning. To control for current IQ in the schizophrenic subjects would be inappropriate as this would not take into account the decline in IQ in the schizophrenic subjects.

iii Performance of groups on cognitive tests

The means and standard deviations of the performance of the schizophrenic, affective disorder and control groups on the cognitive tests are presented in Table 6C. Correlation coefficients of clinical rating scores with performance on the cognitive tests are presented in Appendix A2. One way analyses of covariance with age and premorbid IQ as covariates, followed by Scheffe's range tests were used. Age and IQ were used as covariates where they correlated with performance on cognitive tests for each group of subjects (Appendix A4).

TABLE 6C

ANALYSES OF VARIANCE COMPARING SUBJECTS' PERFORMANCE ON COGNITIVE TESTS, SHOWING MEANS (STANDARD DEVIATIONS) ; USING IQ AND AGE AS COVARIATES WHERE IQ (+) AND AGE (A) CORRELATED WITH COGNITIVE TEST

	1	2	3	4	5	p
	Schizo-phrenic	Bipolar Manic	Bipolar Depressed	Unipolar Depressed	Controls	
	24	10	10	10	24	
WCST (+A)	18.6 (12.6)	19.8 (13.2)	20.6 (13.5)	22.7 (18.1)	9.5 (3.3)	.82
WEFT (+A)	4.8 (2.3)	4.8 (2.3)	5.2 (2.5)	3.2 (1.2)	8.6 (2.1)	.000 1=2=3=
W/A Freq	23.0 (5.6)	21.6 (6.0)	22.1 (6.5)	26.3 (5.7)	26.7 (5.8)	.06
W/A Pair-Ass part II	9.1 (1.1)	8.4 (1.8)	9.2 (1.4)	9.7 (1.5)	10.6 (0.7)	.000 1=2<5
V/R Emotive (+A)	7.9 (2.2)	8.4 (2.8)	8.8 (1.6)	7.4 (2.7)	12.2 (1.1)	.001 1=2=4<
V/R Category (+A)	10.5 (3.1)	10.6 (2.6)	11.9 (3.4)	10.9 (3.2)	15.9 (2.6)	.001 1=2=4<
V/R Isolates	1.3 (1.2)	1.2 (0.9)	1.6 (1.0)	1.0 (0.9)	2.3 (1.1)	.008 (K-W)
V/R Total (+A)	30.3 (8.6)	31.9 (9.6)	33.4 (7.6)	30.5 (8.4)	47.6 (8.5)	.000 1=2=3=
Stroop r.t. col. (+A)	1.54 (1.14)	1.61 (0.56)	1.70 (1.68)	1.85 (1.84)	0.88 (0.16)	.90
Similarities (A)	9.9 (2.6)	8.9 (2.8)	10.8 (2.4)	10.2 (2.2)	13.2 (1.9)	.009 1=2<5
Digit Span (+)	10.3 (3.2)	10.1 (4.1)	11.5 (2.5)	9.0 (2.4)	14.3 (2.9)	.02

WCST = Wisconsin Card Sorting Test
WEFT = Witkins Embedded Figures Test
W/A freq = Word Association Frequent Responses
W/A Pair-Ass part II = Word Association Paired Associate Part 2
V/R Emotive = Verbal Recall Emotive (Positive, Negative) words
V/R Category = Verbal Recall Category ('Animals', 'Education') words
Isolates = Verbal Recall Isolates
V/R Total = Verbal Recall Total Words Recalled
Stroop r.t. col = Stroop Test reaction time for colours

Tables of the analyses of variance are presented in Appendix A5. Performance on the Wisconsin Card Sorting Test was not significantly different between the groups after the effects of age and IQ had been controlled for. However, on the Witkins Embedded Figures Test, the control group's performance was superior to that of all patient groups ($F=16.613$, $df=4,74$).

In the Word Association tests, the differences between the groups approached significance. The numbers of frequent responses given were similar in the control group and unipolar group and greater than in the schizophrenic and bipolar groups ($F=2.39$, $df=4,75$). The frequency rank scores of the responses given by the groups were just significantly different ($p<.05$, $F=2.49$, $df=4,75$). While part I of the Paired-Associates Test was not significantly different between the groups, the schizophrenic and manic patients performed significantly worse than the control group in part II ($X^2=23.29$, $df=76$).

Comparison of the total number of words recalled in the verbal recall tests showed that the control subjects scored significantly higher than all the patient groups ($F=7.77$, $df=4,76$). The performance of the control subjects was superior to that of the schizophrenic, bipolar manic and unipolar subjects but not the bipolar depressed subjects in the recall of emotive words ($F=5.13$, $df=4,76$) and in the recall of category words ($F=5.55$, $df=4,76$).

Reaction time in the Stroop Test was not significantly different between the groups in either the words condition ($p=.94$, $F=0.2$, $df=4,70$) or in the colours condition ($F=.03$, $df=4,72$). The numbers of errors made in the Stroop Test were not significantly different for the word condition ($p=.7$, $X=2.20$, $df=72$) or for the colours condition ($p=.6$, $X=1.79$, $df=71$).

The schizophrenic and manic groups were significantly impaired in the Similarities Test compared with the control subjects ($F=3.67$, $df=1.77$). However, on the Digit Span Test, the schizophrenic and unipolar group were significantly impaired compared with the control group ($F=3.32$, $df=1.77$).

In summary the schizophrenic and manic subjects were significantly impaired in the Witkins Embedded Figures Test, all the verbal recall tests and the Similarities Test, compared with the control group. The unipolar depressed group showed similar impairment in the Witkins Embedded Figures Test, and the verbal recall tests, and impairment in the Digit Span Test but not the Similarities Test. The bipolar depressed group was impaired in the Witkins Embedded Figures Test and in the total number of words recalled.

Inter-test correlations were examined for the patient groups(Table 6D, Table 6E and Appendix A6). Errors on the Wisconsin Card Sorting Test correlated with score on the Similarities test and with total number of words recalled in all groups. Score on the similarities test correlated significantly with score on the Witkins Embedded Figures Test and total number of words recalled in the verbal recall tests in all groups.

TABLE 6D
INTER-TEST CORRELATION COEFFICIENTS FOR SCHIZOPHRENIC PATIENTS (n=24)

	WCST	WEFT	FREQ	PAIR	RCTOT	ERRORS	SIMIL	DIG SP	ST RT	S:N
P3 latency	.36*	-.46*	-.26	-.34*	-.26	-.46*	-.25	.02	.33	-.02
Signal :Noise Ratio (S:N)	-.34*	.26	.14	.23	.49**	-.01	.23	.10	-.27	
Stroop reaction time colour (STRT)	.68**	-.39	-.29	-.22	-.51*	.05	-.48**	-.43*		
Digit Span (DIG SP)	-.65**	.28	.34*	.27	.28	.04	.71**			
Similarities (SIMIL)	-.81**	.38*	.40*	.32	.49**	-.20				
Verbal Recall Errors (ERRORS)	.03	-.17	-.17	-.14	-.04					
Verbal Recall Total (RCTOT)	-.66**	.35*	.16	.05						
Paired-Assoc. Part II (PAIR)	-.22	.17	.48**							
Word Assoc. Frequent (FREQ)	-.45*	.10								
Witkins Embed. Figures (WEFT)	-.43									

Pearson Correlations P3 latency, S:N, STRT, DIGSP, SIMIL, RCTOT, FREQ, WEFT, WCST
Spearman Correlations ERRORS, PAIR

(*p <.05, ** p <.01)

TABLE 6E
INTER-TEST CORRELATION COEFFICIENTS FOR BIPOLAR MANIC SUBJECTS (n=10)

	WCST	WEFT	FREQ	PAIR	RCTOT	ERRORS	SIMIL	DIG SP	ST RT	S:N
P3 latency	.67*	-.26	-.40	-.50	-.79	-.13	-.64*	-.74**	.87**	-.13
Signal:Noise Ratio (S:N)	-.35	-.73**	-.35	-.27	.04	-.43	-.50	-.30	-.17	
Stroop reaction time colour (STRT)	.85**	-.23	-.53	-.61	-.62	.13	-.61	-.49		
Digit Span (DIGSP)	-.44	.41	.12	.28	.77**	-.02	.56*			
Similarities (SIMIL)	-.55	.59*	.71*	.89**	.65*	.34				
Verbal Recall Errors (ERRORS)	.19	.41	.53	.33	-.08					
Verbal Recall Total (RCTOT)	-.86**	.45	.31	.49						
Paired-Associates part II (PAIR)	-.80**	.39	.88**							
Word Association Frequent (FREQ)	-.65	.59								
Witkins Embedded Figures (WEFT)	-.31									

Pearson Correlations P3 latency, S:N, STRT, DIGSP, SIMIL, FREQ, WEFT, WCST
Spearman Correlations ERRORS,PAIR

(* p<.05 ** p<.01)

TABLE 6E (cont.)

INTERTEST CORRELATION COEFFICIENTS FOR BIPOLAR DEPRESSED SUBJECTS (n=10)

	WCST	WEFT	FREQ	PAIR	RCTOT	ERRORS	SIMIL	DIGSP	STRT	S:N
P3 latency	-.05	.26	-.09	.22	.40	-.04	.18	.41	-.11	-.19
Signal : Noise Ratio (S:N)	-.43	.47	-.21	-.18	.56	.60*	.42	.07	-.38	
Stroop reaction time colours (STRT)	.53	-.49	-.42	-.02	-.56	.05	-.71*	-.40		
Digit Span (DIGSP)	-.67*	.33	.37	.27	.20	-.11	.75**			
Similarities (SIMIL)	-.90**	.67*	.35	.58*	.57*	-.23				
Verbal recall errors	.11	-.02	-.29	-.23	-.09					
Verbal recall total (RCTOT)	-.68*	.83**	-.41	.50						
Paired Associates Part II (PAIR)	-.55	.47	.25							
Word Association Frequent (FREQ)	-.14	-.24								
Witkins Embedded Figures (WEFT)	-.64*									

(* p<.05, ** p<.01)

Pearson Correlations : P3latency, Signal : Noise Ratio, Stroop reaction time, Digit Span, Similarities, Verbal Recall totAL, Word Association Frequent Responses, Witkins Embedded Figures Test

Spearman Correlations : Verbal Recall errors, Paired Associates Part II

In the schizophrenic and bipolar manic group errors on the Wisconsin Card Sorting Test also correlated with Stroop Test reaction time and frequent responses in the Word Association Test. In the schizophrenic and manic groups, frequent responses in the Word Association Test correlated with Paired Associates part II. In the bipolar depressed group errors on the Wisconsin Card Sorting Test correlated with digit span. In the unipolar depressed group errors on the Wisconsin Card Sorting Test correlated with errors in the verbal recall tests, Stroop test reaction time and Paired- Associates Part II.

iv Correlations of physiological measures with cognitive scores

The numbers of correlations used in the analysis totalled 15 cognitive variables with each of the three physiological variables. Therefore 2 correlations for each group of subjects may be expected to reach significance at the level of $p < .05$ by chance alone. This suggests that some caution need be used when interpreting these correlations. However, due to the small number of subjects in the affective disorder groups ($n = 10$), the significance of some of the correlations pertinent to these groups may be obscured.

Pearson Product Moment Correlations between P3 latency and state rating measures and IQ scores for the different groups are presented in table 6F.

TABLE 6F

PEARSON CORRELATION COEFFICIENTS OF P3 LATENCY WITH AGE, STATE VARIABLES AND IQ SCORES FOR GROUPS

	1	2	3	4	5
	Schizophrenic	Bipolar Manic	Bipolar Depressed	Unipolar Depressed	Controls
	24	10	10	10	24
Age	.56**	.42	.23	.31	.23
BPRS					
Thought Disorder	.46**				
Anxiety/Depression	.19				
Withdrawal	.41*				
Hostility	-.06				
HRSD	.22		.27	.05	
MMSRS		-.03			
NART IQ	-.11	-.84**	.24	-.14	-.14
WAIS IQ	-.14	-.73**	.29	-.07	-.11
IQ Difference	.04	.02	-.25	-.12	.02

(* $p<.05$, ** $p<.01$)

BPRS = Brief Psychiatric Rating Scale

HRSD = Hamilton Rating Scale for Depression

MMSRS = Modified Manic Rating Scale

NART = National Adult Reading Test

WAIS 0 Wechsler Adult Intelligence Scale

In the schizophrenic group, significant correlations were found for P3 latency with thought disorder and with withdrawal. For the affective disorder patients, no significant correlations for P3 latency with state severity measures were found.

Correlations between P3 latency and IQ scores were negative for all groups except the bipolar depressed group. The only significant correlations found were for P3 latency with premorbid IQ and present IQ in the bipolar manic group increasing P3 latency was associated significantly with decreasing IQ.

Correlations of P3 latency with performance on cognitive tests are presented in Table 6G.

TABLE 6G

PEARSON & SPEARMAN CORRELATION COEFFICIENTS OF P3 LATENCY WITH COGNITIVE VARIABLES FOR ALL GROUPS

	1	2	3	4	5
	Schizophrenic	Bipolar Manic	Bipolar Depressed	Unipolar Depressed	Controls
	24	10	10	10	24
WCST	.36*	.24+	-.05	.38	-.00
WEFT	-.46*	-.26	.26	.21	-.28
WIA Freq.	-.26	-.40	-.09	-.11	.33
W/A Pair Ass.I (Spearman)	-.34*	-.14	-.15	.06	-.07
W/A Pair Ass.II (Spearman)	-.26	-.50+	.22	-.18	-.01
V/R Emotive	-.22	-.71+	.58*	-.52	.22
V/R Category	-.28	-.55+	.48	.03	-.08
V/R Total	-.26	-.79**+	.40	-.30	-.06
V/R Errors	.46*	-.13	-.04	.59*	.36*
Stroop r.t.	.36*	.87*+	-.21	.10	-.17
Similarities	-.25	-.64*+	.18	-.08	-.11
Digit Span	-.02	-.74*+	.41	-.08	-.10

+ indicates that IQ was partialled out

(**p<.01, *p<.05))

WCST = Wisconsin Card Sorting Test
WEFT = Witkins Embedded Figures Test
W/A Freq = Word Association Frequent Responses
W/A Pair Ass I = Word Association Paired Associates Test Part I
W/A Pair Ass II = Word Association Paired Associates Test Part II
V/R Emotive = Verbal Recall Emotive(Positive and Negative words)
V/R Category = Verbal Recall (Animals and Education) words
V/R Total = Total Number of words recalled
V/R Errors = Verbal Recall Errors
Stroop r.t. = Stroop Test Reaction Time

For the schizophrenic group, the significant correlations were found for P3 latency with errors made on the Wisconsin Card Sorting Test, scores on the Witkins Embedded Figures Test, Paired-Associates Test part I, errors made in the verbal recall tests, and Stroop Test reaction time. The correlation of P3 latency with errors made on the Wisconsin Card Sorting Test for the schizophrenic group is presented in Figure 6a.

Partial correlations controlling for IQ were used for the bipolar manic group due to the significant correlation between P3 latency and IQ. Significant correlations were found for P3 latency with performance on the verbal recall tests, similarities, digit span and reaction time on the Stroop Test.

In the bipolar depressed group, the only significant correlation was for P3 latency with number of emotive words recalled in the verbal recall tests. The direction of the correlation shows that recall increases with P3 latency in this group.

In the unipolar depressed group and the control group, the only significant correlation for P3 latency was with errors made in the verbal recall tests.

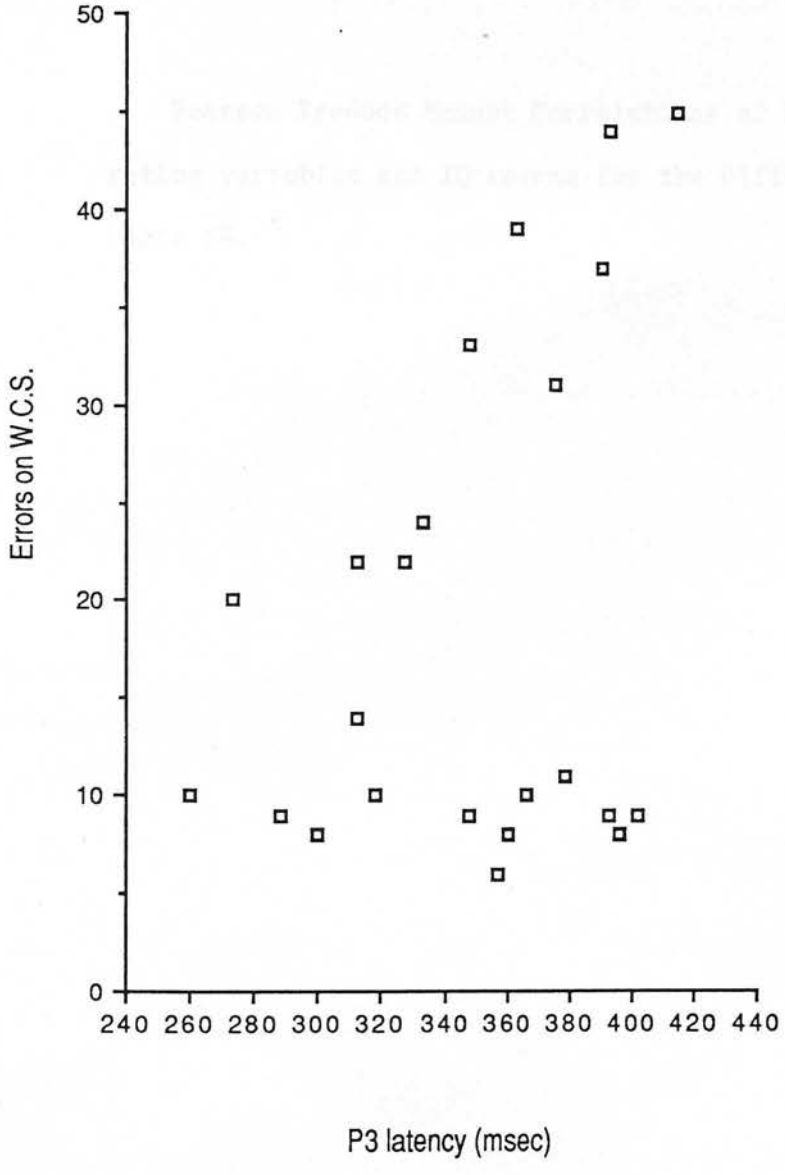

Figure 6a : Plot of Errors on Wisconsin Card Sort Test (W.C.S) by P3 latency for Schizophrenic subjects

Pearson Product Moment Correlations of P3 amplitude with state rating variables and IQ scores for the different groups are shown in Table 6H.

TABLE 6H

PEARSON CORRELATION COEFFICIENTS OF P3 AMPLITUDE WITH AGE, STATE VARIABLES AND IQ SCORES FOR GROUPS

	1	2	3	4	5
	Schizophrenic	Bipolar Manic	Bipolar Depressed	Unipolar Depressed	Controls
	24	10	10	10	24
Age	-.29	-.12	-.16	-.05	
BPRS					
Thought Dis	-.12				
Anxiety/Dep	-.09				
Withdrawal	.00				
Hostility	-.02				
HRSD	-.14		-.74*	.37	
MMSRS		-.60*			
NART IQ	-.21	.05	.12	-.48	-.06
WAIS IQ	.07	.52	.61*	.17	.05
IQ Diff.	-.23	-.59*	-.54*	-.22	-.06

(* $p < .05$)

BPRS = Brief Psychiatric Rating Scale

HRSD = Hamilton Rating Scale for Depression

MMSRS = Modified Manic State Rating Scale

NART = National Adult Reading Test

WAIS = Wechsler Adult Intelligence Scale

Significant negative correlations of P3 amplitude were found for the bipolar manic subjects with scores on the MMSRS, and for the bipolar depressed subjects with scores on the HRSD indicating severity of illness with decreasing P3 amplitude. The correlations of P3 amplitude with IQ scores showed a significant positive correlation with present IQ for the bipolar depressed group indicating increasing current IQ with increasing, P3 amplitude. P3 amplitude correlated significantly with premorbid IQ minus present IQ for the bipolar manic and bipolar depressed group, showing that a decline in IQ is associated with decreasing P3 amplitude in these two groups.

Correlations between P3 amplitude and performance on cognitive tests for the different groups showed only two significant correlations, with part I of the Paired-Associates Test for the schizophrenic subjects and with digit span for the bipolar depressed group (Table 6J).

TABLE 6J

PEARSON & SPEARMAN CORRELATION COEFFICIENTS OF P3 AMPLITUDE WITH COGNITIVE VARIABLES BY GROUPS

	1 Schizophrenic 24	2 Bipolar Manic 10	3 Bipolar Depressed 10	4 Unipolar Depressed 10	5 Controls 24
WCST	-.11	.09	-.36	.27	.22
WEFT	.03	.40	.04	.26	.08
WIA Freq.	.18	-.06	.41	.13	.16
W/A Pair Ass I (Spearman)	.29	.28	.15	.06	-.01
W/A Pair Ass II (Spearman)	.40*	-.28	-.10	-.07	-.01
V/R Emotive	.07	.39	-.29	-.24	.09
V/R Category	-.00	.08	-.27	.07	
V/R Total	-.01	.27	-.01	-.20	.08
V/R Errors (Spearman)	-.21	-.15	-.21	.53	-.04
Stroop r.t.	-.24	.12	-.54	-.16	-.14
Similarities	.10	.31	.44	.15	.06
Digit Span	-.00	.52	.58*	.08	.00

(*p <.05)

WCST = Wisconsin Card Sorting Test
WEFT = Witkins Embedded Figures Test
W/A Freq. = Word Association Frequent Responses
W/A Pair Ass I = Word Association Paired Associates Part I
W/A Pair Ass II = Word Association Paired Associates Part II
V/R Emotive = Verbal Recall Emotive (Positive and Negative) words
V/R Category = Verbal Recall Category (Animals and Education) words
V/R Total = Verbal Recall Total words
V/R Errors = Verbal Recall Errors
Stroop r.t. = Stroop Test Reaction Time

Correlations of signal : noise ratio (SPEM) with state rating measures and IQ scores are presented in Table 6K.

TABLE 6K

PEARSON CORRELATION COEFFICIENTS OF SIGNAL : NOISE RATIO (SPEM) WITH AGE, STATE RATINGS AND IQ SCORES FOR GROUPS

	1	2	3	4	5
	Schizophrenic	Bipolar Manic	Bipolar Depressed	Unipolar Depressed	Controls
	24	10	10	10	24
Age	-.09		-.66*		
BPRS Thought Dis	-.41*				
Anxiety Dep	.11				
Withdrawal	-.23				
Hostility	-.03				
HRSD	.10		-.76*	-.09	
MMSRS		.59			
NART IQ	.16	.09	.20	.49	.40
WAIS IQ	.17	-.41	.14	-.20	.35
IQ Diff. (NART-WAIS)	.04	.72*	.00	.48	-.31

(* P<.05)

BPRS = Brief Psychiatric Rating Scale

HRSD = Hamilton Rating Scale for Depression

MMSRS = Modified Manic State Rating Score

NART = National Adult Reading Test

WAIS = Wechsler Adult Intelligence Scale

Significant negative correlations were found for signal : noise ratio with thought disorder in the schizophrenic subjects, and with depression in the bipolar depressed subjects indicating higher pathology with decreasing signal : noise ratio. A significant correlation was found between signal : noise ratio and premorbid IQ minus present IQ for the bipolar manic subjects indicating increasing signal : noise ratio with greater decline in IQ.

TABLE 6L

PEARSON & SPEARMAN CORRELATION COEFFICIENTS OF SIGNAL : NOISE RATIO (SPEM) WITH COGNITIVE VARIABLES FOR GROUPS

	1	2	3	4	5
	Schizophrenic	Bipolar Manic	Bipolar Depressed	Unipolar Depressed	Controls
	24	10	10	10	24
WCST	-.34*	-.35	-.43	-.55	-.34*
WEFT	.26	-.73*	.47	.12	.31
WIA Freq.	.14	-.35	-.21	-.27	-.23
W/A Pair Ass.I (Spearman)	.23	-.74*	-.35	.27	.24
WIA Pair Ass.II (Spearman)	.21	-.27	-.18	.21	-.14
V/R Emotive	.58**	.19	.32	-.05	.28
V/R Category	.29	-.21	.54	.16	.36*
V/R Total	.49**	.04	.56	.02	.37*
VIR Errors (Spearman)	-.01	-.43	.60	.31	-.37*
Stroop r.t.	-.30	-.01	-.39	-.56	-.15
Similarities	.23	-.50	.42	.30	.10
Digit Span	.10	-.30	.07	-.57*	.41*

(* p<.05 ** p<.01)

WCST = Wisconsin Card Sorting Test
WEFT = Witkins Embedded Figures Test
W/A Freq. = Word Association Frequent Responses
W/A Pair Ass.I = Word Association Paired Associate Test
W/A Pair Ass II = Word Association Paired Association Part II
V/R Emotive = Verbal Recall Emotive (Positive and Negative) words
V/R Category = Verbal Recall Category (Animals and Education) words
V/R Total = Total Number of Words Received
Stroop r.t. = Stroop Test Reaction Time

Correlations of signal : noise ratio with performance on cognitive tests in the schizophrenic group show significant correlations with errors made on the Wisconsin Card Sorting Test, recall of emotive words and total number of words recalled (Table 6L) indicating decreasing signal : noise ratio with decreasing performance on the cognitive tests. For the bipolar manic group, significant correlations were found between signal : noise ratio and score on the Witkins Embedded Figures Test and on the Paired-Associates Test part I, with a poor signal : noise ratio being associated with good performance on the cognitive tests. In the unipolar depressed group, a single significant correlation was found, between signal : noise ratio and digit span, indicating that good signal : noise ratio is associated with impaired digit span. In the control group, significant correlations were found for signal : noise ratio with errors made on the Wisconsin Card Sorting Test, recall of category words, total number of words recalled, number of errors made in verbal recall and digit span, indicating increasing signal : noise ratio with increasing performance on the cognitive tests.

v. Sub-groups within the schizophrenic group

The plot of P3 latency by number of errors made on the Wisconsin Card Sorting Test in schizophrenic subjects (Figure 6a) indicates that performance on the Wisconsin Card Sorting Test may serve to divide schizophrenic subjects into two groups.

Schizophrenic subjects who perform poorly on the Wisconsin Card Sorting Test appear to show a highly significant correlation of this performance with P3 latency, showing increasing P3 latency with increasing number of errors. Schizophrenic subjects who perform well on the Wisconsin Card Sorting Test showed no such association. The schizophrenic group was divided into two subgroups using the mean plus two standard deviations of errors made on the Wisconsin Card Sorting Test for the control group (16.1) as a cut-off point. This resulted in 14 schizophrenic subjects falling into the Good Wisconsin Card Sorting Test group and 10 subjects falling into the Poor Wisconsin Card Sorting Test group.

The means and standard deviations of the physiological variables, state rating measures and IQ scores for the two subgroups are presented in Table 6M. Tables of the analyses of variance comparing the two sub-groups are shown in Appendix A7.

TABLE 6M

COMPARISONS BETWEEN GOOD AND POOR PERFORMERS
ON THE WISCONSIN CARD SORTING TEST IN SCHIZOPHRENIC GROUP,
MEANS (STANDARD DEVIATIONS)

	1 GOOD WCST 14	2 POOR WCST 10	p (Anova)
Age	27.4 (9.5)	32.5 (11.2)	.28
P3 latency	341.4 (45.0)	352.8 (42.8)	.54
P3 amplitude	28.8 (12.6)	36.8 (23.9)	.30
Signal:Noise Ratio	479.4 (124.9)	393.2 (101.0)	.09
BPRS			
Thought Disorder	2.3 (1.4)	4.7 (4.1)	.06
Anxiety/Depression	1.5 (1.6)	1.1 (1.3)	.56
Withdrawal	3.6 (3.8)	4.5 (2.3)	.52
Hostility	1.5 (1.9)	0.4 (1.0)	.13
HRSD	6.3 (7.4)	4.0 (3.9)	.40
Premorbid IQ (NART)	114.4 (8.5)	101.4 (11.2)	.004
Present IQ (WAIS)	110.6 (10.5)	88.2 (13.8)	.0002
IQ Difference (NART-WAIS)	3.5 (10.8)	11.6 (13.5)	.12

WCST = Wisconsin Card Sorting Test
BPRS = Brief Psychiatric Rating Scale
HRSD = Hamilton Rating Scale for Depression
NART = National Adult Reading Test
WAIS = Wechsler Adult Intelligenc Score

The two subgroups do not differ on age, physiological variables or state severity ratings. However, the Poor Wisconsin Card Sorting Test group have a lower premorbid IQ (F=10.46, df=1.23) and current IQ (F=20.63, df=1.23) than the Good Wisconsin Card Sorting Test group. Analyses of covariance using IQ as a covariate where IQ correlated with performance on the cognitive test, were used to compare the performance of the two subgroups on the cognitive tests (Table 6N)

TABLE 6N

COMPARISON OF PERFORMANCE ON COGNITIVE TESTS OF GOOD AND POOR WCST PERFORMERS SHOWING MEANS (STANDARD DEVIATIONS)(+). IQ USED AS A COVARIATE WHERE IQ CORRELATES WITH COGNITIVE TESTS.

	1 GOOD WCST 14	2 POOR WCST 10	P (Anova)
+ WEFT	5.4 (2.5)	4.0 (1.8)	.16
W/A Freq.	24.9 (3.7)	20.3 (6.9)	.05
W/A Partner	9.0 (1.3)	9.3 (0.9)	.63 (K-W)
+ V/R Emotive + Neutral words	8.9 (2.0)	6.5 (1.7)	.08 .05
+ V/R Category	12.3 (2.5)	8.0 (2.0)	.003
+ V/R Total	35.1 (7.0)	23.4 (5.2)	.005
Stroop r.t.	1.08 (0.16)	2.19 (1.6)	.01
+ Similarities	11.4 (1.0)	7.7 (2.5)	.004
+ Digit Span	12.0 (2.8)	7.9 (2.0)	.024

WCST	=	Wisconsin Card Sorting Test
WEFT	=	Witkins Embedded Figures Test
W/A Freq.	=	Word Association Frequent Responses
W/A Partner	=	Word Association Paired Associates Group
V/R Emotive	=	Verbal Recall Emotive (Positive and Negative) words
V/R Category	=	Verbal Recall Category ('Animal', 'Education') words
V/R Total	=	Verbal Recall Total Words Recalled
Stroop r.t. col	=	Stroop Test Reaction time for colours

The Poor Wisconsin Card Sorting Test group was found to be significantly impaired on the number of frequent responses given in the Word Association Test ($F=4.41$, $df=1,23$), recall of neutral words ($F=4.48$, $df=1,23$), recall of category words ($F=11.70$, $df=1,23$) and total number of words recalled ($F=9.90$, $df=1,23$), reaction time in the Stroop Test for the colours condition ($F=7.00$, $df=1,23$), the Similarities Test ($F=10.18$, $df=1,23$) and in the Digit Span Test ($F=5.89$, $df=1,23$).

TABLE 6P

PEARSON & SPEARMAN CORRELATION COEFFICIENTS OF P3 LATENCY WITH AGE, STATE VARIABLES AND COGNITIVE SCORES FOR GOOD AND POOR WCST PERFORMERS IN SCHIZOPHRENIC GROUP

	1 GOOD WCST	2 POOR WCST	$\bar{z}$
Age	.46	.67	0.43
BPRS Thought Disorder	.34	.57*	0.48
Anxiety/Depression	.38	-.05	0.89
Withdrawal	.50*	.19	0.64
Hostility	.01	-.04	0.10
HRSD	.21	.42	0.43
NART IQ	.03	-.07	0.38
WAIS IQ	.33	-.53	1.79
WCST	-.18	.91**	2.25*
WEFT	-.38	-.57*	0.39
Paired Associates Part II (Spearman)	-.01	-.65*	1.32
Verbal Recall 'Short'	-.51*	-.24	0.56
Verbal Recall Emotive	-.08	-.36	0.58
Verbal Recall Category	-.20	-.39	0.39
Verbal Recall Total	-.17	-.38	0.43
Verbal Recall Errors (Spearman)	.44	.41	0.06
Stroop Reaction time	.70**	.41	0.60

(* $p<.05$ ** $p<.01$)

$\bar{z}$ .1.96 $p<.05$

Correlations of P3 latency with state severity ratings and scores on the cognitive tests for the two subgroups show that in the Poor Wisconsin Card Sorting Test group, P3 latency is significantly correlated with thought disorder, errors made on the Wisconsin Card Sorting Test, score on the Witkins Embedded Figures Test, and score on the Paired-Associates Test part II (Table 6P). In the Good Wisconsin Card Sorting Test group, P3 latency correlates significantly with withdrawal, one of the verbal recall tests (recall of short words) and reaction time in the Stroop Test. A significant difference between the correlations was found only for performance on the Wisconsin Card Sorting Test.

vi Factor analysis using cognitive and physiological variables

Factor analysis was carried out to look at the relationships between variables for all the subjects. Variables were selected to include the physiological variables, IQ variables, and a measure of the different cognitive functions being studied. The following variables were included : word association frequency rank of responses, errors on the Wisconsin Card Sorting Test, score on the Witkins Embedded Figures Test, total number of words recalled in the

verbal recall tests, reaction time in the Stroop Test in the colours condition, premorbid IQ, decrease in IQ, P3 latency and signal : noise ratio (SPEM)

Two factors were extracted by principal components analysis. Together they accounted for 60.2% of the variance. Factor 1 accounted for 45.7% of the variance, and factor 2 for 14.5% of the variance.

The rotated factor matrix, using varimax rotation, produced the following loadings for each variable on the two factors :

	Factor 1	Factor 2
Wisconsin C.S. Test	-.83070	.27787
Premorbid IQ	.82091	-.01737
Total Words Recalled	.81583	-.29043
Stroop Test Reaction Time	-.71388	.23941
Signal : Noise Ratio	.65767	.27426
Witkins Embedded Figures Test	.65065	-.41638
P3 latency	-.46473	.37061
IQ Difference	-.07089	.81584
Word Association Rank	-.12492	.71932

Factor 1 appears to be associated with general ability, with high positive loadings for IQ, memory and score on the Witkins Embedded Figures Test and high negative loading for reaction time and errors made on the Wisconsin Card Sorting Test. The physiological measures also have fairly high loadings on this factor with signal noise ratio accounting for 43% of the variance and P3 latency accounting for 22% of the variance. High signal : noise ratio and short P3 latency are associated with good levels of general ability. The relationship is stronger for the signal : noise ratio than for P3 latency. The cognitive tests which load highly on this factor have all been associated with frontal lobe function, which suggests that signal : noise ratio is predominantly associated with frontal lobe function. This also indicates an association of P3 latency with tests of frontal lobe function.

Decrease in IQ, frequency rank of responses given in the word association test, scores on the Witkins Embedded Figures Test and P3 latency have higher loadings on factor 2 than the other variables. P3 latency accounts for 14% of the variance The factor loadings indicate that a large decrease in IQ, uncommon responses in the word association test, a low score on the Witkins Embedded Figures test and a long P3 latency are associated. This factor may reflect thought disorder manifested in uncommon, bizarre associations, intellectual deterioration and impairment in conceptualization. Thought disorder has been associated with temporal

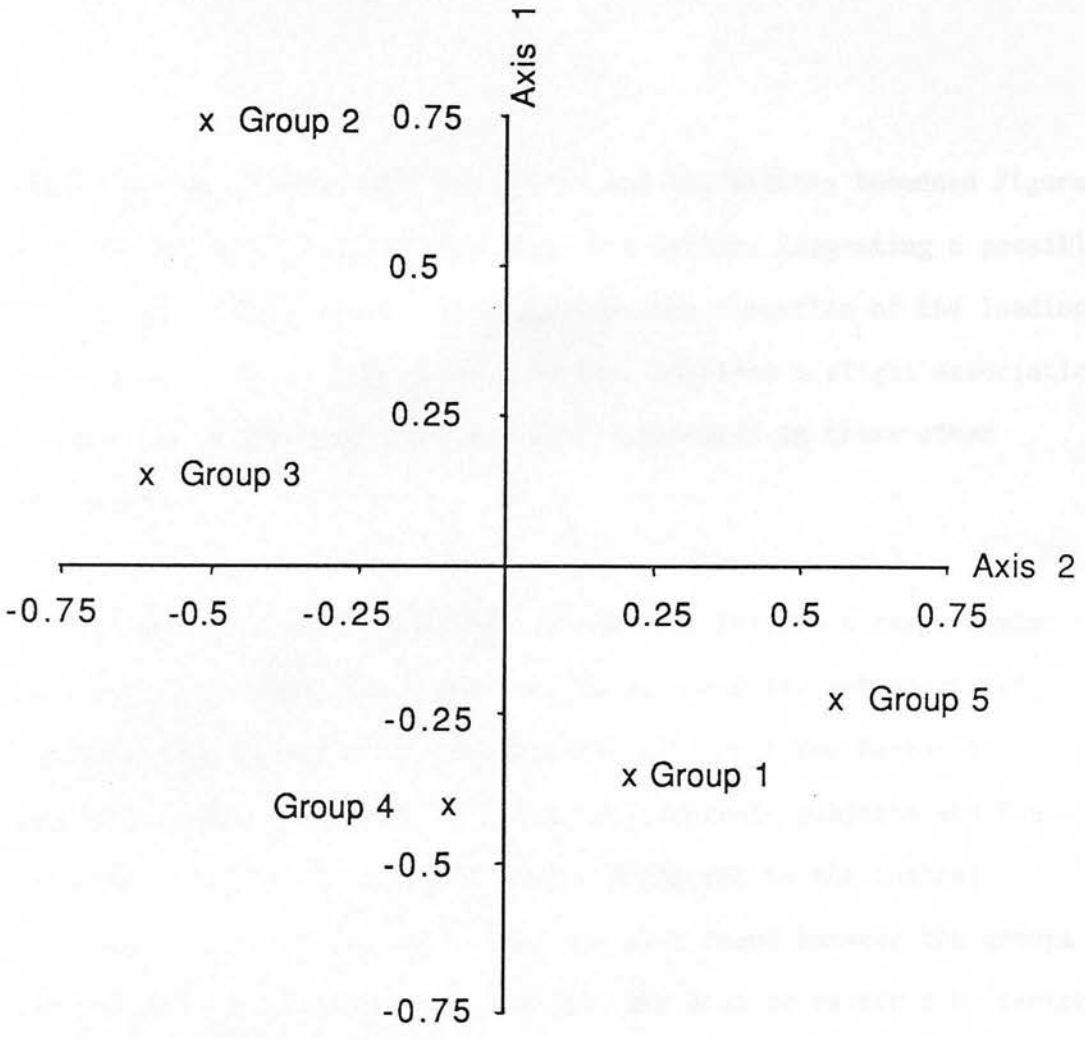

Figure 6b : Plot of factor scores for each group

Groups are: 1. Schizophrenia
2. Controls
3. Unipolar Depressed
4. Bipolar Manic
5. Bipolar Depressed

lobe function as have Word Associates and the Witkins Embedded Figures Test. P3 latency is associated with this factor, suggesting a possible association with temporal lobe function. The direction of the loading for signal : noise ratio on this factor indicates a slight association of good eye tracking performance with impairment in these other variables.

Two way analyses of variance followed by Scheffe's range tests were used to compare the factor scores of the different groups of subjects. The groups were significantly different for factor 1 ($p=.0002$, $F=6.52$, $df=4,65$) with the schizophrenic subjects and the unipolar subjects being significantly different to the control subjects. A significant difference was also found between the groups for factor 2 ($p=.02$, $F=3.04$, $df=4,65$). The plot of factor 1 by factor 2 for the groups is shown in Figure 6b. In Figure 6b axis 1 represents factor 1 and axis 2 represents factor 2.

6.2 Discussion

i Are the physiological variables as predicted for the different groups?

Hypothesis (i) that the P3 latencies of the schizophrenic and bipolar subjects would be prolonged compared with those of the control and unipolar subjects was supported. The P3 latencies of the schizophrenic, bipolar manic and bipolar depressed group were significantly longer than those of the control group and unipolar group. This finding replicates previous reports of increased P3 latency in schizophrenic patients compared with control subjects (Shagass 1980, Blackwood et al 1987) and an increased P3 latency in bipolar subjects compared with unipolar subjects and control subjects (Muir et al in press). No difference was found between the P3 latencies for the schizophrenic group and the bipolar groups supporting hypothesis (ii), as reported by Muir et al (op.cit). Hypothesis (iii) was also confirmed as no difference was found between the P3 latencies of the unipolar subjects and the control subjects, supporting the findings of Blackwood et al (op.cit). P3 latency was found to be more variable for the schizophrenic and

bipolar groups than for the unipolar and control groups, as was reported by Muir et al (op.cit) with respect to schizophrenic subjects.

Hypothesis (iv) that the P3 amplitudes of the schizophrenic, bipolar and unipolar groups would be reduced compared with the control group was only partially supported. The P3 amplitude of the schizophrenic group was smaller than that of the control group, supporting previous findings (Roth et al 1972, Levit et al 1973, Verleger and Cohen 1978, Roth et al 1980, Steinhauer and Zubin 1982, Baribeen-Brown et al 1983, Pfefferbaum et al 1984). The P3 amplitudes of the bipolar groups were not smaller than that of the control group which did not support the findings of Muir et al (op.cit). However, the findings supported their results in so far as the P3 amplitude of the unipolar group was greater than that of the schizophrenic and bipolar groups, with a significant difference for schizophrenic patients only. No significant difference was expected between the unipolar and bipolar groups. The P3 amplitude of the unipolar group was also significantly higher than that of the control group, which was unexpected in the light of the finding by Blackwood et al (op.cit) that P3 amplitude in major depressive disorder subjects was significantly reduced compared with control subjects. They also found that P3 amplitude increased in depressed subjects after treatment and concluded that P3 amplitude was associated with state in unipolar

depressed patients. The groups of unipolar and bipolar subjects in this study were small (n=10), and examination of the P3 amplitudes for the individual subjects in the groups revealed that each group contained some members (in the case of the unipolar depressed group three members) with high P3 amplitudes. Some of the members of the unipolar and bipolar depressed groups were only moderately depressed, with scores of 17 on the HRSD in the unipolar group and 10 in the bipolar group. These factors may explain the lack of reduced P3 ampitude in these groups of depressed subjects. Therefore, it appears that the small numbers and inclusion of moderately ill subjects may have caused the P3 amplitudes of the bipolar and unipolar subjects to be greater than was expected.

Differences in smooth pursuit eye tracking were not found to be significantly different between any of the groups. Therefore hypothesis (v) which stated that ETD would be greater in the schizophrenic group than in the control group was not supported. All the bipolar subjects were taking lithium which has been associated with impaired eye tracking (Lipton et al 1980).

ii Are the cognitive scores as predicted for different groups?

Hypotheses (vi) and (vii) state that the schizophrenic, bipolar manic, bipolar depressed and unipolar depressed subjects would show impairments on the cognitive tests compared with the control subjects. a) Schizophrenic and Bipolar manic subjects. Hypothesis (vi) stated that the schizophrenic and bipolar manic group would show impairments on tests of association, conceptualization and recall. It was predicted that the schizophrenic and manic subjects will show disorganized thinking characterized by loose associations, impairment in conceptualization, and abstract reasoning, perseveration and memory impairments.

1. Loosening of the Associations.

It was predicted that the schizophrenic and bipolar manic subjects would show looser, more bizarre associations due to a dysfunction in the implementation of associative networks. In the Word Association Test, the number of most frequent responses given approached significance ($p<.06$) with the schizophrenic and bipolar manic subjects giving less frequent responses than the control and unipolar groups. The number of infrequent responses given was just significant ($p<.05$) with the schizophrenic and bipolar manic subjects giving more infrequent responses than the other two groups. Similarly,

the ranked scores of the responses were significantly different for the schizophrenic and bipolar manic groups compared with the unipolar and control groups ($p<.05$). In the Paired-Associates test, part I was not significantly different between the groups suggesting that the associative networks of the schizophrenic and bipolar manic subjects are intact as these patients showed that they had the knowledge required for this test. However, in part II where the subjects had to access and use this information themselves, the schizophrenic and bipolar manic subjects were significantly worse than the control subjects. These results support the hypothesis that there is a loosening of the associations in schizophrenic and bipolar manic patients and that the impairments seen in these patients are due to a dysfunction in the implementation of associative networks, although it appears that these networks are intact in these groups.

2. Impairments in conceptualization

It was predicted that the schizophrenic and bipolar manic patients would show impairments in conceptualization due to a dysfunction in the implementation of semantic networks.

The formation and use of concepts was measured using the Wisconsin Card Sorting Test, the Witkins Embedded Figures Test, the Similarities test and the Stroop Test. The performance of the schizophrenic and the

bipolar manic groups was found to be impaired, compared with the control group on the Witkins Embedded Figures Test and the Similarities test. No difference was found between the performance of the schizophrenic and manic groups on these tests. The Similarities test is a measure of verbal conceptualization and abstract reasoning which requires the subject to access acquired knowledge he has about concepts and their attributes. Good performance on the test requires the subject to be able to identify whether the two items are from the same category or have shared attributes or functions, and requires the subject to use information stored in conceptual associative networks in long term memory. Impairment on the test suggests that the structure of these networks is deficient or that the subject is not using these networks efficiently. The Similarities test is a subtest of the WAIS and as such can be used as an indication of IQ compared with normative data. A scaled score of 10 on this subtest would indicate that the subject has an average IQ of 100. The schizophrenic subjects had a mean score of 9.9, with a premorbid IQ of 108.2. The bipolar manic subjects scored 8.9 with a premorbid IQ of 109.2. Both groups showed deterioration in this test relative to their premorbid IQ. The other WAIS subtest, the digit span test which measures attention and concentration showed less deterioration, with a mean score of 10.3 for the schziophrenic subjects and 10.1 for the bipolar manic subjects. Therefore, it appears that intellectual deterioration has occured in both the schizophrenic and bipolar manic subjects in a

selective manner, being due to impaired conceptualization and abstract thinking rather than impaired concentration.

The Witkins Embedded Figures Test is also a test of conceptualization. However, this is a visual test. It requires the subject to identify the essential features of a shape. It also measures the ability of the subjects to separate figure from ground. The test is a good indicator of visual conceptualization, as the test becomes more complex if construed in verbal constructs.

The Wisconsin Card Sorting Test and the Stroop Test did not significantly differentiate the control group from the patient groups after age and IQ were controlled for. In the Wisconsin Card Sorting Test, the variability of performance was much greater in the patient groups than in the control group. Although not all schizophrenic patients were impaired on this test, it will be suggested later that with respect to these patients, this test is effective in identifying subjects who show specific deficits. The Stroop Test measures conceptualization among other things, in that the effective use of concepts should increase the interference effect in the test. Therefore, it was hypothesized that the schizophrenic and bipolar manic patients would find this test easier than control subjects as they would not be susceptible to the interference effect to the same extent. However. there was no significant difference between the

groups on this test, and the mean scores indicated that the schizophrenic and bipolar manic subjects were slower than the control subjects. This may have been affected by the fact that all of the schizophrenic subjects and most of the bipolar manic subjects were taking neuroleptic drugs which may have slowed their reaction time. This test probably involved too many factors, for example decision making and reaction time, to be a good measure of conceptualization.

Therefore the hypothesis that schizophrenic and bipolar manic subjects would show impairment on measures of conceptualization was generally supported.

3. Memory impairments

It was predicted that the schizophrenic and manic patients would show impairments in the recall of related items due to a dysfunction in the implementation of semantic networks.

In the verbal recall tests, the control subjects performed significantly better than the schizophrenic and bipolar manic subjects. However, although this difference occured for emotive words and category words, there was no significant difference between the groups in the recall of neutral words. While the emotive words and the

category words were related within each list the neutral words were not related on any dimension. Recall of related words is aided in normal subjects by the organization of the words into categories or associated groups. It appears that the performance of the control group was significantly aided for recall of related words while the schizophrenic and bipolar manic patients were less able to make use of structuring of the information to enhance recall. In the recall of neutral words, there was no dimension on which to relate the words and so this aid for the control subjects was lost. This was reflected by the lack of significant differences between the control group and the schizophrenic and bipolar manic groups. Therefore, the hypothesis that the schizophrenic and bipolar manic group would show impairments in recall of related words was supported.

b) Bipolar Depressed Subjects

Hypothesis (vii) stated that the performance on the cognitive tests of the bipolar depressed group would be more similar to the bipolar manic group than to the unipolar depressed group.

1 Loosening of the Associations.

It was predicted that the bipolar depressed group would show a similar dysfunction to the bipolar manic group. The bipolar depressed group showed a similar pattern of response to the bipolar manic group in the Word Association Test, giving less 'frequent' responses and more idiosyncratic responses than the control group and the unipolar depressed group. Similarly, in the Paired- Associates test part II, the bipolar depressed group was less able than the control group and the unipolar depressed group to access the correct partner to each target word, although not signifcantly so. This suggests that the bipolar depressed group show a similar dysfunction in the implementation of associative networks as the bipolar manic group, although it suggests that this dysfunction is not as severe in the bipolar depressed group.

2 Impairments in conceptualization

It was predicted that the bipolar depressed group would show similar deficits to the bipolar manic group. The bipolar depressed group was impaired on the Witkins Embedded Figures Test compared to the control group but not on the Similarities test. This indicates that the deficit seen in the bipolar depressed group is more severe for visual conceptualization than for verbal conceptualization, while

in bipolar manic subjects a significant deficit is seen in both tests. However, this bipolar depressed group had a high premorbid IQ of 116.7, indicating that a roughly comparable score on the Similarities test would be 13. As the mean scaled score for the bipolar depressed group was 10.8, this suggests that there is some impairment in this test. The mean score for this group on the digit span test was 11.5, indicating that, as in schizophrenic and bipolar manic subjects, they show a greater dysfunction in conceptualization than in attention.

3. Memory Impairments

Similar impairments were predicted in the bipolar manic and bipolar depressed group in the recall of related words.

In the verbal recall tests, the bipolar depressed group was significantly differentiated from the control group only for total words recalled, and not for emotive or category words separately. The deficit which is seen for the bipolar depressed group in the recall of related words is not as severe as that of the bipolar manic group and only reaches significance when all the words recalled are summed. This only partially supports the hypothesis. It has been shown that there is some deficit in this group, but that it is not as severe as for the bipolar manic group. These findings support the hypothesisis (vii) that the bipolar depressed group will show similar cognitive deficits

to the bipolar manic group. However, in general the deficits of the bipolar depressed group are not as severe as those in the bipolar manic group.

c) Unipolar depressed subjects

Hypothesis (viii) stated that the unipolar depressed group would show a similar performance to control subjects on tests of association and conceptualization, but would be impaired on memory and reaction time tests.

1. Associations.

As predicted, the unipolar depressed group showed very similar performance to the control group in the Word Association Test and Paired-Associates test. No difference was found between the two groups on these tests. This indicates that the associative networks are intact in unipolar depressed patients and that the patients can access the appropriate response.

2. Conceptualization

No significant difference was found between the unipolar depressed subjects and the control subjects in the Similarities test, indicating that there is no significant impairment in conceptualization. However, there was a significant difference between the unipolar depressed and control subjects on the Digit Span test which suggested that attention and concentration were impaired in the unipolar depressed group.

3. Memory Impairments

It was predicted that the unipolar depressed group would show memory impairments but that these would be due to different underlying deficits to those in the bipolar subjects. The unipolar depressed group was significantly impaired on all the verbal recall tests. However, the preceding results may indicate that this is due to different underlying processes in the unipolar depressed and schizophrenic and bipolar manic subjects. Lack of concentration may be the major contributing factor to the poor performance of the unipolar depressed subjects while lack of organization appears to be a major contributing factor for the schizophrenic and bipolar manic subjects. The unipolar depressed group was the only group to show a poorer score for digit span than for the Similarities test. They were slowest on

the Stroop Test and had the lowest score on the Witkins Embedded Figures Test. It is proposed that lack of concentration affected their performance on these tests. However, in the word association tests, the responses they gave were normal, indicating that their use and storage of information is normal when the demands of the test are not great. These findings support the hypothesis (viii) that unipolar depressed subjects would not show cognitive deficits in terms of associative processes and conceptualization, but would be impaired on memory and speed tests.

iii Do the physiological variables correlate as predicted with the cognitive scores?

Hypothesis (ix) states that measures of association, conceptualization and memory will correlate with P3 amplitudes and latencies for the schizophrenic and bipolar groups. It has been hypothesized that P3 abnormalities reflect dysfunctions in the implementation of associative networks. Therefore, it is hypothesized that performance on cognitive tests which require this function in information processing will correlate with P3 measures.

a) P3 latency

The correlation of thought disorder with P3 latency in schizophrenic subjects supported the hupothesis. Dysfunctions in implementing associative networks result in the patient being unable to use structured, coherent cognitive sets and result in loosening of the associations and illogical reasoning. Withdrawal was also found to increase with P3 latency, indicating that with more pronounced physiological abnormality, behavioural symptoms worsen. It is suggested that withdrawal may be used by schizophrenic patients as a means of avoiding situations or information which they cannot impose order upon and cannot cope with. Alternatively, thought disorder has been defined as a positive symptom, and withdrawal as a negative symptom in schizophrenia. As such, they may be predominantly mutually exclusive. If this is the case, it can be seen that P3 latency increases with both increasing positive and negative symptomatology.

P3 latency was not found to correlate with scores on the HRSD or on the MMSRS for any group. This was expected, as P3 latency has been reported to be a stable, robust characteristic and proposed to be indicative of trait (Blackwood et al 1987). Therefore, P3 latency is not affected by mood. P3 latency was not expected to correlate with IQ. This was supported in the schizophrenic, bipolar depressed, unipolar depressed and control groups. However, there was a very

strong negative correlation for P3 latency with premorbid and present IQ in the bipolar manic group showing increasing P3 latency with decreasing IQ. These results are inconclusive, and studies requiring larger numbers of subjects are needed to clarify this.

The hypothesis predicted that correlations would be found for P3 latency with performance on all the cognitive tests for the schizophrenic group, as the cognitive tests which were used involved the implementation of associative networks. Significant correlations were found, as expected, for P3 latency with measures of associative processes in the word association tests, and measures of conceptualization in the Wisconsin Card Sorting Test, the Witkins Embedded Figures Test and the Stroop Test. Number of errors made in the verbal recall tests was also found to be significantly negatively correlated with P3 latency. Errors were made when words which were not included in the recall lists were reported by the subject. In the case of the schizophrenic subjects, these errors were usually perseverations from previous lists or words which sounded like words in the list. Inclusion of extraneous words suggested that the schizophrenic patients were not using category cues to aid recall, but were using phonetic cues or remembering unrelated words from different lists. Therefore, in the schizophrenic subjects the hypothesis that

P3 latency would correlate with measures of association, conceptualization, memory and speed of processing was generally supported.

It was hypothesized that the bipolar subjects would show similar patterns of correlations between cognitive measures and P3 latency to the schizophrenic subjects, as similar processes were proposed to be responsible for the cognitive impairments and physiological abnormalities in both groups of subjects. In the bipolar manic group significant correlations for P3 latency with the verbal recall tests, Stroop Test reaction time and the Similarities and Digit Span tests indicated that P3 latency was associated with measures of conceptualization and memory. While there was no correlation between P3 latency and digit span in the schizophrenic group, the correlation in the bipolar manic group may indicate that concentration may be associated with P3 latency in a manic state, which may lead to stronger correlations of P3 latency with verbal recall and reaction time. Therefore the hypothesis that bipolar manic subjects would show similar correlations of P3 latency with measures of conceptualization, memory and speed of processing as the schizophrenic subjects was generally supported. However, the data also suggest that when ill, attention and concentration may be more related to physiological abnormalities in bipolar manic subjects.

P3 latency would correlate with measures of association, conceptualization, memory and speed of processing was generally supported.

It was hypothesized that the bipolar subjects would show similar patterns of correlations between cognitive measures and P3 latency to the schizophrenic subjects, as similar processes were proposed to be responsible for the cognitive impairments and physiological abnormalities in both groups of subjects. In the bipolar manic group significant correlations for P3 latency with the verbal recall tests, Stroop Test reaction time and the Similarities and Digit Span tests indicated that P3 latency was associated with measures of conceptualization and memory. While there was no correlation between P3 latency and digit span in the schizophrenic group, the correlation in the bipolar manic group may indicate that concentration may be associated with P3 latency in a manic state, which may lead to stronger correlations of P3 latency with verbal recall and reaction time. Therefore the hypothesis that bipolar manic subjects would show similar correlations of P3 latency with measures of conceptualization, memory and speed of processing as the schizophrenic subjects was generally supported. However, the data also suggest that when ill, attention and concentration may be more related to physiological abnormalities in bipolar manic subjects.

The correlations of P3 latency with cognitive variables in the bipolar depressed group were generally non-significant except for recall of emotive words which was associated with longer latency. However, there was a small positive correlation of P3 latency with IQ which may have obscurred any correlations between P3 latency and impairment. Therefore, the hypothesis was only partially supported for the bipolar depressed subjects. It was hypothesized that the unipolar subjects would show a pattern of response which was similar to the control subjects. Only errors made in the verbal recall tests correlated significantly with P3 latency for the unipolar depressed group and the control group. Therefore the hypothesis was supported for the unipolar depressed group.

Therefore, P3 latency appears to reflect better the more permanent changes seen in schizophrenia than the transient changes seen in the affective disorders as a result of change of mood. P3 latency does correlate with clinical symptomatology in schizophrenia but does not correlate with mood in the affective disorders. P3 latency also correlates with performance on cognitive tests in a similar way in the schizophrenic and bipolar manic groups. However, in the schizophrenic group, the correlations are stronger for P3 latency with association and visual conceptualization while in the bipolar manic group the correlations are stronger for verbal conceptualization. In the bipolar depressed group, it is thought that correlations between physiological

abnormalities and any cognitive impairment may have been obscured by the IQ distribution of the subjects in the group. Correlations of P3 latency with cognitive tests in the unipolar group are more similar to those in the control group.

b) P3 amplitude

P3 amplitude correlated with mood in the bipolar manic and bipolar depressed subjects supporting hypothesis (x) and the claim that P3 amplitude may be state dependent (Blackwood et al 1987). P3 amplitude also correlated with decline in IQ in these subjects, indicating that P3 amplitude may also be associated with cognitive impairments in bipolar subjects. However, the lack of strong correlations of P3 amplitude with performance on the cognitive tests suggests that P3 latency is more informative as a gauge for cognitive dysfunction especially in schizophrenia. It has been suggested that P3 latency reflects the amount of time required in the information processing function, while P3 amplitude reflects the amount of processing necessary. While P3 latency differentiates the schizophrenic and control groups, it also appears to be more effectively associated with performance on cognitive tests. Therefore, the delay in processing reflects dysfunction more accurately than the amount of processing which occurs. The amount of processing which occurs seems to be related to the mood of the subject especially in bipolar patients.

Therefore, subjects who are very depressed may not process information as well as patients who are not depressed, effecting a lack of concentration. This may be reflected by the association of P3 amplitude with digit span in the bipolar depressed group. However, the delay of P3 which occurs in schizophrenia and bipolar affective disorder is a robust phenomenon which correlates with performance on cognitive tests, and which may reflect the lack of structure available and used when processing information.

c) ETD

Correlations between ETD and performance on the Wisconsin Card Sorting Test and performance on the verbal recall tests were found in the schizophrenic subjects, and also occured in the control subjects. The Wisconsin Card Sorting Test is a well-used test of frontal lobe function. Some memory functions, and especially recency memory have been associated with frontal lobe function. The inter-test correlations showed strong correlations between performance on the Wisconsin Card Sorting Test and performance on the verbal recall tests for all groups of subjects. In the control group, ETD also correlated with digit span. ETD correlated with thought disorder in the schizophrenic subjects showing that increased physiological abnormality was associated with increased clinical symptomatology.

In the bipolar manic group and unipolar depressed group the significant correlations which were found for ETD with cognitive function indicated that good ETD was associated with poor cognitive function

For the bipolar depressed group, level of depression scored on the HRSD was related to ETD. Therefore, ETD appears to be a better indicator of performance on frontal lobe related tests in schizophrenia, and even in control subjects than in the affective disorder subjects. It is suggested that in affective disorders, factors such as use of lithium, lack of motivation and concentration may obscure any relationship between ETD and performance on cognitive tests.

iv Are there subgroups within the schizophrenic group?

Division of the schizophrenic group into two subgroups on the basis of their performance on the Wisconsin Card Sorting Test, produced two subgroups with similar P3 latency scores, but the Good Wisconsin Card Sorting Test group had a slightly smaller P3 amplitude and the Poor Wisconsin Card Sorting Test group had slightly worse signal : noise ratio. Although the Poor Wisconsin Card Sorting Test group had a lower IQ, after controlling for IQ it was found that this

group had dysfunctions in verbal and visual conceptualization and memory. Their poor performance on the Wisconsin Card Sorting Test suggests that they suffer from frontal lobe deficits. The other tests which they are impaired on, being the Witkins Embedded Figures Test, the verbal recall tests, the Similarities test and the Stroop Test have also been associated with frontal lobe function. However, they are also impaired on Digit Span and slightly impaired on the number of frequent responses given in the Word Association Test. The Good Wisconsin Card Sorting Test group generally performed better than the other group, except on the Paired Associates Test part II although the difference between the groups is not significant. However, it is noteworthy that this group which has a higher IQ and performed better on all the other tests than the Poor Wisconsin Card Sorting Test group performed worse on this one test. This may suggest temporal lobe involvement in this group. Correlations of P3 latency with performance on the cognitive tests for these two subgroups suggest that in the Poor Wisconsin Card Sorting Test group, P3 latency correlates with performance on tests of frontal lobe function, and also with increased thought disorder. However, in the Good Wisconsin Card Sorting Test group prolonged P3 latency correlates with withdrawal and performance on the Stroop test.

The two factors which were produced by principal components analysis were suggested to reflect frontal lobe function and temporal lobe function. P3 latency loaded significantly on both these factors while signal : noise ratio loaded significantly only on the former. While the Wisconsin Card Sorting Test, the Witkins Embedded Figures test and the Stroop test which loaded significantly on factor 1 have been associated with frontal lobe function and the Paired Associates test and Witkins Embedded test which loaded significantly on factor 2 have been associated with temporal lobe function, only the Wisconsin Card Sorting test is an established neuropsychological test. This indicates the need to use specific neuropsychological tests to ascertain whether P3 latency is associated with frontal lobe and temporal lobe function.

Chapter 7

STUDY II METHOD

7.1 Rationale and aims

The second study had two major aims. The first aim was to compare the performance of three groups of subjects; schizophrenic patients, normal controls and the relatives of schizophrenic patients on a battery of neuropsychology tests and IQ tests and to determine to what extent their performance on these tests was related to physiological measures. The second aim was to compare measurements of schizophrenic and control subjects from Magnetic Resonance Imaging (MRI) scans, and to determine whether these measurements correlated with performance on neuropsychological, psychometric and physiological tests.

i Neuropsychology and IQ tests.

The study aimed to compare the performance of the schizophrenic and control subjects on specific neuropsychology tests to extend the findings on cognitive differences between these two groups from study I. Impairments in tests which have been associated with frontal lobe function (Wisconsin Card Sorting Test, Witkins Embedded Figures Test

and Stroop Test), in memory tests and in tests associated with temporal lobe function (Witkins Embedded Figures Test and Paired-Associates test), which were found in the schizophrenic group, indicated the administration of specific neuropsychology tests. The neuropsychology tests which were selected for the second study have been shown to be sensitive to frontal lobe and temporal lobe function.

This study also aimed to examine further the correlations between P3 latency and ETD and performance on the neuropsychology tests. Findings from study I suggested that, within the schizophrenic group, performance on tests of temporal lobe function and performance on tests of frontal lobe function may correlate with P3 latency. In addition, the plan was
to determine whether neuropsychological deficits occured in individuals with abnormally prolonged P3 latency, but who had no clinical symptomology and were not medicated. For this purpose a group of relatives of schizophrenic patients were tested. This was done to determine whether deficits found in the schizophrenic group which related to P3 latency were specific to schizophrenia or occurred also in a control group and whether the deficits were influenced by drug treatment or clinical symptoms.

Findings from study I had indicated that more information was necessary about IQ within the groups, to determine how much effect IQ exerted on performance in the cognitive tests, and to examine deterioration in IQ within the groups and which specific intellectual abilities were affected. Five WAIS subtests were used to obtain Full Scale, Verbal and Performance IQ scores for each subject, and scaled scores for each of the five subtests to indicate ability in different functions.

ii MRI measurements

For the schizophrenic and control groups, MRI scans were recorded. These were to determine structural differences and the relationship between physiological abnormalities and structural abnormalities. Finally, data from the MRI scans were to be used to correlate with performance on the neuropsychology tests.

7.2 Design

This study was designed to be carried out in two sessions for the schizophrenic and control subjects, and in one session for the relatives. For the schizophrenic and control subjects, the original

forty-eight subjects who took part in the first study also participated in the second study. Twelve additional schizophrenic and control subjects were included.

The MRI scans were carried out in the first session, for the schizophrenic and control subjects. The scans were peformed at the Royal Infirmary in Edinburgh. For most of the subjects, the two sessions occured on different days. This was because the MRI scanning was a long procedure, which lasted approximately one and a half hours, and necessitated a journey from the Royal Edinburgh Hospital to the Royal Infirmary. Many patients and even some control subjects complained that they found the length of time and procedure involved quite stressful and wearisome. Therefore, to avoid further stress and fatigue, the second session was carried out on a subsequent day.

The physiological tests and cognitive tests were administered in the second session. All three groups participated in these tests. The relatives were also interviewed on the same day by a psychiatrist using the SADS-LA. The schizophrenic subjects were interviewed for the purpose of scoring the BPRS.

7.3 Subjects

Thirty schizophrenic patients, thirty control subjects and thirty relatives of schizophrenic patients participated in the study. The twenty-four schizophrenic patients from study I were included with six other schizophrenic patients. The circumstances of some of the patients had changed from study I. The period of time which elapsed between patients being tested for study I and for study II ranged from six months to one year. Therefore, all patients were completely assessed for study II. The resulting group of schizophrenic patients consisted of in-patients and out-patients who were being treated at the Royal Edinburgh Hospital. In-patients consisted of patients from both acute admission wards and long-stay rehabilitation wards. Out-patients were seen on a regular basis by medical staff. They consisted of patients who lived at home, or in hostels or supported accomodation. Appendix B1 lists age of first onset, length of time in hospital for current episode of illness, and medication taken.

The relatives belonged to families in which at least one of the members suffered from schizophrenia. They were not relatives of the schizophrenic subjects in the study. These families were located in different regions in Scotland and England. One member of this group was unemployed, the rest were in employment, students or housewives. No subject was taking psychotropic medication.

Six other control subjects were added to the twenty-four who participated in study I to comprise the group of control subjects for study II. This group contained normal control volunteers from hospital staff, students and members of the local community. No subject was taking psychotropic medication.

i Criteria for selection

The schizophrenic group and control group each consisted of twenty-three males and seven females. These two groups had fairly similar age distributions although subjects were not strictly age-matched. Consequently, the schizophrenic and control subjects fell roughly into the same age range. No specific criteria were established for selection of relatives on the basis of age or sex. Only three relatives had ages which fell outside the range for the schizophrenic and control groups; these relatives were aged 63, 65 and 67.

The schizophrenic patients were required to have fulfilled RDC and DSM--III-R criteria for a diagnosis of schizophrenia. Severity of symptoms were not specified, as the study aimed to examine the effect of severity of illness on cognitive functioning. Measures of state

were made using the BPRS. Subjects with evidence of neurological brain damage were excluded from the study including one subject who was found to have a colloid cyst.

The control subjects were required to have no past history of or current evidence of psychiatric illness. They were interviewed by a psychiatrist.

The relatives were also interviewed by a psychiatrist using the SADS-LA to determine that they had not suffered from schizophrenia. Three relatives were given diagnoses on the lifetime version of the SADS of major depressive disorder, and one was given a diagnosis of minor depressive disorder. The remaining twenty-six relatives were given no diagnoses. The relatives were required to be free of psychotropic medication, as an additional exclusion criterion for psychotic illness.

ii Description of subjects

The ratio of female : male subjects in the relatives group was greater than in the schizophrenic and control groups. The relatives were significantly older than the other two groups (p=.001). However, there was no age difference between the sexes. (Table 7a).

TABLE 7

AGE, MEANS (STANDARD DEVIATIONS) AND SEX RATIOS OF SUBJECTS

	1 Schizophrenic 30	2 Relatives 30	3 Controls 30	P
M/F	23/7	12/18	23/7	.003 (+)
Age	29.3 (8.7)	38.7 (15.1)	28.7 (9.2)	.001 (++)

(+) $X^2 = 11.73$, df=2

(++) ANOVA F=7.73, df=2,89

7.4 Measures and rating scales

i Diagnostic and state rating scales

The same diagnostic and state rating scales were used for study II as were used for study I, that is for diagnosis the SADS, RDC and DSM-III-R were used. These have been described in 5.4.i. For measures of state, the BPRS and HRSD were used which have been described in section 5.4.ii.

ii Physiological

Auditory ERPs were recorded using the same procedure as described in section 5.4.iii. However, the recordings were made using a purpose built micro-computer averaging system in place of the Nicolet-Ca1000 clinical averager. The same filter settings were used. This micro-computer averaging system had facilities for multi-channel averaging, and enabled recording of EOG as well as EEG during the auditory task. Averaging was carried out from Cz and a bipolar pair of electrodes with one at the lateral canthus of the left eye and the other above the mid-point of the left eye. No evidence of time-locked eye movement induced artefact was found.

The data were stored on floppy disc on completion of recording and averaging ERPs in each trial. This meant that the data could be rated on a separate occasion, rather than immediately after the end of the trial as was necessary with the Nicolet-Ca1000 which had no enduring memory storage capacity and no facilities for transferring the data to floppy disc. Otherwise, the procedure for measuring the ERP components was the same for both systems. The latencies and amplitudes of the potentials recorded with both systems were not significantly different.

Smooth pursuit eye movements were recorded in the same way as described in section 5.4.iii.

iii MRI measures

MRI scans were performed using the same procedure on all subjects. An M & D Technology Limited 0.08 Tesla resistive magnetic resonance imaging system was used, and two series of scans were performed. In a preliminary study a pulse sequence was chosen which produced the clearest images of medial temporal lobe structures. For this high resolution scan, a saturation recovery pulse sequence with a repetition time (TR) of 800 msec and a reduced flip angle (60) was

used. Matrix size was 256 , slice thickness was 8 mm, and six averages were performed. In the same preliminary study, the settings which gave the clearest images of the ventricular system were identified. The low resolution scan used a saturation recovery pulse sequence with a TR of 500 msec and a flip angle of 90 . Matrix size was 128 , slice thickness was 12 mm and one average was done. Ten serial coronal sections were performed first at the low resolution settings, then the high resolution settings, with the subject's head held still in a light headrest. The coronal sections began at the anterior of the temporal lobes and extended posteriorly. All measurements were done without knowledge of subject identity or group membership. The MRI images were fed to a Quantimet 800 Image Analysis System via a Plumbicon scanner, from films placed on a transilluminating macroviewer. The analogue image acquired by the Quantimet was converted to a digital matrix. Areas for measurement were outlined on the monitor screen using a light pen and the data on them extracted from the digital matrix. To ensure consistency five repeated measurements of each area were made and the mean taken. The coefficient of variation for the measurements was less than 7% and for measurements on the high resolution was less than 6%. Repeated measurements over the course of the study indicated no significant operator difference in measurement. The measurements were given in mm and sq mm of the actual photographic image. Measurements were made on both the low resolution and high resolution scan. The total

intracranial area was taken as the area delineated by the inner table of the skull. A straight line was extrapolated across the lower margin, occupied by the brain stem, to complete the delineation. The cerebral size was taken as the area delineated by the surface of the brain at the level of the amygdala, measured from the medial aspect of the temporal cortex around the surface of the brain to the opposite medial aspect of the temporal cortex. A straight line was extrapolated to connect the two opposing medial temporal cortices. The intracranial area and cerebral size were measured on the low resolution scan.

Cerebral atrophy was calculated for each subject from the difference between cerebral size and intracranial area. All other measurements were converted into a ratio relative to the intracranial area for that subject. The ventricular brain ratio was taken from the low resolution scan section in which the lateral ventricles had the greatest area; the right and left sides were added together to give a total area which was then expressed as a ratio of the intracranial area to give the ventricular brain ratio. All other measurements were carried out on the high resolution scan.

iv Cognitive tests

a) Tests sensitive to frontal lobe function.

1) Verbal fluency

There are a number of different versions of verbal fluency tests. These vary in the types of verbal associative fluency which they measure but broadly speaking they fall into two categories; those which measure the number of words a subject can give which begin with a certain letter, and those which measure the number of items which the subject can name that belong to a certain category.

The letter fluency test was developed by Borkowski et al (1967) and Benton (1968), on the basis of Thurstone's (1938) verbal fluency tests. This test requires the subject to say as many words as he can think of beginning with a given letter, excluding proper names, numbers and the same word with a different suffix for one minute. Three letters are used; the most widely used have been F, A and S. The score is the sum of all acceptable words produced in the three trials. Borkowski et al tested sixty-six adult subjects. They found that the number of words produced correlated with the frequency count for each

letter in the Thorndike-Lorge norms, and with the estimates derived from the dictionary of the number of words beginning with each letter. They showed that IQ affected verbal recall but that age did not.

Benton (1976) developed the Controlled Oral Word Association Test which used the letters C, F and L or P, R and W. These combinations offered trials of increasing difficulty. Benton reported associative norms for these letters.

There are various category fluency tests. Rosen (1980) measured subjects' responses when asked to produce items in three different categories for one minute each. Talland (1965) asked subjects to name as many objects in the street and animals as they could. Newcombe (1969) recorded subjects' responses for objects, animals and birds and colours alternatively.

Schaie and Strother (1968) estimated that the test-retest reliability coefficient after seven years for verbal fluency tests was 0.86.

There is evidence that impairment in verbal fluency tests is associated with left prefrontal brain damage (Benton 1967, Milner 1964). Milner showed that neither right prefrontal nor left temporal lesions resulted in the same impairment. Milner and Petrides (1984)

measured verbal fluency in patients with focal lesions, dementing patients and normal control subjects. A regression equation was derived to predict fluency from an index of verbal intelligence. When verbal intelligence was taken into account, the fluency scores remained depressed in subjects with frontal lesions. However, for dements the obtained fluency score was as predicted from the verbal IQ. Newcombe (1969) showed that verbal fluency tests discriminated between left and right sided lesions in war veterans who had sustained penetrating missile wounds.

Benton (1968) found that patients with left frontal lesions produced on the average almost one third fewer FAS words than patients with right fontal lesions. Bilateral lesions tended to lower the number of responses even further.

Verbal fluency for the letters S A and F and for categories animals, fruit and flowers was used in this study.

2) Visuoconstructive Test

The Copying of Designs Test (Benton 1967) is a visuoconstructive test, which is associated with right hemisphere function. The test requires the subject to copy the designs of the Benton Visual Retention Test, and the test is scored by the number of errors of

specific types made by the subject. Benton standardized this test to show that performance can be rated as normal to grossly defective. No correlations in score for age or educational level are made. Benton found that there was a high frequency of failure among right hemisphere damaged patients, and among bilateral patients, but not among left hemisphere patients.

3) The Wisconsin Card Sorting Test has been described in section 5.4.iv.

b) Tests sensitive to temporal lobe function.

1) Hebb's Recurring Digits Test

Hebb's Recurring Digits Test (Milner 1970, 1971) and Corsi's Block Tapping Test (Corsi, 1967, Milner 1971) involve similar learning processes, although the former uses verbal material and the latter visuo-spatial material. In the Hebb's Recurring Digits Test, the subject's digit span is evaluated using the procedure as described for Digits Forwards (section 5.4.iv). He is then presented with a series of sequences of digits comprising his present digit span plus one, and is required to repeat the sequence. The subject is not informed that every third sequence is repeated while the intervening two are novel. Normal subjects tend to show a learning curve for the repeated

sequence. This test is sensitive to left hippocampal function. Gruzelier (1988) found that a ceiling effect was reached at approximately the fourth trial for control subjects. Impairment on this test was shown by patients with left temporal lobectomies but not by patients with right temporal lobectomies. The extent of the impairment was shown to vary with the amount of hippocampal involvement. Gruzelier proposed that the failure of patients with tempero-hippocampal deficits to demonstrate a learning curve was due to dysfunction in memory consolidation or to retrieval deficits.

2) Corsi's Block Tapping Test

Corsi's Block Tapping Test was devised by P.Corsi to test memory impairment in patients who had undergone temporal lobe surgery. Administration of the test requires nine one and a half inch block cubes which are positioned randomly on a black board. The examiner taps out a sequence of blocks and the subject is required to copy this sequence. The procedure is the same as for the Recurring Digits Test, in that the examiner evaluates the subject's block tapping span, and then presents a series of sequences which exceed the subject's span by one. Every third sequence is repeated. Milner showed that normal subjects gradually learn the recurring pattern. The test is sensitive to right hippocampal function. Patients who had undergone extensive right temporal lobe excision which involved significant amounts of the

hippocampus showed no learning on this test. Left and right sided anterior temporal lobectomy cases were differentiated by impairment on the Recurring Digits Test and Block Tapping Test respectively.

c) Verbal Recall and Recognition

The verbal recall tests were described in section 5.4.iv. A test which involved recognition of the words used in the verbal recall tests was also administered. A list of twenty-eight words was prepared which consisted of two words taken at random from each of the verbal recall lists and fourteen new words which were not included in the verbal recall tests, and which were selected randomly from Toglia and Battig's (1978) word lists. The old and new words were presented in a random sequence in the list, and subjects were required to tick the words that they had seen before.

d) Intellectual level

To obtain estimates of present Full Scale, Verbal and Performance IQ, five subtests of the WAIS were administered. The WAIS was developed from the Wechsler-Bellevue Intelligence Scale (1939) for the purpose of providing a valid and reliable estimate of IQ in adults. Prior to the Wechsler-Bellevue Intelligence Scale, the IQ tests

available were developed for children and the concepts of mental age and chronolgical age were used to assess the level of performance. Standardization of the WAIS is described in section 5.4.iv.

A validation study compared the performance of 52 white male adults from the Annandale reformatory in New Jersey on the WAIS and the Stanford-Binet. Correlations between the Stanford-Binet and the WAIS Verbal, Full Scale IQ and Performance IQ were 0.86, 0.85 and 0.69 . Two functionally discrete subtest groups have emerged on factor analysis of the WAIS. The first group shares a common verbal factor. The second group shares a common factor termed perceptive organization, non-verbal organization or space performance. A general intellectual factor has been extracted (Russell 1952) and also a memory factor.

Complete WAIS assessment consists of the administration of six verbal subtests and performance subtests. Each subtest is scored separately to produce a raw score. The raw scores are then converted into scaled scores for each subtest. One conversion table is used at this stage for all age groups so that scaled scores provide a comparison of the subject's performance with the reference group as a whole. The six verbal scaled scores are summed and the five performance scaled scores are summed so that performance on each test contributes with equal weight to the overall IQ score. The verbal

total score and the performance total score are converted into verbal IQ and Performance IQ using conversion tables which refer to the subject's age group specifically. A total IQ score is obtained by adding the verbal scaled score and performance scaled score totals and again using the appropriate age-related scale to convert this to a full scale IQ score. Thus the subject's IQ can be compared with other members of his own age group. It is permissible to use a shortened version to obtain a prorated IQ score. Wechsler recommended using four,five or six subtests. The use of the shortened version reduces the amount of time necessary for assessment, which in the case of the full WAIS is approximately one and a half to two hours, without significantly reducing the validity or reliability of the IQ score. Three verbal subtests and two performance subtests were administered. To reach the verbal total scaled score, the scaled scores for the three tests were added and then doubled. The scaled scores for the performance subtests were added and then multiplied by two and a half.

The five subtests which were administered were : Vocabulary, Similarities, Digit Span, Picture Completion and Block Design. The first three are verbal subtests and the last two are performance subtests. All these subtests were selected as they had high reliability coefficients and were quick to administer.

Vocabulary was selected as it has been designated as one of the 'hold' tests and the purpose was to compare performance on the Vocabulary subtest with the NART, and also to enable evaluation of how much deficit there was between the Vocabulary subtest and the other subtests.

The Vocabulary subtest consists of a list of forty words. The examiner reads each word and points to the word when necessary on the list which is also in front of the subject. The subject is required to explain the meaning of the word. The meaning for each word can be awarded two, one or no points. The score obtained on the Vocabulary subtest reflects the patient's recall vocabulary, and the effectiveness of his speaking vocabulary. Lezak (1985) reported that patients with thought disorder may reveal a thinking problem in idiosyncratic associations or personalized or confabulatory responses. Gonen and Brown (1968) reported that when brain injury is diffuse or bilateral, Vocabulary tends to be among the least affected of the WAIS battery subtests. However, Parsons et al (1969) stated that it is relatively sensitive to lesions in the left hemisphere. Reliability coefficients for the 18 - 19, 25 - 34, and 45 - 54 age groups are 0.94,0.95 and 0.96.

The Similarities Test and Digit Span Test have been described in section 5.4.iv.

The Picture Completion Test consists of a booklet of twenty-one pictures. The subject is shown each picture in succession. Some necessary item is missing from each picture and the subject is required to identify what the missing feature is, within twenty seconds. Every correct response is awarded one point. This is a test of visual recognition and long term memory. There are also reasoning components to this test, involving judgements about practical and conceptual relevancies (Saunders 1960). Lezak (op.cit) reported that of all the performance scale subtests, the Picture Completion subtest has the highest weighting of the general ability factor with modest weightings on both verbal and visuospatial factors (Lansdell and Donelly 1977, Maxwell 1960, Russell 1972). Lezak (op.cit) stated that this subtest is very resilient to the effects of brain damage, and reported that lateral damage does not have any significant differentiating effect. It may serve as another good indicator of previous ability levels. reliability coefficients for the 18 -19, 25 - 34, and 45 - 54 age groups are 0.82, 0.85 and 0.83.

The Block Design subtest requires the subject to copy a series of ten designs using initially four and then nine blocks. The blocks are identical and each comprises two red sides, two white sides and two diagonal red and white sides. The subject is timed in copying each design.

This is a test of level of visuospatial conceptualization. It is the best subtest to measure visuospatial organization, and it also reflects general ability.

Lezak (op.cit) claimed that any type of brain damage results in a lower score on this subtest. McFie (1975) stated that performance is least affected by lesions in the left hemisphere, except when the parietal lobe is involved. It is moderately affected by diffuse or bilateral brain lesions, or diffuse degenerative processes that do not involve cortical tisue. It is most severely affected by diffuse loss of cortical neurons, severe damage to prefrontal cortex, or extensive right hemisphere damage that involves the parietal lobe. Reliability coefficients for the 18 -19, 25 -34 and 45 - 54 age groups are 0.86, 0.83 and 0.82.

The NART has been described in section 5.4.iv.

7.5 Procedure

The schizophrenic and control subjects were accompanied to the Edinburgh Royal Infirmary by a psychiatrist from the Royal Edinburgh Hospital for the MRI scans. Scanning lasted approximately one hour.

During the second session, the schizophrenic and control subjects who had not participated in the first study and all the relatives were administered the auditory ERP recordings and smooth pursuit eye tracking recordings as described in section 5.5. The forty-eight schizophrenic and control subjects who were tested for study I were not required to undergo repeat physiological recordings. Data from their previous recordings were used. Blackwood et al (1987) showed that P3 latency is stable over time.

All the schizophrenic subjects were interviewed for the purpose of rating the BPRS by a psychiatrist. All subjects were administered the battery of cognitive tests. The tests were carried out in random order, except that verbal recall was always followed by Benton's Copying of designs and then recognition. It was decided to use a test involving visuospatial stimuli between the verbal recall tests and recognition test, as it was necessary to have an intervening test, but one which did not involve the use of different sets of words which would have a confounding effect on the recognition test. The variability of time taken to complete the Benton's Copying of Designs Test was less than that for other tests, except that of Verbal fluency, which, however, was a test of verbal recall.

The cognitive tests were administered in the same sitting-room used in Study I. The examiner and the subject were seated in armchairs, separated by a table which was used to place test materials on. The responses required from the subject were oral, except for the recognition test and Copying of Designs Test which were written, and the Block Design Test and Corsi's Block Tapping Test which required manipulation of test materials. The examiner recorded the responses of the subject for each test where appropriate, and where necessary times taken to complete each test were recorded.

7.6 Hypotheses

i Scores on tests of frontal lobe and temporal lobe function will be significantly different between schizophrenic and control subjects.

ii Scores on tests of frontal lobe function and temporal lobe function will be significantly different between relatives with abnormal P3 and relatives with normal P3.

iii There will be no difference in the performances on these tests of schizophrenic subjects and relatives with abnormal P3.

iv There will be no difference in the performances on these tests of control subjects and relatives with normal P3.

v P3 latency will correlate with performance on the tests of frontal lobe and temporal lobe function in the schizophrenic and relatives groups.

vi Sub-groups in the schizophrenic group which may be identified by performance on the Wisconsin Card Sorting Test will show different deficits.

vii There will be differences in the MRI measurements between schizophrenic subjects and control subjects.

viii MRI measurements will correlate with physiological and neuropsychological measures.

7.7 Statistical analyses.

Two way analyses of variance using groups and sex as factors were used to compare differences in P3 latency, P3 amplitude, ETD, premorbid IQ, present IQ and decline in IQ. Scores on the neuropsychological tests were compared between groups using one way

analyses of covariance using IQ as a covariate. For tests of hippocampal function, two way repeated measures analyses of variance were used using group and laterality as factors. Kruskal-Wallis analyses of variance were used where the data were not normally distributed. Inter-test correlations between scores on the neuropsychology and psychometric tests were analysed using Pearson Product Moment Correlations and non-parametric correlations. Stepwise discriminant function analysis was used to identify which cognitive variables most effectively differentiated schizophrenic and control subjects. The same discriminant function scores were used to differentiate relatives with abnormal P3 and relatives with normal P3. Pearson Product Moment Correlations and non-parametric correlations were used to correlate physiological variables with scores on cognitive tests. Paired t-tests were used to compare MRI measurements between the schizophrenic and control groups as they were fairly well matched for age and were matched for sex. Pearson Product Moment Correlations and partial correlations controlling for age and IQ were used to correlate MRI measurements with physiological variables and scores on cognitive tests. Factor analysis was used to examine correlations between scores on the cognitive tests and physiological measures. One way analyses of variance compared the factor scores of the different groups.

Chapter 8

STUDY II RESULTS AND DISCUSSION

8.1 Results

i. Description of subjects on physiological variables

The means and standard deviations for the physiological variables for the three groups are presented in Table 8A. Two way analyses of variance (Group by Sex) followed by Scheffe's range tests showed a significant difference in P3 latency between the control group and the other two groups ($F=10.50$, $df=2,82$). There was no significant difference between the schizophrenic group and the relatives. Similar findings were shown for P3 amplitude ($F=5.86$, $df=2,75$). No significant differences were found between the groups for signal : noise ratio. No sex differences and no interaction effect (Group by Sex) were found for any of the physiological variables, indicating that the differences found between the relatives and the control groups were not significantly influenced by the different sex ratios in the groups. Tables of the analyses of variance are presented in Appendix B2

TABLE 8A

DESCRIPTION OF SUBJECTS BY PHYSIOLOGICAL VARIABLES;
MEANS (STANDARD DEVIATION

	1 Schizophrenic 30	2 Relatives 30	3 Controls 30	p ANOVA	
P3 latency (msec)	343.9 (40.5)	338.4 (40.3)	299.5 (24.5)	.000	1=2>3
P3 amplitude (uV)	38.8 (27.6)	26.1 (17.7)	52.7 (16.5)	.004	1=2<3
Signal:Noise Ratio (SPEM)	444.0 (117.8)	461.9 (106.7)	493.4 (111.7)	.24	

The relatives were divided into two subgroups, which consisted of those with abnormal P3 latency and those with normal P3 latency. Abnormal P3 latency was defined as greater than the mean plus two standard deviations of the P3 latency of the control group (348.5). This resulted in a group of 11 relatives with abnormal P3 latency and 19 relatives with normal P3 latency. The relatives with normal P3 latency served as a second control group to test whether any differences found in the relatives with abnormal P3 latency were due to their abnormal physiological responses, and not due to the fact that they were relatives of schizophrenic patients.

The age and sex distributions of the two groups of relatives compared with the schizophrenic group and the control group are presented in Table 8B. The numbers of males and females in the groups, and the ages of the groups were significantly different. No significant difference was found in age between males and females and no interaction effect (Groups by Sex) for age.

The means and standard deviations of the physiological variables for the groups of relatives compared with the schizophrenic and control subjects are presented in Table 8C. One way analyses of variance by Groups followed by Scheffe's range tests showed that the P3 amplitude of the control group was significantly greater than that of both groups of relatives ($F=20.49$, $df=3,88$) and that there was no

TABLE 8B

AGE, MEANS (STANDARD DEVIATIONS) AND SEX RATIOS OF SUBJECTS

	1 Schizophrenic 30	2 Relatives Abnormal p3 11	3 Relatives Normal p3 19	4 Controls 30	p
MF	23/7	4/7	8/11	23/7	.008 (+)
Age (years)	29.3(8.7)	35.7(12.1)	40.4(16.6)	28.7(9.2)	.002(++)3>1=4

(+) X^2 = 11.84 df = 3

(++) ANOVA f = 5.80 df = 1,89

TABLE 8C

DESCRIPTION OF SUBJECTS ON PHYSIOLOGICAL VARIABLES, MEANS (STANDARD DEVIATIONS)

	1 Schizophrenic 30	2 Relatives Abnormal P3 11	3 Relatives Normal P3 19	4 Controls 30	P ANOVA
P3 latency (msec)	343.9 (40.5)	379.5 (31.6)	314.6 (21.0)	299.5 (24.5)	
P3 amplitude (uV)	38.8 (27.6)	18.6 (7.4)	30.1 (20.3)	52.7 (16.5)	.0001 2=3<4
Signal:Noise Ratio (SPEM)	444.0 (117.8)	478.5 (84.9)	452.4 (118.7)	493.4 (111.7)	.36

significant difference between the two groups of relatives. No significant differences were found between the groups for signal : noise ratio. Tables of the analyses of variance are presented in Appendix B2.

ii Description of subjects on IQ scores

The means and standard deviations of IQ scores for the schizophrenic and control and two relatives groups are presented in Table 8D. Two way analyses of variance (Groups by Sex) followed by Scheffe's range tests showed that the control group had a higher premorbid IQ ($F=11.01$, $df=3,89$) and a higher present IQ ($F=17.34$, $df=3,76$) than the schizophrenic and both relatives groups (Appendix B2). Decline in IQ was found to be significantly greater for the schizophrenic and abnormal P3 relatives groups than for the control group ($F=7.42$, $df=3,76$). No sex differences and no interaction effect (Groups by Sex) were found. The lack of differences between males and females for age, physiological variables and IQ scores enabled the exclusion of sex as a significant factor in further analyses. The effects of IQ and age differences between the groups were examined in subsequent analyses.

TABLE 8D

DESCRIPTION OF SUBJECTS BY IQ SCORES, MEANS (STANDARD DEVIATIONS)

	1 Schizophrenic 30	2 Relatives Abnormal p3 11	3 Relatives Normal p3 19	4 Controls 30	p ANOVA
Premorbid IQ (NART)	109.7 (10.5)	110.0 (6.5)	112.5 (8.1)	120.8 (4.9)	.0001 1=2=3<4
Present IQ (WAIS)	104.7 (14.2)	110.8 (9.5)	115.1 (11.5)	128.3 (9.7)	.0001 1=2=3<
IQ Difference (NART - WAIS	6.0 (6.3)	3.1 (3.3)	1.3 (3.3)	0.8 (1.7)	.0002 1>3=4

iii Differences between the groups on cognitive scores

Means and standard deviations of performance on cognitive tests for the groups are presented in Table 8E. Analyses of covariance using IQ as a covariate were used, followed by Scheffe's range tests. IQ was used as a covariate where IQ correlated significantly with performance on the cognitive tests for all the groups (Appendix B3). Age did not correlate consistently with performance on cognitive tests for the groups. Tables of the analyses of covariance are shown in Appendix B4.

a) Tests sensitive to frontal lobe function.

Performance on the Wisconsin Card Sorting Test significantly differentiated the schizophrenic group but not the relatives groups from the control group ($F=3.34$, $df=3,88$). In the verbal recall tests, the control subjects remembered significantly more words than the schizophrenic subjects and the abnormal P3 relatives for total number of words recalled ($F=10.92$, $df=3,87$), emotive words ($F=8.50$, $df=3,87$), and category words ($F=11.54$, $df=3,87$). The normal P3 relatives remembered significantly more category words than the schizophrenic subjects. Separate one way analyses of variance comparing the schizophrenic and the normal P3 relatives only found a significant difference for total words ($p<.01$) and for emotive words ($p<.03$). The

TABLE 8E

ANALYSES OF VARIANCE COMPARING PERFORMANCES OF GROUPS IN COGNITIVE TESTS SHOWING MEANS (STANDARD DEVIATION); WITH IQ USED AS A COVARIATE WHERE IQ CORRELATES WITH COGNITIVE TESTS +

	1 Schizophrenic 30	2 Relatives Abnormal p3 11	3 Relatives Normal p3 19	4 Controls 30	p
+WCST	20.4 (15.8)	12.0 (6.5)	12.1 (6.7)	9.3(3.0)	.023 1>4
+VIR Emotive	8.3 (2.4)	8.9 (1.7)	9.9 (2.2)	12.7(2.7)	.000 4>1=2 3>1 (0.3)
+VIR Category	9.8 (2.9)	11.2 (2.5)	12.1 (2.7)	15.8(2.6)	.000 3>1=2<4
+VIR Total	30.9 (8.2)	34.2(7.8)	36.6 (6.0)	47.4(7.6)	.000 4>1=2 3>1(.01)
+VIR Recognition	12.2 (4.6)	13.4 (3.1)	14.6 (3.4)	14.6(2.5)	.40
HRD; CBT Span	12.4 (1.7)	12.2 (1.7)	12.5 (1.5)	14.0(1.1)	.001 4>1=2
Times to learn	9.3 (3.3)	10.2 (1.9)	7.0 (2.3)	7.2(2.1)	.028 3=4<2=1
+Verbal Fluency Letters	39.1 (11.6)	38.5 (11.4)	46.8 (9.9)	55.5(11.1)	.01 4>1=2 3>2
Categories	31.7 (8.4)	41.1 (7.4)	48.9 (11.8)	54.8(10.8)	.000 1<3=4 2<4 1=2
Benton's C.D.	9.4 (1.5)	9.1 (1.3)	9.3 (1.1)	9.8(0.4)	.43

WCST = Wisconsin Card Sorting Test
VIR Emotive = Verbal Recall Emotive (Positive and Negative) words
VIR Category = Verbal Recall ('Animal' and 'Education') words
VIR Total = Total words recalled (Verbal Recall)
VIR Recognition = Verbal Recall Recognition of Presented Words
HRD = Hebb's Recurring Digits Test
CBT = Coisi's Bioch Tapping Test
Benton's C.D. = Benton's Copying of Designs Test

number of isolates recalled by the control group and the normal P3 relatives was greater than that of the other two groups (p=.004, X =13.62, df=87). No differences were found between the groups for recognition.

In the verbal fluency letters tests, the control group performed significantly better than the schizophrenic group and the abnormal P3 relatives (F=3.82, df=3,79) The normal P3 relatives were significantly better than the abnormal P3 relatives. In the categories tests, the schizophrenic group performed worse than the normal P3 relatives and the control groups (F=14.51, df=3,71). The abnormal P3 relatives group performed worse than the control group, and there was no difference between the schizophrenic group and the abnormal P3 relatives group.

b) Tests sensitive to hippocampal function

In Hebb's Recurring Digits Test and Corsi's Block Tapping Test, two way analyses of variance (Groups by Test) were used. Group differences were found for span (F=6.01, df=3,77) and for times to learn the repeated sequence (F=5.29, df=3,77). The control group had a higher span than the schizophrenic group and the abnormal P3 relatives group. There was a significant main effect for Test (F=207.00, df=3,77) showing a superior digit span compared with block tapping span, and no interaction effect (Groups by Test). The number of times

the repeated sequence was presented before it was learned was significantly greater in the schizophrenic and abnormal P3 relatives groups than in the control and normal P3 relatives groups. There was no significant Test main effect and no interaction effect (Groups by Test), indicating that the differences found between the groups applied to both Hebb's Recurring Digits Test and Corsi's Block Tapping Test.

In summary, performance of the schizophrenic group and of the abnormal P3 relatives group was equally impaired compared with the control subjects on the recall tests, Hebb's Recurring Digits Test, Corsi's Block Tapping Test and the verbal fluency tests. The normal P3 relatives group showed superior performance compared with the schizophrenic group on the verbal recall tests, times to learn in Hebb's Recurring Digits Test and Corsi's Block Tapping Test, and verbal fluency categories tests. In no test was their performance significantly different to that of the control group.

Inter-test correlations showed significant correlations for errors made on the Wisconsin Card Sorting Test with verbal fluency categories and total number of words recalled in all three groups (Appendix B5). In the schizophrenic group, errors made on the Wisconsin Card Sorting Test also correlated with Benton's Copying of Designs Test and verbal fluency letters (Table 8F).

TABLE 8F
INTER-TEST CORRELATIONS FOR SCHIZOPHRENIC SUBJECTS (n = 30)

	WCST	RCTOT	RECOG	SPAN	TIMES	VFLET	VFCAT	BENTON	S:N
P3 latency	.26	-.17	.16	-.09	.28	-.40	-.14	-.23	-.00
Signal: Noise Ratio (S:N)	-.43**	.36*	-.12	.40*	.26	.26	.42*	.41	
Benton Copying of Designs (Benton)	-.65**	.28	.12	.48**	.31	.21	.37		
Verbal Fluency Categories (VF Cat)	-.57**	.73**	.00	.49*	.32	.47*			
Verbal Fluency Letters (VF Let)	-.38*	.47**	.12	.03	-.14				
Hebb's Recurring Digits Corsi's Block Tapping Times to Learn (Times)	-.21	-.19	.14	.25					
Span	-.70**	.55**	.15						
Verbal Recall Recognition (Recog)	.03	.32							
Verbal Recall Total (RC Tot)	.57**								

(* p < .05 ** p < .01)

All these tests are sensitive to frontal lobe function.

Times to learn the repeated sequences in Hebb's Recurring Digits Test and Corsi's Block Tapping Test did not correlate with any of the other cognitive tests for any of the groups. This suggests functional and local specificity of these tests.

iv Discriminant Function Analysis

Discriminant function analysis was applied to the data to determine whether performance on the cognitive tests would correctly classify subjects into schizophrenic and control groups. The second part of this analysis used the derived classification coefficients from the schizophrenic and control subjects to classify the relatives into normal and abnormal P3 groups.

The following variables were entered into a stepwise discriminant function analysis for the schizophrenic and control subjects : errors made on the Wisconsin Card Sorting Test, total words recalled in verbal recall tests, verbal fluency category tests, times to learn in Hebb's Recurring Digits Test and Corsi's Block Tapping Test, and signal : noise ratio(SPEM). These variables were selected to include one measure of each of the cognitive functions, and ETD. P3 latency was

not included as the same classification coefficients were to be used to discriminant the relatives on the basis of P3 latency. Three of these variables were selected by stepwise discriminant function analysis to be included in the analysis :

Variables	Wilk's Lambda	Sig
Verbal fluency categories tests	.40299	.00001
Times to learn repeated sequence	.34589	.00001
Total words recalled	.33223	.00001

The classification function coefficients fo the two groups were :

	1	2
Total words recalled	0.5772384	0.6877628
Verbal fluency categories tests	-0.0033373	0.2251223

Times to learn repeated sequences	1.472196	1.004013
Constant	-15.82840	-26.42431

The standardized canonical discriminant function coefficients were :

Total words recalled	0.29786
Verbal fluency categories tests	0.80163
Times to learn repeated sequences	-0.41203

The analysis correctly classified 92% of the schizophrenic and control subjects.

The classification coefficients were used to classify the relatives into two groups according to P3 latency. Scores for group 1 (abnormal P3) and for group 2 (normal P3) were calculated by multiplying the appropriate classification coefficient by the score on the three variables and subtracting the constant. If the subject's

classification score for group 1 exceeded his classification score for group 2, he was placed in group 1, and vice versa. The classification scores and P3 latency for each subject are presented in Appendix B6.

The analysis correctly classified 79.3% of the relatives by P3 category.

v. Correlations of physiological variables with performance on cognitive tests.

For each group of subjects 12 cognitive variables were correlated with each of the three physiological variables. Therefore for the three groups combined, 5 of the existing correlations would be expected to reach significance at the .05 level by chance. Therefore, it is necessary to use some caution in interpreting these correlations.

a) P3 latency

Correlations of P3 latency with state rating variables and cognitive scores for the schizophrenic, relatives and control groups are presented in Table 8G.

TABLE 8G
PEARSON CORRELATIONS OF P3 LATENCY WITH AGE, IQ SCORES, STATE VARIABLES AND COGNITIVE VARIABLES FOR SUBJECTS

	1 Schizophrenic	2 Relatives	3 Controls
	30	30	30
Age	.56**	.05	.19
BPRS Thought Disorder	.42*		
Anxiety/Depression	-.13		
Withdrawal	.24		
Hostility	.11		
HRSD	.43**		
NART IQ	-.06	-.06	-.04
WAIS IQ	-.01	-.08	.03
IQ Diff.	-.06	.10	.15
WCST	.26	.08	-.01
Verbal Recall Recognition	.16	-.28	-.34
Hebb's Recurring Digits Span	.04	-.13	-.16
Times to learn	.16	.66 **	-.78 **
Corsi's Block Tapping Test Span	-.21	.13	.18
Times to learn	.32*	.27	-.05
Verbal Fluency Letters	.40*	.12	.30
Verbal Fluency Categories	-.14	-.09	.34*
(Fruit)	-.41*	-.34*	-.21
Benton Copying of designs (Spearman)	-.23	-.11	-.10

(* p<.05 ** p <.01)

NART = National Adult Reading Test
WAIS =Wechsler Adult Intelligence Scale
WCST = Wisconsin Card Sorting Test

The schizophrenic and relatives groups showed significant positive correlations with times to learn the repeated sequence in Hebb's Recurring Digits Test and Corsi's Block Tapping Test respectively indicating increasing P3 latency with increasing number of presentations required to learn the sequence. The schizophrenic group showed a significant negative correlation of P3 latency with one of the verbal fluency categories tests indicating increasing P3 latency with decreasing number of items named. The relatives group showed a similar correlation for this verbal fluency categories test. The correlations for P3 latency with Hebb's Recurring Digits Test and with verbal fluency category tests for the control subjects occur in the opposite direction, suggesting that poorer scores on these tests are associated with earlier P3 latency in the control group. Figure 8a shows the plot of P3 latency by errors made on the Wisconsin Card Sorting Test for the three groups. This highlights the difference in degrees of severity of physiological abnormality and cognitive impairment in the three groups.

b) P3 amplitude

Correlations of P3 amplitude with state variables and performance on cognitive tests are shown in Appendix B7. Significant negative correlations were found for P3 amplitude with premorbid IQ and current

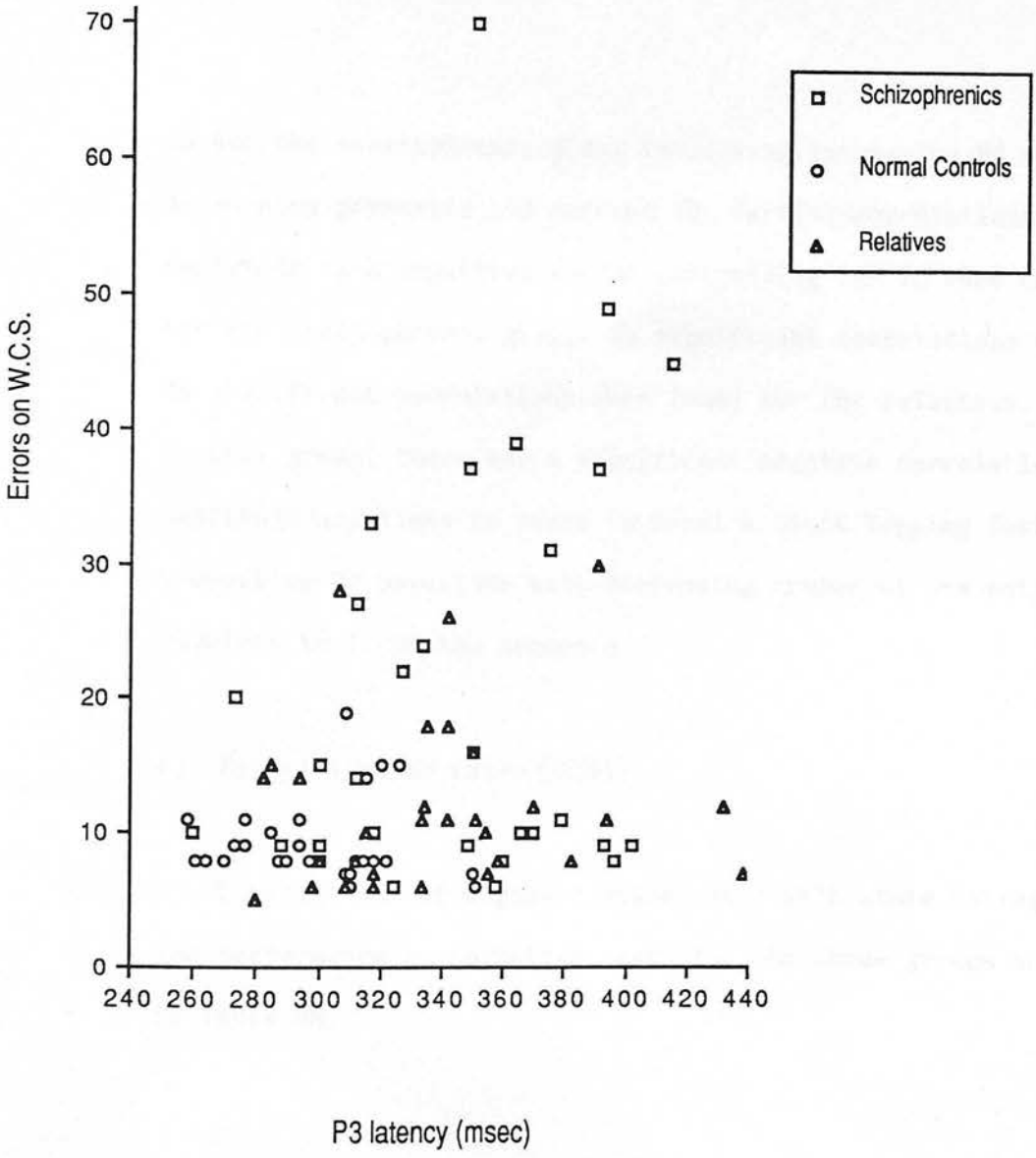

Figure 8a : Plot of Errors made on Wisconsin Card Sort Test (W.C.S.) by P3 latency in Schizophrenics, Relatives and Control Subjects

IQ for the schizophrenic group indicating increasing P3 amplitude with decreasing premorbid and current IQ. Partial correlations of P3 amplitude with cognitive scores controlling for IQ were carried out for the schizophrenic group. No significant correlations were found. No significant correlations were found for the relatives. For the control group, there was a significant negative correlation between P3 amplitude and times to learn in Corsi's Block Tapping Test indicating increasing P3 amplitude with decreasing number of presentations required to learn the sequence

c) Signal : noise ratio (SPEM)

Correlations of signal : noise ratio with state rating variables and performance on cognitive tests for the three groups are presented in Table 8H.

TABLE 8H
CORRELATIONS OR SIGNAL:NOISE RATIO (SPEM) WITH AGE, IQ SCORES, STATE VARIABLES AND COGNITIVE VARIABLES FOR SUBJECTS

	1 Schizophrenic	2 Relatives	3 Controls
	30	30	30
Age	-.09	-.36*	-.04
BPRS Thought Disorder	-.48**		
Anxiety/Depression	.06		
Withdrawal	-.37*		
Hostility	.02		
HRSD	.09		
NART IQ	.19	-.23	.33*
WAIS IQ	.29	-.24	.20
IQ Diff.	-.26	.08	-.21
WCST	-.43**	-.28	.01
Verbal Recall Recognition	-.12	-.12	-.36
Hebb's Recurring Digits Span	.34*	-.17	.18
Times to learn	.33*	-.02	-.13
Corsi's Block Tapping Test Span	.34*	-.05	.44*
Times to learn	.11	-.07	.07
Verbal Fluency Letters	.26	-.24	.38*
Verbal Fluency Categories	-.05	-.07	.21
Benton Copying of Designs (Spearman)	.40*	.28	-.05

(* p<.05 ** p <.01)

NART = National Adult Reading Test
WAIS = Wechsler Adult Intelligence Test
WCST = Wisconsin Card Sorting Test

For the schizophrenic group, significant correlations were found for signal : noise ratio with thought disorder, errors made on the Wisconsin Card Sorting Test, span in Hebb's Recurring Digits Test and Corsi's Block Tapping Test, and Benton's Copying of Designs showing that decreasing signal:noise ratio was associated with increasing symptomatology and cognitive impairment. However, a significant correlation was found for signal:noise ratio with times to learn in Corsi's Block Tapping Test and Hebb's Recurring Digits Test which showed that decreasing signal:noise ratio was associated with decreasing number of presentations required to learn the sequence. In the control group, premorbid IQ, span in Corsi's Block Tapping Test and verbal fluency letters tests correlated significantly with signal : noise ratio. indicating increasing signal:noise ratio with increasing performance on the cognitive tests.

vi Comparison of Good and Poor Wisconsin Card Sorting Test performers in the schizophrenic group.

The schizophrenic subjects were divided into two groups on the basis of errors made on the Wisconsin Card Sorting Test, using the control mean and two standard deviations (15.3) as the cut-off point. Means and standard deviations for age and physiological variables for the two subgroups are presented in Table 8J.

TABLE 8J

COMPARISONS OF PHYSIOLOGICAL VARIANCES AND POOR WCST PERFORMERS IN THE SCHIZOPHRENIC GROUP, MEANS (STANDARD DEVIATIONS)

	1	2	
	GOOD WCST	POOR WCST	p
	17	13	
P3 latency (msec)	339.6 (42.6)	349.5 (38.4)	.51
P3 amplitude (uV)	30.4 (12.1)	49.8 (37.5)	.05
Signal:Noise Ratio	487.2 (114.1)	387.5 (100.3)	.02

WCST = Wisconsin Card Sorting Test

The groups were not significantly different on age or P3 latency. P3 amplitude was significantly lower in the good WCST group ($F = 4.07$, $df = 1.29$). Signal : noise ratio was significantly impaired in the Poor Wisconsin Card Sorting Test group ($F=6.24$, $df=1,29$). Tables of the analyses of variance comparing the sub-group are presented in Appendix B8.

The means and standard deviations for state rating scores, and performance on the cognitive tests are presented in Table 8K.

TABLE 8K

COMPARISONS OF GOOD AND POOR WCST PERFORMERS IN THE SCHIZOPHRENIC GROUP, MEANS (STANDARD DEVIATIONS) (±) USING IQ AS A COVARIATE WHERE IQ CORRELATES WITH COGNITIVE TEST

	1 GOOD WCST 17	2 POOR WCST 13	p
BPRS Thought Disorder	2.0 (1.4)	4.5 (4.0)	.02
Anxiety/Depression	1.2 (1.5)	0.9 (1.2)	.62
Withdrawal	3.0 (3.5)	4.8 (3.3)	.15
Hostility	1.4 (1.8)	0.4 (0.9)	.08
HRSD	4.6 (4.1)	4.3 (3.7)	.82
Witkins Embedded Figures Test (+)	5.3 (2.3)	4.2 (1.6)	.94
Verbal Recall Emotive (+)	9.6 (2.1)	6.7 (1.6)	.001
Verbal Recall Category (+)	1.4 (2.5)	7.6 (1.6)	.005
Verbal Recall Total (+)	36.0 (6.9)	24.2 (3.7)	.000
Verbal Recall Recognition	13.1 (4.3)	11.3 (5.0)	.37
Hebb's Recurring Digits Corsi's Block Tapping Span	13.5 (1.2)	11.2 (1.5)	.000
Times to learn	9.3 (2.9)	9.3 (3.8)	.98
Verbal Fluency Letters	43.5 (9.9)	34.7 (11.8)	.05
Verbal Fluency Categories (+)	36.3 (7.3)	26.1 (6.1)	.03
Copying of Benton Designs	9.9 (0.3)	8.8 (2.0)	.08 (K-W)
NART IQ	115.5 (6.6)	102.0 (9.8)	.0001
WAIS IQ	115.0 (8.5)	92.8 (8.9)	.0000
IQ Difference	3.5 (4.0)	10.0 (6.1)	.0006

NART = National Adult Reading Test
WAIS = Wechsler Adult Intelligence Scale
WCST = Wisconsin Card Sorting Test

One way analyses of variance were used to compare the two subgroups on state rating scores and IQ. The Poor Wisconsin Card Sorting Test group had a higher level of thought disorder (F=5.65, df=1,29), a significantly lower premorbid IQ (F=20.36, df=1,29), lower present IQ (F=45.74, df=1,27) and a greater decline in IQ (F=15.03, df=1,27) than the Good Wisconsin Card Sorting Test group.

Analyses of covariance were used controlling for IQ to compare the performance of the two subgroups on the cognitive tests. (Appendix B8). The Poor Wisconsin Card Sorting Test group were significantly poorer on the recall of emotive words (F=12,57, df=1,29), recall of category words (F=19.66, df=1,29), total words recalled (F=17.44, df=1,29), span in Hebb's Recurring Digits Test and Corsi's Block Tapping Test (F=19.66, df=1,29), verbal fluency letters (F=4.20, df=1,25), and verbal fluency categories (F=5.35, df=1,19). Means and standard deviations for the two subgroups on the MRI measures are presented in Table 8L.

vii Differences between schizophrenic and control subjects on MRI measures.

No overall differences between the schizophrenic and control group were found in any of the brain structures studied. In both the control and schizophrenic groups the temporal lobe was significantly larger on the right compared to the left. The right-left difference effect for the temporal lobes did not differ between the groups ($t = 0.74$, $df = 59$) indicating that both the schizophrenic group and control group had a similar left-right asymmetry of the temporal lobe measurement. Paired
t-tests comparing right and left amydalae revealed that the amygdala was larger on the right than the left in control subjects but not in schizophrenic subjects. The right-left difference score for the amygdala was significantly different between controls and schizophrenics ($t = 2.03$, $df = 41$ $p < .05$).

Significant differences were found for ventricular brain ratio ($F=7.94$, $df=1,29$). The poor WCST group had a significantly higher ventricular brain ratio than the good WCST group.

viii Correlations of MRI measures with physiological and cognitive variables

Correlations of MRI measures with physiological variables, state rating variables and cognitive scores for the schizophrenic subjects are presented in Table 8M.

TABLE 8L
COMPARISONS OF MRI MEASURES FOR GOOD AND POOR WCST PERFORMERS IN SCHIZOPHRENIC GROUP MEANS (STANDARD DEVIATIONS)

	Good WCST 17	Poor WCST 13	P (ANOVA)
VBR	259.6 (86.8)	392.7 (168.3)	.01
TL DIFF	97.88 (74.2)	51.8 (48.8)	.06
CAUD DIFF	10.3 (7.6)	5.4 (5.2)	.06

WCST = Wisconsin Card Sorting Test

VBR = Ventricular Brain Ratio, High Res.

TL DIFF = Temporal Lobe Absolute Right-Left Difference

CAUD DIFF = Caudate Absolute Right-Left Difference

TABLE 8M

PEARSON CORRELATION COEFFICIENTS OF MRI VARIABLES WITH P3 LATENCY, SIGNAL: NOISE RATIO, STATE VARIABLES AND COGNITIVE TESTS FOR SCHIZOPHRENIC SUBJECTS CONTROLLING FOR AGE(A) AND IQ(+) WHERE AGE AND IQ CORRELATE WITH DEPENDENT VARIABLE

	Ventricular Brain Ratio (A+)	Amygdala Absolute Right-Left Difference	Caudate Absolute Right-Left Difference
P3 latency	.36*	.46*	-.37*
Signal:Noise	-.39*	-.24	.47**
BPRS Thought Dis	.48**	-.39*	-.27
Anxiety/Dep	.13	.35	.07
Withdrawal	.04	.10	.01
Hostility	.22	.32	-.04
HRSD	.27	.51*	.13
Duration	.48**	-.03	-.15
Wisconsin Card Sorting Test	.11	.25	-.34*
Wilkins Embedded Figures Test	-.14	-.63**	.36
Verbal Recall Emotive	-.47*	-.34	.21
Verbal Recall Category	-.29	-.23	.10
Verbal Recall Total	-.41	-.29	.19
Verbal Recall Recognition	-.29	.11	-.19
Hebb's Recurring Digits Span	-.57**	-.02	-.11
Times to learn	-.24	.03	-.03
Corsi's Block Tapping Test	-.09	-.05	.15
Times to Learn	.00	-.06	-.09
Verbal Fluency Letters	-.34	-.52*	.23
Verbal Fluency Categories	-.51*	-.26	.04
Benton's Copying of Designs	-.43*	-.12	.00
Premorbid IQ	-.34*	-.33	.20
Current IQ	-.40*	-.30	.20

* $p < .05$ ** $p < .01$

All these MRI measures correlated significantly with P3 latency. Ventricular brain ratio and absolute caudate difference also correlated significantly with signal : noise ratio. The data suggest that the Poor Wisconsin Card Sorting Test group show abnormalities which are associated with frontal lobe impairment. This is evident in the significant correlations of ventricular brain ratio with signal : noise ratio, verbal fluency category tests and Benton's Copying of Designs Test.

Absolute difference in right and left measures for amygdala and caudate did not differentiate the two subgroups, indicating that both Poor and Good Wisconsin Card Sorting Test subjects have abnormalities on these measures which increase with P3 latency. The data suggest that prolonged P3 latency may be associated with high ventricular brain ratio, involvement of the caudate and frontal lobe impairment, or with involvement of the amygdala or with both.

Correlations of the MRI variables with physiological variables and cognitive scores for the control subjects are presented in Table 8N.

TABLE 8N

PEARSON CORRELATION COEFFICIENTS OF MRI VARIABLES WITH P3 LATENCY, SIGNAL:NOISE RATIO, STATE VARIABLES AND COGNITIVE TESTS FOR CONTROL SUBJECTS, CONTROLLING FOR AGE(A) WHERE AGE CORRELATES WITH DEPENDENT VARIABLE

	Ventricular Brain Ratio (A+)	Hippocampus Right-Left Difference
P3 latency	.42*	-.35*
Signal:Noise	.20	.01
Wisconsin Card Sorting Test	-.20	-.13
Wilkins Embedded Figures Test	-.00	-.04
Verbal Recall Emotive	.06	-.25
Verbal Recall Category	-.12	-.00
Verbal Recall Total	-.09	-.11
Verbal Recall Errors	-.05	.15
Verbal Recall Recognition	-.42	.46*
Hebb's Recurring Digits Span	-.38	-.15
Times to learn	-.30	.36*
Corsi's Block Tapping Test	-.31	-.14
Times to learn	-.13	.50**
Verbal Fluency Letters	-.04	.15
Verbal Fluency Categories	-.09	-.06
Benton's Copying of Designs	.16	
Premorbid IQ	.15	-.18
Current IQ	.05	.07

* $p < .05$ ** $p < .01$

Ventricular brain ratio also correlated significantly with P3 latency for the control subjects. However, the difference between right and left hippocampus rather than amygdala correlated significantly with P3 latency for these subjects. Times to learn in Hebb's Recurring Digits Test and Corsi's Block Tapping Test correlated significantly with this hippocampus measure.

Correlations of temporal lobe structures with performance on tests which are sensitive to temporal lobe function, and with tests which are sensitive to frontal lobe function in the schizophrenic subjects are presented in Table 8P.

TABLE 8P

PEARSON CORRELATION COEFFICIENTS OF TEMPORAL LOBE STRUCTURES WITH PERFORMANCE ON TESTS SENSITIVE TO FRONTAL LOBE AND TEMPORAL LOBE FUNCTION IN SCHIZOPHRENIC SUBJECTS, CONTROLLING FOR IQ (+) WHERE IQ CORRELATES WITH TEST

	Amygdala Right	Amygdala Left	Parahippocampal gyrus Right	Parahippocampal gyrus Left	Parahippocampal gyrus Absolute Right-Left Difference (+)	Temporal lobe Absolute Right-Left Difference
P3 latency	.12	-.05	.31	.15	-.34	-.22
BPRS Thought Dis	-.29	-.34	.09	.01	.02	-.35*
Anxiety/Dep	-.01	.08	.35*	.41*	.05	.13
Withdrawal	.01	-.03	.19	.06	.09	-.24
Hostility	-.32	-.30	-.12	-.10	-.05	.00
HRSD	.03	-.11	.36*	.06	-.62	-.06
Wisconsin Card Sorting Test	-.06	-.04	.12	-.08	-.02	-.29
Verbal Fluency Letters	-.01	.06	-.24	-.19	.13	.39*
Verbal Fluency Categories	.01	.05	-.15	-.04	-.11	.68**
Benton Copying of Designs	.08	.05	-.12	.01	.12	.20
Hebb's Recurring Digits Times to learn	-.38*	-.32	-.34	-.31	-.40*	.25
Corsi's Block Tapping Test Times to learn	-.35	-.41*	-.38*	-.34	-.38*	.26
Premorbid IQ	.06	-.02	-.26	-.05	-.44*	.12
Current IQ	.13	.01	-.16	-.02	-.46*	.43*
IQ Difference	-.16	-.04	-.10	-.15	.21	-.60**

(* $p<.05$ ** $p<.01$)

The stronger correlations between these temporal lobe structures and the tests of temporal lobe function; times to learn in the Hebb's Recurring Digits Test and Corsi's Block Tapping Test add some validity to these tests, and also suggest that there is some degree of temporal lobe impairment in schizophrenia for these relationships to be evident.

ix Factor analysis using physiological and cognitive variables

Factor analysis was carried out for the schizophrenic and control subjects using the following variables : total words recalled in the verbal recall tests, verbal fluency category tests, errors made on the Wisconsin Card Sorting Test, times to learn the repeated sequences in Hebb's Recurring Digits Test and Corsi's Block Tapping Test, premorbid IQ, IQ difference, P3 latency and signal : noise ratio (SPEM). These variables were selected to include the physiological variables, IQ variables and a measure of each cognitive function. Principal components analysis produced two factors which accounted for 65.6% of the variance. Factor 1 accounted for 50.4% of the variance and factor 2 accounted for 15.3% of the variance. Varimax rotation was used to produce the following loadings for each variable on the two factors :

	Factor 1	Factor 2
Wisconsin Card Sorting Test	-.84095	.12192
Verbal fluency	.82178	-.26200
IQ difference	-.77310	.06504
Total words recalled	.75841	-.50840
Premorbid IQ	.71319	.20670
Signal : noise ratio (SPEM)	.62795	.20670
Times to learn sequences	.11145	.86099
P3 latency	-.35545	.62074

Factor 1 appears to reflect general ability with a high positive loading on IQ and a high negative loading on decline in IQ. It focuses on frontal lobe functions with a high negative loading on the Wisconsin Card Sorting Test, and high positive loadings on verbal

fluency and signal : noise ratio. The tests which have high loadings on factor 1 are those which differentiated the schizophrenic subgroups. P3 latency has a moderate negative loading on this factor and accounts for 13% of the variance.

P3 latency has a high positive loading on factor 2 and accounts for 39% of the variance. Times to learn the repeated sequences in Hebb's Recurring Digits Test and Corsi's Block Tapping Test have the highest positive loadings on this factor. Verbal recall also has a fairly high loading on this factor. This factor may represent temporal lobe function.

One way analyses of variance showed highly significant differences between the schizophrenic and control groups for factor scores. The two groups were significantly different on factor 1 ($F=24.59$, $df=1,40$) and on factor 2 ($F=12.20$, $df=1.41$).

8.2 Discussion

i Is there a difference in the cognitive scores for the different groups?

a) IQ

Although the normal controls had a higher IQ than the other two groups, the schizophrenic and relatives groups were fairly well matched for premorbid IQ. When the relatives were divided into two subgroups on the basis of P3 latency it was evident that the schizophrenic subjects suffered a significantly greater decline in IQ than both the normal controls and the normal P3 relatives. There was no difference in amount of decline in IQ between the schizophrenic subjects and the abnormal P3 relatives, suggesting that relatives with abnormal physiological response have suffered some intellectual impairment even though they do not manifest clinical symptoms.

b) Cognitive tests

Hypothesis (i) stated that performance on the tests of frontal lobe function and temporal lobe function would differentiate the schizophrenic and control subjects.

1) Performance of the schizophrenic subjects on tests sensitive to frontal lobe function.

Performance of the schizophrenic group on the cognitive tests compared with the control group was as expected supporting hypothesis (i). With increased numbers of subjects in each group, the difference between the groups on the Wisconsin Card Sorting Test became significant. The two groups were also significantly differentiated on all the verbal free recall tests as in Study I. However, in the tests of left and right frontal lobe function, the schizophrenic subjects showed left sided deficits but not right sided deficits. The schizophrenic subjects were impaired relative to the control subjects on both the verbal fluency letters and verbal fluency categories tests.

2. Performance of the schizophrenic subjects on tests sensitive to temporal lobe function.

As expected, there was no difference in verbal recognition between the two groups. Recognition has been shown to be independent of hippocampal function, while other types of memory such as paired-associates have been associated with hippocampal function. Thus the hypothesis that abilities associated with medial temporal lobe

function and especially hippocampal function would be impaired in schizophrenia while other memory capacities not related to the hippocampus or to the frontal lobes would be intact was supported.

Evidence for possible impairment of the hippocampus in the schizophrenic patients was provided by the significant difference in times to learn the repeated sequence in Hebb's Recurring Digits Test and Corsi's Block Tapping Test for these subjects compared with the control subjects. No main effect for test was found, suggesting that the schizophrenic subjects were impaired on both tests relative to control subjects. Span was also significantly reduced for the schizophrenic subjects compared with the control subjects. There was a main effect for test indicating that subjects generally had a superior digit span compared with block span. However, lack of interaction effect for Group by Test showed that span for either test was not affected differentially by group membership. The data suggest that the schizophrenic subjects showed deficits related to both left and right hippocampus.

Hypotheses (ii) to (iv) stated that the schizophrenic and abnormal P3 relatives would show similar performance on tests of frontal and temporal lobe function, while the performance of the normal P3 relatives would be significantly different, but similar to that of controls.

3) Performance of the relatives on tests sensitive to frontal lobe function.

Hypothesis (iii) stated that the abnormal P3 relatives would show similar performances on the cognitive tests to the schizophrenic subjects,and hypothesis (iv) stated that the normal P3 relatives would show similar performances to the control subjects. The relatives were not differentiated from each other or from the controls by the Wisconsin Card Sorting Test. However, on all the verbal recall tests, the abnormal P3 relatives were significantly differentiated from the normal control group and the normal P3 relatives were significantly differentiated from the schizophrenic group. The frontal lobe function tests suggested left hemisphere involvement in the abnormal P3 relatives. The abnormal P3 relatives were significantly differentiated from the control subjects on both the verbal fluenecy letters and verbal fluency categories tests. Normal P3 relatives were significantly differentiated from the abnormal P3 relatives on the verbal fluency categories tests. No difference was found between the groups of relatives on Benton's Copying of Designs Test, indicating no difference in right frontal lobe function.

4) Performance of the relatives on tests sensitive to temporal lobe function.

As expected there was no difference between the two groups of relatives on verbal recognition.

The abnormal relatives were differentiated from the control subjects on the hippocampal tests, both on span and on times to learn the repeated sequence. Again deficits were found on tests indicating both right and left hippocampal impairment. The normal P3 relatives were significantly differentiated from the schizophrenic subjects on times to learn the repeated sequence but not on span. Therefore hypotheses (ii), (iii) and (iv) were supported.

In conclusion the data suggest specific left frontal lobe and bilateral medial temporal lobe deficits in schizophrenia. Deficits in free recall are also suggested to be associated with frontal lobe impairment. Performance on tests sensitive to left frontal lobe function was more impaired in the schizophrenic group than in any of the other groups. Performance on the test which has been associated with right frontal lobe function was not impaired in schizophrenic subjects. Performance on tests sensitive to both right and left hippocampal function was impaired in the schizophrenic subjects. Lack

of impairment in tests of recognition suggest that these deficits are specific to the hippocampus and do not reflect global memory impairments in schizophrenia.

The abnormal P3 relatives show similar deficits to the schizophrenic subjects. They are impaired on tests of left frontal lobe function, though to a lesser extent than the schizophrenic subjects on the verbal fluency categories tests. They are also impaired on the free recall tests. However, performance on the Wisconsin Card Sorting Test was not impaired suggesting that frontal lobe impairment in the abnormal P3 relatives is not as severe or can be compensated for to a greater extent than in the schizophrenic subjects. Left and right hippocampal impairment is as pronounced as that found in the schizophrenic subjects. In comparison, the normal P3 relatives showed no significant impairments compared with the control subjects. They were significantly differentiated from the abnormal P3 relatives on the basis of left frontal lobe function as measured by the verbal fluency letters test, and on the basis of hippocampal function as measured by times to learn the repeated sequence. Therefore, the impairments seen in the abnormal P3 relatives appear to be due to their abnormal physiological response rather than to the fact that they are relatives of schizophrenic patients.

The most discriminating variables for classifying the schizophrenic and control subjects included verbal fluency categories tests, times to learn the repeated sequences and total words recalled in the verbal recall tests. Performance on the Wisconsin Card Sorting Test and signal : noise ratio were excluded from the analysis. The same discriminant function correctly classified 79.3% of the relatives into abnormal P3 latency and normal P3 latency groups, supporting the hypothesis that the abnormal P3 relatives and the normal P3 relatives differ on the same criteria as the schizophrenic subjects and the control subjects. Therefore, it is proposed that the cognitive performance of the abnormal P3 relatives is no different to that of the schizophrenic subjects, while the cognitive performance of the normal P3 relatives is no different to that of the control subjects. The results indicate that the cognitive functions which have been studied are associated with abnormal P3 latency rather than specifically with schizophrenia. However, this supports the view that delayed P300 latency is a biological marker for the schizophrenia trait in these families.

ii Do the physiological variables correlate with the cognitive scores?

a) P3 latency

Hypothesis (v) stated that P3 latency would correlate with performance on the frontal lobe and temporal tests in the schizophrenic and relatives groups. P3 latency was significantly correlated with times to learn in Corsi's Block Tapping Test in the schizophrenic subjects and for times to learn in Hebb's Recurring Digits Test in the relatives. This suggests that in the schizophrenic subjects, abnormal physiological response is associated more with right sided hippocampal impairment while in the relatives abnormal physiological response is associated more with left sided hippocampal impairment. However, correlations for the contralateral tests for both the schizophrenic and relatives groups respectively approached significance, indicating bilateral impairment in both groups.

Correlations of P3 latency with left frontal lobe related tests were significant for both the schizophrenic and relatives groups. Significant correlations were found in both groups for the verbal fluency 'fruit' category, which is intermediate in level of difficulty. There was no significant correlation of P3 latency with the easiest verbal fluency category 'animals'. It is suggested that

this category is a very common category and that it is relatively easy to recall names of animals without a great deal of demand on memory functions or search of associative networks in long term memory. However, naming different fruits is more difficult and requires search of the appropriate associative networks. The hypothesis states that subjects with normal P3 latency will be able to access and use associative networks to impose structure and order on their search, while subjects with abnormal P3 latency will be limited to recalling the more easily accessible responses. Verbal fluency 'flowers' did not correlate significantly with P3 latency for the schizophrenic and control subjects and it is thought that this category may have required too much specialized knowledge to make it a valid study of memory retrievability. A significant correlation was found for P3 latency with verbal fluency letters for the schizophrenic group.

Therefore, the data suggest that within both the schizophrenic and relatives groups, P3 latency correlates with left frontal lobe and bilateral hippocampal impairment supporting hypothesis (v). In contrast, the correlations of P3 latency for the control group suggest that the more prolonged the P3 latency is, the better the performance on the verbal fluency test and times to learn the repeated sequences. However, the range of P3 latency and also of performance on the cognitive tests was much narrower for the control group than for the other two groups, and it is proposed that the possible frontal lobe

and hippocampal impairment which is suggested in the schizophrenic and relatives groups occur only with the gross physiological abnormalities which are not seen in the control group. It could be argued that the correlations between P3 latency and cognitive scores in the schizophrenic group, because they are not supported in the control group, are due to the fact that the subjects are schizophrenic patients. However, the correlations of P3 latency with cognitive scores in the relatives group support those found in the schizophrenic group suggesting that cognitive deficits are found when P3 latency is sufficiently prolonged.

b) P3 amplitude

P3 amplitude was found to correlate significantly with times to learn in Corsi's Block Tapping Test for the control subjects. As has already been suggested, P3 amplitude may reflect the attention or concentration given by a subject or the amount of processing of the stimulus. Changes in P3 amplitude have been stated to be more transient and perhaps related to mood than P3 latency which is a robust trait and hypothesized to be indicative of enduring cognitive change. Therefore, P3 latency is a better predictor of cognitive performance in the schizophrenic group and also in the relatives group, while P3 amplitude seems to be informative about a subject's mental state and level of attentiveness.

c) Signal : noise ratio (SPEM)

Signal : noise ratio correlated significantly with tests of frontal lobe function, being the Wisconsin Card Sorting Test and Benton's Copying of Designs Test in the schizophrenic subjects. However, it did not correlate with performance on the verbal fluency tests, suggesting that ETD may reflect right frontal lobe dysfunction in schizophrenic patients to a greater extent than left frontal lobe dysfunction. Correlations with signal : noise ratio were not significant in the relatives group, reflecting the relative lack of ETD compared with the schizophrenic group.

iii Are there subgroups in the schizophrenic group showing different deficits?

Hypothesis (vi) stated that sub-groups in the schizophrenic group identified by performance on the Wisconsin Card Sorting Test would show different deficits.

Subgroups within the schizophrenic group were compared to test whether the proposed frontal lobe and hippocampal impairments which were indicated in study I were found. While both subgoups showed similar P3 latencies, the Good Wisconsin Card Sorting Test group had a

smaller P3 amplitude while the Poor Wisconsin Card Sorting Test group had a poorer signal : noise ratio. Poor signal : noise ratio (SPEM) is associated with frontal lobe impairment and performance on the cognitive tests also supported this. The Poor Wisconsin Card Sorting Test group was impaired on the recall tests, and the verbal fluency letters and verbal fluency categories tests compared with the Good Wisconsin Card Sorting Test group.

The findings indicate that the Poor Wisconsin Card Sorting Test group suffer from a frontal lobe impairment which is more severe on the left side than on the right side. This group also showed a large decrease in IQ suggesting that intellectual deterioration is associated with frontal lobe involvement in schizophrenia.

Times to learn the repeated sequences in Corsi's Block Tapping Test and Hebb's Recurring digits Test were the same for both subgroups. The prediction that the good Wisconsin Card Sorting Test group would show more hippocampal impairment than the Poor Wisconsin Card Sorting Test group was not supported. However, it has been established that hippocampal impairment is found in the schizophrenic patients compared with the control subjects. Therefore, both subgroups seem to manifest hippocampal impairment to the same extent.

If two subgroups within the schizophrenic population can be identified on the basis of these data, it appears that one subgroup manifests more
frontal lobe impairment but the same degree of hippocampal impairment compared with the other subgroup. However, the Good Wisconsin Card Sorting Test group was impaired on the the frontal lobe function tests compared with the control subjects even though they performed significantly better than the Poor Wisconsin Card Sorting Test group on these tests. On the other hand no significant difference was found between the Good Wisconsin Card Sorting Test group and the control group on decrease in IQ. Therefore, both groups are impaired on the tests of frontal lobe function and hippocampal function compared to normal controls but the Poor Wisconsin Card Sorting Test group is more impaired than the Good Wisconsin Card Sorting Test group on tests of frontal lobe function. Therefore, hypothesis (vi) was partially supported but it may be more appropriate to describe these subjects as lying on a continuum with temporal lobe dysfunction being stable and with frontal lobe dysfunction increasing in severity.

iv Are there differences in the MRI scores between schizophrenic and control subjects?

Hypothesis (vii) stated that there would be differences in the MRI measurements between schizophrenic subjects and control subjects.

In both the control and schizophrenic groups, the left temporal lobe was significantly smaller than on the right. The size of the right-left difference in the temporal lobes did not differ between the groups indicating that both the schizophrenic and control groups had a similar right-left asymmetry of the temporal lobe measurement. However, when the schizophrenic group was sub-divided into good and bad Wisconsin Card Sorters, the former had a larger right-left difference in size of the temporal lobe than the control subjects, while the latter had a smaller right-left difference than the control subjects. A similar pattern was found for right-left caudate differences. The left amygdala was smaller than the right in control subjects but not in schizophrenic subjects. The absolute right-left difference score for the amygdala was significantly different between the control and schizophrenic subjects. However, the absolute right-left difference score for the amygdala was not significantly different between the Good Wisconsin Sorters and the Poor Wisconsin Sorters. In the schizophrenic group, but not in controls, the parahippocampal gyrus was smaller on the left than on the right. However, the absolute right-left difference score did not differ significantly between the two groups.

Ventricular brain ratio significantly differentiated the two subgroups but it did not differentiate them from the control group. The Poor Wisconsin Card Sorting Test group had a higher ventricular brain ratio than the other subgroup, and the difference was slightly greater for the right side.

This difference in ventricular brain ratio between the subgroups suggest that there may be an association between this measures and frontal lobe function and intellectual function. The Poor Wisconsin Card Sorting Test group performed worse than the Good Wisconsin Card Sorting Test group on the tests of frontal lobe function indicating that changes in ventricular size may be associated with gross cognitive impairment and that lesser degrees of impairment may occur without significant structural change. The tests of hippocampal function were not significantly different between these two subgroups suggesting that ventricular brain ratio does not affect hippocampal function, but that hippocampal impairment can occur without significant structural changes to the ventricles.

The MRI data suggest that structural changes are found in schizophrenic brains and these are evident as disturbances in asymmetry in temporal lobe structures which occcur in schizophrenic

patients as a whole, and in ventricular brain ratio which occurred in about one-half of the schizophrenic subjects in this study, supporting hypothesis (vii).

v Do the MRI measures correlate with the physiological and cognitive variables?

Hypothesis (vii) stated that MRI measurements would correlate with physiological and neuropsychological measusres.

The MRI measure which differentiated the schizophrenic patients from the control subjects, the right-left difference in the amygdala, correlated with P3 latency. The ventricular brain ratio, and the absolute right-left difference in caudate also correlated with signal : noise ratio. As expected, the right-left difference in amygdala did not correlate with signal : noise ratio Therefore, the structural changes which were found in the schizophrenic subjects correlated with the physiological abnormalities.

Ventricular brain ratio and right-left difference in amygdala correlated with thought disorder, indicating that these measures are associated with positive symptoms. However, right-left difference in amygdala also correlated with depression.

Performance on cognitive tests also correlated with the structural changes in schizophrenia. Performance on tests of frontal lobe function correlated significantly with ventricular brain ratio. Tests of right and left hippocampal function did not correlate with ventricular brain ratio. Therefore, ventricular brain ratio predominantly reflects frontal lobe function. Tests of hippocampal function were more strongly correlated with measures of right and left parahippocampal gyrus difference. These structures were found to show abnormalities in the schizophrenic subjects.

Correlations betweem MRI measures and P3 latency in the control subjects showed the same patterns as those found in the schizophrenic subjects. P3 latency was significantly associated with ventricular brain ratio and right-left hippocampal difference, thus implicating the frontal lobes and temporal lobes with P3 latency. Times to learn the repeated sequences in Hebb's Recurring Digits Test and Corsi's Block Tapping Test correlated with right-left hippocampal difference. However, the fact that only a few significant correlations between MRI measures and cognitive scores were found in the control subjects suggests that these subjects may not have shown sufficient impairment on cognitive tests and structural change to demonstrate the relationships as they were shown in the schizophrenic group. Therefore, hypothesis (vii) was supported more strongly in the schizophrenic group than in the control group.

Chapter 9

STUDY III METHOD

9.1 Rationale and aims

Study III aimed to compare visual ERP responses to word stimuli of different emotive tone in depressed, recovered depressed and control subjects. It aimed to examine whether any differences found in the P3 response to emotive stimuli were associated with level of depression.

i Physiological measures

Having established in Study I that there were no significant differences in the latencies of P3 components in ERPs evoked in neutral auditory tasks between unipolar depressed patients and normal control subjects, study III aimed to compare the P3 responses of these two groups in different emotive conditions. Although it has been determined that P3 latency is a relatively stable trait, which is not vulnerable to the effects of time, state or drug treatment, the findings of Study I suggested that P3 amplitude may be affected by state in auditory ERP recordings. This study aimed to examine whether

P3 amplitudes and latencies to visual word stimuli would differ in unipolar patients and control subjects, and whether the two groups would show differential responses to emotive words of varying hedonic tone. The study also aimed to examine whether physiological changes correlated with severity of depression.

The rationale for testing a group of subjects who had recovered from the same illness which was currently being manifested by the depressed group was to determine whether the recovered depressed group showed any residual features of their depressive episode and hence any physiological vulnerability marker. Previous studies have looked for evidence of abnormalities in cognition in subjects who have rcovered from a depressive illness with conflicting results, indicating that recovered depressed subjects may be vulnerable to dysfunctional cognitions particularly in times of stress. This study aimed to test whether the recovered depressed subjects showed physiological responses which were more similar to the depressed subjects than to the control subjects, when exposed to emotive stimuli.

ii Relationship between physiological variables and cognitive function

The aim was to test the hypothesized relationship between P3 abnormalities and cognitive dysfunctions with regard to depressed patients. The hypothesis concerning the relationship of P3 to

information processing claims that P3 is evoked by an unexpected stimulus and that a normal P3 response is the manifestation of activating unprimed chains of associations. Therefore, when comparing the P3 responses evoked by two stimuli, it should be possible to infer that the stimulus which evokes the largest amplitude of the P3 response will be the most unexpected. The study hypothesizes that due to their cognitive styles, depressed subjects and normal control subjects have different expectations. The study aimed to test whether these different expectations will be manifested in their different physiological responses.

iii Cognitive theories of depression

This study aims to support cognitive theories of depression. Beck's (1967) cognitive theory of depression proposed that depressed individuals' style of thinking is determined by irrational dysfunctional beliefs and attitudes which act as the schemata by which he construes his world. Weissman and Beck (1978) reported a significant relationship between the strength of an individual's dysfunctional attitudes and the intensity of his depression. Beck stated that, central to the depressed subject's way of thinking were negative views of the self, the world and the future, and generally pervasive negative content of thought. The depressed person exaggerates the negative content of a situation and overgeneralizes it

to other situations. Events are interpreted in a negative way, and even distorted to fit in with pervasive negative themes. The negative bias in thinking is maintained through the operation of basic schemata (attitudes) which lead the individual to process information in particular biased ways. Cognitive theories of depression (Beck, 1967) and the learned helplessness theory of depression (Seligman 1981) propose that depressed patients expect negative events more than positive or neutral events. The study aimed to support this assumption by providing physiological evidence that depressed patients expect negative events more than positive events, and that recovered depressed subjects show physiological responses which are more similar to those of depressed subjects than to control subjects due to their cognitive vulnerability.

9.2 Design

The study was designed to compare the visual ERPs and scores on subjective and objective rating scales of three groups of subjects. All the tests were administered in one session for all subjects. Different subjects were used for the depressed and recovered depressed groups. The depressed patients were at least moderately depressed at the time of testing, and the recovered depressed group had been clinically recovered for at least three months and in most cases

considerably longer at the time of testing. It was decided to use two separate groups of subjects for the depressed and recovered depressed groups as the depressed group may not have reached a sufficient level of recovery within the time span allowed for this study.

9.3 Subjects

Fifteen unipolar depressed patients, fifteen recovered unipolar depressed subjects and fifteen control subjects participated in the study. The depressed subjects were mainly in-patients in the Professorial Unit at the Royal Edinburgh Hospital except for two who were being treated as out-patients on a regular basis. All were taking antidepressant medication.

The normal control subjects consisted of a cross-section of hospital staff, who were interviewed by a clinical psychologist to determine that they had no past history of, nor current evidence of psychiatric disorder.

The group of recovered depressed subjects consisted of subjects who had previously been in- or out-patients at the Royal Edinburgh Hospital. They had subsequently not been clinically depressed for at

least the three months preceding the study. Seven of these subjects were taking prophylactic antidepressant medication. Five had been treated with cognitive therapy.

i Criteria for selection

The depressed subjects and the recovered depressed subjects at the time of illness were required to fulfill RDC for primary major depressive disorder. The depressed group was required to score seventeen or over on the HRSD, and therefore, to be suffering from at least a moderate level of depression. The recovered depressed group was required to score ten or less on the HRSD and therefore, to have recovered sufficiently from their depressive illness to score only up to a mild level of depression, and thus not to be considered as clinically depressed. They were required to have been recovered from a clinical level of depression for at least three months at the time of testing. In fact, all except one had been recovered for six months or more.

The control subjects were required to consist of the same numbers of males and females as the depressed group and to be fairly closely matched for age. The number of recovered depressed subjects who were willing to participate in the research project within the space of

time allowed for the study was too small to allow matching of these subjects with the other two groups. Many of the recovered depressed subjects who were contacted expressed the wish not to have to be reminded of their previous episode of illness.

Subjects with evidence of neurological disease were excluded from the study.

ii Description of subjects

The depressed group and the control group each consisted of four males and eleven females. The mean age for the depressed group was 42.3 (standard deviation 14.3), and for the control group the mean age was 42.3 (standard deviation 13.5). The recovered depressed group consisted of three males and twelve females. This group had a mean age of 44.5 (standard deviation 10.2).

9.4 Measures and rating scales

i Diagnostic

The RDC was used for diagnosing the subjects in the depressed and recovered depressed groups. The RDC has been described in section 5.4.i.

ii Rating scales

Two rating scales were used to measure severity of depression in all subjects. The HRSD which is an observer-rated scale and the Beck Depression Inventory (BDI) which is a self-rated scale were used. The HRSD has been described in section 5.4.ii.

The BDI (Beck et al 1961) was derived from Beck's cognitive theory of depression. It consists of a list of twenty-one descriptive symptoms which were found to discriminate between depressed and non-depressed psychiatric patients. These symptoms refer to characteristic aspects of depression for example, pessimism, social withdrawal, suicidal wishes, a sense of failure and physical symptoms. For each symptom, there are four or five statements in the first person,

ranging from a mild or neutral statement to one indicating a severe form of that particular symptom. Each statement is assigned a score of 0, 1, 2 or 3 to indicate the degree of severity of the symptom. The maximum score on the BDI is 63. There is evidence for the construct and concurrent validity of the BDI.

A significant relationship has been found for self-reported depression on the BDI with masochistic dreams (Beck and Ward 1961 in Beck 1967); with high scores indicating a negative self concept on a self-concept test (Beck and Stein 1960); with a tendency to see self as a failure in response to pictorial stimuli (Beck et al 1963, Beck 1967); the tendency to make extremely pessimistic predictions about future performance following inefficient task performance (Loeb et al 1964); and the tendency to underestimate successful performance (Loeb et al 1966).

Beck et al (1961) reported correlations of BDI scores with physicians' ratings of 0.65 to 0.67 in an American population, and Metcalfe and Goldman (1965) reported correlations between the same two variables of 0.61 in a British population. Little and McPhail (1973) found that the BDI correlates highly with the other self-rating scales.

Beck et al (1961) reported that the reliability of the scale has been found to range from 0.86 to 0.93. With regard to concordance rates between the BDI and observer rating scales such as the HRSD, correlations of 0.75 (Schwab et al 1967) and 0.82 (Williams et al 1972) have been reported. Other investigators have noted that these correlations were highest near recovery and lowest at the acute stage of illness (Carrol et al 1973, Paykel 1973). Possible explanations for this finding are the distorting effects of illness on self-perception, lack of insight and response sets. As Prusoff (1972) states, the physicians' rating may be more reliable than the BDI self-rating score when the patient is acutely ill. Therefore, the importance of including an observer rating scale such as the HRSD is evident.

iii Physiological measures

Visual ERP recordings were made using three lists varying in emotive content as stimuli. Twenty negatively toned words, twenty positively toned words and twenty neutral words were used. These words were matched for length and initial letters and for frequency of usage in the English language (Thorndike and Lorge 1944). The lists of words were compiled by Beck as being salient for autonomous and socially dependent personalities. Each word was duplicated so that the final three lists each consisted of forty words. This was done so that, when

the ERP reponses were recorded to these words, enough words would be presented per list to ensure a high signal : noise ratio. A slide was prepared for each word. The words were written in white lower case letters against a blue background. The slides were projected by tachistoscope through a one way mirror. Precise time of projection of slides was determined by microcomputer. Each word was presented for 40 msec. and the interstimuli interval was 8 seconds.

A pilot study had shown that the optimal time of presentation of the stimulus to both enable the subject to read the word fairly easily and to produce a large amplitude P3 response was 40 msec. The large interstimuli interval was necessary to ensure that the subject's response to a word was not contaminated by his response to the previous word.

A multi-channel averaging system also controlled by micro-computer was used to record the ERPs for each word. Bipolar recordings were made between EEG electrodes at standard frontal, vertex and occipital midline positions and an indifferent earclip electrode at the left earlobe. A reference ground electrode was positioned at the right earlobe. Measured impedances were less than 5 k in all cases. The EOG was recorded between electrodes at the lateral canthus and at the supraorbital ridge above the midline of the left eye.

The EEG signal was amplified 10,000 times and passed through analogue filters with a bandpass of 0.05 to 30 Hz (-3 db points with roll-off of 6 db per octave). The signal was amplified over one second time epochs at 250 Hz sampling rate and digitized by an 8 bit analogue-to-digital converter. A total of 250 msec. of EEG was captured prior to the presentation of the visual stimulus to serve as a baseline. The EEG epochs for each electrode were averaged and on-line monitoring of the signal was facilitated by use of an oscilloscope. For each lead, the responses to target and to non-target stimuli were averaged separately. One second epochs of EOG were averaged in a similar manner to the EEG and no time-locked responses could be found to target or non-target stimuli in any subject. An artefact-rejection mechanism was implemented that excluded all sweeps exceeding $\pm$ 45 microvolts in amplitude on any EEG lead or $\pm$ 450 microvolts on the EOG leads. All data collection was performed in an adjacent room; the EEG leads from the subject passing through a connecting port.

All averaged data were stored on a floppy disc. Responses to negative, positive and neutral word stimuli were averaged and stored separately. Computer generated cursors allowed measurement of the latencies and amplitudes of the P3 with respect to the prestimulus baseline.

iv Cognitive measures

a) The Dysfunctional Attitude Scale (DAS)

The DAS (Weissman and Beck 1978) was developed to elicit information on the individual's irrational, dysfunctional beliefs. The theoretical background for the development of the scale was provided by Beck's cognitive theory of depression. The scale aimed to describe the depressogenic schemata by which the patient construes his world. Beck (1967) proposed that 'the affective response is determined by the way an individual structures his experience', and that the depressed individual tends to distort his experiences in a negative way. They misinterpret specific irrelevant events to mean personal failure, deprivation, or rejection. They exaggerate or overgeneralize any negative information about themselves. The DAS aimed to meet the lack of objective methods at the time to quantify the relative presence or absence of these cognitive distortions in individuals. The DAS aimed to identify the common assumptions underlying depressogenic cognitions which act as schemata with which the individual construes his world. The DAS aimed to provide a valid and reliable measure by which the relationship between attitudes and depressive tendency could be evaluated.

Weissman collected together an initial pool of items to reflect the common distorted beliefs of depressed individuals. This was administered to a group of residents in psychiatry at the University of Pennsylvania for their opinions on face validity and comprehensibility of the items. The resulting list consisted of 100 items. For each belief or attitude, a choice of seven response categories were presented ranging from totally agree to neutral to totally disagree. Weissman determined whether agreement or disagreement indicated an adaptive or maladaptive reaction. The items were scaled on a modified Likert (1932) model, with the most adaptive end of the range scoring the lowest number of points. The DAS score is the total for all the items. Therefore, the higher the score the more distorted is the individual's way of thinking.

275 undergraduate students completed this first draft of the DAS. Factor analysis of their responses resulted in two parallel forms of the test (DAS-A and DAS-B) consisting of 40 items with a maximum score of 280. Seventy undergraduate students completed DAS-A and a week later DAS-B. The correlation between the total scores on DAS-A and DAS-B was 0.79. The reliability scores for DAS-A and DAS-B were 0.86 and 0.87.

A validation and reliability study was carried out using 355 students. Half the students completed DAS-A followed by DAS-B. The other half completed DAS-B followed by DAS-A. All completed the BDI, the Profile of Mood States (McNair et al 1971) and the Story Completion Test (Hammen-Krantz 1976) as a measure of idiosyncratic thinking.

Each item correlated significantly with total DAS score, ranging from 0.25 to 0.76. Coefficient alpha for pretest and posttest for DAS-A and DAS-B ranged from 0.89 to 0.92. Test-retest reliability after eight weeks was 0.84. The DAS correlated with the Story Completion Test 0.52; with the Profile of Mood States 0.40; and with the BDI 0.36. This supported the assumption that individuals who endorse a greater number of depressogenic cognitions tend to feel more depressed. Hamilton and Abramson (1983) found that depressed in-patients evidenced higher scores than non-depressed psychiatric controls or a non-depressed normal control group.

Cane (1986) used the DAS to test 664 University students. A factor analysis of the responses showed that 61% of the variance was accounted for by two factors : performance evaluation and approval by others.

Factors that represent concerns about performance evaluation and interpersonal approval were recorded by Beck (1983b) to underly different vulnerabilities to depression. To examine the question of whether differential depressogenic attitudes occur in two different types of personality, Beck developed the Sociotropy-Autonomy Subscale (SAS, Beck 1983). Beck hypothesized that for those autonomous and socially dependent personalities, different events would precipitate depression.

b) The Sociotropy-Autonomy Scale (SAS).

The SAS was developed to provide a measure of sociotropic and autonomous personality traits. Beck hypothesized that in addition to cognitions and schemata, each individual has an even more stable personality structure that can a) predispose him to depression in response to particular categories of environmental stressors b) determine the pattern of symptoms i.e. cognitions and behaviours in depression and c) influence response to particular forms of treatment.

These personality characteristics represent central value systems or superordinate schemata. Beck hypothesized that these 2 major personality characteristics: sociotropy and autonomy describe modes

that can dominate an individual's psychological functioning. An individual may be predominantly sociotropic or autonomous or may be a mix of the two.

The autonomous individual is described as investing in independent functioning, mobility, choice, and achievement and integrity of his domain. Blocking of these valued conditions is perceived as a major loss by the autonomous individual. The sociotropic individual invests in positive interchange with others, focusing on acceptance, intimacy, support and guidance. Obstruction of these interpersonal resources is seen as a loss to these individuals. As with other personality measures, autonomy and sociotropy are considered to be long standing, stable characteristics developed from an early age.

A questionnaire consisting of 65 sociotropy and 65 autonomy items was developed at the Centre for Cognitive Therapy in Philadelphia. These two scales were based on patients' self-reports and clinical material collected from therapists. The items were selected according to clarity of wording and content validity with an attempt to represent the range of content suggested by Beck's definitions of the two personality modes.

Initial item analyses were conducted on samples of 66 outpatients at the Centre for Cognitive Therapy and 72 non-clinical individuals comprising undergraduates and older adults from community college classes. The internal consistency of each scale was high, with the alpha coefficients for the autonomy scale being .86 and .91 for the clinical and non-clinical samples respectively, and .93 for both groups for the sociotropy subscale. Item-total correlations ranged from .07 to .61 for the autonomy scale and from .03 to .65 for the sociotropy scale. The correlations between the sociotropy and autonomy totals was -.13.

Factor analyses on each of the sets of sociotropy and autonomy items produced factors of sensitivity to rejection, sharing with others, subordinating one's own needs to those of others, concern about being alone, dependence on others' love and support, and dependence on others' advice and guidance for the sociotropy scale. The autonomy factors included desire for independent standards and action, dislike of intrusions and restrictions, resisting help, desire for freedom and self control and freedom from others' influence.

Beck claimed that clinical use of the SAS has indicated a noteable correspondence between patients' questionnaire responses and independent personality ratings by their therapists. He concluded that the SAS appears to have good promise as a research and clinical

tool. The present scale consists of 60 items, half of which have relevance for sociotropy and the other half for autonomy. The items appear in random order. The items take the form of statements and the subject is required to indicate how much of the time he feels that the statement applies to him. He may tick one of the columns to indicate 0%, 25%, 50%, 75% or 100%. Each item can obtain a score of 0 to 4. 0 indicates a low degree of sociotropy or autonomy while 4 indicates a high degree. Separate scores for sociotropy and autonomy are yielded by summing the scores for the relevant items for both categories. The minimum score that can be obtained for both the sociotropy and autonomy subscales is 0 and the maximum score is 120.

c) The Mill Hill Vocabulary Scale (MHVS)

The MHVS (Raven 1958) is generally used to give an estimate of verbal IQ. It is a well-standardized test, and Mill Hill raw scores convert to percentiles for age levels from 20 to 65. The test consists of Part A and Part B. Part A comprises a list of 40 words increasing in level of difficulty, which requires the subject to explain the meaning of each given word in his own words. Part B is a multiple choice test, consisting of 40 words with a choice of 6 alternative words. The subject is required to pick the word whose meaning most closely corresponds to the meaning of the target word. The level of

difficulty increases throughout the list. Either Part A or Part B can be administered to yield an estimated age-related IQ score. For the purpose of this study, Part B was selected as it is generally quicker to administer than Part A.

The MHVS has been shown to be sensitive to dominant hemisphere disease (Costa and Vaughan 1962). The performance of patients with left hemipsphere disease on the MHVS was found to be significantly poorer than that of right hemisphere disease patients and control subjects of comparable IQ levels. Performance of the right hemisphere lesion patients and the control subjects was not significantly different. In patients with left hemisphere disease performance on the MHVS was found to correlate highly with performance on the Raven's Matrices Test, which indicates performance IQ, (r=0.72). Together, these scores indicate a general intellectual impairment in left hemisphere lesion patients.

9.5 Procedure

The visual ERP recordings were carried out first. Subjects were seated in a comfortable chair, in a sound-attenuated, darkened room. The electrodes were positioned after skin preparation. Subjects were asked to sit as still as possible and to fixate on the opposite wall,

where the words would be projected very briefly. They were instructed to read each word silently as it appeared and to avoid blinking while reading and that there would be a few seconds gap between each word.

The subject was left alone in the room while the tester went into the next room to initiate the trials. The experiment consisted of two trials for each subject. In the first trial, negative and neutral words were presented, and in the second trial positive and neutral words were presented, with a short interval between trials. Each trial consisted of the presentation of the 40 emotive words (negative or positive) and the 40 neutral words in a random sequence generated by the micro-computer. At the end of both trials, the electrodes were removed.

The subject was then asked to complete the BDI, the DAS, the SAS and the MHVS, and was interviewed for the purpose of scoring the HRSD by a clinical psychologist. The sequence of physiological tests and rating scales was determined to ensure that the physiological measurements would not be affected by any influence on mood which these rating scales may exert.

9.6 Hypotheses

The hypotheses of this study were:

i. Depressed patients expect negative events more than positive events (Seligman 1981). Therefore, they will show a larger amplitude of the P3 to positive word stimuli relative to neutral word stimuli than to the negative word stimuli relative to neutral word stimuli. Normal controls expect positive stimuli more than negative stimuli (Abramson et al 1981). Therefore, they will show a larger amplitude of P3 to negative than to positive stimuli relative to neutral stimuli. Recovered depressed patients will show a pattern of response which is closer to that of the depressed group than to that of the normal controls, thus showing a vulnerability to depressive illness.

ii. Latencies of P3 will not be different between the three groups.

9.7 Statistical analyses

Repeated measures analyses of variance with groups and emotive conditions as factors were used to compare the differences in amplitudes of P3's for negative and neutral stimuli and for positive and neutral stimuli. An interaction effect of group by condition was

expected. Latencies were also analysed by repeated measures analyses of variance for negative, positive and the two neutral presentations. No group differences were expected for latencies. Scores on all rating scales were analysed by one-way analyses of variance and Pearson's product-moment correlations were used to examine the association between physiological parameters and scores on the psychological measures.

Chapter 10

STUDY III RESULTS AND DISCUSSION

10.1 Results

i Description of subjects on rating scales

The mean scores on rating scales for the depressed, recovered depressed and control groups are presented in Table 10A.

TABLE 10A
DESCRIPTION OF SUBJECTS ON SEVERITY RATINGS AND ON PSYCHOLOGICAL MEASURES, MEANS (STANDARD ERRORS)

	1 DEPRESSED	2 CONTROLS	3 RECOVERED DEPRESSED	p
N	15	15	15	
HRSD	20.5 (0.7)	0.9 (0.3)	1.7 (0.8)	.00001 (1>2=3)
BDI	27.3 (2.9)	2.7 (0.8)	4.1 (1.4)	.00001 (1>2=3)
MHV (IQ)	100.9 (2.6)	118.7 (2.6)	103.9 (2.9)	.00001 (2>1=3)
DAS	150.5 (8.1)	109.9 (3.1)	117.3 (9.5)	.001 (1>2=3)
SAS A	71.3 (4.9)	63.5 (3.4)	66.2 (3.2)	N.S.
SAS S	74.7 (5.0)	56.2 (4.7)	59.9 (5.4)	.03 (1>2=3)

HRSD = Hamilton Rating Scale for Depression - 17 items
BVI = Beck Depression Inventory
DAS = Dysfunctional Attitude Scale
SAS A = Sociotropy-Autonomy Scale, Autonomy scale
SAS S = Sociotropy-Autonomy Scale, Sociotropy scale
MHV = Mill Hill Vocabulary Scale

One way analyses of variance followed by Scheffe's range tests found significant differences between the depressed group and the other two groups (Appendix C1). As expected, the recovered depressed patients did not differ from normal controls on observer-rated or self-rated levels of depression as measured by the HRSD and BDI, or on level of depressogenic attitudes indicated in the DAS scores, whereas the depressed group was highly differentiated from the control group and recovered depressed groups on scores on HRSD ($F=290.03$, $df=2,44$), scores on BDI ($F=51.5$, $df=2,44$), and scores on the DAS ($F=8.86$, $df=2,44$). Verbal IQ, as measured by the MHV differentiated normal controls from the depressed and recovered depressed group ($F=12.74$, $df=2,44$). Of the two personality variables, autonomy did not differentiate the groups, but sociotropy did. Depressed patients were more sociotropic than the two other groups ($F=3.89$, $df=44$).

ii Physiological variables

a) Amplitudes

The mean P3 amplitudes for the three groups for positive, negative and neutral stimuli for the three electrode sites are shown in Figure 10a. Neutral amplitudes for each individual were averaged from the two trials as the same words were used in both trials. One way analyses of

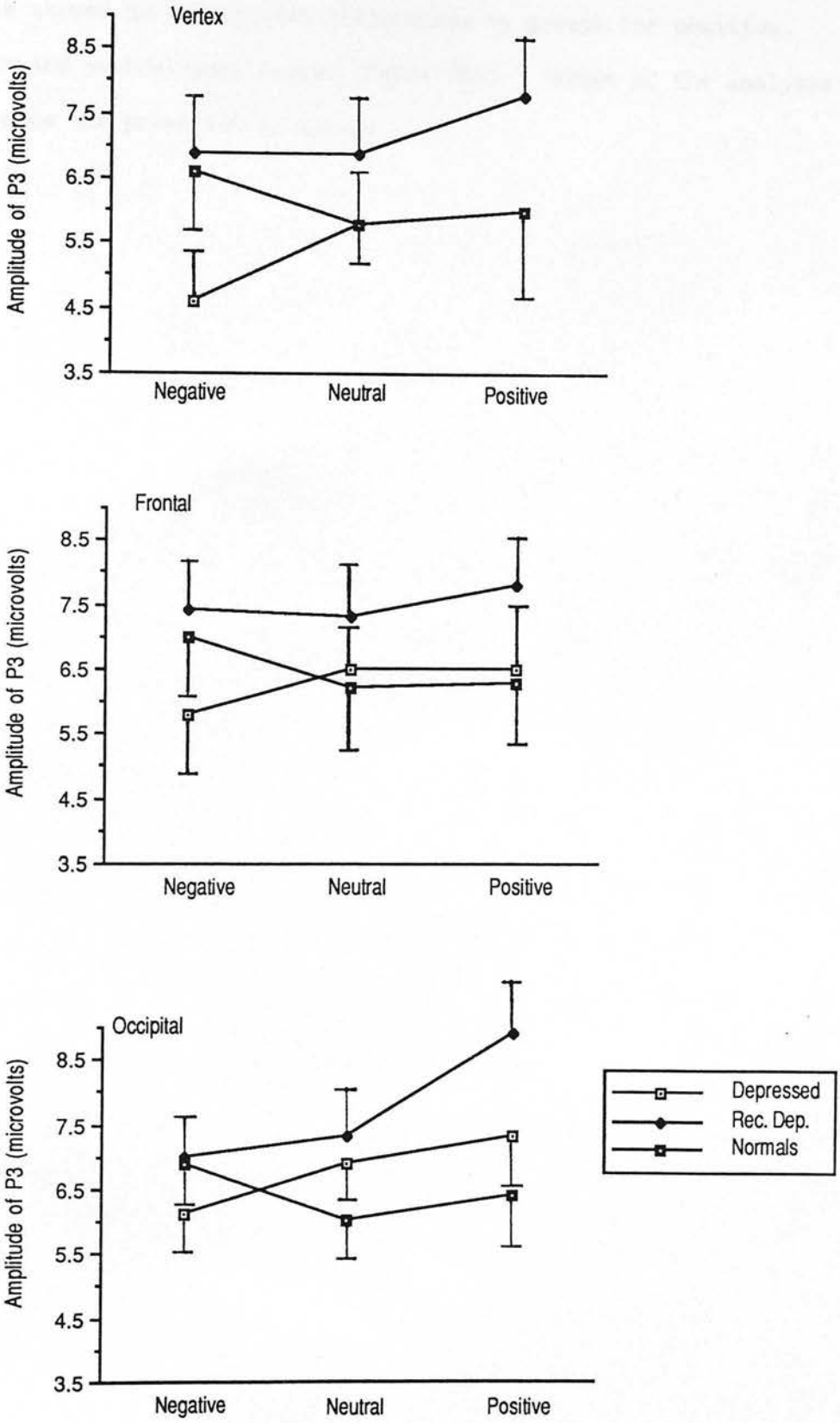

Figure 10a : Means (S.E.) of P3 amplitudes for three electrode sites and three emotion conditions

variance showed no significant differences by groups for positive, negative and neutral amplitudes. (Table 10B). Tables of the analyses of variance are presented in Appendix C2.

TABLE 10B

AMPLITUDES FOR NEGATIVE, POSITIVE AND NEUTRAL STIMULI FOR THE THREE ELECTRODE SITES, MEANS (STANDARD ERRORS)

		1 Depressed 15	2 Controls 15	3 Recovered 15	p
Negative	Vertex	4.6 (0.8)	6.6 (0.9)	6.9 (0.9)	ns
	Frontal	5.8 (0.8)	7.0 (1.0)	7.4 (0.8)	ns
	Occipital	6.1 (0.6)	6.9 (0.8)	7.0 (0.6)	ns
Positive	Vertex	6.0 (1.0)	6.0 (0.8)	7.3 (1.0)	ns
	Frontal	6.5 (1.0)	6.3 (0.8)	7.8 (0.8)	ns
	Occipital	7.3 (0.8)	6.4 (0.8)	8.9 (0.9)	ns
Neutral	Vertex	5.8 (0.6)	5.8 (0.9)	6.9 (0.9)	ns
	Frontal	6.5 (0.7)	6.2 (1.0)	7.3 (0.8)	ns
	Occipital	6.9 (0.6)	6.0 (0.6)	7.3 (0.8)	ns

Figure 10a indicates that depressed subjects had a larger amplitude of the P3 to positive than to negative stimuli for all three electrode sites. The reverse was true for controls. Like the depressed group, the recovered depressed group also had a larger P3 amplitude to positive than to negative stimuli. With reference to neutral stimuli, P3 amplitude was larger than for negative stimuli in depressed patients at all three electrode sites and in the recovered depressed patients at the occipital electrode only. Again the converse was true for normal controls.

The means and standard errors for the differential P3 amplitudes (negative minus neutral and positive minus neutral) for the three groups for the three emotive conditions at three electrode sites is given in Table 10C.

TABLE 10C

DIFFERENCES IN AMPLITUDE FOR NEGATIVE AND POSITIVE STIMULI RELATIVE TO NEUTRAL FOR THE THREE ELECTRODE SITES

		1 DEPRESSED	2 CONTROLS	3 RECOVERED	
	N	14	15	15	P Anova
Negative	Vertex	-1.96	0.71	0.63	.003
minus	Frontal	-1.39	0.66	1.03	.02
Neutral	Occipital	-1.43	0.89	-0.37	.02
Positive	Vertex	0.94	0.17	0.43	ns
minus	Frontal	0.69	0.23	-0.35	ns
Neutral	Occipital	0.91	0.38	1.53	ns

A repeated measures analysis of variance for the two trials, looking at the difference for negative minus neutral and positive minus neutral was carried out. Significant differences were obtained for the groups for P3 amplitude to negative stimuli relative to neutral stimuli for all three electrode sites but not for positive stimuli relative to neutral stimuli.

The responses to the neutral stimuli of each trial were used for the appropriate comparison and not the average of both neutral conditions as shown in Figure 10a. An interaction effect was obtained for all three electrode sites indicating that the groups reacted to emotive stimuli differently. Duncan's range tests following one way analyses of variance by Groups indicated that the main effect was in the negative minus neutral amplitudes, with depressed patients being significantly differentiated from normal controls only ($F=4.65$, $df=2,44$) for the occipital electrode, and from normal controls and recovered depressed patients for the vertex ($F=6.50$, $df=2,44$) and frontal ($F=4.46$, $df=2,44$) electrodes.

A one way analysis of variance by emotive conditions indicated a significant difference between negative minus neutral and positive minus neutral amplitudes only for the occipital electrodes. IQ was not related to the differential measures of amplitude, with correlations ranging from 0.03 to 0.19 (n=45).

Two-way repeated measures analysis of variance (group by electrode site) showed a main effect for group ($F=4.84$, $df=2$, $p=.01$) and site ($F=4.07$, $df=2$, $p=.02$) and an interaction effect ($F=2.82$, $df=4$, $p=.08$) for negative minus neutral amplitude. However, there were no significant main effects nor interaction effect for positive - neutral amplitude.

b)Latencies

The mean P3 latencies for the three emotive conditions for the three groups for the three electrode sites are shown in Figure 10b. Figure 10b indicates that normal controls had shorter latencies of the P3 for all three classes of stimuli than the depressed patients and recovered depressed patients. The recovered depressed patients appear slower than the depressed patients for all three electrode sites. The relative latencies within group for the three emotive conditions did not show the clear pattern obtained for the relative amplitudes.

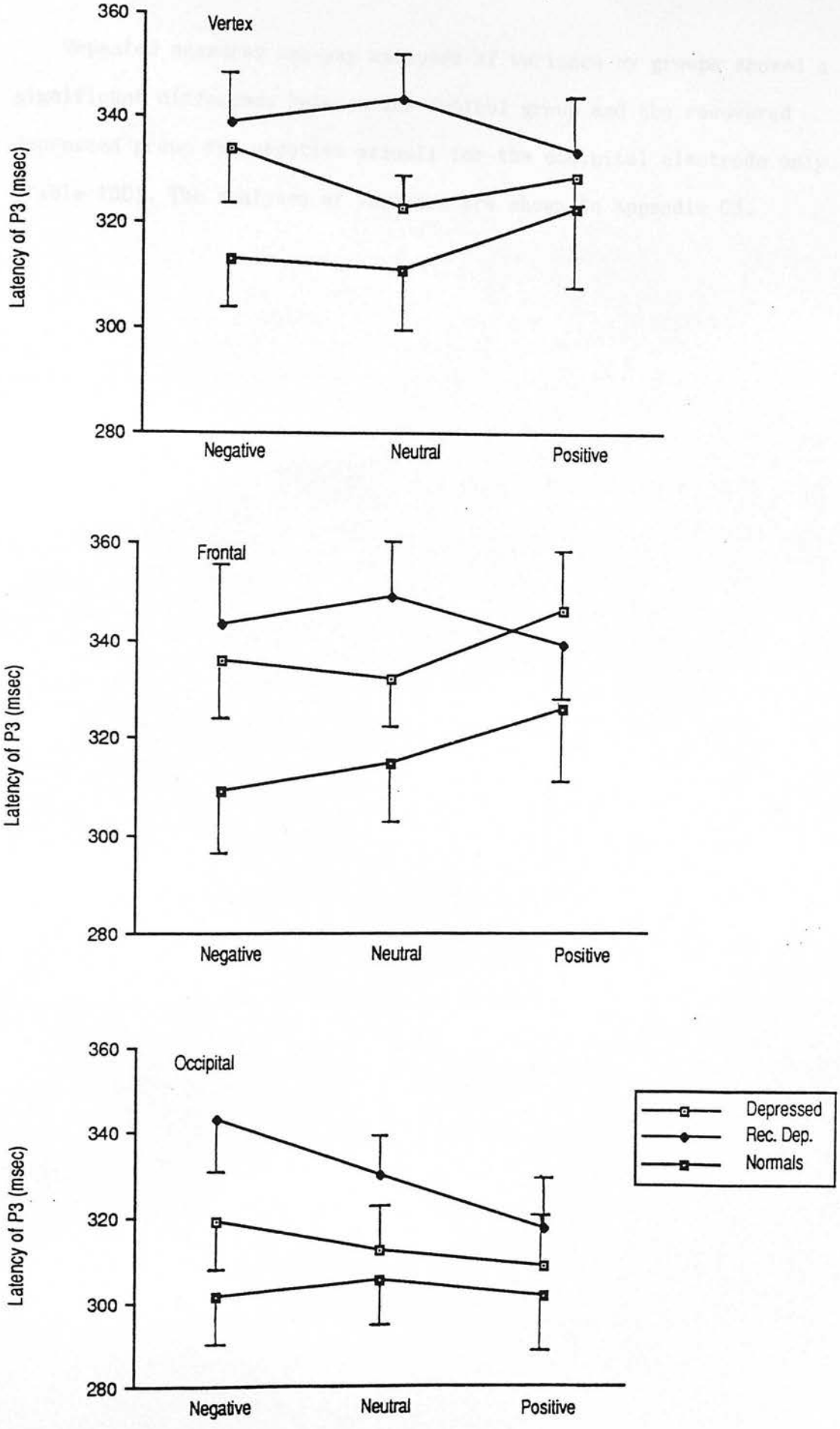

Figure 10b : Means (S.E.) of P3 latencies for three electrode sites and three emotion conditions

Repeated measures one-way analyses of variance by groups showed a significant difference between the control group and the recovered depressed group for negative stimuli for the occipital electrode only. (Table 10D). The analyses of variance are shown in Appendix C3.

TABLE 10D

LATENCIES FOR NEGATIVE, POSITIVE AND NEUTRAL STIMULI FOR THE THREE ELECTRODE SITES; MEANS (STANDARD ERRORS)

		1 Depressed 15	2 Controls 15	3 Recovered 15	p
Negative	Vertex	333.6 (9.9)	312.7 (9.3)	339.1 (10.6)	ns
	Frontal	336.1 (12.3)	308.9 (10.3)	342.8 (11.8)	ns
	Occipital	319.2 (9.8)	300.9 (9.0)	342.8 (10.2)	.01 2<
Positive	Vertex	329.1 (8.0)	322.8 (15.1)	334.0 (10.1)	ns
	Frontal	346.8 (9.9)	325.7 (14.2)	339.3 (12.3)	ns
	Occipital	308.0 (9.9)	300.7 (10.6)	316.7 (9.6)	ns
Neutral	Vertex	323.2 (6.7)	311.1 (12.0)	344.1 (8.8)	ns
	Frontal	332.5 (9.9)	315.5 (12.6)	348.8 (11.1)	ns
	Occipital	311.8 (9.6)	304.8 (9.1)	329.7 (7.1)	ns

Repeated measures two-way analyses of variance (groups by condition) showed a significant main effect for condition only for the occipital electrode ($F = 3.91$, $df=2$, $p = 0.02$). Repeated measures two-way analyses of variance (groups by electrode site) showed a significant group effect for negative stimuli ($F = 3.61$, $df=2$, $p = 0.04$), and a significant effect for site for positive stimuli ($F = 13.80$, $df=2$, $p = .0001$) and for neutral stimuli ($F = 6.16$, $df=2$, $p = .003$). IQ was not significantly correlated with latencies ranging from -.04 to -.27 except for one significant result for negative stimuli at the frontal electrode ($r = -.27$, $df=43$, $p < .05$, Appendix C4).

iii. Correlations of P3 amplitude (negative-neutral) with cognitive scores

Table 10E shows the correlations for all subjects combined (n=45) between psychological variables and the most discriminatory variable, the difference between amplitudes for negative and neutral stimuli. It can be seen that level of depression as self-rated (BDI) or observer-rated (HRSD) was significantly associated with this differential measure of P3 amplitude. The lower the amplitude ofP3 for negative stimuli relative to neutral stimuli, the higher was the level of depression. Similarly, the lower the amplitude for negative stimuli, the higher was the level of depressogenic attitudes (DAS), the higher the level of sociotropy (SAS-S) and for frontal electrode only, the higher was the level of autonomy.

TABLE 10 E

CORRELATIONS OF P300 AMPLITUDE (NEGATIVE-NEUTRAL) WITH PSYCHOLOGICAL VARIABLES FOR ALL SUBJECTS (N = 45)

	BDI	HRSD	DAS	SAS-A	SAS-S
VERTEX	-0.38**	-0.46***	-.32*		-0.29*
FRONTAL	-0.37**	-0.36**		-0.28*	-.33**
OCCIPITAL	-0.32*	-0.34**	-0.52***		

(*p < 0.05; **P< 0.01; *** P <0.001)

BDI = Beck Depression Inventory
HRSD = Hamilton Rating Sclae for Depression
DAS = Dysfunctional Attitude Scale
SAS-A = Autonomy
SAS-S = Sociotropy

10.2 Discussion

i Do the groups have different physiological responses to the emotive conditions?

The hypotheses related to the the P3 amplitude for emotive stimuli in depressed patients were supported by the results of this study. The depressed subjects showed smaller P3 amplitudes to the negative words relative to the neutral words. The depressed and control subjects showed little difference in their response to the positive and neutral words. The recovered depressed subjects showed a larger response to the positive words relative to the neutral words. Both depressed and recovered depressed subjects showed a smaller response to the negative words than to the positive words. A significant interaction effect between groups and emotive stimuli was obtained for the vertex, frontal and occipital electrode sites. Univariate analyses of variance by groups indicated that the difference for all three sites lay in the responses of the depressed group to the negative stimuli relative to the neutral stimuli but not in the difference between responses for positive and neutral stimuli. Therefore, although the depressed subjects' P3 amplitude response was significantly different from that of the control subjects to the negative words relative to the neutral words, their response to the positive words relative to the neutral

words was not equally abnormal. Thus the depressed subjects responded to the negative and neutral words as being more different than the positive and neutral words, which elicited a more similar response.

The depressed group was always differentiated from the normal controls, but they were differentiated from the recovered depressed group for the vertex and frontal electrodes only. Recovered depressed subjects were not differentiated from normal controls.

The only significant difference between the groups in P3 latency was between the control group and the recovered depressed group for negative word stimuli. The differences between the groups in P3 latency for positive and neutral stimuli were not significant. The controls had slightly faster P3 latencies for all emotive conditions at all electrode sites than the depressed and recovered depressed subjects. This may be due to a slowness in information processing which occurs in depression. However, the recovered depressed subjects were generally slower than the depressed subjects, except for their P3 latency to positive words for the frontal electrode. This was unexpected and it was not thought that once recovered these subjects would experience any retardation in information processing.

ii Do the physiological scores correlate with the rating scores?

The depressed group was significantly differentiated from the other two groups on severity of depression, as measured by the HRSD and the BDI as expected. They were also differentiated from the control group and the recovered depressed group on the DAS and the sociotropy subscale of the SAS.

Correlations of these scores with the most discriminating physiological variable, the difference in P3 amplitude for negative and for neutral words, for the three groups combined, together showed significant correlations with level of depression and level of depressogenic attitudes. This indicated that the more depressed and dysfunctional an individual was, the lower was his P3 amplitude for negative stimuli relative to neutral stimuli. Sociotropy showed more association with the central measure of depressive information processing, indicating that excessive dependency on social gratification is a vulnerability depression measure.

iii Is there a vulnerability marker for depression?

Lack of significant difference between the control group and the recovered depressed group for scores on the DAS and the SAS-A and SAS-S indicate that while depressogenic attitudes and excessively dependent personality measures are found in depressed subjects, they disappear after recovery.

However, the larger amplitude and longer latency of the P3 response which was found generally for all emotive conditions and for all electrode sites in recovered depressed subjects compared with control subjects suggests that this may indicate a psychophysiological vulnerability marker of depression. The recovered depressed subjects showed a generally higher level of response in terms of higher P3 amplitudes for all three classes of emotive stimuli. It appears that recovered depressed subjects have a tendency to show a stronger response to stimuli of any emotive tone relative to depressed patients and to controls, indicating possibly more unexpectedness or more effortful processing. The regular trend for longer response latencies for all stimuli supports this interpretation. However, these were only trends in the results. Although the differences were not significant, they were consistent It may be that recovered depressed subjects process emotive stimuli more slowly and more actively than normal control subjects as these stimuli may be more meaningful to them in

some way. If these emotive stimuli are incorporated into the associative networks which, as proposed by Bower consist of semantic and emotional information, during remission these networks may be inactive and therefore require more processing time and activity to locate the appropriate information node.

Chapter 11

GENERAL DISCUSSION

Schizophrenic patients were differentiated from control subjects by physiological and cognitive measures in Study I. Significantly prolonged P3 latency was found in the schizophrenic group, which was consistent with previous findings (Blackwood et al 1987). The schizophrenic patients were significantly impaired on tests of associative and conceptual cognitive functions which supported previous reports (Rattan and Chapman 1973, Hamlin 1977, Gregg 1988, Hemsley 1977, Goldberg and Weinberger 1988). Significant correlations between P3 latency and performance on tests which involved these cognitive functions were found.

The results for the bipolar affective disorder groups were similar to those for the schizophrenic group in terms of the physiological and cognitive tests. These groups had significantly prolonged P3 latency compared with control groups, thus supporting previous findings (Muir et al, in press). P3 and other biological markers have been generally found to be abnormal in schizophrenia and bipolar affective disorders, and have not significantly differentiated the two. Cognitive impairments found in the bipolar manic subjects were very similar to those found in the schizophrenic subjects. The impairments found in the bipolar manic subjects were consistent with previous findings indicating dysfunction in

associative and conceptual cognitive functions (Weingartner 1980, Henry et al 1971, Wolfe 1987, Savard et al 1980, Harrow 1986, Breakey and Goodell 1982). Correlations found for P3 latency and performance on the cognitive tests were similar in the bipolar manic group and schizophrenic group. The bipolar depressed group showed the largest decline in IQ and significant impairment in visual conceptualization. They did not differ significantly from bipolar manic subjects on any test. However, performance on the cognitive tests did not correlate significantly with P3 latency in the bipolar depressed group, while level of depression, decline in IQ and level of attention as indicated by performance on the Digit Span Test correlated significantly with P3 amplitude. The schizophrenic and bipolar groups were not significantly differentiated by any of the measures used in Study I, showing that schizophrenia and bipolar affective disorders share many features and may involve similar dysfunctions. However, separation of the two disorders rests on the basis of symptoms, outcome and family and twin studies.

Findings for the unipolar depressed subjects were generally dissimilar to those of the bipolar groups in terms of P3 latency and performance on the cognitive tests. The unipolar and bipolar groups were significantly differentiated by P3 latency, which supports previous results (Muir et al, op.cit.). The performance of the unipolar depressed subjects on the cognitive tests was impaired relative to the control subjects, but analysis of the deficits indicated that the impairment found in the unipolar

depressed subjects was largely due to lack of attention and motivation. Impairments on the cognitive tests did not correlate with P3 latency. Therefore, the study provides some evidence of clear-cut boundaries between unipolar and bipolar affective disorders.

P3 latency and performance on the cognitive tests appear to be related in the schizophrenic and bipolar manic groups. This supports the hypothesis that P3 reflects an implementation of associative networks in long term memory. P3 abnormalities manifest a dysfunction in the activation of associative networks, which is evident in impairments in producing associations and using associations to form concepts.

Schizophrenic patients were also found to be significantly impaired on neuropsychological tests associated with frontal lobe and temporal lobe function in Study II, supporting previous findings (Gruzelier 1988, Keilp 1988, Golden et al 1981). Although the localizing power of neuropsychological tests is limited, the results were consistent with previous findings and supported the implication of the frontal lobes and temporal lobes in schizophrenia. Results from the neuropsychological tests were supported by the imaging (MRI) data, where performance on tests associated with frontal lobe and temporal lobe function correlated significantly with ventricular brain ratio and temporal lobe structures respectively. No reliable measures of frontal lobe structures were obtained from the MRI scans but the measures of temporal lobe structures

significantly differentiated schizophrenic patients from control subjects, supporting the findings of Johnstone (1976) and de Lisi (1988). Specific changes in the amygdala and parahippocampal gyrus were also found in schizophrenic patients with prolonged P3 latency, with significant correlations between the variables. Performance on neuropsychological tests was shown to be more impaired in schizophrenic subjects with long P3 latency for tests of both frontal lobe and temporal lobe function. In about half the schizophenic subjects, impairment on tests of frontal lobe function was gross and correlated significantly with P3 latency and ventricular brain ratio.

The neuropsychological and physiological data from the schizophrenic patients were possibly affected by drugs and clinical status. All the schizophrenic patients were taking psychotropic drugs and their ratings on the four measures which were taken from the BPRS varied. Therefore, relatives with normal and abnormal P3 latency provided important groups for comparison, as none of the relatives were taking psychotropic medication and none had been diagnosed as having a psychotic illness. Relatives with abnormally prolonged P3 latency were found to perform as schizophrenic subjects on the neuropsychological and psychometric tests, and were significantly differentiated from normal control subjects. Schizophrenic patients and abnormal P3 relatives both showed a significant decline in IQ compared with control subjects. The performance of the relatives with normal P3 latency was similar to that of the control subjects on all tests,

and was significantly different from that of the schizophrenic subjects. These findings may lend some support to the evidence for a schizophrenic spectrum. However, this is a contentious issue, and it is only possible to state that P3 latency differentiates relatives with specific cognitive abnormalities from those without. It is as yet unknown whether the relatives with abnormal P3 are likely to develop schizophrenia in the future, or whether schziophrenia is a disorder with multifactorial inheritance and while a certain number of individuals inherit a predisposition to the condition, only a certain proportion of these encounter the precipitating factors which result in a psychosis.

P3 amplitude to negative stimuli relative to neutral stimuli significantly differentiated unipolar depressed patients from control subjects in Study III, indicating that depressed subjects expect negative stimuli more than positive or neutral stimuli, while the converse is true for control subjects, supporting Beck's cognitive theory of depression. This also supports Wenzlaff's (1988) hypothesis that information processing deficits in unipolar depressed subjects are due to pervasive interconnected negative thoughts. The physiological measure was significantly associated with self-rating and observer-rating levels of depression, depressogenic attitudes and a measure of depression-prone personality, suggesting that P3 amplitude is a valid indicator of state. Recovered depressed subjects were significantly differentiated from control subjects at the occipital electrode site, suggesting that there may be a physiological vulnerability

marker for depression, supporting the hypothesis that recovered depressed subjects possess depressotypic negative schemata but that these are generally dormant until the subject becomes depressed (Blackburn 1981).

Results from the three studies showed that physiological measures and cognitive measures are related and can be used to examine types of dysfunction evident in different groups of subjects. However, interpretation of the results must be made with some caution due to the small numbers of subjects in the affective disorders groups. Further work is needed to compare these groups using larger numbers of subjects. A further criticism of the study is that BPRS ratings were not taken for the affective disorder groups, and it would have been useful to have had scores on measures such as thought disorder as well as measures of affective state. Suggestions for future research include a more extensive comparison of schizophrenic and bipolar affective disorder patients with larger numbers of subjects in each group. These preliminary results suggest that the relationship between schizophrenia and bipolar affective disorder is closer than that between bipolar and unipolar affective disorders. It would be useful to study the performance of bipolar subjects on the neuropsychological tests which were used with the schizophrenic subjects, and to do MRI scans on the bipolar subjects. The results also suggest that SPECT imaging studies may produce differences between schizophrenic and control subjects when these subjects are scanned while performing neuropsychological tests which are sensitive to frontal

lobe and temporal lobe function. Finally, these results also suggest that it may be worthwhile to test larger numbers of relatives of schizophrenic subjects to attempt to define the schizophrenia phenotype and to understand the genetic transmission of schizophrenia in families.

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APPENDIX A1

AGE AT FIRST ONSET, LENGTH OF HOSPITALIZATION FOR CURRENT EPISODE AND MEDICATION FOR SCHIZOHRENIC AND AFFECTIVE DISORDER PATIENTS.

SUBJECT	AGE AT FIRST ONSET	LENGTH OF HOSPITALIZATION (MONTHS) CURRENT EPISODE	MEDICATION (mg/day) (NEUROLPETICS DOSE AS CPZ EQUIVALENT)	
SCHIZOPHRENIC PATIENTS				
1	26	OP	FPX DEC	150
2	19	2	FPX DEC	400
			CPZ	600
3	20	4	TFPZ	600
4	23	OP	DRUG FREE	
5	18	3	CPZ	600
6	29	OP	TFPZ	200
7	33	11	ZPX DEC	200
8	39	OP	TFPZ	200
9	34	2	CPZ	100
			FPX DEC	190
10	19	0.25	FPX DEC	70
11	22	OP	FPX DEC	190
12	23	OP	FPX DEC	40
13	23	OP	ZPX DEC	270
14	24	2	TFPZ	200
			TDZ	800
15	19	OP	CPZ	300
			FPX DEC	190
16	20	2	FPX DEC	140
17	19	4	TFPZ	400
18	20	0.25	SPD	600
			FPX DEC	70
19	19	9	TFPZ	100
			FPX DEC	140
20	19	2	FPX DEC	140
21	18	4	CPZ	400
22	19	1	CPZ	600
			FPX DEC	90
23	37	8	CPZ	600
24	21	1	CPZ	600
			CPZ	400

BIPOLAR MANIC PATIENTS

1	21	1	CPZ	400
2	40	1	CPZ	1000
			DPD	450
3	35	1.5	HPD	360
			TFPZ	200
4	39	3	CPZ	100
			CMZ	800
5	33	2.25	LTH	1200
			CPZ	600
6	17	2	CPZ	200
7	25	1.5	CPZ	1200
8	23	1.75	CPZ	100
			LTH	1000
9	22	0.25	CPZ	300
			FPZ DEC	420
10	23	4.25	LTH	1200
			CMZ	1200

BIPOLAR DEPRESSED SUBJECTS

1	22	0.5	AMI	100
			LTH	1000
2	35	1	LTH	800
			HPD	430
3	37	1.5	AMI	200
			TDZ	100
4	18	6.25	LTH	1200
			CPZ	1200
5	31	3.75	LTH	1200
			AMI	100
			SPD	400
6	42	1	AMI	200
7	41	1	LTH	1000
			IMI	100
8	45	0.5	L-TP	3000
9	56	0.5	SPD	800
10	25	OP	AMI	100

UNIPOLAR DEPRESSED SUBJECTS

1	43	1	TDZ	100
2	37	0.25	DRUG FREE	
3	33	0.5	DRUG FREE	
4	27	0.5	DRUG FREE	
5	51	1	AMI	200
6	57	OP	IMI	50
7	48	1.5	AMI	150
8	40	2	AMI	200
9	36	1	LTH	800
			IMI	150
			TDZ	100
10	56	2	PLZ	30

OP = Outpatient
FLX DEC = Flupenthixol decanoate
CPZ = Chlorpromazine
TFPZ = Trifluoperazine
ZPX DEC = Zuclopenthixol decanoate
SPD = Sulpiride
TDZ = Thioridazine
DPD = Droperidol
HPD = Haloperidol
CMZ - Carbamazepine
LTH = Lithium
FPZ DEC = Fluphenazine decanoate
AMI = Amitriptyline
IMI = Imipramine
L-TP = L-Tryptophan
PLZ = Phenelzine

APPENDIX A2

CORRELATION COEFFICIENTS OF RATING SCALES WITH COGNITIVE VARIABLES

Pearson and Spearman correlation coefficients of brief psychiatric rating scale (BPRS) and Hamilton rating scale for depression (HRSD) with performance on cognitive tests in schizophrenic subjects.

	Thought Disorder	Anxiety/ Depression	Withdrawal	Hostility	HRSD
Age	-.10	-.12	-.00	-.30	-.07
Premorbid IQ	-.23	-.19	-.22	-.06	-.29
Current IQ	-.39*	-.25	-.01	.35*	.01
Similarities	-.46*	-.25	-.06	.37*	-.04
Digit Span	-.21	-.15	.11	.35	.05
Word Association Frequent Responses	-.64**	-.06	-.09	.20	-.04
Word Association Rank	.63**	-.02	.03	-.16	.02
Paired Associates Part I(Spearman)	-.35	.12	-.25	.05	-.13
Paired Associates Part II(Spearman)	-.38*	.01	-.12	.00	-.37*
Wisconsin Card Sorting Test	-.49**	-.14	.15	-.33	-.05
Witkins Embedded Figures Test	-.33	.06	-.38*	.37*	-.41*
Verbal Recall Emotive Words	-.38*	.07	-.17	-.06	-.06
Verbal Recall Category Words	-.19	.16	-.13	.16	.15
Verbal Recall Total Words	-.29	.17	-.17	.06	.08
Verbal Recall Errors (Spearman)	.30	.45*	.42*	-.43*	.34
Verbal Recall Isolates(Spearman)	-.12	.27	-.04	.02	.06

Stroop Reaction Time Words	.05	-.22	-.03	-.19	-.16
Stroop Reaction Time Colours	.05	-.22	-.03	-.19	-.16

(*p<.05; **p<.01)

Pearson and Spearman Correlation Coefficients of Hamilton Rating Scale for Depression (HRSD) and Modified Manic State Rating Scale (MMSRS) with performance on cognitive tests in bipolar and unipolar subjects.

	MMSRS Bipolar Manic	HRSD Bipolar Depressed	MRSD Unipolar Depressed
Age	.44	-.02	.23
Premorbid I.Q.	.08	-.01	-.32
Current I.Q.	-.54	-.24	.29
Similarities	-.22	-.43	.60*
Digit Span	-.47	-.65	-.21
Word Association Frequent Responses	-.23	-.76*	.35
Word Association Rank	.10	.74*	-.44
Paired Associates Part I (Spearman)	-.20	.39	.26
Paired Associates Part II (Spearman)	-.36	.21	-.02
Winsconsin Card Sorting Test	.19	.40	.08
Witkins Embedded Figures Test	-.41	-.24	.22
Verbal Recall Emotive Words	-.32	.77*	.07
Verbal Recall Category Words	-.43	.33	-.08
Verbal Recall Total Words	-.38	.50	-.02
Verbal Recall Errors (Spearman)	-.15	-.15	.15
Verbal Recall Isolates (Spearman)	.17	-.42	-.42
Stroop Reaction Time Words	-.08	.28	-.22

Stroop Reaction Time Colours	.06	.32	-.20

(* $p<.05$)

APPENDIX A3

Analysis of Variance of Age, Physiological Variables and I.Q. by Group

Age by Sex by Group

Source	df	Mean Square	F Ratio	p
Sex	1	244.83*	2.20	.14
Group	4	494.52	4.45	.003
Sex x Group	4	105.24	0.95	.44
Residual	63	111.21		
Total	72			

Analysis of Variance

P3 Latency by Sex by Group

Source	df	Mean Square	F Ratio	p
Sex	1	1875.49	1.28	.26
Group	4	10343.95	7.04	.000
Sex x Group	4	421.58	0.29	.89
Residual	63	1468.88		
Total	72	1901.62		

P3 Amplitude by Sex by Group

Source	df	Mean Square	F Ratio	p
Sex	1	873.06	1.85	.18
Group	4	4161.27	8.82	.0001
Sex x Group	4	282.61	0.60	.67
Residual	63	472.02		
Total	72			

Signal : Noise Ratio (ETD) by Sex by Group

Source	df	Mean Square	F Ratio	p
Sex	1	4867.23	0.32	0.57
Group	4	24680.27	1.62	0.18
Sex x Group	4	33383.62	2.19	0.08
Residual	63	27339.25		
Total	72			

Analysis of Variance

Nart VIQ by Sex by Group

Source	df	Mean Square	F Ratio	p
Sex	1	8.08	0.07	.79
Group	4	622.70	5.45	.001
Sex x Group	4	52.17	0.45	.77
Residual	68	114.29		
Total	77			

WAIS VIQ by Sex by Group

Source	df	Mean Square	F Ratio	p
Sex	1	74.83	0.36	.55
Group	4	1898.86	9.14	.0001
Sex x Group	4	111.12	0.54	.71
Residual	68	207.75		
Total	77			

IQ Difference by Sex by Group

Source	df	Mean Square	F Ratio	p
Sex	1	33.72	0.27	.61
Group	4	543.70	4.28	.004
Sex x Group	4	61.36	0.48	.75
Residual	68	126.97		
Total	77			

APPENDIX A4

Pearson and Spearman Correlation Coefficients of Premorbid I.Q. (National Adult Reading Test) and Age with Performance on Cognitive Tests

(a) All Subjects

	Premorbid I.Q.	Age
Similarities	.72**	-.21*
Digit Span	.62**	-.22
Word Association Frequent Responses	.21	-.17
Word Association Rank	-.15	.13
Paired Associates Part I (Spearman)	.32**	-.03
Paired Associates Part II (Spearman)	.43*	-.15
Wisconsin Card Sorting Test	-.66**	.33**
Verbal Recall Emotive Words	.63**	-.26*
Verbal Recall Cateogry Words	.65**	-.27**
Verbal Recall Total Words	.69**	-.33**
Verbal Recall Errors (Spearman)	-.24*	.10
Verbal Recall Isolates (Spearman)	-.39**	-.22*
Stroop Reaction Time (Words)	-.51**	.36**
Stroop Reaction Time(Colours)	-.50**	.39**

(b) Pearson and Spearman Correlation Coefficients of Premorbid I.Q. (National Adult Reading Test) and Age with Performance on Cognitive Tests in Schizophrenic Subjects

	Premorbid I.Q.	Age
Similarities	.67**	-.19
Digit Span	.59**	-.17
Word Association Frequent Responses	.04	-.40
Word Association Rank	.03	.41*
Paired Associates Part I (Spearman)	.23	-.42
Paired Associates Part II (Spearman)	.01	-.30
Winsconsin Card Sorting Test	-.52**	.39*
Watkins Embedded Figures Test	.42	-.17
Verbal Recall Emotive Words	.48**	-.14
Verbal Recall Category Words	.44*	-.34
Verbal Recall Total Words	.51**	-.35*
Verbal Recall Errors (Spearman)	.11	.33
Verbal Recall Isolates (Spearman)	.13	-.27
Stroop Reaction Time (Words)	-.39*	.56**
Stroop Reaction Time(Colours)	-.36	.58**

(* $p<.05$; ** $p<.01$)

(c) Pearson and Spearman Correlation Coefficients of Premorbid I.Q. (National Adult Reading Tests) and Age with Performance on Cognitive Tests in Bipolar Manic subjects

	Premorbid I.Q.	Age
Similarities	.70*	-.35
Digit Span	.68*	-.22
Word Association Frequent Responses	.32	-.40
Word Association Rank	-.17	.13
Paired Associates Part I (Spearman)	.25	.18
Paired Associates Part II (Spearman)	.44	-.48
Wisconsin Card Sorting Test	-.68*	.55
Witkins Embedded Figures Test	.34	.01
Verbal Recall Emotive Words	.78**	-.69*
Verbal Recall Category Words	.84**	-.48
Verbal Recall Total Words	.89	-.62
Verbal Recall Errors (Spearman)	.02	-.50
Verbal Recall Isolates (Spearman)	.45	.35
Stroop Reaction Time (Words)	-.79*	.33
Stroop Reaction Time (Colours)	-.63	.67

(* $p<.05$)

(d) Pearson and Spearman Correlation Coefficients of Premorbid I.Q. (National Adult Reading Test) and age with performance on cognitive Tests in Bipolar Depressed Subjects

	Premorbid I.q.	Age
Similarities	.76**	-.01
Digit Span	.33	.25
Word Association Frequent Responses	.21	.28
Word Assocation Rank	-.22	-.23
Paired Associates Part I (Spearman)	.81**	.16
Paired Associates Part II (Spearman)	.62*	.31
Wisconsin Card Sorting Test	.73*	-.03
Witkins Embedded Figures Test	.60*	-.21
Verbal Recall Emotive Words	.51	-.20
Verbal Recall Category Words	.56*	-.33
Verbal Recall total Words	.68*	-.40
Verbal Recall Isolates (Spearman)	.05	-.18
Stroop Reaction Time (Words)	-.73*	.48
Stroop Reaction Time (Colours)	-.70*	.53

(e) Pearson and Spearment Correlation Coefficients of Premorbid I.Q. (National Adult Reading Test) and Age with Performance on Cognitive Tests in Unipolar Depressed Subjects

	Premorbid I.Q.	Age
Similarities	.47	-.10
Digit Span	.21	-.15
Word Association Frequent Responses	.23	-.10
Word Association Rank	-.14	.18
Paired Associates Part I (Spearman)	.41	.17
Paired Associates Part II (Spearman)	.61*	-.50
Winsconsin Card Sorting Test	-.89**	.10
Witkins Embedded Figures Test	.50	-.31
Verbal Recall Emotive Words	.66*	-.06
Verbal Recall Category Words	.76**	.10
Verbal Recall Total Words	.73**	-.11
Verbal Recall Errors (Spearman)	.71*	.54
Verbal Recall Isolates (Spearman)	.58*	-.47
Stroop Reaction Time (Words)	-.66*	-.06
Stroop Reaction Time (Colours)	-.68*	-.08

(f) Pearson and Spearman Correlation Coefficients of Premorbid I.Q. (National Adult Reading Test) and Age with Performance on Cognitive Tests in Control Subjects

	Premorbid I.Q.	Age
Similarities	.56**	-.20
Digit Span	.43*	-.43*
Word Association Frequence Responses	.07	-.11
Word Association Rank	-.06	.08
Paired Associates Part I (Spearman)	.46	.08
Paired Associates Part II (Spearman)	-.02	.34
Wisconsin Card Sorting Test	-.70**	.25
Witkins Embedded Figures Test	.16	-.47*
Verbal Recall Emotive Words	.47*	.02
Verbal Recall Category Words	.48**	-.10
Verbal Recall Total Words	.53**	-.10
Verbal Recall Errors (Spearman)	-.64**	.04
Verbal Recall Isolates (Spearman)	.33	-.08
Stroop Reaction Time (Words)	-.26	.28
Stroop Reaction Time (Colours)	-.27	.40*

Appendix A5

Analysis of Variance of Cognitive Scores by Group Wisconsin Card Sorting Test by Group

Source	df	Mean Square	F Ratio	p
Covariate I.Q.	1	5119.64	66.49	.0001
Covariate Age	1	930.05	12.08	.001
Between Groups	4	29.32	0.38	.82
Within Groups	68	76.99		
Total	74			

Witkins Embedded Figures Test by Group

Source	df	Mean Square	F Ratio	p
Covariate I.Q.	1	1612.12	43.77	.0001
Covariate Age	1	61.55	16.61	.0001
Between Groups	4	27.66	7.47	.0001
Within Groups	68	3.71		
Total	74			

Word Association Frequent Responses by Group

Source	df	Mean Square	F Ratio	p
Between Groups	4	81.99	2.35	.06
Within Groups	71	34.27		
Total	75			

Word Association Infrequent Responses by Group

Source	df	Mean Square	F Ratio	p
Between Groups	4	82.22	2.51	.05
Within Groups	71	32.73		
Total	75			

Word Association Rank by Group

Source	df	Mean Square	F Ratio	p
Between Groups	4	3.16	2.49	.05
Within Groups	71	1.27		
Total	75			

Verbal Recall of Emotive Words by Group

Source	df	Mean Square	F Ratio	p
Covariate I.Q.	1	275.63	61.78	.0001
Covariate Age	1	31.99	7.17	.009
Within Groups	70	4.46		
Total	76			

Verbal Recall of Category Words by Group

Source	df	Mean Square	F Ratio	p
Covariate I.Q.	1	425.51	69.86	.0001
Covariate Age	1	52.46	8.61	.005
Between Groups	4	33.78	5.55	.001
Within Groups	70	6.09		
Total	76			

Total Words Recalled by Group

Source	df	Mean Square	F Ratio	p
Covariate I.Q.	1	4345.55	100.16	.0001
Covariate Age	1	758.19	17.48	.0001
Between Groups	4	336.95		
Within Groups	70	43.39		
Total	76			

Stroop Reaction Time (Words) by Group

Source	df	Mean Square	F Ratio	p
Covariate I.Q.	1	19.77	26.13	.0001
Covariate Age	1	9.69	12.81	.001
Between Groups	4	0.15	0.20	.94
Within Groups	64	0.76		
Total	70			

Stroop Reaction Time (Colours) by Group

Source	df	Mean Square	F Ratio	p
Covariate I.Q.	1	20.82	22.88	.0001
Covariate Age	1	12.24	13.45	.001
Between Groups	4	0.24	0.26	.90
Within Groups	67	2.02		
Total	72			

Similarities by Group

Source	df	Mean Square	F Ratio	p
Covariate I.Q.	1	308.85	91.48	.0001
Between Groups	4	12.40	3.67	.009
Within Groups	72	3.38		
Total	77			

Digit Span by Group

Source	df	Mean Square	F Ratio	p
Covariate I.Q.	1	388.74	54.11	.0001
Between Groups	4	23.86	3.32	.02
Within Groups	72	7.19		
Total	77			

Kruskal-Wallis One Way Analysis of Variance

Paired Associates Part I by Group

Mean Rank	Cases = 77
37.08	
40.58	x^2 = 3.47 sig = .48
48.70	
31.00	correctedf x^2 = 4.95 sig = 0.29
38.00	

Paired Associates Part II by Group

Mean Rank	Cases = 77
29.67	
55.88	x^2 = 23.29 sig = .0001
41.65	
23.75	corrected x^2 = 24.88 sig = .0001
32.89	

Verbal Recall Errors by Group

Mean Rank	Cases = 77
36.13	
40.25	x^2 = 5.44 sig = .25
52.35	
30.33	corrected x^2 = 8.62 sig = .23
37.35	

Verbal Recall Isolates by Group

Mean Rank	Cases = 78
33.77	
52.40	x^2 = 12.84 sig = .01
28.10	
32.45	corrected x^2 = 13.76 sig = .008
40.75	

INTERTEST CORRELATION COEFFICIENTS FOR ALL SUBJECTS (n=78)

	WCST	WEFT	FREQ	PAIRASS	RCTOT	ERRORS	SIMIL	DIG SP	STRT	S : N
P3 Latency	.40**	-.40**	-.27**	-.45**	-.43**	.18	-.41**	-.31**	.29*	-..21
Signal : Noise Ratio (S:N)	-.44**	.28**	-.05	.18	·40**	-·08	·23	·16	-·34**	
Stroop Reaction Time Colours (STRT)	.71**	-.46**	-.33**	-.40**	-.53**	.10	-.55**	-.41**		
Digit Span (DIGSP)	-.55**	.56**	.28**	.55**	.63**	-.14	.64**			
Similarities (SIMIL)	-.72**	.65**	.50**	.55**	.70**	-.13				
Verbal Recall Errors (Errors)	.20*	-.08	-.09	-.06	-.15					
Verbal Recall Total (RCTOT)	-.68**	.66**	.30**	.51**						
Paired Associates Part II (PAIRASS)	-.40**	.46**	.43**							
Word Association Frequent Responses (FREQ)	-.34**	.28**								
Witkins Embedded Figures Test (WEFT)	-.52**									

(* p<.05; ** p <.01)

Pearson Correlations : P3 Latency; Signal : Noise Ratio; Stroop Reaction Time; Digit Span; Similarities; Verbal Recall Total; Word Association Frequent Responses; Witkins Embedded Figures.
Spearman Correlations: Verbal Recall Errors; Paired Associates Part II

INTER TEST CORRELATION COEFFICIENTS FOR UNIPOLAR DEPRESSED SUBJECTS (n=10)

	WCST	WEFT	FREQ	PAIASS	RCTOT	ERRORS	SIMIL	DIGSP	STRT	S:N
P3 Latency	.38	.21	-.12	-.18	-.30	.59*	-.08	-.08	.07	.18
Signal : Noise Ratio (S : N)	-.55	.12	-.27	.22	.02	.31	.30	-.57	-.45	
Stroop Reaction Time Colours (STRT)	.82**	-.65*	-.39	-.82**	-.72*	.59	-.71*	-.30		
Digit Span (DGTSP)	-.14	.15	.21	.20	.55*	-.50	-.06			
Similarities (SIMIL)	-.61*	.76**	.71*	.45	.61	-.11				
Verbal Recall Errors (ERRORS)	.69*	-.20	-.31	-.24	-.46					
Verbal Recall Total (RCTOT)	-.75**	.50	.62*	.32						
Paired Associates PART II (PAIRASS)	-.59*	.74**	.34							
Word Association Frequent Responses (FREQ)	-.24	.67*								
Witkins Embedded Figures Test(WEFT)	-.44									

(* p<.05; ** p <.01)

Pearson Correlations : P3 Latency; Signal; Noise Ratio, Stroop Reaction Time, Digit Span; ½similarities; Verba Recall Total; Word Association Frequent Response; Witkins Embedded Figures

Spearman Correlations: Verbal Recall Errors; Paired Associates Part II.

INTER TEST CORRELATION COEFFICIENTS FOR CONTROL SUBJECTS (n = 24)

	WEST	WEFT	FREQ	PAIRASS	RCTOT	ERRORS	SIMIL	DIGSP	STRT	S:N
P3 Latency	-.00	-.28	.33	-.01	-.06	-.36*	-.11	-.11	.03	-.23
Signal : Noise Ratio (S:N)	-.34	.31	-.23	-.14	.37*	-.37*	.10	.41*	-.22	
Stroop Reaction Time Colours (STRT)	-.32	-.44*	-.46*	.49**	-.52**	.31	-.40*	-.54**		
Digit Span (DIGSP)	-.45	.33	.06	-.22	.50**	-.39	.31			
Similarities (SIMIL)	-.58**	.47*	.33	-.05	.51**	-.33				
Verbal Recall Errors (ERRORS)	.19	-.17	-.25	-.15	-.58**					
Verbal Recall Total (RCTOT)	-.58**	.21	.24	.12						
Paired Associates Part II (PAIRASS)	.10	-.23	.02							
Word Association Frequent Responses (FREQ)	-.12	.28								
Witkins Embedded Figures Test (WEFT)	-.29									

(* p<.05; ** p<.01)

Pearson Correlations : P3 Latency; Signal : Noise Ratio; Stroop Recation Time; Digit Span; Similarities; Verbal Recall Total; Word Association Frequent Responses; Witkins Embedded Figures.
Spearman Correlations: Verbal Recall Errors; Paired Associates Part II.

APPENDIX A7 Analysis of Variance by Sub-Groups

P3 Latency by Sub Group

Source	df	Mean Square	F Ratio	p
Between Groups	1	763.8107	.3933	.5371
within Group	22	1942.7643		
Total	23			

P3 Amplitude by Sub-Groups

Source	df	Mean Square	F Ratio	p
Between Groups	1	374.6679	1.1432	.2966
Within Groups	22	327.7253		
Total	23			

Signal : Noise Ratio by Sub-Groups

Source	df	Mean Square	F Ratio	p
Between Groups	1	43372.9714	3.2409	.0855
Within Groups	22	13382.8649		
Total	23			

Age by Sub-Groups

Source	df	Mean Square	F Ratio	p
Between Groups	1	129.6429	1.2461	.2763
within Groups	22	104.0390		
Total	23			

Analysis of Variance

Thought Disorder by Sub-Group

Source	df	Mean Square	F Ratio	p
Between Groups	1	32.35	3.80	.06
Within Groups	21	8.52		
Total	23			

Anxiety/Depression by Sub-Group

Source	df	Mean Square	F Ratio	p
Between Groups	1	0.74	0.35	.56
within Groups	21	2.10		
Total	22			

Withdrawal by Sub-Group

Source	df	Mean Square	F Ratio	p
Between Groups	1	4.42	0.42	.52
Within Groups	21	10.55		
Total	22			

Hostility by Sub-Group

Source	df	Mean Square	F Ratio	p
Between Groups	1	6.37	2.49	.13
Within Groups	21	2.55		
Total	22			

Hamilton Rating Scale for Depression by Sub-Group

Source	df	Mean Square	F Ratio	p
Between Groups	1	28.13	0.75	.40
Within Groups	21	37.73		
Total	22			

NART By Sub-Group

Source	df	Mean Square	F Ratio	p
Between Groups	1	990.17	10.46	.0004
Within Groups	22	94.63		
Total	23			

WAIS I.Q. By Group

Source	df	Mean Square	F Ratio	p
Between Groups	1	2938.14	20.63	0.0002
Within Groups	21	142.40		
Total	23			

I.Q. Difference by Sub-Group

Source	df	Mean Square	F Ratio	p
Between Groups	1	209.0012	2.4290	.13
Within Groups	22	86.0435		
Total	23			

Word Association Frequent Responses by Sub Groups

Source	df	Mean Square	F Ratio	p
Between Groups	1	121.14	4.41	0.05
Within Groups	22	27.45		
Total	23			

Word Association by Sub Group

Source	df	Mean Square	F Ratio	p
Between Groups	1	4.18	3.65	0.69
Within Groups	22	1.14		
Total	23			

Witkins Embedded Figures by Sub Group

Source	df	Mean Square	F Ratio	p
Covariate I.Q.	1	21.00	4.49	.05
Between Groups	1	0.67	.14	.71
Within Groups	21	4.68		
Total	23			

Verbal Recall Emotive Words by Sub Group

Source	df	Mean Square	F Ratio	p
Covariate I.Q.	1	25.52	7.32	.01
Between Groups	1	11.78	3.37	.08
Within Groups	21	3.49		
Total	23			

Verbal Recall Category Words by Sub Group

Source	df	Mean Square	F Ratio	p
Covariate I.Q.	1	43.13	7.80	.01
Between Groups	1	64.72	11.70	.003
Within	21	5.53		
Total	23			

Verbal Recall Total Words by Sub Group

Source	df	Mean Square	F Ratio	p
Covariate I.Q.	1	442.56	11.01	.003
Between Groups	1	397.76	9.98	.005
Within Groups	21	40.20		
Total	23			

Verbal Recall Neutral Words by Sub-Group

Source	df	Mean Square	F Ratio	p
Covariate I.Q.	1	12.00	7.46	.01
Between Groups	1	7.20	4.48	.05
Within Groups	21	1.61		
Total	23			

Similarities by Sub-Group

Source	df	Mean Square	F Ratio	p
Covariate I.Q.	1	67.99	25.03	.0001
Between Groups	1	27.59	10.15	.004
Within Groups	21	2.72		
Total	23			

Digit Span by Sub-Group

Source	df	Mean Square	F Ratio	p
Covariate I.Q.	1	81.71	14.34	.001
Between Groups	1	38.58	5.89	.02
Within Groups	21	5.70		
Total	23			

Stroop Reaction Time (Words) by Sub Group

Source	df	Mean Square	F Ratio	p
Covariate I.Q.	1	6.95	4.16	.05
Between Groups	q	3.35	2.01	.17
Within Groups	21	1.67		
Total	23			

Stroop Reaction Time (Colours) by Sub-Group

Source	df	Mean Square	F Ratio	p
Between Groups	1	7.17	7.00	.01
Within Groups	22	1.03		
Total	23			

Kruskall-Wallis One Way Analysis of Variance

Paired Associates Part I by Sub-Group

Mean Rank	Cases = 24
13.89 10.55	x^2 = 1.31 sig = .25 corrected x^2 = 1.74 sig= .19

Paired Associates Part II by Sub-Group

Mean Rank	Cases = 24
11.93 13.30	x^2= 0.22 sig = .64 corrected x^2 = 0.24 sig = .63

Verbal Recall Errors by Sub-Group

Mean Rank	Cases = 24
12.36 12.70	x^2 = 0.01 sig = .91 corrected x^2 = 0.01 sig = .90

Verbal Recall Isolates by Sub-Group

Mean Rank	Cases = 24
14.14 10.20	x^2 = 1.81 sig = .18 corrected x^2 = 1.95 sig = .16

APPENDIX B1
AGE AT FIRST ONSET, LENGTH OF HOSPITALIZATION FOR CURRENT EPISODE AND MEDICATION FOR SCHIZOPHRENIC PATIENTS

JECT	AGE AT FIRST ONSET	LENGTH OF HOSPITALIZATION (MONTHS) CURRENT EPISODE	MEDICATION (mg/day) (NEUROLEPTICS DOSE AS CPZ EQUIVALENT)'	
1	26	OP	FPX DEC	150
2	26	OP	DRUG FREE	
3	19	1.5	CPZ	700
			FPX DEC	300
4	20	20	HPD	250
5	23	4.5	FPX DEC	600
			CPZ	300
6	18	1.5	FPX DEC	550
			CPZ	600
7	29	OP	FPZ DEC	150
8	33	30	SPD	400
9	39	1	TFPZ	400
10	34	2	FPX DEC	190
			CPZ	100
11	21	1	CPZ	400
12	19	OP	FPX DEC	70
13	22	OP	FPX DEC	190
14	23	OP	FPX DEC	150
15	23	OP	ZPCX DEC	190
16	17	OP	SPD	300
17	24	OP	TFPZ	400
18	19	OP	FPX DEC	190
			CPZ	300
19	20	OP	FPX DEC	150
20	19	18	FPZ DEC	300
21	20	OP	FPX DEC	70
22	19	22	TDZ	25
23	19	OP	FPX DEC	300
24	18	24	CPZ	400
25	19	OP	FPX DEC	190
26	19	66	HPD	300
			ZPX DEC	450
27	24	32	PZ	750
28	21	4	CPZ	600
			FPX DEC	600
29	24	1.5	TFPZ	200
30	37	8	CPZ	600

OP = Outpatient
PX DEC = Flupenthixol decanoate
PZ DEC = Fluphenazine decanoate
PX DEC = Zuclopenthixol decanoate
Z = Pimozide

CPZ = Chlorpromazine
HPD = Haloperidol
TFPZ = Trifluoperazine
SPD = Sulpiride

APPENDIX B2

Analyses of Variance of Age, Physiological Variables and I.Q. by Group

Age by Sex by Group

Source	df	Mean Square	F Ratio	p
Sex	1	101.20	0.80	.37
Group	2	975.10	7.73	.001
Sex by Group	2	241.19	1.91	.15
Total	89			

P3 Latency by Sex by Group

Source	df	Mean Square	F Ratio	p
Sex	1	1026.47	0.80	.87
Group	2	16080.30	11.98	.0001
Sex by Group	2	72.04	0.54	.95
Within Cells	82	1342.77		
Total	87			

P3 Amplitude by Sex by Group

Source	df	Mean Square	F Ratio	p
Sex	1	120.44	0.27	.61
Group	2	14408.21	9.78	.0001
Sex by Group	2	668.89	1/48	.23
Within Cells	82	450.95		
Total	87			

Signal : Noise Ratio by Group

Source	df	Mean Square	F Ratio	p
Sex	1	1766.37	0.14	.71
Group	2	17863.94	1.46	.24
Sex by Group	2	32589.65	2.66	.08
Within Cells	82	12232.05		
Total	87			

Age by Sex by Group

Source	df	Mean Square	F Ratio	p
Sex	1	92.59	.77	.38
Relgp	3	698.36	5.80	.001
Sex x Relgp	3	354.14	2.94	.04
Within Cells	82	120.38		
Total	89			

Relgp = Schizophrenics, Controls, Relatives with abnormal P3 latency and relatives with normal P3 latency

P3 Latency by Sex by Group

Source	df	Mean Square	F Ratio	p
Sex	1	766.06	0.77	.38
Relgp	3	20400.07	20.49	.0001
Sex by Relgp	3	259.67	.26	.85
Within Cells	81	995.65		
Total	88			

P3 Amplitude by Sex by Group

Source	df	Mean Square	F Ratio	p
Sex	1	112.36	.25	.62
Relgp	3	3222.55	7.24	.0001
Sex by Relgp	3	619.06	1.39	.25
Within Cells	80	445.09		
Total	87			

Signal : Noise Ratio by Sex by Group

Source	df	Mean Square	F Ratio	p
Sex	1	1983.59	.16	.69
Relgp	3	13572.98	1.09	.36
Sex by Relgp	3	21780.10	1.75	.16
Within Cells	80	12473.45		
Total	87			

NART I.Q. by Sex by Group

Source	df	Mean Square	F Ratio	p
Sex	1	9.02	.14	.71
Relgp	3	726.45	11.01	.0001
Sex by Relgp	3	26.63	.40	.75
Within Cells	82	65.96		
Total	89			

Current I.Q by Sex by Group

Source	df	Mean Square	F Ratio	p
Sex	1	16.99	.12	.73
Reigp	3	2470.35	17.34	.0001
Sex by Relgp	3	128.31	.90	.45
Within Cells	69	142.43		
Total	76			

I.Q. Difference by Sex by Group

Source	df	Mean Square	F Ratio	p
Sex	1	13.64	.71	.40
Relgp	3	142.28	7.42	.0001
Sex by Relgp	3	5.52	.29	.83
Within Cells	69	19.12		
Total	76			

APPENDIX B3

Pearson and Spearman Correlation Coefficients of Premorbid I.Q. (National Adult Reading Test) and Age with Performance on the Cognitive Tests

(a) All Subjects

	Premorbid I.Q.	Age
Wisconsin Card Sorting Test	-.57**	.15
Verbal Fluency Letters	.55**	.02
Verbal Fluency Categories	.58**	-.06
Benton's Copying of Designs (Spearman)	.27**	-.23*
Witkins Embedded Figures Test	.60**	-.20
Verbal Recall Emotive Words	.51**	-.26
Verbal Recall Category Words	.63**	-.15
Verbal Recall Total Words	.63**	-.26**
Verbal Recall Recognition	.36**	-.07
Hebb's Recurring Digits Span	.49**	-.16
Times to Learn	.25*	-.08
Corsi's Block Tapping Test Span	.45**	-.12
Times To Learn	-.04	.04
Word Association Frequent Responses	.14	-.28*
Word Association Rank	-.15	.25

(* $p<.05$; ** $p<.01$)

(b) Pearson and Spearman Correlation coefficients of Premorbid I.Q. (National Adult Reading Test) and Age with Performance on the Cognitive Tests in Schizophrenic Subjects

	Premorbid I.Q.	Age
Wisconsin Card Sorting Test	-.53**	.31*
Verbal Fluency Letters	.34*	-.11
Verbal Fluency Categories	.44*	-.05
Benton Copying of Designs (Spearman)	.39	-.07
Witkins Embedded Figures Test	.41*	-.06
Verbal Recall Emotive Words	.32*	-.11
Verbal Recall Caategory Words	.52**	-.02
Verbal Recall Total Words	.47**	-.11
Verbal Recall Recognition	.36*	.08
Hebb's Recurring Digits Span	.46**	-.16
Times to Learn	-.15	-.11
Corsi's Block Tapping Test Span	.29	-.49**
Times to Learn	.14	.05
Words Association Frequent Responses	-.04	-.39*
Word Association Rank	.08	.41*

(* $p<.05$; **$p<.01$)

(c) Pearson and Spearman Correlation Coefficients of Premorbid I.Q. (National Adult Reading Tests and Age with Performance on the Cognitive Tests in Relatives

	Premorbid I.Q.	Age
Wisconsin Card Sorting Test	-.51**	.07
Verbal Fluency Letters	.50**	.18
Verbal Fluency Categories	.56**	-.08
Benton Copying of Designs (Spearman)	-.02	-.38
Verbal Recall Emotive Words	.11	-.50**
Verbal Recall Category Words	.30	-.15
Verbal Recall Emotive Words	.11	-.50**
Verbal Recall Category Words	.30	-.15
Verbal Recall Recognition	.26	-.27
Hebb's Recurring Digits Span	.42*	.18
Times to Learn	-.09	-.07
Corsi's Block Tapping Span	.44**	.10
Times to Learn	.10	-.03

(*p<.05; **p<.01)

(d) Pearson and Spearman Correlation Coefficients of Premorbid I.Q. (National Adult Reading Test) and Age with Performance on the Cognitive Tests in Control Subjects

	Premorbid I.Q.	Age
Wisconsin Card Sorting Test	-.69**	.26
Verbal Fluency Letters	.32	.11
Verbal Fluency Categories	.60**	-.14
Benton Copying of Designs (Spearman)	.36*	-.46**
Witkins Embedded Figures Test	.36*	-.46**
Verbal Recall Emotive Words	.44	-.13
Verbal Recall Category Words	.50**	-.19
Verbal Recall Total Words	.58**	-.14
Verbal Recall Recognition	.20	-.15
Hebb's Recurring Digit Span	.10	-.43
Times to Learn	.02	-.11
Corsi's Block Tapping Test Span	.15	-.19
Times to Learn	-.14	-.11
Words Association Frequent Responses	.26	-.14
Word Association Rank	-.28	.11

(*$p<.05$; **$p<.01$)

APPENDIX B4

Analyses of Variance of Cognitive Variables by Groups

Wisconsin Card Sorting Test by Group

Source	df	Mean Square	F Ratio	p
Covariate I.Q.	1	3510.85	42.96	.0001
Between Groups	3	255.27	3.34	.02
Within Groups	84	76.40		
Total	88			

Verbal Recall Emotive Words by Group

Source	df	Mean Square	F Ratio	p
Covariate I.Q.	1	204.46	38.1	.0001
Between Groups	3	45.50	8.50	.0001
Within Groups	83	5.35		
Total	87			

Verbal Recall Category Words by Group

Source	df	Mean Square	F Ratio	p
Covariate I.Q.	1	472.61	79.30	.0001
Between Groups	3	68.78	11.54	.0001
Within Groups	83	5.96		
Total	87			

Verbal Recall Total Words by Group

Source	df	Mean Square	F Ratio	p
Covariate I.Q.	1	3565.00	76.20	.0001
Between Groups	3	511.08	10.92	.0001
Within Groups	83	46.80		
Total	87			

Verbal Recall Recognition by Group

Source	df	Mean Square	F Ratio	p
Covariate I.Q.	1	131.70	10.71	.0002
Between Groups	3	12.30	1.00	.40
Within Groups	67	12.30		
Total	71			

Hebb's Recurring Digits Test and Corsi's Block Tapping Test

(a) Span by Test by Group

Source	df	Mean Square	F Ratio	p
Groups	3	6.71	6.01	.001
Test	1	117.52	207.00	.0001
Groups x Test	3	1.40	2.47	.07
Within Cells	70	0.57		
Total	77			

(b) Times to Learn by Group

Source	df	Mean Square	F Ratio	p
Groups	3	18.44	5.29	.002
Test	1	.04	.03	.87
Groups x Test	3	1.39	.87	.46
Within Cells	70	1.59		
Total	77			

Verbal Fluency Letters by Group

Source	df	Mean Square	F Ratio	p
Covariate I.Q.	1	4059.93	38.15	.0001
Between Groups	3	406.32	3.82	.01
Within Groups	75	106.43		
Total	79			

Verbal Fluency Categories by Group

Source	df	Mean Square	F Ratio	p
Covariate I.Q.	1	4354.29	56.08	.0001
Between Groups	3	1126.50	14.51	.0001
Within Groups	67	77.62		
Total	71			

Kruskal-Wallis One Way Analysis of Variance

Benton's Copying of Designs by Group

Mean Rank	
40.56	Cases = 77
34.84	x^2 = 2.78 sig = 0.43
32.10	
43.89	corrected x^2 = 4.07 sig = 0.25

Verbal Recall Errors by Group

Mean Rank	
45.30	Cases = 89
46.34	x^2 = 0.13 sig = 0.99
45.25	
43.77	corrected x^2 = 0.13 sig = 0.99

Verbal Recall Isolates by Group

Mean Group	
34.40	Cases = 88
43.11	x^2 = 13.62 sig = 0.004
38.00	
58.10	corrected x^2 = 14.48 sig = 0.002

INTER TEST CORRELATION COEFFICIENTS FOR RELATIVES (n = 30)

	WCST	RCTOT	RECOG	SPAN	TIMES	VFLET	VFCAT	BENTON	S:N
P3 Latency	.08	-.30	-.28	.05	.66**	-.30	-.34*	-.11	-.20
Signal : Noise Ratio (S:N)	-.28	-.00	-.12	-.10	.02	-.24	.07	.28	
Benton Copying of Designs (BENTON)	-.04	.34*	-.08	.13	-.16	-.02	-.12		
Verbal Fluency Categories (VFCAT)	-.40*	.30	.23	.30	-.30	.45**			
Verbal Fluency Letters (VFLET)	.00	.22	.21	.27	-.34				
Times to Learn (TIMES)	.13	-.33	-.10	.34					
Span	-.11	.09	-.14						
Recognition (RECOG)	-.13	.42							
Verbal Recall Total Words (RCTOT)	-.40*								

INTER TEST CORRELATION COEFFICIENTS FOR CONTROL SUBJECTS (n = 30)

	WCST	RCTOT	RECOG	SPAN	TIMES	VFLET	VFCAT	BENTON	S:N
P3 Latency	-.01	-.17	-.34	.00	-.51**	.12	-.09	-.10	-.13
Signal : Noise Ratio (S:N)	-.31	.14	-.36	.43*	-.04	.38*	.21	-.05	
Benton Copying of Designs (BENTON)	.33	-.41*	.71	-.12	-.14	-.33	-.30		
Verbal Fluency Categories (VFCAT)	-.43*	.40*	.23	.38*	.22	.48*			
Verbal Fluency Letters (VFLET)	-.16	.37*	.12	.28	.01				
Times to Learn (TIMES)	.30	.08	.32	-.03					
Span	.18	.15	-.17						
Recognition (RECOG)	-.09	.38							
Verbal Recall Total Words (RCTOT)	-.57**								

APPENDIX B6

Discriminant Function Analysis

Classification Scores for Relatives

	Group 1	Group 2	P3 Latency	Predicted Group	Actual Group
01	19.5406504	17.3810728	394	1	1
02	18.4061974	14.6548134	335	1	1
03	16.96888403	13.3456239	438	1	1
04	13.5120845	9,2190471	432	1	1
05	M I S S I N G	V A L U E S			
06	21.6382729	18.3174275	351	1	1
07	15.8210381	11.9700983	342	1	1
08	30.8540635	30.6723661	384	1	1
09	19.8249966	19,2607832	342	1	1
10	26.8033828	26.5333934	350	1	1
11	14.9294178	11.4278258	382	1	1
12	10.7356387	11.9526175	358	2	1
13	22.1591827	17.8145649	370	1	1
14	19.8583696	17.0095602	355	1	1
15	22.0490518	25.2436008	280	2	2
16	22.1706605	19.5354891	294	1	2
17	12.4740285	13.5644513	285	2	2
18	11.7355185	7.6860575	282	1	2
19	16.2599813	19.4918943	300	2	2
20	15.3750356	18.4999672	315	2	2
21	17.399643	19.371808	333	2	2
22	16.8624522	15.9821776	309	1	2
23	5.8400599	4.1202501	306	1	2
24	18.4873738	25.2483796	333	2	2
25	17.6891979	18.4044827	318	2	2
26	16.2136646	17.624692	312	2	2
27	14.1156366	21.7069418	298	2	2
28	14.1375318	17.7348946	318	2	2
29	18.2946006	19.6876582	342	2	2
30	24.750611	25.0667399	334	2	2

79.3% cases classified correctly

Classification Function Coefficients

	1	2
RCTOT	.5772384	.6877628
VFCAT	-.0033373	.2251223
TIMES	1.472196	1.004013
CONSTANT	-15.82840	-26.42341

APPENDIX B7

Pearson and Spearman Correlation Coefficients of P3 Amplitude with Age, Rating Scores and Cognitive Scores

	1 Schizophrenic	2 Relatives	3 Controls
Age	-.32*	.25	-.14
Brief Psychiatric Rating Scale Thought Disorder	-.08		
Anxiety Depression	-.18		
Withdrawal	.10		
Hostility	-.08		
Hamilton Rating Scale for Depression	.03		
Premorbid I.Q.	-.42*	.11	.12
Current I.Q.	-.35*	.04	.15
I.Q. Difference	.02	-.08	-.12
Wisconsin Card Sorting Test	-.11 (+)	-.02	-.10
Verbal Recall Recognition	.19 (+)	-.18	.28
Hebb's Recurring Digits Test Span	-.03 (+)	.25	.05
Times to Learn	.30	-.20	.16
Corsi's Block Tapping Test Span	.05	-.01	-.07
Times to Learn	-.05	-.13	-.50**
Verbal Fluency Letters	-.03 (+)	.04	.11
Verbal Fluency Categories	-.04 (+)	.24	-.26
Benton's Copying of Designs (Spearman)	.10	.15	-.05

(*p<.05;** p<.01)

(+) controlling for I.Q. where I.Q. correlates with cognitive variables

APPENDIX B8

Analysis of Variance Comparing Sub-Groups in Schizophrenic Group

Age by Sub-Group

Source	df	Mean Square	F Ratio	p
Between Groups	1	76.03	1.01	.32
Within Groups	28	75.09		
Total	29			

P3 Latency by Sub-Group

Source	df	Mean Square	F Ratio	p
Between Groups	1	729.35	.44	.51
Within Group	28	1699.69		
Total	29			

P3 Amplitude by Sub-Group

Source	df	Mean Square	F Ratio	p
Bwteen Group	1	2799.23	4.07	.05
Within Groups	28	688.48		
Total	29			

Signal : Noise Ratio by Sub-Group

Source	df	Mean Square	F Ratio	p
Between Groups	1	73333.71	6.24	.01
Within Groups	28	11757.37		
Total	29			

Analyses of Variance Comparing State Rating Scales for Sub-groups in Schizophrenic Group

Thought Disorder by Sub-Group

Source	df	Mean Square	F Ratio	p
Between Groups	1	44.64	5.65	.01
Within Groups	28	7.90		
Total	29			

Anxiety/Depression by Sub-Group

Source	df	Mean Square	F Ratio	p
Between Groups	1	.47	.25	.62
Within Groups	28	1.84		
Total	29			

Withdrawal by Group

Source	df	Mean Square	F Ratio	p
Between Groups	1	25.11	2.15	.15
Within Groups	28	11.70		
Total	29			

Hostility by Sub-Group

Source	df	Mean Square	F Ratio	p
Between Groups	1	6.91	3.28	.08
Within Groups	28	2.11		
Total	29			

Hamilton Rating Scale for Depression

Source	df	Mean Square	F Ratio	p
Between Groups	1	.85	.05	.82
Within Groups	28	15.45		
Total	29			

Premorbid I.Q. by Sub-Group

Source	df	Mean Square	F Ratio	p
Between Groups	1	1348.43	20.36	.0001
Within Groups	28	46.22		
Total	29			

Current I.Q. by Sub-Group

Source	df	Mean Square	F Ratio	p
Between Groups	1	3441.80	45.74	.00001
Within Groups	26	75.24		
Total	27			

I.Q. Difference by Sub-Group

Source	df	Mean Square	F Ratio	p
Between Groups	1	388.27	15.03	.0006
Within Groups	26	25.84		
Total	27			

Verbal Recall Emotive Words

Source	df	Mean Square	F Ratio	p
Covariate I.Q.	1	17.15	4.46	.04
Between Groups	1	46.22	12.52	.001
Within Groups	27	8.68		
Total	29			

Verbal Recall Category Words by Sub-Group

Source	df	Mean Square	F Ratio	p
Covariate I.Q.	1	65.40	13.82	.001
Between Groups	1	44.16	9.33	.005
Within Groups	27	4.73		
Total	29			

Verbal Recall Total Words by Sub-Group

Source	df	Mean Square	F Ratio	p
Covariate I.Q.	1	427.43	12.57	.001
Between Groups	1	592.97	17.44	.0001
Within Groups	27	34.01		
Total	29			

Verbal Recall Recognition by Sub-Group

Source	df	Mean Square	F Ratio	p
Between Groups	1	18.38	.85	.37
Within Groups	22	21.71		
Total	23			

Verbal Recall Letters by Sub-Group

Source	df	Mean Square	F Ratio	p
Between Groups	1	499.85	4.20	.05
Within Groups	24	119.00		
Total	25			

Verbal Fluency Categories by Sub-Group

Source	df	Mean Square	F Ratio	p
Covariate I.Q.	1	257.73	5.35	.03
Between Groups	1	265.73	5.52	.03
Within Groups	17	48.16		
Total	19			

Hebb's Recurring Digit Test. Corsi's Block Tapping Test

(a) Span by Test by Sub-Group

Source	df	Mean Square	F Ratio	p
Groups	1	17.41	19.66	.0001
Test	1	80.92	135.62	.0001
Groups x Test	1	0.92	1.53	.23
Within Cells	26			
Total	29			

(b) Times to Learn by Test by Sub-Group

Source	df	Mean Square	F Ratio	p
Groups	1	0.00	0.00	.98
Test	1	3.20	1.49	.23
Groups x Test	1	0.63	0.29	.59
Within Cells	26			
Total	29			

Kruskal-Wallis One Way Analysis of Variance

Benton Copying of Designs by Sub-Group

Mean Rank	cases = 24		
16.15			
10.85	x^2 = 3.3	sig = 0.08	
	corrected x^2 = 5.15		sig = 0.02

Analyses of Variance

Ventricular Brain Ratio by Sub-Group

Source	df	Mean Square	F Ratio	p
Between Groups	1	130512.98	9.94	.009
Within Groups	28	16449/53		
Total	29			

Absolute Right-Left Caudate Difference

Source	df	Mean Square	F Ratio	p
Between Groups	1	177.56	3.96	.06
Within Groups	28	44.81		
Total	29			

Absolute Right-Left Temporal Lobe Difference

Source	df	Mean Square	F Ratio	p
Between Groups	1	15664.63	3.75	.06
Within Groups	28	4171.79		
Total	29			

APPENDIX C 1

Analyses of Variance

Age by Group of Age and Cognitive Measures by Group

Source	df	Mean Square	F Ratio	p
Between Groups	2	23.49	0.14	.89
Within Groups	42	163.95		
Total	44			

Mill Hill Vocabulary Scale by Group

Source	df	Mean Square	F Ratio	p
Between Groups	2	1325.96	12.74	.00
Within Groups	42	104.06		
Total	44			

Hamilton Rating Scale for Depression by Group

Source	df	Mean Square	F Ratio	p
Between Groups	2	1839.62	290.03	.00001
Within Groups	42	6.34		
Total	44			

Beck Depression Inventory by Group

Source	df	Mean Square	F Ratio	p
Between Groups	2	2851.69	51.5	.00001
Within Groups	41	55.36		
Total	43			

Dysfunctional Attitude Scale by Group

Source	df	Mean Square	F Ratio	p
Between Groups	2	6981.45	8.86	.0006
Within Groups	41	788.04		
Total	43			

Sociotropy-Autonomy Scale (Autonomy) by Group

Source	df	Mean Square	F Ratio	p
Between Groups	2	238.78	1.05	.36
Within Groups	41	227.25		
Total	43			

Sociotropy-Autonomy Scale (Sociotropy) by Group

Source	df	Mean Square	F Ratio	p
Between Groups	2	1434.45	3.89	.03
Within Groups	41	368.84		
Total	43			

APPENDIX C2

Analyses of Variance of P3 Amplitude by Group

Negative Stimuli

(a) Vertex

Source	df	Mean Square	F Ratio	p
Between Groups	2	22.84	2.01	.15
Within Groups	41	11.35		
Total	43			

(b) Frontal

Source	df	Mean Square	F Ratio	p
Between Groups	2	10.62	0.99	.38
Within Groups	41	10.74		
Total	43			

(c) Occipital

Source	df	Mean Square	F Ratio	p
Between Groups	2	3.51	0.50	.61
Within Groups	41	7.08		
Total	43			

Positive Stimuli

(a) Vertex

Source	df	Mean Square	F Ratio	p
Between Groups	2	16.81	1.28	.29
Within Groups	41	13.10		
Total	43			

(b) Frontal

Source	df	Mean Square	F Ratio	p
Between Groups	2	10.30	0.92	.41
Within Groups	41			
Total	43			

(c) Occipital

Source	df	Mean Square	F Ratio	p
Between Groups	2	22.84	2.24	.12
Within Groups	41	10.21		
Total	43			

Neutral Stimuli

(a) Vertex

Source	df	Mean Square	F Ratio	p
Between Groups	2	5.28	0.51	.60
Within Groups	41	10.36		
Total	43			

(b) Frontal

Source	df	Mean Square	F Ratio	p
Between Groups	2	4.64	0.46	.63
Within Groups	41	10.05		
Total	43			

(c) Occipital

Source	df	Mean Square	F Ratio	p
Between Groups	2	6.92	0.95	0.39
Within Groups	41	7.28		
Total	43			

P3 Amplitude Negative-Neutral by Group

(a) Vertex

Source	df	Mean Square	F Ratio	p
Between Groups	2	35.05	6.50	.003
Within Groups	42	5.39		
Total	44			

(b) Frontal

Source	df	Mean Square	F Ratio	p
Between Groups	2	20.93	4.46	.02
Within Groups	42	4.69		
Total	44			

(c) Occipital

Source	df	Mean Square	F Ratio	p
Between Groups	2	16.27	4.65	.02
Within Groups	42	3.50		
Total	44			

P3 Amplitudes Positive-Neutral by Group

(a) Vertex

Source	df	Mean Square	F Ratio	p
Between Groups	2	16.50	1.91	.16
Within Groups	41	8.64		
Total	43			

(b) Frontal

Source	df	Mean Square	F Ratio	p
Between Groups	2	4.00	0.61	.55
Within Groups	41	6.57		
Total	43			

(c) Occipital

Source	df	Mean Square	F Ratio	p
Between Groups	2	4.99	0.84	.44
Within Groups	41	5.96		
Total	44			

P3 Amplitude (Negative-Neutral) by Group by Site

Source	df	Mean Square	F Ratio	p
Group	2	40.90	4.84	.01
Site	2	15.48	4.07	.02
Group x Site	4	10.73	2.82	.03
Within Cells	82	3.80		
Total	90			

P3 Amplitudes (Positive-Neutral) by Group by Site

Source	df	Mean Square	F Ratio	p
Group	2	5.56	0.47	.63
Site	2	6.88	1.49	.23
Group x Site	4	9.97	2.16	.08
Within Cells	82	4.62		
Total	90			

APPENDIX C3

Analyses of Variance of P3 Latencies by Group

Negative Stimuli

(a) Vertex

Source	df	Mean Square	F Ratio	p
Between Groups	2	2912.62	1.98	.15
Within Groups	42	1474.43		
Total	44			

(b) Frontal

Source	df	Mean Square	F Ratio	p
Between Groups	2	4828.09	2.43	.10
Within Groups	42	1988.22		
Total	44			

(c) Occipital

Source	df	Mean Square	F Ratio	p
Between Groups	2	6608.62	4.72	.01
Within Groups	42	1399.71		
Total	44			

Positive Stimuli

(a) Vertex

Source	df	Mean Square	F Ratio	p
Between Groups	2	472.62	0.24	.79
Within Groups	42	1966.79		
Total	44			

(b) Frontal

Source	df	Mean Square	F Ratio	p
Between Groups	2	1618.40	0.71	.50
Within Groups	42	2266.86		
Total	44			

(c) Occipital

Source	df	Mean Square	F Ratio	p
Between Groups	2	962.22	0.64	.53
Within Groups	42	1513.21		
Total	44			

Neutral Stimuli

(a) Vertex

Source	df	Mean Square	F Ratio	p
Between Groups	2	4183.51	3.14	>.05
Within Groups	42	1330.60		
Total	44			

(b) Frontal

Source	df	Mean Square	F Ratio	p
Between Groups	2	4167.47	2.20	.12
Within Groups	42	1894.04		
Total	44			

(c) Occipital

Source	df	Mean Square	F Ratio	p
Between Groups	2	2480.69	2.22	.12
Within Groups	42	1119.66		
Total	44			

Repeated Measures Analysis of Various P3 Latency by Group by Emotive Condition

(a) Vertex

Source	df	Mean Square	F Ratio	p
Group	2	6256.24	1.65	.21
Condition	2	85.76	.18	.84
Group x Condition	4	656.26	1.35	.26
Within Cells	84	487.56		
Total	88			

(b) Frontal

Source	df	Mean Square	F Ratio	p
Group	2	9196.92	1.95	.16
Condition	2	735.67	1.03	.36
Group x Condition	4	754.96	1.05	.38
Within Cells	84	715.71		
Total	88			

(c) Occipital

Source	df	Mean Square	F Ratio	p
Group	2	8698.87	2.78	.07
Condition	2	1775.27	3.91	.02
Group x Condition	4	767.33	1.49	.21
Within Cells	84	453.80		
Total	88			

APPENDIX C4

Pearson Correlation Coefficients of I.Q. with Physiological Variables

Negative - Neutral P3 Amplitude

Vertex	.19
Frontal	.07
Occipital	.02

P3 Latency :

	Negative	Positive	Neutral
Vertex	-.13	-.11	-.23
Frontal	-.27*	-.13	-.19
Occipital	-.19	-.04	-.20

(*p<.05)