ELECTROPHYSIOLOGICAL AND NEUROPSYCHOLOGICAL MEASURES IN PATIENTS WITH SCHIZOPHRENIA AND THEIR UNAFFECTED BIOLOGICAL SIBLINGS: A FAMILY STUDY

DISSERTATION SUBMITTED FOR PARTIAL FULFILLMENT

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DOCTOR OF MEDICINE

BRANCH - XVIII (PSYCHIATRY)

THE TAMILNADU

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CHENNAI, TAMIL NADU.

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CERTIFICATE

This is to certify that the dissertation titled, "**ELECTROPHYSIOLOGICAL AND NEUROPSYCHOLOGICAL MEASURES IN PATIENTS WITH SCHIZOPHRENIA AND THEIR UNAFFECTED BIOLOGICAL SIBLINGS: A FAMILY STUDY"** is the bonafide work of **Dr. VIJAYA RAGHAVAN D**, in part fulfillment of the requirements for the M.D. Branch – XVIII (Psychiatry) examination of The Tamilnadu Dr. M. G. R. Medical University, to be held in April 2015. The period of study was from Aug 2014 – Sep 2014.

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CERTIFICATE OF GUIDE

This is to certify that the dissertation titled, **"ELECTROPHYSIOLOGICAL AND NEUROPSYCHOLOGICAL MEASURES IN PATIENTS WITH SCHIZOPHRENIA AND THEIR UNAFFECTED BIOLOGICAL SIBLINGS: A FAMILY STUDY"** is the original work of **Dr. VIJAYA RAGHAVAN D,** done under my guidance submitted in partial fulfilment of the requirements for M.D. Branch – XVIII [Psychiatry] examination of The Tamilnadu Dr. M. G. R. Medical University, to be held in April 2015.

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DECLARATION

I, **Dr. VIJAYA RAGHAVAN D**, solemnly declare that the dissertation titled, "**ELECTROPHYSIOLOGICAL AND NEUROPSYCHOLOGICAL MEASURES IN PATIENTS WITH SCHIZOPHRENIA AND THEIR UNAFFECTED BIOLOGICAL SIBLINGS: A FAMILY STUDY"** is a bonafide work done by me at the Madras Medical College, Chennai, during the period from Aug 2014 - Sep 2014 under the guidance and supervision of **Dr. JEYAPRAKASH R. MD, DPM**, Professor of Psychiatry, Madras Medical College.

The dissertation is submitted to The Tamilnadu Dr. M. G. R. Medical University towards part fulfilment for M.D. Branch XVIII (Psychiatry) examination.

Place:

Date: **Dr. VIJAYA RAGHAVAN D**

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INSTITUTIONAL ETHICS COMMITTEE
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CERTIFICATE OF APPROVAL

To
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Dear Dr. J.Jeyasudha,

The Institutional Ethics Committee has considered your request and approved your study titled **"Electrophysiological and Neuropsychological measures in patients with schizophrenia and their unaffected biological siblings: A family study" No.02082014.**

The following members of Ethics Committee were present in the meeting held on 05.08.2014 conducted at Madras Medical College, Chennai-3.

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2.	Dr.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
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10.	Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
11.	Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

MEMBER SECRETARY
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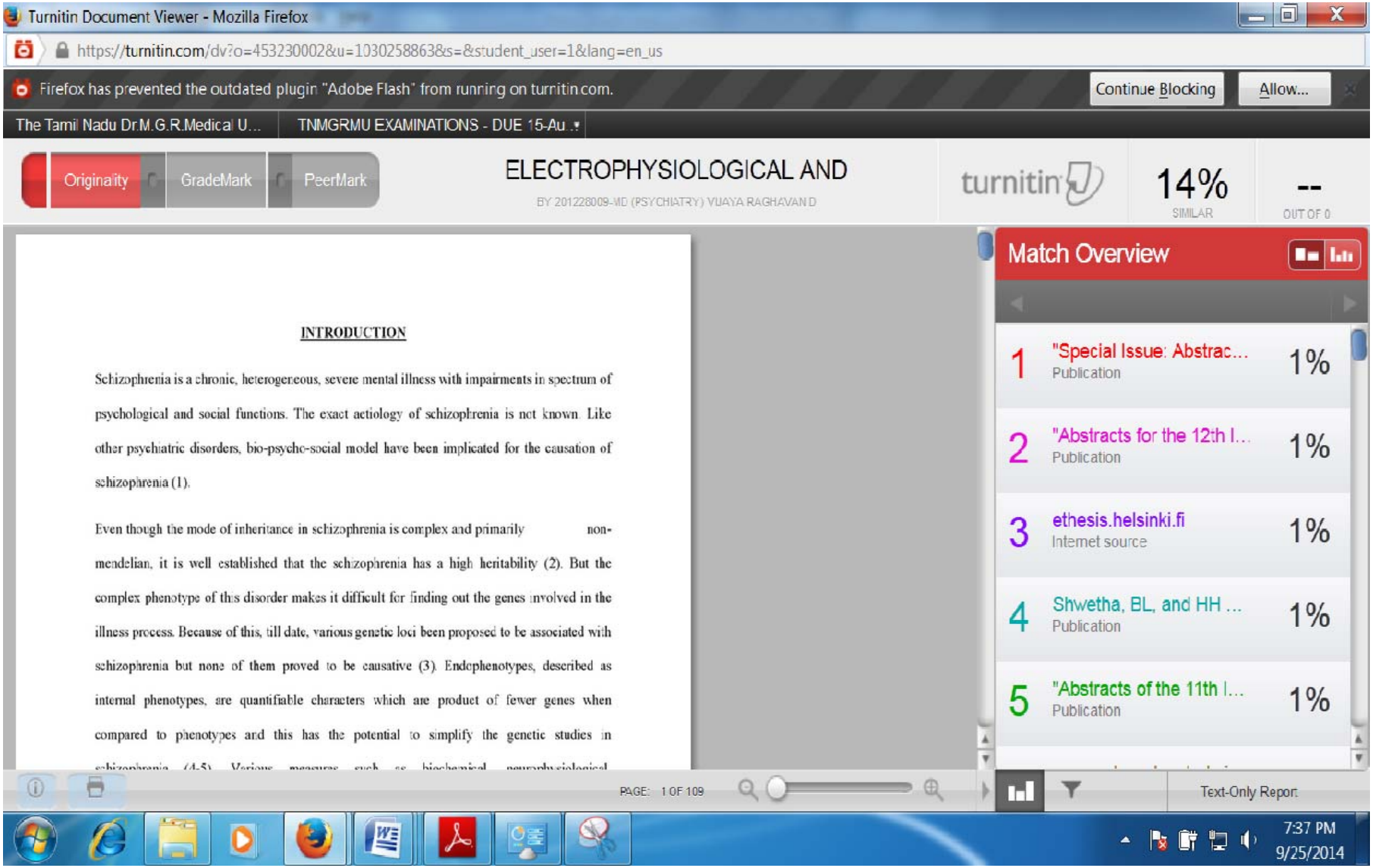
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INTRODUCTION
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Even though the mode of inheritance in schizophrenia is complex and primarily non-mendelian, it is well established that the schizophrenia has a high heritability (2). But the complex phenotype of this disorder makes it difficult for finding out the genes involved in the illness process. Because of this, till date, various genetic loci been proposed to be associated with schizophrenia but none of them proved to be causative (3). Endophenotypes, described as internal phenotypes, are quantifiable characters which are product of fewer genes when compared to phenotypes and this has the potential to simplify the genetic studies in
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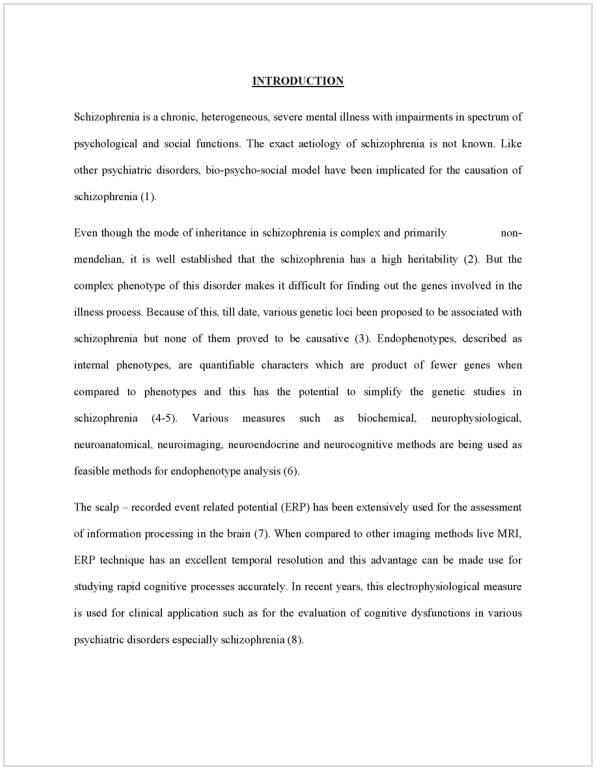

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The scalp – recorded event related potential (ERP) has been extensively used for the assessment of information processing in the brain (7). When compared to other imaging methods live MRI, ERP technique has an excellent temporal resolution and this advantage can be made use for studying rapid cognitive processes accurately. In recent years, this electrophysiological measure is used for clinical application such as for the evaluation of cognitive dysfunctions in various psychiatric disorders especially schizophrenia (8).

CONTENTS

ELECTROPHYSIOLOGICAL AND NEUROPSYCHOLOGICAL MEASURES IN PATIENTS WITH SCHIZOPHRENIA AND THEIR UNAFFECTED BIOLOGICAL SIBLINGS: A FAMILY STUDY

ABSTRACT:

Background: Various neuropsychological domains and P300 auditory event related potentials exhibit abnormalities in patients with schizophrenia and their first-degree relatives. The aim of the study is to compare the cognitive and P300 measurements in patients with schizophrenia, their unaffected biological siblings and normal controls. Also, to find the correlation between the clinical variables in patients with schizophrenia and P300 event related potentials and neuropsychological test.

Methods: 30 patients with paranoid schizophrenia according to ICD-10, 30 unaffected biological siblings of patients with schizophrenia and 30 normal controls were able to complete all neuropsychological test and P300 event related potential assessments. All participants were administered SCAN and the patients were also evaluated regarding the symptom severity.

Results: Both patients with schizophrenia and the unaffected biological siblings of patients with schizophrenia showed lower P300 amplitude and longer P300 latency when compared with the normal controls. When compared between them, patient and sibling groups showed a statistical difference in P300

event related potentials. The three groups showed statistically significant differences in Digit vigilance test, Visual 2-back test, Controlled oral word association test, Animal names test and Stroop test. PANSS total score and psychopathology scores were having a statistically significant correlation with the P300 event related potential and neuropsychological tests.

Conclusion: The patients with schizophrenia and the unaffected biological siblings of patients with schizophrenia showed abnormalities in P300 event related potentials and neuropsychological test. These tests were also correlated well with the illness characteristics of patients with schizophrenia.

Keywords: Schizophrenia, Siblings, P300, Neuropsychological tests, PANSS.

INTRODUCTION

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The scalp – recorded event related potential (ERP) has been extensively used for the assessment of information processing in the brain (7). When compared to other imaging methods live MRI, ERP technique has an excellent temporal resolution and this advantage can be made use for studying rapid cognitive processes accurately. In recent years, this electrophysiological measure is used for clinical application such as for the evaluation of cognitive dysfunctions in various psychiatric disorders especially schizophrenia (8).

The most important and well researched component of auditory event related potential that shows abnormality in is the P300 (9). P300 is correlated with information processing in the brain and considered as an index of the same. In most of the studies, P300 is elicited by oddball paradigm. In the oddball paradigm, an odd stimulus is inserted in between a regularly occurring stimulus and the person taking the test responds for the odd stimulus while not the regular stimulus. Various endogenous cognitive processes like attention and working memory are correlated well with P300 and taken as their index of measure (10).

Since its first report in 1972, various studies have shown that various event related potential abnormalities manifest in persons suffering from schizophrenia, namely the reduced P300 amplitude. Similar results are seen in studies conducted on the first degree relatives with schizophrenia probands. Hence, event related potential abnormalities are considered as the biological vulnerability marker of schizophrenia (11).

The cognitive defects in schizophrenia has been represented in eight different domains namely processing speed, attention/vigilance, working memory, verbal and visual learning/memory, reasoning and problem solving, verbal comprehension and social cognition (12). Moreover, it is observed that these deficits are also found to be present in unaffected relatives and twins of schizophrenic patients. Research suggests that the cognitive deficits have a strong genetic linkage, tends to run in families and predispose the unaffected first degree relatives of patients with schizophrenia to develop the disorder in future (13).

Cognitive impairments and event related potential changes are established endophenotype markers in schizophrenia. First-degree relatives of schizophrenic

patients are having a high risk for the disorder and they show evidence of deficits in endophenotype markers well before the onset of illness. Hence, early assessment of high risk persons for various endophenotype abnormalities may lead to early identification, regular follow-up, acute management of illness and prevention of future illness (6).

Studies on schizophrenia in which the electrophysiological and neurophysiological variables measured in combination in persons with schizophrenia and their unaffected siblings are few. Hence the purpose of this current study is to assess these two variables, event related potentials and neuropsychological performance, in combination in patients and their unaffected biological siblings and to compare between and with normal controls.

This study's hypothesis is that the event related potential and neuropsychological measures would show a continuum between the persons suffering with schizophrenia and their unaffected biological siblings with most significant abnormalities in patients followed by siblings and the normal controls. This may also throw light on the heritability of the neuropsychological and electrophysiological measures among siblings of patients with schizophrenia.

REVIEW OF LITERATURE

The review of literature is dealt in three sections. Section A deals with the studies relating to the intermediate endophenotypes in genetic studies of schizophrenia. Section B deals with the studies examining the electrophysiological measures in patients suffering with schizophrenia and their siblings and section C deals with the cognitive functions and neuropsychological test measures in schizophrenic patients and their siblings.

SECTION (A):

Now a days, the genes for simple Mendelian disorders could be identified and characterized easily but it is not the case with the psychiatric disorders (14). This is because the psychiatric disorders are not produced by the defect in single gene but by the influence of various genes from different foci, interacting among themselves and with the environment (epigenetics) (15). To circumvent this problem of identifying the susceptibility genes involved in complex disorders, the trait like variables associated with the complex psychiatric disorders can be taken phenotypes for the genetic studies. The clinical features of the psychiatric illnesses are heterogeneous and overlap with one another and hence finding the genetic basis for the clinical profile is very difficult and not prudent. This has rose the interest in finding the traits that directly index the underlying pathology and which are more closed to the genes involved in their manifestation (16). Also, these traits are seen not only in persons with schizophrenia but in their relatives also. Some relatives of the patients carry the susceptible genes in them but not manifesting the disorder. These relatives may show abnormalities in the brain structure and functioning which are not attributed to the illness but rather to the effects of the susceptible genes on the brain in the absence of

the disorder. These traits which are intermediate between the genotype and phenotype are called the intermediate phenotypes or endophenotypes (6).

SECTION (A) I: The concept of endophenotype

Endophenotypes are described as “internal phenotypes discoverable by microscopic examination or biochemical test but is not seen without an aided eye”. This term was first used by John et al. and Lewis et al. in their research paper which was published in the year 1966 (17). Hence the study of endophenotypes will be helpful in identifying the culprit genes readily in the polygenic systems offering vulnerability to disorders.

Many methods have been described for the study of endophenotypes in literature. Most important and most studied are neurochemical (18), neurophysiological (16), neuroendocrinological (19), neuroanatomical, cognitive (20) and neuroimaging (21). Endophenotypes are also called by various other names like “intermediate phenotype”, “biological marker”, “subclinical trait” and “vulnerability marker” (5).

Gottesman et al. gave the criteria for particular methods to be called an endophenotype (22). The method/test must satisfy the following criteria to be taken up as an endophenotype:

1. Associated with illness in the population.
2. Heritable.
3. State – independent.
4. Co – segregate within families

5. Found in the affected family members and also in the non – affected family members, the rate being higher in comparison with the general population.

The search for the candidate endophenotype have been described well in the literature for many of the psychiatric illnesses including schizophrenia, mood disorders, Alzheimer's disease, attention deficit hyperactivity disorder and personality disorders.

Endophenotypes are helpful in finding the genes which are related to the biological processes that are taking place internally which is manifesting externally as the phenotypes of schizophrenia (23). Endophenotype mapping of susceptibility genes for psychiatric disorders may help in identifying the specific domains of brain function, influenced by relevant risk gene variants of disorders (24). They help us to find out single or multiple genes are involved in a particular disorder and how they interact to produce the particular phenotype. Biology of the neural circuits underling a particular symptom can be studied using the endophenotype (25). Endophenotypes could inform the evolution of psychiatric nosology. They help in classifying patients on the basis of similar biological deficits into homogenous bio-cognitive subtypes across diagnostic categories (26).

Various endophenotypes that are observed in schizophrenia that have fitting criteria for an endophenotype have been proposed. These are eye tracking abnormalities, electrophysiological markers like event related potentials measuring P300 amplitude, neurochemical abnormalities and positive and negative symptom scores. Now, neuroimaging endophenotypes have also been studied.

SECTION (A) II: Electrophysiological Endophenotypes

In early 1970s, electrophysiological measures were first used to assess and investigate the information processing deficits in schizophrenia (27). This led to recognition of various abnormalities in information processing not only in patients but also in the first-degree relatives (28). The most studied electrophysiological processes are event-related potentials and startle response.

Event-related potential studies were mostly done using the auditory oddball paradigm but some studies were also done using the visual stimuli evoked event-related potentials (29). In all these experiments, the primary outcomes were the amplitude and latency of the specific wavelength that was studied.

Studies involving the P50 waveform, also called as the mid latency waveform since it occurs 50 milliseconds after the stimulus, have shown that it was reduced to the second auditory stimulus in healthy controls showing that sensory gating of the irrelevant stimulus in them. But in the case of patients with schizophrenia there were impaired gating. At first, it was found that in schizophrenics and nearly 50% of first degree relatives of patients with schizophrenia have impaired sensory gating mechanism (30). This was used in the linkage studies and was found that it had a strong genetic inheritance. This was linked to the markers on the 15q13 in the linkage studies.

Mismatch negativity (MMN) is another important event related potential wave which has been studied as an endophenotype (31). No specific attentional process is required for the production of MMN as in the case of some other measures like P300. The basis of the reduced auditory MMN in the subjects would be due to the impairment in the processing of primary auditory stimuli. Turetsky et al. showed that

the neuroleptics have limited effect on the MMN (32). Magno et al. showed that the MMN abnormalities in the patients with schizophrenia were not found at the start of the illness but emerged as the illness process proceeded (33). Bruggemann et al. observed that the mismatch negativity deficits were found in the high-risk subjects (34). The heritability of MMN is not very evident and the overall data regarding the heritability is also limited. A twin study by Hall et al. showed that there was significant heritability of MMN in the family.

P300 is the most studied intermediate phenotype in schizophrenia and many features of P300 satisfy the criteria for an ideal phenotype. Many studies involving the P300 had used the auditory oddball paradigm for conducting the experiment (35). P300 reflects many cognitive processes which include attention, working memory and context updating (36). P300 had been distinguished into two components, namely the P3a and P3b, by some studies. Most consistent finding in many of the studies involving the P300 were the reduced P300 amplitude and to a lesser extent, the increased latency in schizophrenia (37). Several meta-analyses have reported the same findings. Reduced P300 amplitude has also been seen in the persons with high risk of schizophrenia and also in first degree relatives of patients with schizophrenia (38). Another important finding regarding the reduced amplitude of P300 in patients with schizophrenia is that it does not change with the start of the antipsychotic medication. This is seen as a proof that P300 is indeed a trait marker of schizophrenia. Family studies involving the P300 component suggests that it has a very strong genetic component (39). Many twin studies and other genetic studies have shown that there is a substantial correlation between the P300 amplitude and genetic risk of schizophrenia (10). Association studies have come up with positive findings linking P300 and several candidate genes like the D_3 dopamine receptor and COMT (40). The

major issue with the P300 amplitude is that it is not specific to schizophrenia but is also impaired in various other disorders like the dementia, depression, alcoholism and bipolar affective disorder.

SECTION (A) III: Neuropsychological endophenotypes

Egan et al. expressed that the importance of schizophrenia endophenotypes is "to inform genetic studies of psychiatric disorders is never as productive and exciting as in neuropsychological studies". This is due to the fact that the cognitive deficits in schizophrenia are trait like core features of this illness and these deficits play an important role in clinical and functional outcome (41). It is suggested that there may be several endophenotypes derived from neuropsychological test data. Results from twin and family studies by Park et al. and Cannon et al. had observed that visuo-spatial working memory functions, related to prefrontal neural systems, but also verbal working memory functions may be potentially valid endophenotypes that can be taken up for the genetic analyses (42). In another study, Egan et al. had observed that the relative risk of impairment in siblings of schizophrenia patients was elevated not only in verbal learning and memory functions but also in executive functions (41). The studies assessing the relative risk of impairments in first-degree relatives of patients with schizophrenia had shown that the deficits were present in multiple domains of cognitive functions and this suggested that multiple test scores were needed to study the genetic linkage analysis (43).

Executive function is one’s ability to plan, initiate, sequence, monitor and inhibit complex goal-directed behaviour. International neuropsychological society (INS) defines executive functions as: “cognitive abilities necessary for complex goal directed behaviour and adaptation to a range of environmental changes and demands”.

Executive functions include the ability to plan and anticipate out comes (cognitive flexibility) and to direct attentional resources to meet the demands of non-routine events. Many conceptualizations of executive functions also include self-monitoring and self-awareness since they are necessary for behavioural flexibility and appropriateness (44).

Executive functions are needed to carry out the day today activities but also to plan and execute higher activities which are more goals oriented. Executive skills are most important for dealing novel or complex situation. Goldberg et al. referred to the loss of meaningful, directed behaviour resulting from the frontal lobe lesions (45). Pre-frontal cortex is the seat for the executive functions (46). Executive functions play a major role in activities of daily life including the ability to work or attend school, functional responsibility in the home or have appropriate social relationships (47). Hutton et al. observed that patients with first episode schizophrenia were particularly impaired on selected executive function and also had poor verbal memory (48). Joyce et al. found that deficits in executive functions play an important role in the prognosis of the patient and also they act as the determinants of functional outcome (49)**.**

SECTION (B):

The first person to observe that the electrical responses could be evoked from the brain was Caton (1895). Hans Berger, in 1929, reported the first recordings of the EEG from the scalp of human subjects. He coined the term “electroencephalogram” or EEG (50). He measured the electrical activity by placing the electrodes on the scalp of the human subjects, then amplifying the signals and recording them as changes in the voltage over time. He also showed the relationship between the mental processes in the subjects and the EEG signal changes. After this the field of electrophysiology

grew fast. Evoked potentials were first observed by Davis in 1939 and showed the changes in the EEG associated with a particular sensory stimulus. To improve the signal to noise ratio, Dawson in 1954, averaged a number of evoked potentials and obtained the desired results. This averaging of the signals helped to eliminate the unwanted muscle movement artefacts and showed only the most consistent voltage changes in the EEG. This was the starting point of Event-Related Potentials (ERPs). The first peak in ERP was discovered by Walter, which was called as the Contingent variation or CNV. Sutton (1965) discovered the positive peak in amplitude elicited by infrequent stimulus and it was called as P300 (51).

Before 1950s, there was no standard system for the placement of electrodes on the scalp of the human subjects for the measurement of EEG. This led to the development of a committee and it produced the international 10-20 placement system (52). After this, ERPs are measured using different number of electrodes like 32, 64, 128 and 256 channels (53).

SECTION (B) I: Event related potential

Event related potentials are the positive and negative voltage deflections in the voltage of the ongoing electroencephalogram (EEG) signal. This event related potentials (ERP) are produced by the activity of brain while it is undergoing a cognitive, motor or sensory event (8).

There are two types of electrical activity generated by the neurons. They are the action potentials and post-synaptic potentials and thus they could be the neural basis of event related potentials (54). Action potentials are the voltage spikes that are generated from the beginning of the axon and they travel towards the terminals. When the voltage spike reaches the terminal, they cause the release of the neurotransmitter

into the synapse. This release of the neurotransmitters into the cleft causes the excitation of the post-synaptic neuron. Post-synaptic potentials are also voltage spikes that are produced in the post-synaptic neuron when the neurotransmitters bind to the receptors present on the post-synaptic neuron. Among these two potentials, action potentials are negligible contribution to the production ERP signal because they last about a millisecond, produced at different times and travels fast down the axon. But in contrast, post-synaptic potentials occur at fixed locations of the cell membrane and present for hundreds of milliseconds. These occurrences of the post-synaptic activity in millions of neurons which are spatially aligned produce the signal measurable in the scalp after summation. These are mostly done by the pyramidal cells lying in the perpendicular direction to the scalp. Thus it is taken for granted that the ERP peaks are produced mostly by pyramidal neurons post-synaptic potentials (55).

In the ongoing EEG, timed triggers are placed which elicit a response in form of activity of the brain. These are recorded in the EEG as voltage deflections. These recording of the deflections in the EEG activity can be later extracted and measured as ERP after filtering and averaging the EEG data. ERPs are extracted from the EEG data by averaging a number of epochs which are time locked to a particular event. An epoch is the time frame where the response for a particular stimulus occurs in the ERP, which can be either stimulus locked or response locked.

Since the voltage variations evoked by the brain during the activity in response to the target stimuli is very small when compared with the ongoing background EEG, signal averaging is the most common technique used to extract the signal which is the time-locked ERP from the noise which is the background EEG. Signal-to-noise ratio is enhanced by the signal averaging technique. Since the background EEG activity

randomly varies when the average is taken, its sum becomes zero. The remaining will be the non-random, stimulus locked brain activity.

The advantages and disadvantages of the ERP technique are many. The post-synaptic potentials, which are waxing and waning, are volume conducted to the scalp. From the scalp, these potentials are picked up by the EEG electrodes. The conduction delay between the brain activity and its reflection in the EEG signal is below a millisecond. Hence, the ERP technique is superior when compared to the neuroimaging technique in its temporal resolution as it allows detecting the brain activity in millisecond to millisecond basis. But at the same time, ERPs are poor in their spatial resolution when compared with the neuroimaging techniques. This disadvantage of the ERP can be attributed to the weak conductive capacity of the scalp leading to the marked blurring of signal.

Event related potentials are very much used in the investigations pertaining to attention and information processing. As the information processing ability of the humans lie in the brain, it is prudent to explore them it in vivo to promote further understanding of the cognitive processes. Thus, ERPs provide a platform for the research which explores the neuropsychological mechanisms underlying the cognitive deficits in schizophrenia.

SECTION (B) II: Different ERP waveforms

Pre-pulse inhibition

The startle response is evoked by the sudden occurrence of an unexpected stimulus which could be auditory and this stimulus could be suppressed by another stimulus which is presented before it (pre-pulse stimulus) usually occurring 60- 120

ms earlier. The importance of this wave pattern is that it reflects the sensorimotor gating mechanism (56).

P50 wave

The basic mechanism used by the central nervous system to deal with numerous external stimuli is filtering or gating the stimuli called the sensory gating. When two identical stimuli are given to an individual, the amount of attenuation in the neural pathway for the second identical stimulus measures the strength of the sensory gating or the inhibitory pathway. Sensory gating is very important for selecting the salient stimuli and to ignore the irrelevant, repetitive stimulus. This reduces the person's response to low information stimuli and directs the attention towards the high information stimuli (57). P50 is a positive peak which usually occurs between the 40 and 75 milliseconds after the presentation of the stimulus.

N100

This is the negative deflection that is peaking around 90 – 200 ms after the stimulus and it is observed that is produced after an unexpected stimulus. This is produced as an orienting response or a "matching process" since in this the presenting stimulus is compared with previously given stimulus (58).

P200

It is a positive peak that occurs around 100 – 250 ms after the presentation of the stimulus. Recent research indicates that this wave form may reflect the sensation seeking behaviour of humans (59).

N200

This is the negative wave occurring around 200 ms after the stimulus (60). It has 3 components:

1. N2a/Mismatch negativity

Mismatch negativity is a short latency brain event occurring after the presentation of an odd stimulus in a series of repetitive standard stimuli. The mismatch negativity occurs between 100-220 ms after presentation of the odd stimulus. The most important thing that differentiates the mismatch negativity from the P300 is that the P300 requires the attention of the subject to consciously process the deviant stimulus while it is not required in the case of mismatch negativity. Hence, the mismatch negativity is called as the “pre-attentive”. It is thought that it reflects the operations of the sensory memory.

2. N2b

It is later in latency and occurs when the physical quality of the stimulus is changed.

N2c

It is elicited when classification of disparate stimulus is required.

P300

This is separately dealt in the next section.

N400

It is observed in the context of semantic incongruency (61). It is produced 300 – 600ms after the presentation of the stimulus and it is related inversely to the expectancy of completing a sentence with a given word.

P600

It is seen in relation with the language processing. It wave form is usually seen in the ERP if the language contains violations to syntax or when the syntactic structure is very complex (62).

SECTION (B) III: P300

The P300 event related potential (ERP) has received special interest in the field of information processing research. The long latency P300 is described as a correlate for attention and basic cognitive information processing in the brain. P300 is a positive wave in the ERP and it occurs approximately 300 milliseconds after the presentation of significant, rare stimuli to the individual. There are two components in P300. One is the latency and other is the amplitude (63). While the amplitude component of P300 is representative of the amount of attention allocated for carrying out the task in hand, the latency of P300 indicates stimuli evaluation time by the individual. The traditional site for the measurement of P300 is the midline site particularly in the parietal region because maximal response is consistently found in this site. By using functional MRI, many cerebral structures have been identified as the potential sites for the generation of P300. Most studies have shown that the consistent site for the generation of P300 in the brain is the temporal lobe with few contributions from frontal lobe, inferior parietal lobe, amygdala, hippocampus and brainstem. When the attention is used actively to discriminate between two different stimuli, P300 is produced. This can be readily elicited by using the “oddball” paradigm. In this “oddball” paradigm, the individual is instructed to select low probability stimuli which occur randomly when a volley of high probability stimuli are presented.

Many cognitive constructs have been implicated for the variations in the amplitude and latency of P300 when recorded (36). These cognitive constructs include attention, decision making and speed of processing. The variations in P300 by these variables can be observed in various experimental procedures. But till date, the exact functional role of P300 is not clear. However, various theories by researches prevail to explain the generation of P300. Posner et al., proposed the "channel-limited information processing" in which P300 reflects the allocation of limited attentional resources to serve the task in hand which is relevant for the situation (64). This has been shown by studies where the amplitude of the P300 is attenuated when the individual is not attending to the target stimuli while there is a robust increase in the amplitude when the stimuli is given attention. Another researcher has conceptualized the P300 as a measure of "physiological correlate of updating of a cognitive hypothesis" (65). It suggests that the P300 reflects a change in the mental model of the environment produced by working memory.

SECTION (B) IV: The P300 ERP in schizophrenia

The first report of the reduction in the amplitude of P300 event related potential in patients with schizophrenia was given by Roth and Cannon in 1972. In their study, the recordings were done using the electrodes placed in midline of the head (66). Most of the studies that had been done after this had reported a similar reduction in amplitude of P300 when measured over the central plane in patients with schizophrenia. Some studies have reported onset delay in P300 occurrence (67). In a meta-analysis by Bramon et al., it was found that an effect size of 0.85 for amplitude and 0.57 for latency (for both, $p < 0.001$) and this effect was not due to the influence of the antipsychotic medications taken by the subjects or the duration of the illness (9). O'Donnell et al. in a cross-sectional study observed that there was a greater rate

of decrease in latency of P300 with increasing age in patients with schizophrenia (68). This finding of this study is compatible with the idea of progression of the abnormalities in P300 in patients with schizophrenia with age but definitive evidences could be obtained only by longitudinal studies.

The reduction in the amplitude of P300 in patients with schizophrenia have no relation with the absence of motivation in them to follow the task during the test (69). Ford et al. proved that in their studies, P300 remains reduced even when the patients were able to detect the tone as comparable to controls. The P300 latency varies with the difficulty of the task while the amplitude of P300 remains reduced irrespective of the difficulty of the task (70). Hence, it is observed that the reduction in amplitude of P300 is a robust finding in patients with chronic schizophrenia.

Weisbord et al. showed that even though there were reductions in the amplitude of P300 over both hemispheres, there was asymmetry in P300 with smaller voltage over the left when compared with the temporal lobe (71). Strik et al. observed that this selective reduction in the amplitude of P300 in schizophrenia was relatively specific when compared with affective psychosis patients (72)**.**

P300 as a marker of cognitive functioning

P300 can be considered as an important objective marker of cognitive functioning of the brain. Many research conducted assess the relationship between the cognitive functioning, measured by neuropsychological tests, and P300 in patients with schizophrenia (36). Dichter and colleagues reported that overall intelligence and amplitude of P300 is reduced in comparison with the normal controls. In the patient group, while the latency of P300 is negatively correlated with the verbal and performance IQ, the amplitude of P300 is positively correlated with the verbal and

total IQ (73). In patients with chronic schizophrenia, P300 amplitude is positively correlated with the short-term memory and with non-perseverative errors (74).

P300 and psychopathological symptoms

Research findings have reported that the abnormalities in the P300 amplitude and latency were correlated with the negative symptoms but not positive symptoms (75). Liu et al., assessed the PANSS scores in patients with schizophrenia and found that the patients with more negative symptom score had abnormalities in P300 in the form of increased latency and decreased amplitude. Predominant negative symptom patients had prolonged latency in N1, P2, N2 and P3 waves and reduced amplitude in P300 when compared to the patients with predominant positive symptoms. When compared to normal group, P300 amplitude is reduced in both positive and negative symptom group of schizophrenia but P300 latency is prolonged significantly only in negative symptom group (76). Some studies compared the relationship between the positive symptoms and P300 abnormalities. It was found that the patients with auditory hallucinations had increased latency of P300 and reduced amplitude of P300 (77). When patients with aggressive behaviour compared with non aggressive patients, the former group had more prolonged latency and more decreased amplitude in P300 indicating that aggressive behaviour patients has more cognitive deficits (78).

The effect of different types of interventions on P300

Gonul et al., assessed the amplitude and latency changes in P300 of schizophrenia and depression who were on the treatment with medications. They found out that in the case of patients with schizophrenia, after clinical improvement with treatment, there were only few changes in P300 amplitude and latency but in the case of patients with depression, after clinical improvement with antidepressants,

there were shortened latency and increased amplitude in P300 (79). Molina and colleagues did a follow up study of the patients with schizophrenia and depression for two years. During the acute phase of the disorder, there were abnormalities in both the disorder groups. In the follow up, with the resolution of clinical symptoms in both groups, P300 abnormities resolved over time in the depression patients but not in the patients with schizophrenia. This result suggests that the P300 abnormalities noted are stable over time. This finding was confirmed by other studies (80). In another study, it was found that the no difference in the P300 amplitude and latency in patients with schizophrenia before and after treatment (81). Some studies which followed up the first-episode patients for changes in P300 found changes in P2 and P3 in correspondence with clinical improvement. Most studies which compared the effects of different medications on the P300 amplitude and latency have found out that there is little difference between different antipsychotics (82).

SECTION (B) V: The P300 ERP in the first-degree relatives of patients with schizophrenia

The data from the family studies investigating the heritability of P300 amplitude, it was found that it has a substantial genetic component (0.4 – 0.6). A meta-analysis by Broman et al. showed that P300 amplitude and latency had a moderate effect size. Further studies also mostly accepted this result (9). Hall et al. done a twin study and showed that substantial correlation between the amplitude of P300 and genetic risk of schizophrenia (83). In an association study by Mulert et al. it was reported that P300 amplitude had positive finding with several candidate genes like D_3 dopamine receptor and *COMT* (40). P300 reduction in amplitude is also associated with DISC1 translocation (84).

SECTION C:

The cognitive deficits in schizophrenia are very important and of much clinical relevance. The study in the field of cognitive deficits in schizophrenia and their relatives has produced numerous publications. Therefore, selective articles have been reviewed and emphasis is given for those publications which have relevance to this thesis. These areas include cognitive deficits as risk factors, deficits in different cognitive domains, relationship between cognition and clinical symptoms and deficits in unaffected first-degree relatives of patients with schizophrenia.

SECTION (C) I: Cognitive deficits in schizophrenia

Patients suffering with schizophrenia have deficits in many cognitive domains: attention, working memory, verbal declarative memory and executive functions (85). However, no specific neurocognitive deficit profile present (86). Patients with schizophrenia present with wide combination of cognitive deficits, no particular profile can be expected in all the patients (86). Attenuated impairment in cognitive functions is present well before the onset of the illness. Even though attention is the frequent cognitive deficit seen in the prodromal phase of the illness, no one specific cognitive function can be used to predict the onset of the disorder. The impairments in the cognition do not directly correlate with the age, severity of symptoms, medication or duration of illness. Similarly the cognitive deficits do not progress but remain stable. Sometimes, executive functions may show an accelerated decline (87). It is still unresolved that whether some cognitive functions are specific for schizophrenia. In a meta-analysis, it is shown that patients with schizophrenia score well below the normal controls in different neuropsychological tests (88). Some patients do not show

differences in the cognitive functions when compared with normal controls bit it may be that their cognitive function have deteriorated from a high pre-morbid level (89).

Cognitive impairment and clinical symptoms in schizophrenia

The severity of the deficits in various domains of cognitive functions correlates well with the negative symptoms and to a lesser degree with the disorganized symptoms (90). Many studies show that there is usually no correlation between the positive symptoms like delusions and hallucinations with the cognitive functions. Improvement in the symptoms is not associated with the concurrent improvement of the cognitive functions in patients with schizophrenia (91). Negative symptom patients have poor performance in impaired conceptual thinking, object naming, verbal fluency and memory. The cognitive dysfunctions can be related to the various aspects of symptometology and these underlying cognitive deficits prevent the patients from attaining the optimal adaptation required for the day today activities. Impairments in the executive functions, like the planning and problem solving, play an important role in disabling the patients from psychosocial functioning. Functional outcome of the patients with schizophrenia is better correlated with the cognitive deficits than the positive or negative symptoms (92).

Speed of processing

Various cognitive tests are used to measure the speed of processing (93). Verbal fluency was measured by the number of words starting with a given letter that was generated in a brief time period. The cognitive processes tapped by these tests measured the speed of performance (94). Reaction time was used in the speed of processing domain. The measure of reaction time is the elapsed time between the presentation of a sensory stimulus and the subsequent response.

Speed of information processing is considered a core cognitive deficit in schizophrenia. Dickinson, Ramsey & Gold made a comparison of digit symbol coding tasks with executive functions, concluded that the largest single impairment in schizophrenia was on such tasks (95). The reaction time deficits in schizophrenia have shown a systematic association with intelligence and many cognitive processes, such as executive functions, working memory, and inferential processes (96).

Rodriguez-Sanchez et al. found that cognitive deficits in schizophrenia may be fundamentally determined by a slow speed of information processing (97). This fundamental deficit may also account for the broad diversity of symptoms and reduced functional capacity in schizophrenia. Andreasen et al., 1998 found that disruption in the circuitry connecting the thalamus, frontal cortex and cerebellum produced difficulty in prioritizing, processing, coordinating, and responding to information, the very hallmarks of schizophrenia (98). It might also be rooted in white matter alteration, because Dwork et al. found that processing speed is heavily dependent on the integrity of white matter which is abnormal in schizophrenia (99).

Ojeda et al., and Sánchez et al., found that slowing of processing speed performance was related to social, clinical and functional outcomes in schizophrenia and specific correlates between performance and clinical symptoms were also found to be modulated by persistence and fluctuation of the illness (100-101). The more persistent the illness produces more negative impact on processing speed. In a study by Eberhard et al., found deficits in processing speed to deteriorate linearly with the number of psychotic episodes (102).

Vigilance and attention

Attentional dysfunctions are a core feature in schizophrenia. The impairments include different aspects of attentional functioning such as the ability to detect

relevant stimuli and to focus attention on certain relevant stimuli, while ignoring irrelevant stimuli at the same time, as well as to maintain attention on a stimulus until it is processed.

In schizophrenia, attentional deficits mainly include problems with sustained attention (103), selective attention (104), and cognitive control of attention (105). It is found that the cognitive control of attention and selective attention has strong relationships to working memory while sustained attention is separable from other cognitive factors (106).

The most prominent test for sustained attention is the Continuous Performance Test (CPT) that evaluates the ability to maintain a focused readiness to detect and respond to selected target stimuli over a prolonged time period (107). This typically involves presentations of a random series of stimuli at a rapid rate over 5-15 minutes with instructions to respond to a predestinated stimulus. An example of a CPT is the computerized Rapid Visual Information Processing (RVIP) test (108-109). Performance results of the CPT usually include the number of correct detections, the number of detection errors and reaction times for correct detections.

Nuechterlein et al., found that performance on the CPT was consistently found impaired in patients with schizophrenia in target detection rates and signal/noise discrimination independent of clinical state and across various stages of the illness (107). Cornblatt et al., and Caspi et al., observed that even prior to the first psychotic episode and at presentation poor ability to maintain attention were typically present (110-111). Liu et al., found evidence for a progressively deteriorating course of deficits, from moderate impairment in first episode to severe impairment in chronic stages (112). Kurtz et al., found poor performance in first-degree relatives of

schizophrenics, including the children, siblings, and parents, as well as in non-clinical subjects with high schizotypy scores (113). Based on these findings, it has been suggested that the deficit in sustained attention represents a stable trait schizophrenics.

Gur et al., observed that a deficit in sustained attention might serve as a possible cognitive endophenotype for schizophrenia and therefore be a useful in understanding the neurobiological and genetic aspects of the illness (114). Siedman et al., investigated the neurobiological substrate of CPT performance using functional neuroimaging (115). There is an abnormally low glucose metabolic rate in medial frontal cortex, cingulate gyrus, medial temporal lobe, and ventral caudate during CPT in schizophrenic patients. Snitz, Macdonald & Carter, found that poor performance of CPT was related to the estimated risk for the later development of schizophrenia and is noticeably marked in siblings and parents of schizophrenia patients (116). Hallmayer et al. found that poor performance was related to specific genes and subtypes of schizophrenia (117).

Green et al., observed that deficits in sustained attention resulted in difficulty to follow social conversations and an inability to follow important instructions regarding treatment and simple activities such as reading or watching television became laboured or impossible (118). Deficits in patients with schizophrenia are significant predictors of outcome, including social deficits, community functioning, and skills acquisition (119).

Working memory

Barch observed that the concept of working memory was far from unitary and was either an immediate memory held for a brief period or a manipulation of a limited amount of information (120). Goldman-Rakic et al., and Barch et al., demonstrated

that schizophrenia patients had deficits on a variety of verbal and spatial working memory tasks (120-121). McGurk et al., found that verbal working memory impairments were common and often moderate to severe in magnitude. Spatial working memory deficits were also found in schizophrenia (122). Working memory performance deficits occurred more severe on tasks.

Hutton et al., found that the working memory deficits in schizophrenia patients showed associations with clinically important features of the illness (123). The difficulty in encoding and then arranging information makes it difficult for schizophrenia patients to handle social and interpersonal situations that require attention to information. Kopelowicz et al., observed that working memory impairments caused poor functional outcome and impairments also caused less goal-oriented behaviour, disorganized cognitions, and failure of self-monitoring (124).

Smith, Park & Cornblatt, found that impaired performance on working memory tasks predicted the development of psychotic symptoms in high-risk subjects and marked deficits in the prodromal phase announce the transition to psychosis (125). Tan, Callicott & Weinberger, observed that functional abnormalities of prefrontal cortex have been well established in schizophrenia and proposed in etiological theories of this illness (126). Working memory deficits also relate strongly to a variety of other cognitive domains impaired in schizophrenia that are mediated by prefrontal cortical regions.

Verbal learning and memory

The abilities involved in memory functioning includes learning new information, retaining newly learned information over time, and recognizing previously presented material. Saykin et al., found that the ability to encode and retain

verbally presented information tended to be the most severely impaired in patients with schizophrenia (127). This is evidenced in reduced rates of immediate and delayed recall on verbal list-learning tasks such as the Buschke Selective Reminding Test. Smith et al., 1999 found that verbal memory performance predicted success in various forms of verbal therapy and was associated with social, adaptive, and occupational success. Bozikas et al., found that the degree of impairment in verbal learning and memory, unlike in other cognitive domains, is different between male and female schizophrenia patients, with women outperforming men, which is typical of the healthy population as well (128).

Gur et al., observed that deficits in verbal learning and memory were related to the deficits in medial temporal and the frontal lobes (114). Both of these brain regions mediate component processes contributing to this cognitive dimension, and both are structurally and functionally impaired in schizophrenia. According to Leeson et al., impaired encoding and retrieval implicates abnormal involvement of prefrontal cortex whereas accelerated forgetting is attributable to medial temporal lobe dysfunction (129).

Visual learning and memory

This area of cognitive function is partially separate from verbal learning and memory and schizophrenia patients retain less visual information. The tests developed to be sensitive to this deficit of schizophrenia usually require recognition of faces either immediately or after a delay, memory for non familiar figures, and reproduction of line drawings. By Rey-Osterrieth Complex Figure Test (RCFT) one is asked to reproduce a complicated line drawing, first by copying and then from memory. A study by Kim et al., on the differences in RCFT performance between schizophrenia

patients and healthy controls suggested that schizophrenia patients were deficient in visual retention and retrieval, and that a poor organizational strategy seems related to this visual memory deficit (130).

On the contrary, visual learning and memory has been found by some studies by Gold et al., and Buchanan et al., to correlate modestly with functional outcome measures such as employment status, job tenure, psychosocial rehabilitation success, social functioning, and quality of life ratings (131-132).

Reasoning and problem solving

The concept of reasoning and problem solving is used to describe a loosely defined collection of processes involved in planning, cognitive flexibility, abstract thinking, and rule acquisition, initiating appropriate actions and inhibiting inappropriate actions, and selecting relevant sensory information (133).

There are many neuropsychological tests which are used to test reasoning and problem solving. The most well known and most widely used is the Wisconsin Card Sorting Test (WCST). Addington et al., found that chronic patients with schizophrenia achieve fewer sorting categories than control subjects and display significantly more perseverative errors (134). Pantelis et al., observed that it was important to note that the difficulty of the WCST requires the contribution and coordination of numerous complex cognitive processes for successful completion (135).

According to Elvevåg & Goldberg, the neural mechanisms by which schizophrenic psychopathology and dysfunctions in reasoning and problem solving arise have traditionally been associated with the frontal lobes (136). This view has been prominent ever since functional imaging studies correlated poor performance of patients with schizophrenia on the WCST to reduced activity of the dorsolateral

prefrontal cortex. However, more recent reviews indicate that functions are far more distributed across the cortex. Activated areas during WCST performance thus include dorsolateral prefrontal, parietal, orbitofrontal and temporal cortex (133, 137).

The deficits in reasoning and problem solving are unique in schizophrenia. Bryson et al., found that they were present in most patients, regardless of the global level of cognitive function and independently of intelligence and are not confounded by education, medication, and duration of illness (138). Tan et al., observed that the co-occurrence of deficits with the exacerbation of clinical symptoms and the clinical onset of illness may be explained by the fact that the prefrontal cortex, the centre of reasoning and problem solving, does not develop fully until young adulthood, where the first signs of illness usually occur (126). This synchronicity in clinical symptoms, specific cognitive dysfunction and neurodevelopment may be a critical determinant of schizophrenia morbidity. Reduced capacity in reasoning and problem solving might thus be a cognitive endophenotype in individuals at genetic high risk for schizophrenia. Meta-analysis by Sitskoorn et al., showed that the frontal-lobe tasks were the most consistent deficit in relatives of the patients (139).

Hutton et al., found that patients with schizophrenia often have impaired ability to solve problems, to formulate strategies, and to evaluate their usefulness (123). This has numerous practical implications for everyday life and social activities and for performing tasks. Patients with impaired ability thus have difficulty in daily activities. Impairments are also associated with less engagement in therapy, medication compliance, and longer hospital stays.

SECTION (C) III: Cognitive deficits in relatives of patients with schizophrenia

Studies in the past 25 years on the first-degree relatives of patients with schizophrenia have produced lot of results in the cognitive domain specifically in the memory and executive functions. Due to various methodological issues with these studies, it is not yet clear whether these results can be taken as a conclusive evidence that the cognitive dysfunction runs in the families (140).

Cognitive deficits are present in schizophrenics at the time of onset of the illness and even predate it in patients. It is independent of the psychotic symptoms, related to the underlying neuronal dysfunction and also stable over the period of time (12, 141). Because of these merits of cognitive deficits, it has gained the attention as an endophenotype of the disorder. The importance of the endophenotype is that they could be used to discriminate the patients from controls (5, 142).

The majority of the studies that have studied the cognitive function in the patients with schizophrenia have shown that the cognitive processes are affected in the relatives but to a lesser extend when compared to the patients (143). Studies dealing with the cognitive functions on the first-degree relatives of patients with schizophrenia suggest that the deficits in cognitive functions could be familial or genetic. In many of the studies, the cognitive deficits in relatives of schizophrenia found to be similar to that in patients but in a milder degree (144-146). Twin studies studying the cognitive deficits have shown that the deficits correlate well with the discordant monozygotic twins than discordant dizygotic twins (147-149).

In a meta-analysis, Sitskoorn et al. analyzed 34 peer-reviewed studies that compared the cognitive functions between the patients with schizophrenia, their unaffected first-degree relatives and controls and it was reported that the first-degree relatives of patients with schizophrenia showed lesser cognitive efficacy when

compared to the normal controls (139). These cognitive deficits were seen in different cognitive domains like the memory and executive functions, with mean effect size being in the moderate range. Kang et al. analyzed similar studies and reported a small to moderate effect size of the cognitive deficits in the first-degree relatives of patients with schizophrenia (150). In a review done on the studies pertaining to the declarative memory in the relatives of patients with schizophrenia, Apples et al. reported that the relatives showed greater deficits on tests which required greater demand for the effective encoding and retrieval of the given material (145). Snitz et al., using the most robust methodologies, conducted a meta-analysis on the cognitive deficits in the first-degree relatives of patients in schizophrenia. In that it was reported that group differences in the individual tasks of cognitive function with effect size ranging from small to moderate. Test of span of apprehension showed a small effect size ($d = 0.17$) while CPT-AX/-IP false alarm test showed a medium effect size ($d = 0.66$) (116). The other areas of cognitive functions that showed strong deficits were the language, spatial ability, executive functions and attention/working memory.

Significant differences in the tasks which require the continuous processing tasks has led to the proposal that they they require higher effort from the central executive functioning (144). Similarly, deficits in face recognition, working memory and declarative memory in the first-degree relatives of patients with schizophrenia have implicated the possible dysfunction in the front-temporal region of the brain (146). A verbal memory deficit in the relatives of patients with schizophrenia is stable over time and it has the strongest discriminative capacity (151). The relatives also showed deficits in other areas like the attention, vigilance and psychomotor response in the initial assessments but later there were some improvement in these deficits (152). These findings have been instrumental in further studies that needed to see the stability of the deficits in relatives of patients with schizophrenia.

AIMS AND OBJECTIVES

AIM:

The current study attempts to measure the event related potentials and neuropsychological performance in the patients with schizophrenia and their unaffected biological siblings and to compare them between the two groups and with the normal control group.

OBJECTIVES:

1. To measure and compare the P300 component of event related potential in patients with schizophrenia, their unaffected biological siblings and normal controls.

2. To measure and compare the speed of processing, attention, working memory and executive functions performance in patients with schizophrenia, their unaffected biological siblings and normal controls.

3. To identify the relationship between the P300 component of event related potential and neuropsychological tests in patients with schizophrenia, their unaffected biological siblings and normal controls.

4. To identify the relationship between the P300 component of event related potential and severity of symptoms in patients with schizophrenia.

5. To identify the relationship between the neuropsychological tests and severity of symptoms in patients with schizophrenia.

NULL HYPOTHESIS

1. There is no difference in the P300 component of event related potential in patients with schizophrenia, their unaffected biological siblings and normal controls.

2. There is no difference in the speed of processing, attention, working memory and executive functions performance in patients with schizophrenia, their unaffected biological siblings and normal controls.

3. There is no relationship between the P300 component of event related potential and neuropsychological tests in patients with schizophrenia, their unaffected biological siblings and normal controls.

4. There is no relationship between the P300 component of event related potential and severity of symptoms in patients with schizophrenia.

5. There is no relationship between the neuropsychological tests and severity of symptoms in patients with schizophrenia.

MATERIALS AND METHOD

Section (A): Sample selection:

The current study was a case control study, conducted at the Institute of Mental Health, Rajiv Gandhi Government General Hospital, Chennai. The participants, 30 consecutive patients with paranoid schizophrenia and biological siblings of patients with schizophrenia, were taken from the outpatient and inpatient departments of Institute of Mental Health. 30 normal controls with no family history of psychiatric illness were selected from the general population.

Inclusion criteria:

1. Patients with paranoid schizophrenia according to ICD-10 using SCAN.
2. Biological siblings of patients with schizophrenia without any psychiatric disorder.
3. Normal controls with no family history of psychiatric illness.
4. Subjects between 25 – 35 years of age.
5. Minimum of eight years of formal education.
6. Normal hearing by history and clinical examination.
7. Giving informed consent.

Exclusion criteria:

1. Mental retardation.
2. H/o any psychiatric illness (sibling and control group) using SCAN.

3. H/o concurrent neurological illness or systemic illness known to impair cognition.

4. H/o head injury with loss of consciousness.

5. H/o any substance dependence.

6. H/o benzodiazepine or any other medication use known to impair cognition in the last 1 month period.

Section (B): Instruments

Clinical assessments

I. Socio-demographic data sheet (Appendix 1):

A structured proforma was designed to elicit information about the demographic details about the patients with schizophrenia, unaffected biological siblings of patients with schizophrenia and normal controls.

II. Schedules for Clinical Assessment in Neuropsychiatry (WHO, 1999) (153):

Schedules for Clinical Assessment in Neuropsychiatry (SCAN) are a manuals created by the World Health Organization (WHO) for assessing, measuring and classifying the mental illnesses. It can be used in variety of settings like the clinical and research settings. Its stability and validity has been proven by various studies.

SCAN is a semi structured standardized clinical interview with provision for cross examination of the subject. There is no fixed order of the flow of the interview which makes this instrument flexible and versatile. Each section of the schedules starts with the important questions about the symptoms pertaining to that section. If

these questions are answered positively, then the questions below the cut-off point are also asked to the patient.

III. Positive and negative syndrome scale (kay, 1987) (154):

The patients with schizophrenia were administered the positive and negative syndrome scale (PANSS) to measure the severity of psychopathology. The PANSS, developed by SR Kay et al., is a 30-item rating scale developed to assess the symptoms in patients with schizophrenia and finds application in various clinical and research settings. This scale is based on the premises that schizophrenia has two distinct syndromes, positive and negative syndrome. The patient is rated from 1 to 7 on 30 different symptoms based on the interview as well as reports of family members. The scale is divided into three sections, namely positive scale, negative scale and general psychopathology scale. PANSS is relatively a brief interview which takes about 40 minutes to complete.

Neuropsychological assessments

Test for speed of processing:

The tests for speed of processing can be divided into two types, namely motor speed and mental speed. Mental speed is a composite measure which needs rapid information processing. In any modality, even for simple stimulus, information processing speed depends on the coordination of different brain circuits. The measurement of mental speed is used to document the efficiency of the rate of information processing.

I. Digit symbol substitution test (155):

It is a test for visual motor coordination, motor persistence and most importantly response speed. The test consists of sheet in which numbers 1 – 9 are randomly arranged in 4 rows of 2 squares each. The subject substituted each number with a symbol using number symbol key given on the top of the page. The test sheet was placed in front of the person and asked to perform the test after explaining it. The subject was explained that he would be given 90 seconds and he had to as many symbols as possible by that time. The number correct responses were taken as the score of the test.

Tests for attention:

Attention is very basic for higher order cognition. Attention can be viewed either as a resource/capacity or as a skill of resource deployment. Attention is divided into three types namely, focused attention, sustained attention and divided attention.

A. Sustained attention

I. Digit vigilance test (156):

It consists of numbers from 1 to 9 arranged randomly in rows on a page. Each test page contains 50 rows, each row containing 30 digits. The subject was asked to strike the target digits namely 6 and 9. The subjects were asked to cancel the digits as fast as possible without missing them or striking the wrong digits. Time taken and error score were calculated from the test.

B. Focused attention

I. Trail making test A and B (157):

Trail Making Test has two parts A and B. While Trail Making Test A is used to measure the attentional process, Trail Making Test B is used to measure the executive function domain. Each part consists of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1 – 25, and the subject was asked to draw lines connecting the numbers in ascending order. In Part B, the circles include both numbers (1 – 13) and letters (A – L); the subject was asked to connect the circles in an ascending order, but the additional task is alternating between numbers and letters (i.e., 1-A-2-B-3-C, etc.). The subject was instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper. Time taken to complete the trail was noted. If the subject makes an error, it was pointed out immediately and correction allowed.

C. Divided attention

I. The triads test (158):

The triads test was developed in NIMHANS. It combines a verbal triad task with a tactual number identification test. For this test, the subject is blindfolded. The verbal triads consist of 16 triads. In each triad, two words belong to a particular category and the other will be the odd one. The subject had to identify the odd word from the triad. At the same time, a number was written with a finger in the non dominant hand of the subject. The subject had to identify the number also. This task required the divided attention to answer both the question correct at the same time. The number of errors committed in the each task was counted.

Tests for working memory:

The main function of working memory is to hold the information at hand and to manipulate it according to the needs of the ongoing process. Working memory is externally and internally guided.

A. Verbal working memory

I. Verbal N – back test (Smith and Jonides, 1999) (159):

The N back tests used for verbal working memory, are the 1 back and 2 back version of the N back test. This test measures the externally guided working memory. In this test 30 randomly ordered consonants common to multiple Indian languages were presented to the subjects. One word was given to the subject per second. Of these 9 consonants are repeated. The constantans were repeated at random. In the case of 1 back test, the subject was asked to respond when a consonant was repeated consecutively. Whereas in the 2 back test, the subject was instructed to respond when a consonant was repeated after an intervening consonant. The number of hits was scored along with the errors. Errors included the number of omission and commission errors. The total number of errors was taken for computation.

B. Visual working memory

I. Visual N – back test (Smith and Jonides, 1999) (159):

For testing visual working memory N back test with 1 back version, from the NIMHANS neuropsychology battery, 2004 is used. It consists of 36 cards. A black dot is placed randomly along the circle imagined to be on the card, in each card. The subject was asked to respond when they would see the location of the dots in the subsequent cards was repeated. The number of hits was scored along with the errors.

Errors included the number of omission and commission errors. The total number of errors was taken for computation.

Tests for executive functions

A. Fluency

I. Phonemic fluency

Controlled Oral Word Association Test (Benton & Hamsher, 1989)

The Controlled Oral Word Association Test (COWA) is a test to measure the phonemic fluency. In this test the subjects generate words that are phonetically similar. The subject generates words that are beginning with the letters F, A, S. while generating words starting with these letters, the subject should exclude proper nouns and names of numbers. The same word should not be repeated again. In the subjects, whose mother tongue is not English, they are asked to generate words starting with “Ka”, “Pa” and “Ma”. The total number of acceptable new words produced by the subject in one minute for each trail is noted down and the average number of new words produced at the end of three trails is taken as the score.

II. Category fluency

Animal names test (Lezak, 1995)

Category fluency is another form of verbal fluency. In category fluency the content of the words are regulated by the participant. In this type of tests, participant generates words that are belonging to a particular semantic category. The Animal names test requires the subject to generate names of the animals for one minute. The subject is asked to exclude the names of the fish, birds and insects. The number of

animal names generated by the subject in one minute forms the score of the fest. This test approximately takes three minutes to complete.

B. Response inhibition

I. Stroop test (Alexander, Benson and Stuss, 1989) (160):

This test measures the response inhibition ability. The name of the colors “blue”, “green”, “red” and “yellow” are in the capital letters printed on the paper. The color in which the word written occasionally corresponds with the meaning of the color the word designated to. In this test, the words were printed in 16 rows and 11 columns in a sheet of paper. The sheet of paper containing this was placed before the subject. In the first trail, the subject was asked to read the word in column wise ignoring the color in which the word was written. The subjects were encouraged to read as fast as possible. The time taken to complete the whole words was noted down in seconds. Once the trail was over, now the subject was asked to read the color in which each word was written ignoring the color represented by the word. In this trail also, the subjected is encouraged to read as fast as possible in column wise. The time taken to complete was noted down in seconds. Errors in both the trails were also noted. The test was given in the mother tongue of the subjects while English version was given to the subjects preferred it. Stroop effect score = Time taken to name – Time taken to read the words .

Electrophysiological assessments

P300 event related potential recording (161):

RMS neuro diagnostic system was used to record P300 auditory event related potentials. For the purpose of this study, the oddball paradigm was developed in the

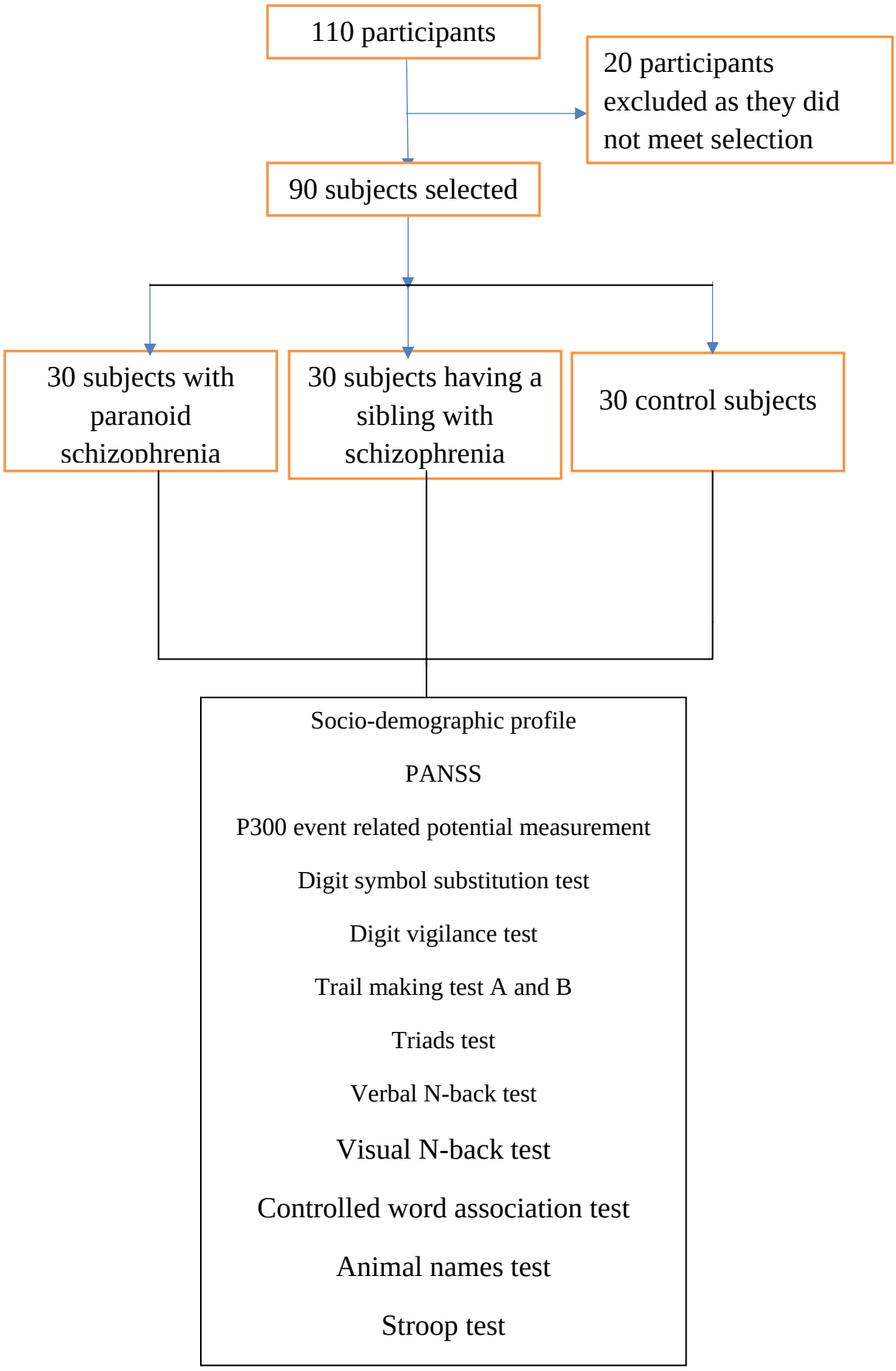
following manner. The auditory stimuli were presented to the subjects in both the ears using head phones. The auditory stimuli were pure tones presented to the subjects at the rate of 1.25 s for 10 min. Each tone was 100 ms in duration at an intensity of 70-db sound level. The pure tones were of 1000 and 2000 hz in which the rare frequency would be the 2000hz. The probability of the occurrence of the rare frequency pure tone was set at 0.2. The subjects who were being tested were instructed to press a button using the right thumb as soon as they hear the rare target stimuli.

Using the copper electrodes, the EEG of the subject was recorded at three sites namely, Fz, Cz and Pz. The electrodes were placed in the scalp of the subjects according to the 10-20 international system of electrode placement. The reference electrode was the electrode attached to the earlobes or mastoids while the ground electrode was placed on the left side of the forehead.

In this, first the subjects were explained about the procedure and the doubts regarding it were explained. Before the start of the procedure, the subjects were asked to have their head washed with water and it was made sure that it was not greasy since it can affect the conductance. Then the subject was comfortably seated in front of the computer and asked to relax. The 3 electrodes were placed on the head according to the 10-20 international system. Ear phones were given and asked the subject to wear it. Any discomfort was asked for and rectified. The subject was instructed to press a button or to count in his head whenever he hears the odd frequency sound and not respond to the repetitive, non-target sound. The recordings were stored in the computer and were used for further analysis.

Methodology of selection and administration of tests:

Subjects were selected from the psychiatry OPD, Institute of Mental Health, Madras Medical College, Chennai. The subjects were selected by using the inclusion and exclusion criteria mentioned above. The subjects who were satisfying the criteria were included in the study after explaining about the study. Written informed consent was obtained from them before the start of the study. The neuropsychological tests and electrophysiological tests were done in two separate days. The neuropsychological tests were performed by the subjects in the Institute of Mental Health, Madras Medical College. The tests were given in the afternoon from 3 pm to 5 pm. Any difficulties in the subject were asked for and were eliminated at that time. The electrophysiological tests were performed on the subjects in the Institute of Physiology, Madras Medical College. The electrophysiological and neurophysiological tests were conducted in distraction free silent rooms. The test results were recorded in the proforma as soon as the tests were finished by the subjects. Digital stop watch was used to measure the time taken by the subjects to complete the neurophysiological tests.


110 participants
20 participants excluded as they did not meet selection
90 subjects selected
30 subjects with paranoid schizophrenia
30 subjects having a sibling with schizophrenia
30 control subjects
Socio-demographic profile
PANSS
P300 event related potential measurement
Digit symbol substitution test
Digit vigilance test
Trail making test A and B
Triads test
Verbal N-back test
Visual N-back test
Controlled word association test
Animal names test
Stroop test

DATA ANALYSIS

The results were tabulated and analyzed using the statistical package, SPSS 16.0.

Descriptive statistics was used to get the mean and standard deviations with respect to different variables of socio-demographic profile of the three groups and the illness characteristics of the patients with schizophrenia. Age across the three groups was compared using ANOVA while the other socio-demographic variables were compared between the three groups by chi-square test.

The event related potentials, P300 amplitude and latency were compared between the three groups using ANOVA. Post hoc comparisons between two different were also done. Similarly, neuropsychological test scores were also compared between the groups using ANOVA. Means score plot was used to represent the means of the test scores in the three groups.

Pearson correlation was used to assess the relationship between the P300 variables and the neuropsychological test scores. Similarly, Pearson correlation was used to assess the relationship between the clinical variables of the illness and event related potentials and neuropsychological test scores.

RESULTS

The current study is case control study. Here, controls represent the subjects with no psychiatric illness and with no family history of psychiatric illness. Siblings group represent the subjects who do not have any psychiatric illness but have a patient with schizophrenia as their sibling. Patient group represents the subjects with paranoid schizophrenia.

90 subjects were included in the current study with 30 subjects in each group. The subjects were selected from the outpatient department, Institute of Mental Health, Madras Medical College, Chennai.

Socio-demographic data:

Age:

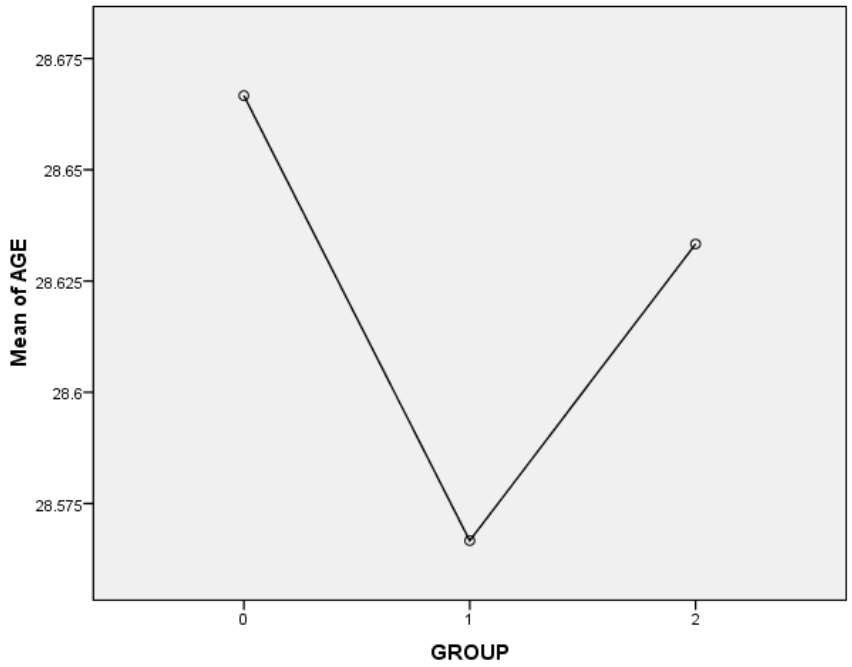
Table 1: comparison of age between the three groups

Group	N	Mean age	S.D.	F	Sig.
Controls	30	28.67	3.044	.008	.992
Siblings	30	28.57	3.059		
Patients	30	28.63	3.090		
Total	90	28.62	3.030		

Significance $p < 0.05$

The mean age of the group was 28.62±3.03. The mean age of the control group was 28.67, while it was 28.57 for siblings and 28.63 for the patient group. The above table shows that there was no statistical difference between the three groups with respect to age and hence they were comparable with respect to age.

Chart 1: Means graph for the age among the three groups



Gender:

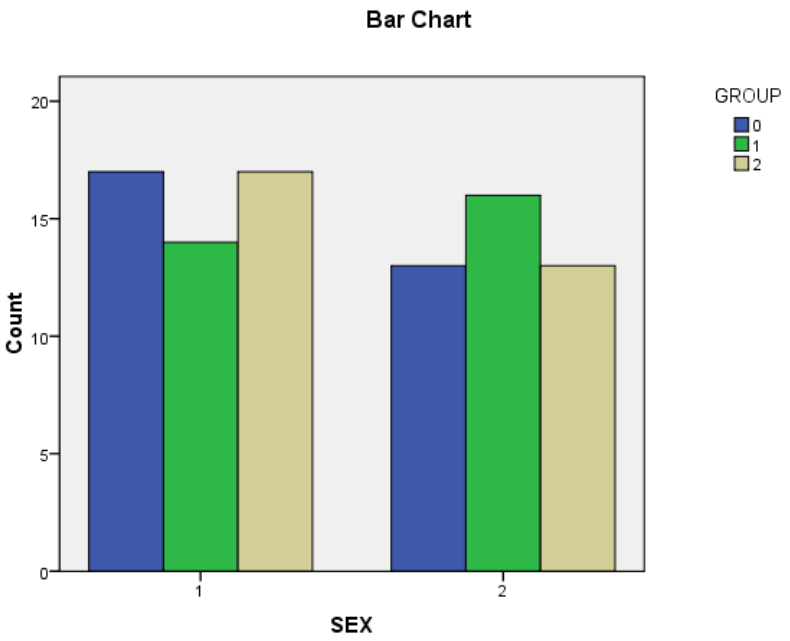
Table 2: comparison of gender between the three groups

Gender	Controls N	Siblings N	Patients N	Total N	Sig.
Male	17	14	17	48	.669
Female	13	16	13	42	
Total	30	30	30	30	

Significance p< 0.05

The total number of males in the study population was 48 while the number of female in the study population was 42. The above table shows that the three groups were not statistically different with respect to gender as the chi-square valve was 0.669 and hence comparable.

Chart 2: bar diagram for the distribution of sex in the three groups



Education:

Chart 3: Bar diagram for the distribution of education in years between the groups

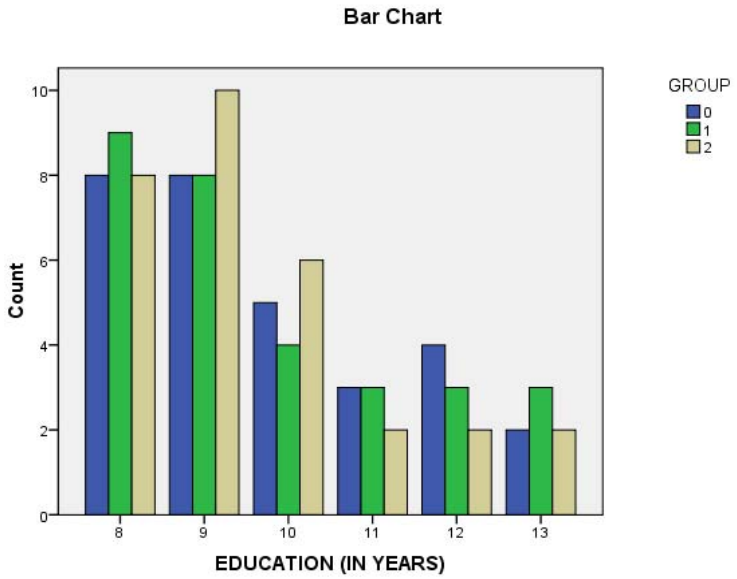


Table 3: Comparison of education between the three groups

Education (in years)	Controls N	Siblings N	Patients N	Total N	Sig.
8	8	9	8	25	.996
9	8	8	10	26	
10	5	4	6	15	
11	3	3	2	8	
12	4	3	2	9	
13	2	3	2	7	
Total	30	30	30	90	

Significance $p < 0.05$

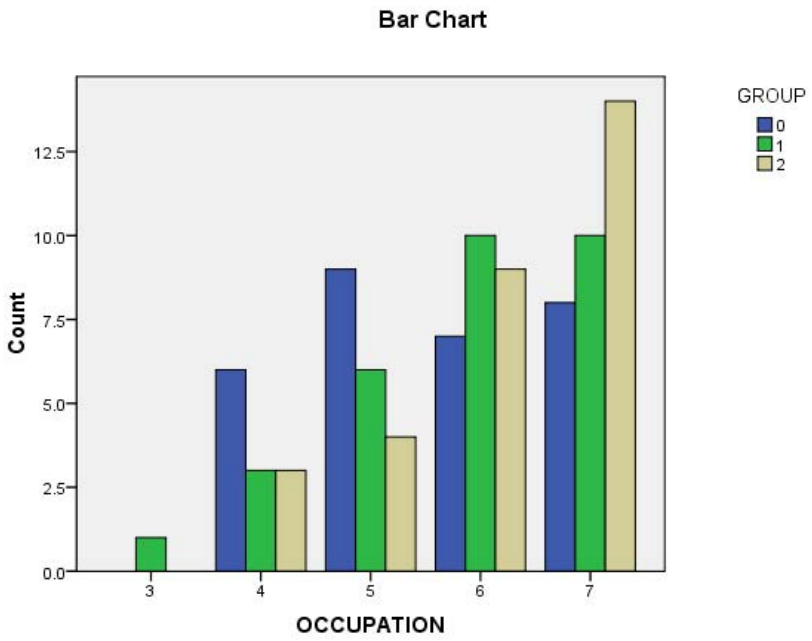
The above table shows that there was no statistical difference between the three groups with respect to education.

Occupation:

Table 4: comparison of occupation between the three groups

Occupation	Controls N	Siblings N	Patients N	Total N	Sig.
Clerical	0	1	0	1	.454
Skilled	6	3	3	12	
Semiskilled	9	6	4	19	
Unskilled	7	10	9	26	
Unemployed	8	10	14	32	
Total	30	30	30	90	

Chart 4: Bar diagram for the distribution of occupation between the groups



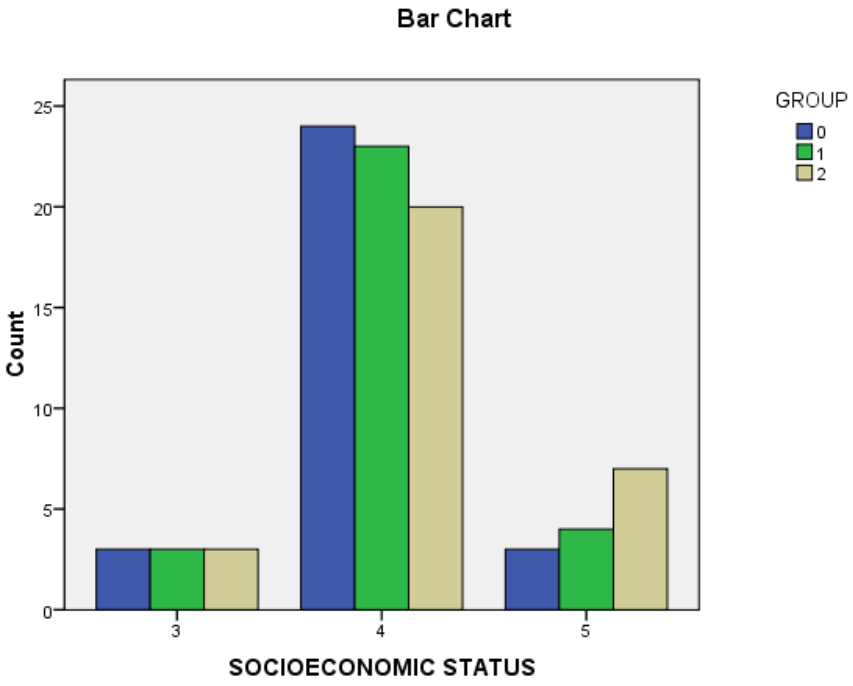
When compared to the control group, more number of unemployed persons was there in the patient group but there was no statistical difference between the groups as the P value is > 0.05.

Socio-economic status:

Table 5: comparison of socio-economic status between the groups

Socio-economic status	Controls N	Siblings N	Patients N	Total N	Sig.
Lower middle	3	3	3	9	.691
Upper lower	24	23	20	67	
Lower	3	4	7	14	
Total	30	30	30	90	

Chart 5: Bar diagram for the distribution of socio-economic status between the groups

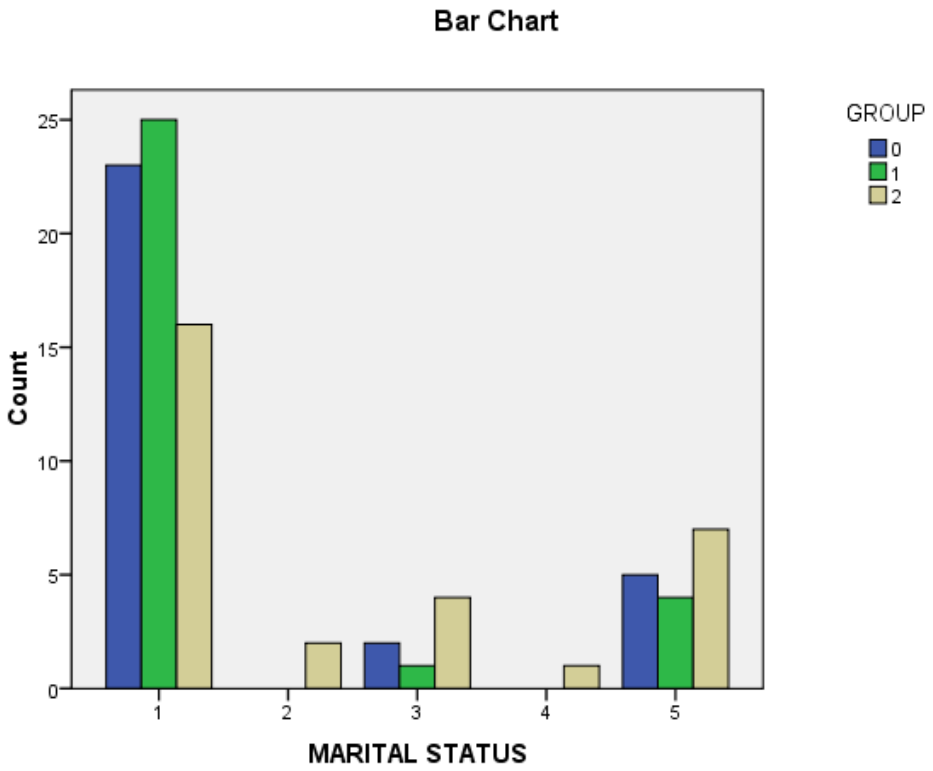


Marital status:

Table 6: comparison of marital status between the groups

Marital status	Controls N	Siblings N	Patients N	Total N	Sig.
Married	23	25	16	64	.203
Divorced	0	0	2	2	
Separated	2	1	4	7	
Widowed	0	0	1	1	
Single	5	4	7	16	
Total	30	30	30	90	

Chart 6: Bar diagram for the distribution of marital status between the groups

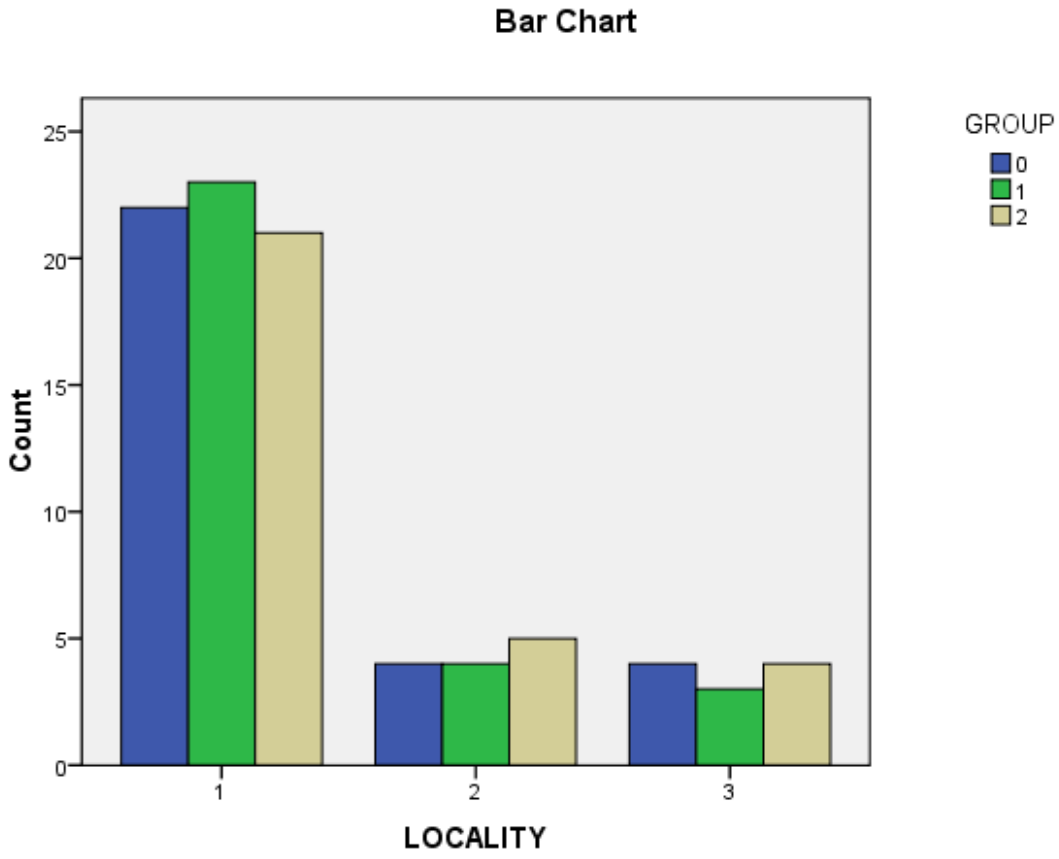


Locality:

Table 7: comparison of locality between the groups

Locality	Controls N	Siblings N	Patients N	Total N	Sig.
Urban	22	23	21	66	.980
Semi urban	4	4	5	13	
Rural	4	3	4	11	
Total	30	30	30	90	

Chart 7: Bar diagram for the distribution of locality between the groups

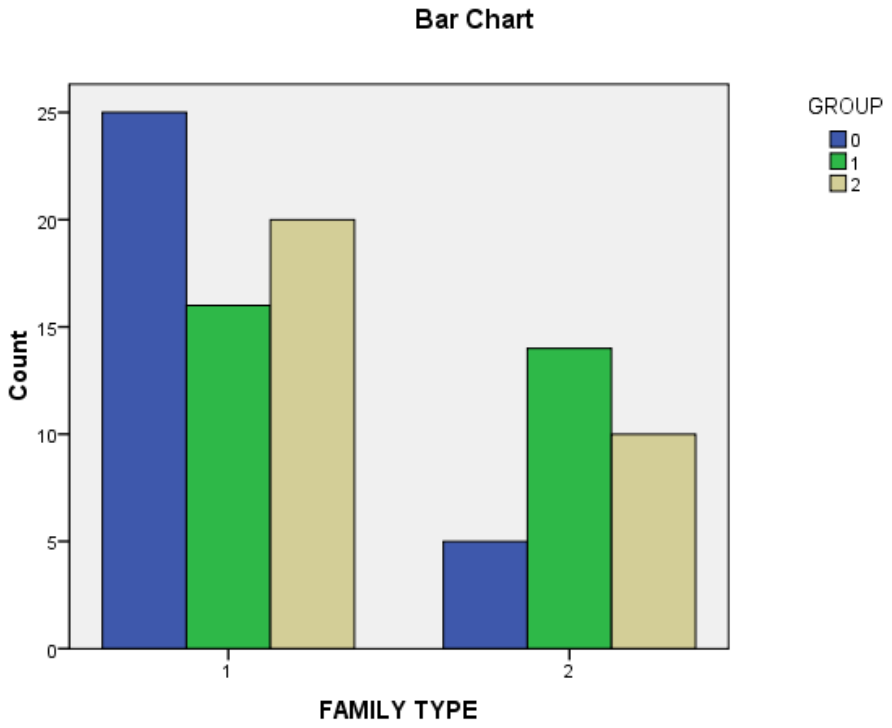


Family type:

Table 8: comparison of family type between the groups

Family type	Controls N	Siblings N	Patients N	Total N	Sig.
Nuclear	25	16	20	61	.045
Joint	5	14	10	29	
Total	30	30	30	90	

Chart 8: Bar diagram for the distribution of family type between the groups



The three group of the subjects were compared among themselves for the socio-demographic profile. There is no significant difference between the three groups with respect to age, sex and education. Hence the three groups are comparable for the further analysis and there is a lesser chance that the other variables would be affected by these confounding factors.

Similarly, the other socio-demographic variables were also compared between the three groups. The three groups are comparable in the marital status, socio-economic status and locality. There is a statistical difference between the three groups only in the variable of family type.

Illness characteristics of patients with schizophrenia:

Table 9: Illness characteristics data of the patients with schizophrenia

Illness characteristics	N	Mean	S.D.
Age of onset of illness (years)	30	21.83	2.321
Duration of illness (months)	30	81.60	45.384
Lag period for treatment (months)	30	30.47	20.217
Duration of treatment (months)	30	51.13	29.251
PANSS positive score	30	20.80	3.943
PANSS negative score	30	24.90	8.239
PANSS general psychopathology score	30	52.53	13.549
PANSS total score	30	98.23	20.433

The mean age of the illness onset in the patient group was 21.83 years. The mean duration on the illness is 81.60 months. Most of the patient group was on anti-psychotics during the study period and the mean duration of treatment was 51.13 months. The severity of the illness was assessed by PANSS scale. The mean positive and negative score in the PANSS was 20.80±3.943 and 24.90±8.239. The mean total score of PANSS was 98.23±20.433.

Comparison of P300 variables across groups:

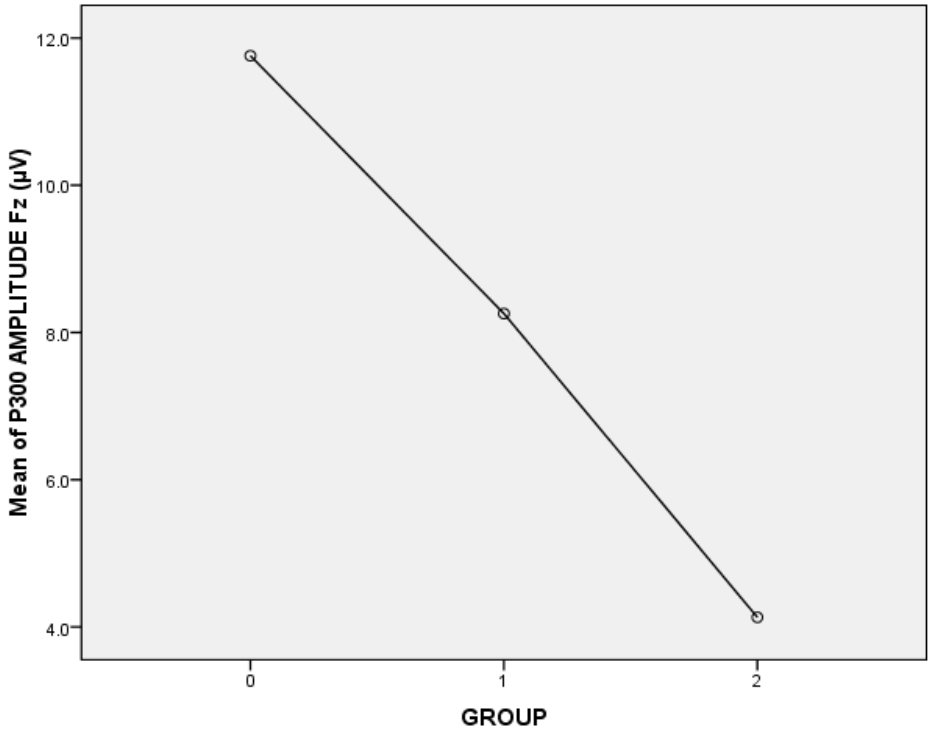
P300 amplitude Fz (µV):

Table 10: Comparison of P300 amplitude Fz (µV) among the three groups

Group	N	Mean	S.D.	F	Sig.
Controls	30	11.760	3.1883	77.587	.000
Siblings	30	8.257	2.2334		
Patients	30	4.130	1.3293		
Total	90	8.049	3.9175		

Significance P < 0.05

Chart 9: Means graph of P300 amplitude Fz (µV) among the three groups



The above table shows that the three groups are statistically different from one another with respect to P300 amplitude Fz (µV).

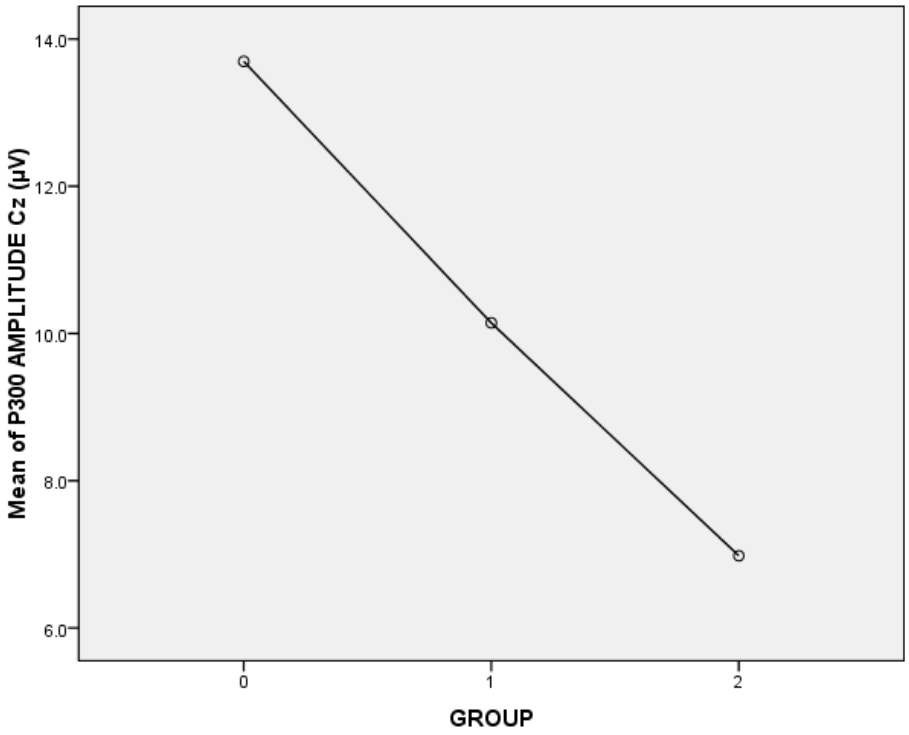
P300 amplitude Cz (µV):

Table 11: Comparison of P300 amplitude Cz (µV) among the three groups

Group	N	Mean	S.D.	F	Sig.
Controls	30	13.697	2.9122	58.131	.000
Siblings	30	10.143	2.2531		
Patients	30	6.980	1.9808		
Total	90	10.273	3.6480		

Significance $P < 0.05$

Chart 10: Means graph of P300 amplitude Cz (µV) among the three groups



There is a statistical difference between the three groups in the mean score of the amplitude Cz. The value in the patient group is reduced when compared with the other two groups. Similarly, siblings too have reduced value in relation to controls.

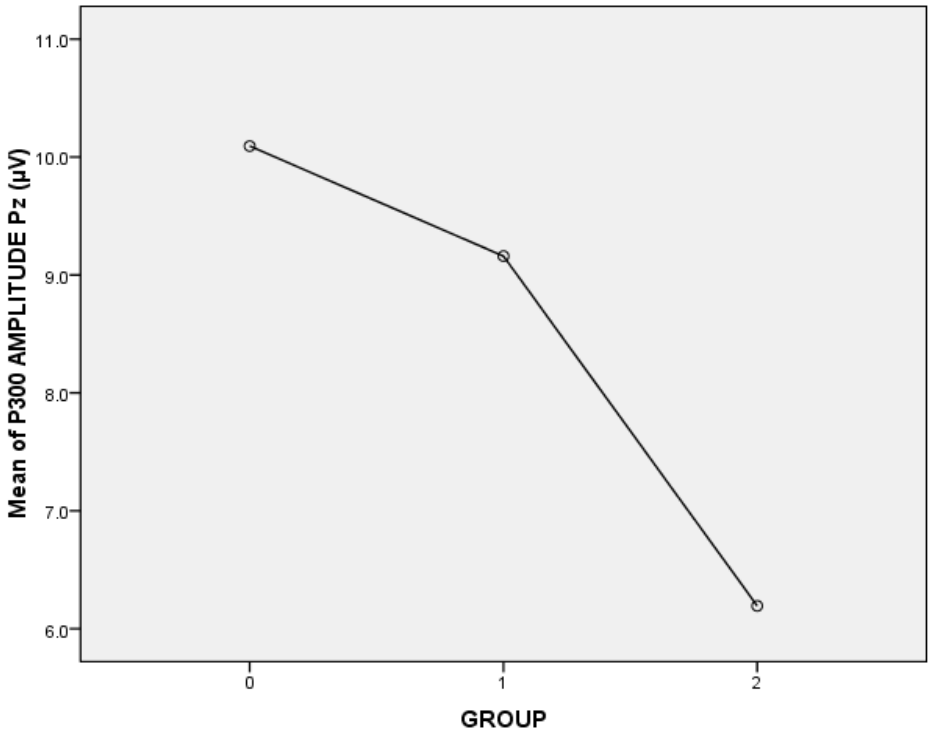
P300 amplitude Pz (µV)

Table 12: Comparison of P300 amplitude Pz (µV) among the three groups

Group	N	Mean	S.D.	F	Sig.
Controls	30	10.093	1.5642	33.691	.000
Siblings	30	9.160	2.0399		
Patients	30	6.193	2.1143		
Total	90	8.482	2.5309		

Significance P < 0.05

Chart 11: Means graph of P300 amplitude Pz (µV) among the three groups



The mean score for the patient group is 6.193±2.11 while for sibling group, it is 9.160±2.03. There is a statistical difference between the three groups with regard to this score.

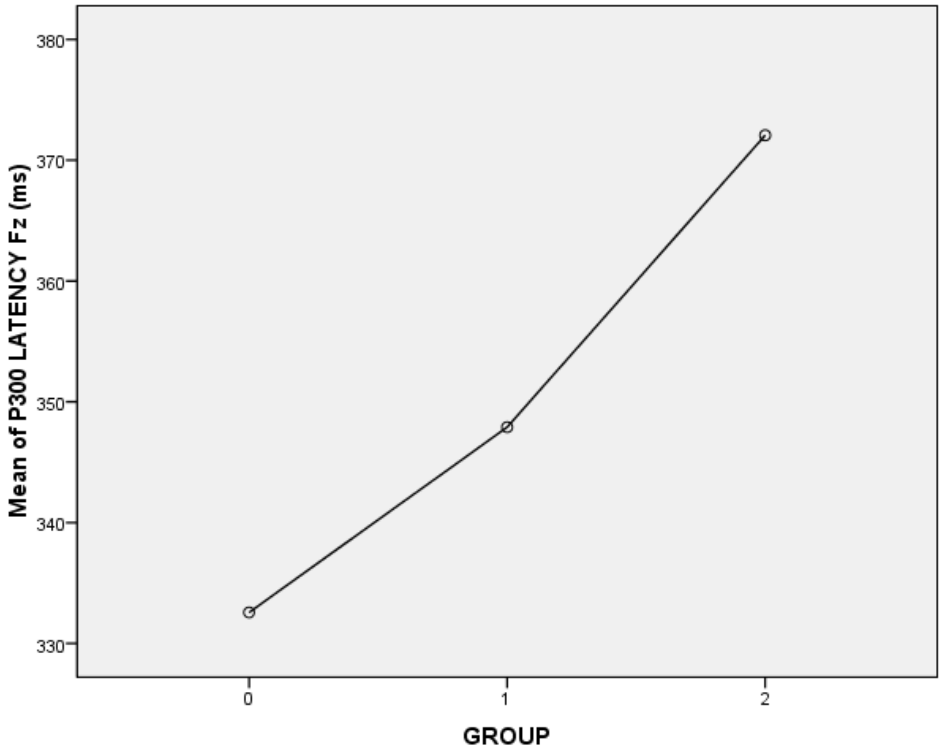
P300 latency Fz (ms):

Table 13: Comparison of P300 latency Fz (ms) among the three groups

Group	N	Mean	S.D.	F	Sig.
Controls	30	332.57	2.512	31.281	.000
Siblings	30	347.90	11.195		
Patients	30	372.07	19.099		
Total	90	350.84	25.281		

Significance $P < 0.05$

Chart 12: Means graph of P300 latency Fz (ms) among the three groups



There is a statistical difference between the three groups with regard to this variable.

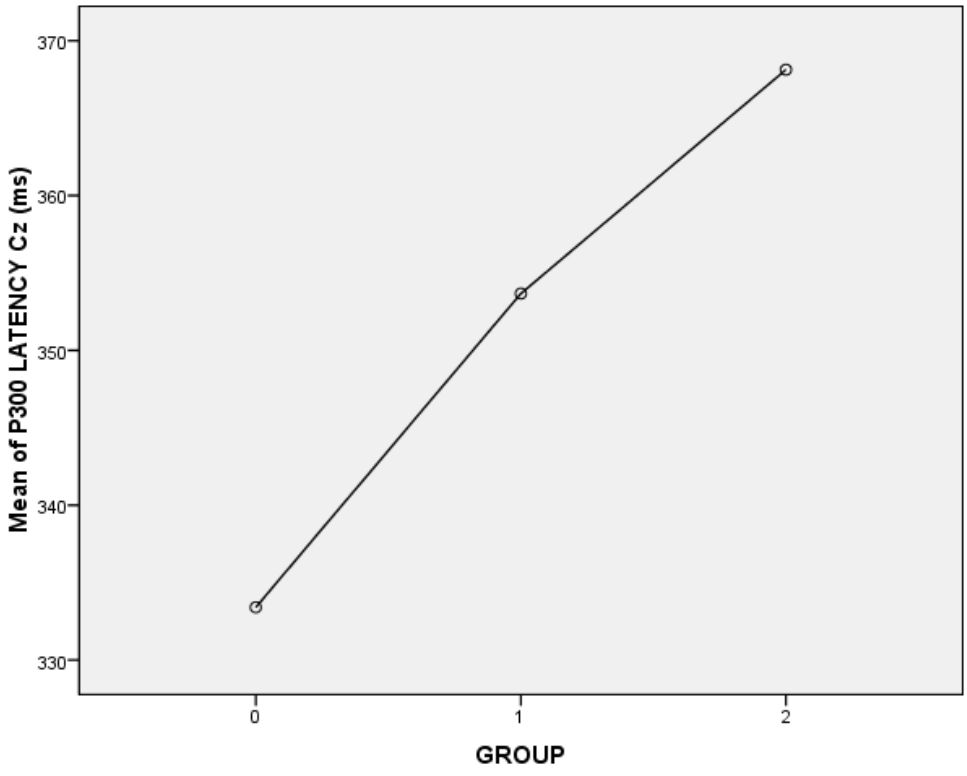
P300 latency Cz (ms):

Table 14: Comparison of P300 latency Cz (ms) among the three groups

Group	N	Mean	S.D.	F	Sig.
Controls	30	333.40	39.893	9.014	.000
Siblings	30	353.67	32.677		
Patients	30	368.13	19.493		
Total	90	351.73	34.577		

Significance $P < 0.05$

Chart 13: Means graph of P300 latency Cz (ms) among the three groups



When P300 latency Cz (ms) was compared between the three groups, there is a statistical difference among them with longer latency for the patient group.

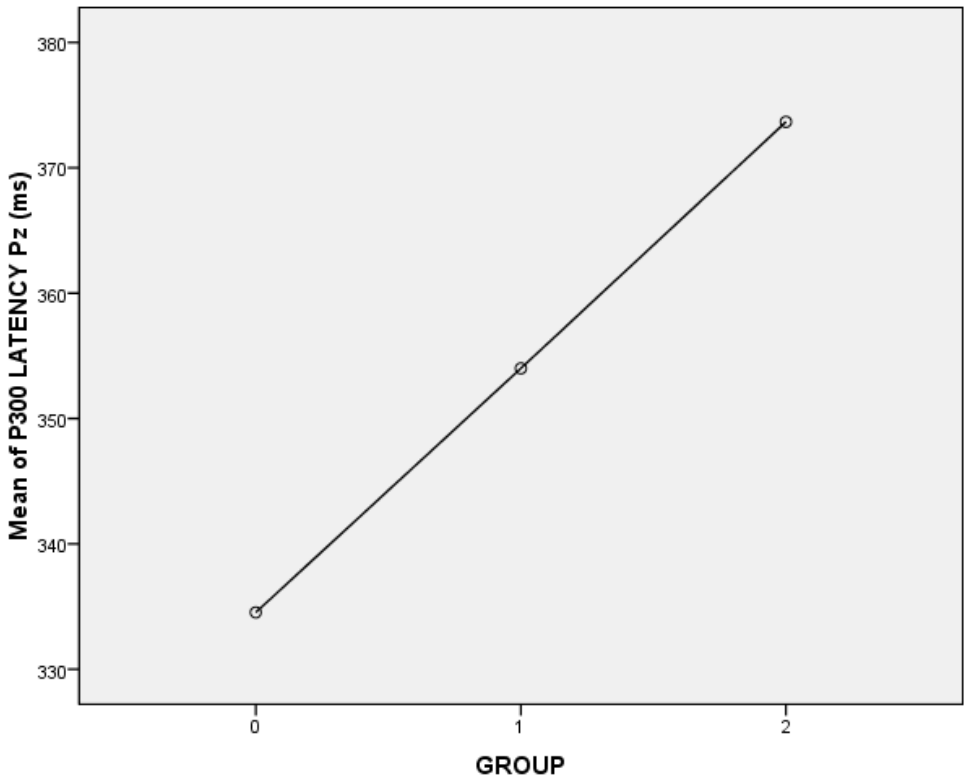
P300 latency Pz (ms):

Table 15: Comparison of P300 latency Pz (ms) among the three groups

Group	N	Mean	S.D.	F	Sig.
Controls	30	334.53	15.874	58.089	.000
Siblings	30	354.00	12.889		
Patients	30	373.67	13.231		
Total	90	354.07	21.246		

Significance $P < 0.05$

Chart 14: Means graph of P300 latency Pz (ms) among the three groups



There is a statistical difference between the three groups. The sibling group is intermediate in latency when compared with the patient and control group.

Comparison of neuropsychological variables across groups:

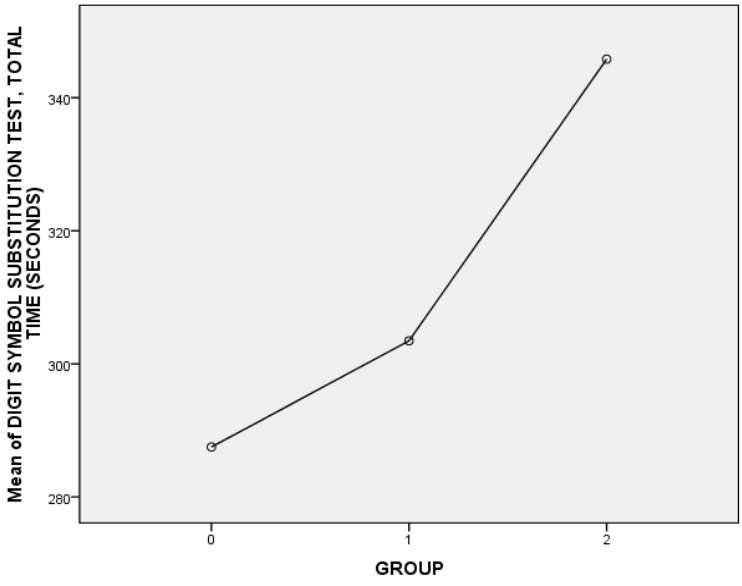
Digit symbol substitution test, total time (seconds):

Table 16: Comparison of Digit symbol substitution test total time (seconds) among the three groups

Group	N	Mean	S.D.	F	Sig.
Controls	30	287.50	59.167	12.368	.000
Siblings	30	303.47	47.394		
Patients	30	345.80	29.287		
Total	90	312.26	52.574		

Significance $P < 0.05$

Chart 15: Means graph of Digit symbol substitution test total time (seconds) among the three groups



There is a statistical difference between the three groups with respect to digit symbol substitution test.

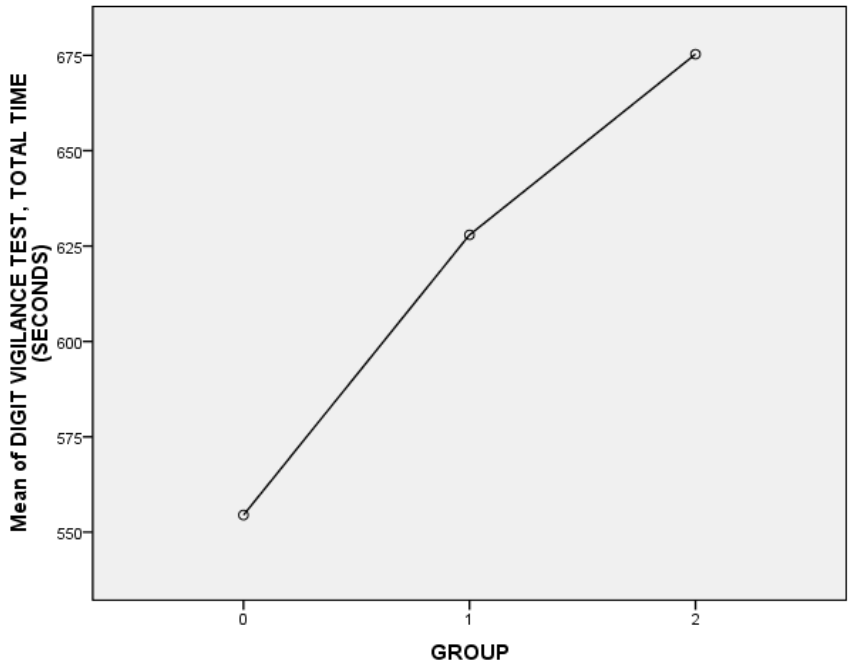
Digit vigilance test, total time (seconds):

Table 17: Comparison of Digit vigilance test, total time (seconds) among the three groups

Group	N	Mean	S.D.	F	Sig.
Controls	30	554.50	81.533	17.179	.000
Siblings	30	627.93	93.653		
Patients	30	675.30	63.163		
Total	90	619.24	93.924		

Significance P < 0.05

Chart 16: Means graph of Digit vigilance test, total time (seconds) among the three groups



When three groups were compared with the above said test, there is a statistical difference among the three groups.

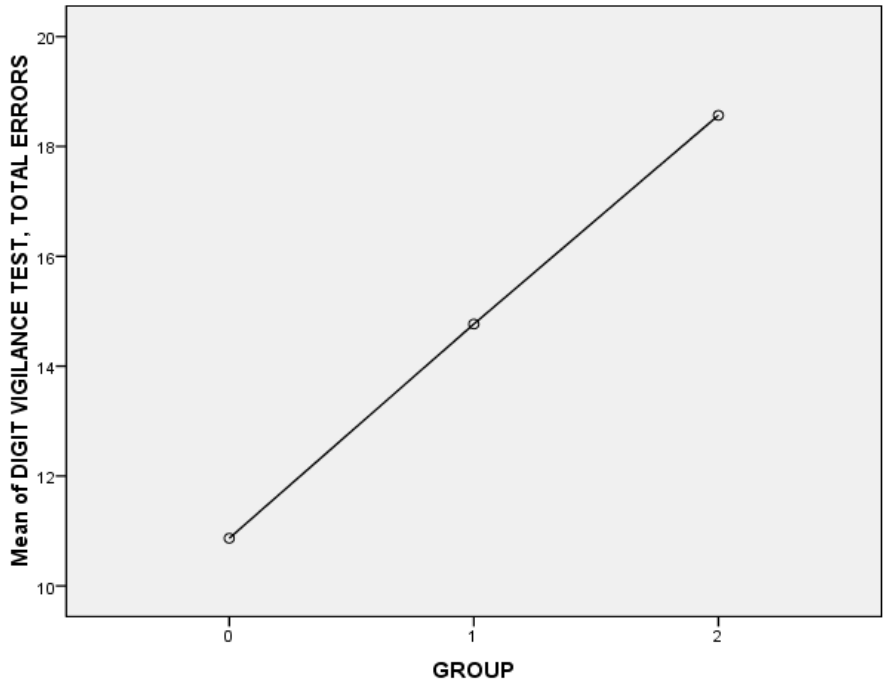
Digit vigilance test, total errors:

Table 18: Comparison of Digit vigilance test, total errors among the three groups

Group	N	Mean	S.D.	F	Sig.
Controls	30	10.87	2.886	54.171	.000
Siblings	30	14.77	2.315		
Patients	30	18.57	3.308		
Total	90	14.73	4.245		

Significance P < 0.05

Chart 17: Means graph of Digit vigilance test, total errors among the three groups



In the three groups, the total errors made by the patient group is more when compared with the other two groups while siblings were having more errors than the controls. There is a statistical difference between the three groups present.

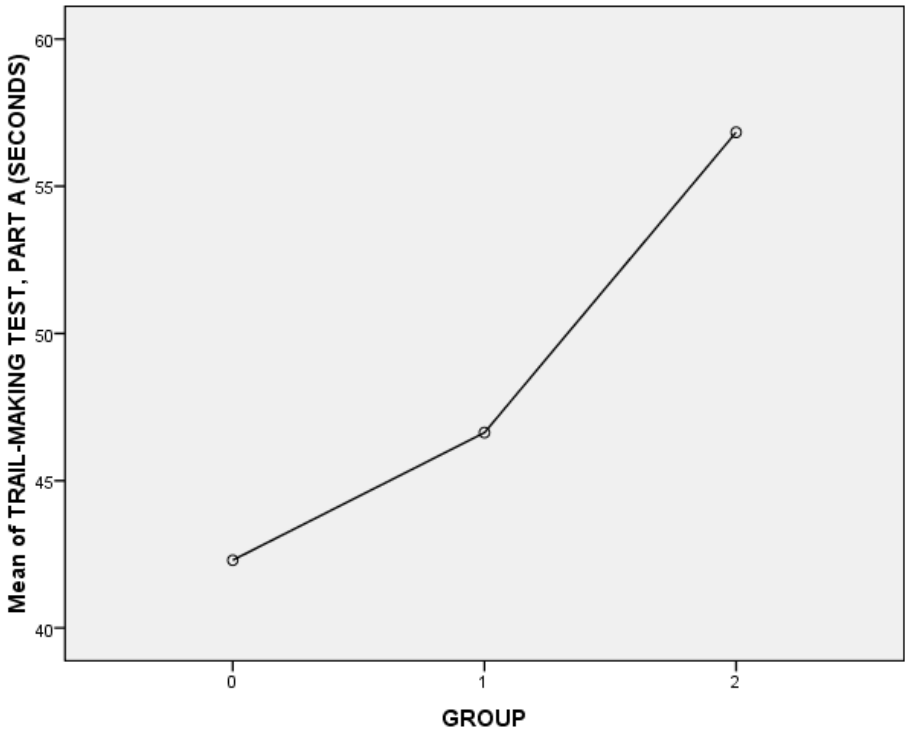
Trail-making test, part A (seconds):

Table 19: Comparison of Trail-making test, part A (seconds) among the three groups

Group	N	Mean	S.D.	F	Sig.
Controls	30	42.30	12.301	20.572	.000
Siblings	30	46.63	6.105		
Patients	30	56.83	7.414		
Total	90	48.59	10.812		

Significance $P < 0.05$

Chart 18: Means graph of Trail-making test, part A (seconds) among the three groups



Trail making test, part A shows a statistical difference among the three groups of subjects with more time taken by the patients to complete the test when compared with others. The time taken by the siblings is intermediate between the other groups

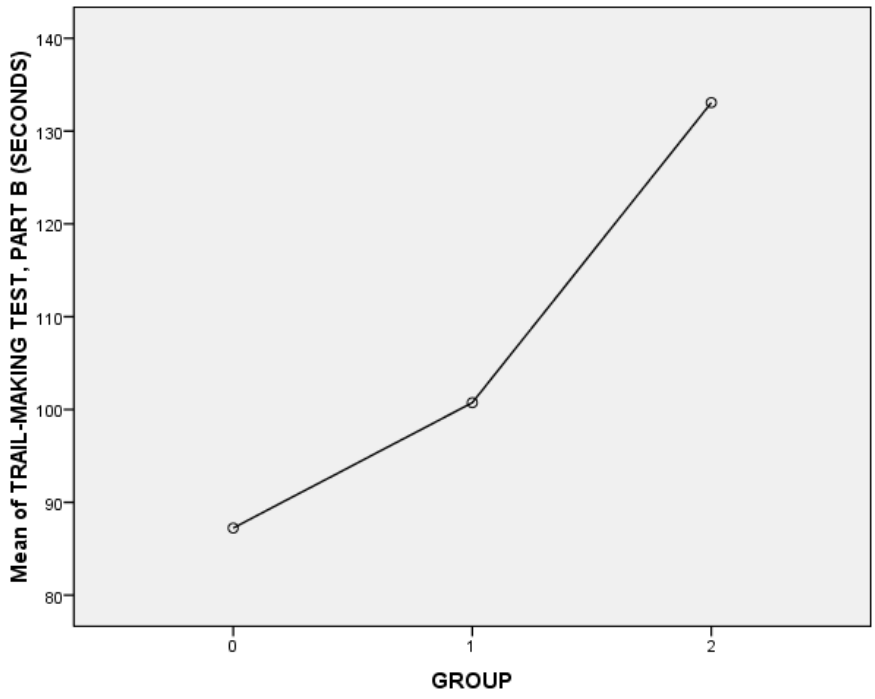
Trail-making test, part B (seconds):

Table 20: Comparison of Trail-making test, part B (seconds) among the three groups

Group	N	Mean	S.D.	F	Sig.
Controls	30	87.23	20.903	67.251	.000
Siblings	30	100.73	11.429		
Patients	30	133.07	13.222		
Total	90	107.01	24.817		

Significance $P < 0.05$

Chart 19: Means graph of Trail-making test, part B (seconds) among the three groups



There is a statistical difference among the three groups with respect to the Trail making test, part B.

Trail-making test, part B – part A (seconds):

Table 21: Comparison of Trail-making test,

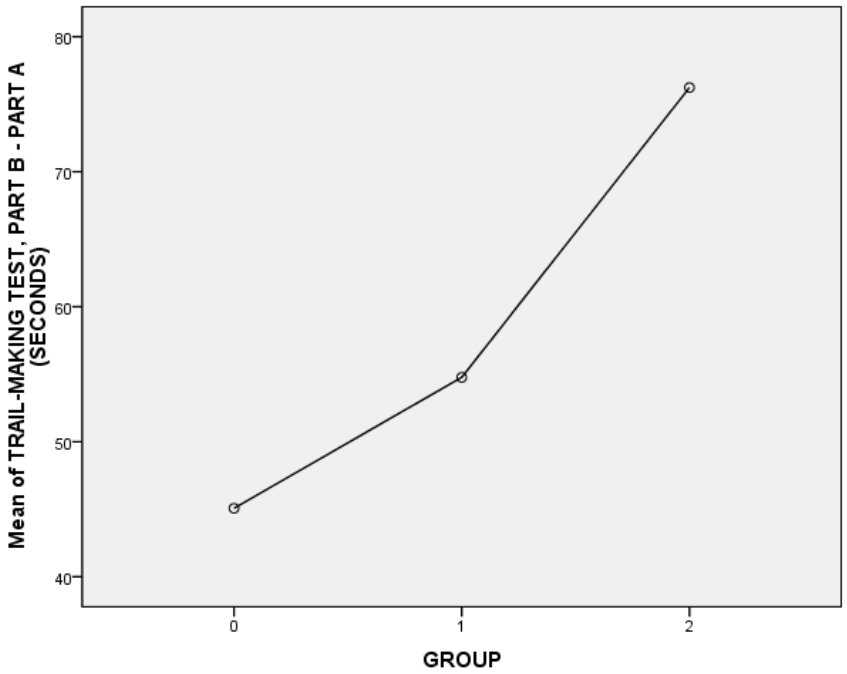
part B – part A (seconds) among the three groups

Group	N	Mean	S.D.	F	Sig.
Controls	30	45.07	11.507	92.771	.000
Siblings	30	54.77	7.934		
Patients	30	76.23	7.171		
Total	90	58..69	15.871		

Significance P < 0.05

Chart 20: Means graph of Trail-making test,

part B – part A (seconds) among the three groups



The difference between the Trail making test B and Trail making test A can be taken as an indicator of the executive function of the subjects. There is a statistical difference among the three groups when scores were compared.

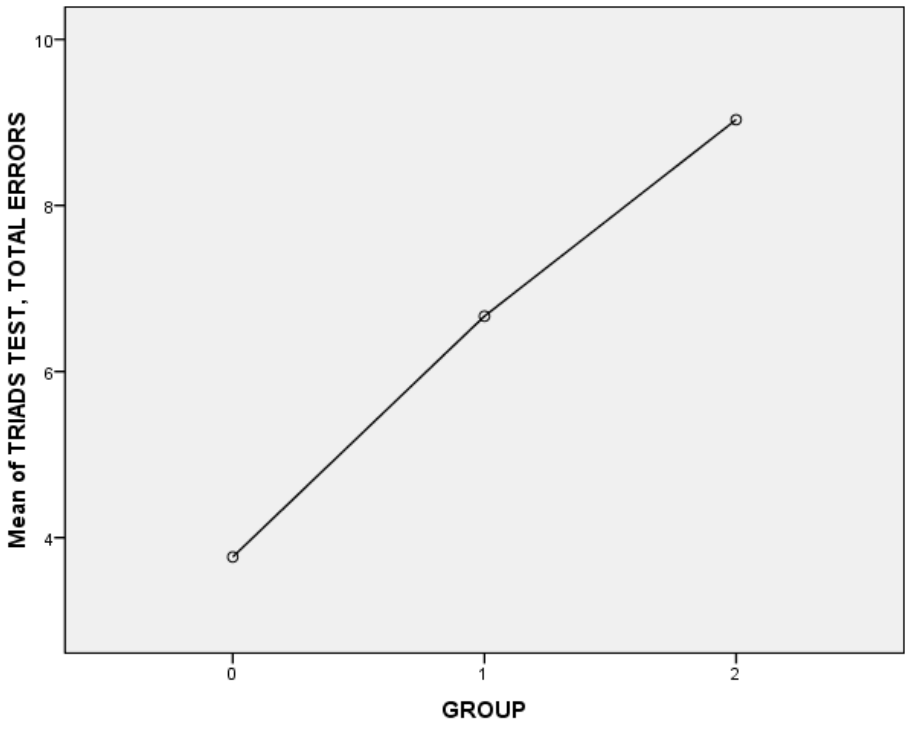
Triads test, total errors:

Table 22: Comparison of Triads test, total errors among the three groups

Group	N	Mean	S.D.	F	Sig.
Controls	30	3.77	1.591	61.562	.000
Siblings	30	6.67	2.040		
Patients	30	9.03	1.866		
Total	90	6..49	2.829		

Significance P < 0.05

Chart 21: Means graph of Triads test, total errors among the three groups



When the three groups were compared to the scores of the Triads test, there is a statistical difference between the three groups is observed. The total errors made by the patients and siblings are more when compared with normal group.

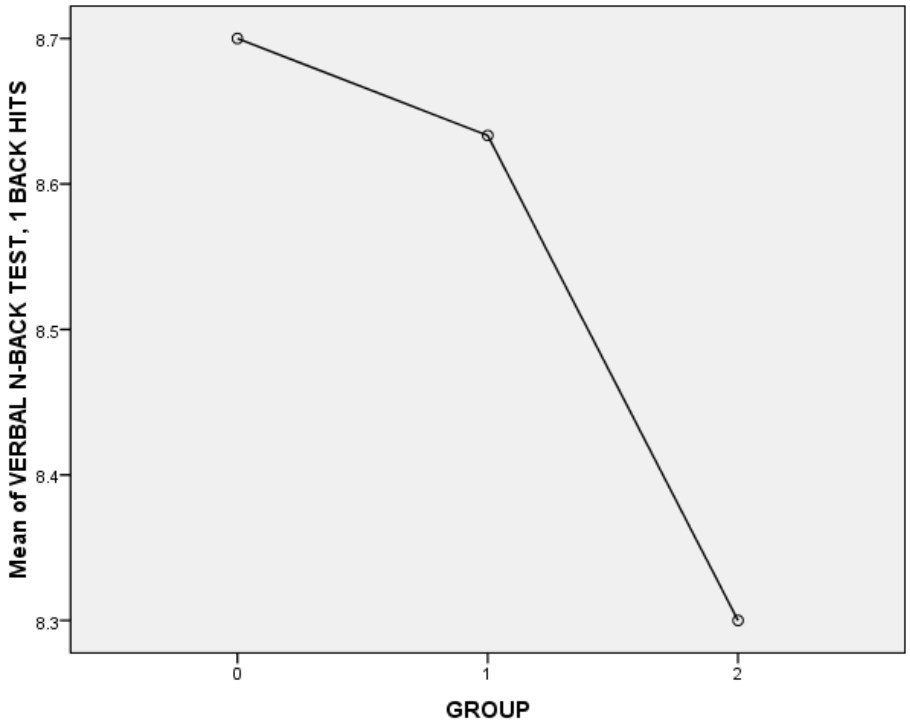
Verbal N-back test, 1 back hits:

Table 23: Comparison of Verbal N-back test, 1 back hits among the three groups

Group	N	Mean	S.D.	F	Sig.
Controls	30	8.70	.535	3.370	.000
Siblings	30	8.63	.615		
Patients	30	8.30	.750		
Total	90	8.54	.656		

Significance P < 0.05

Chart 22: Means graph of Verbal N-back test, 1 back hits among the three groups



Even though the scores among the three groups were comparable, there is a statistical difference between the three groups with regard to this test. The sibling and normal group were more comparable than the patient group with regard to this test.

Verbal n-back test, 1back errors:

Table 24: Comparison of Verbal n-back test,

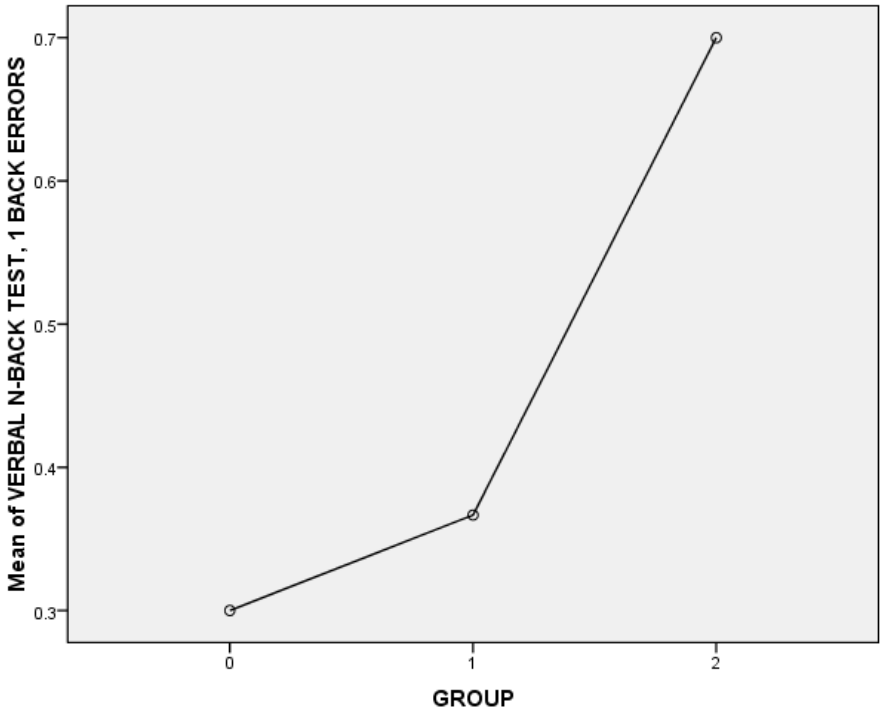
1back errors among the three groups

Group	N	Mean	S.D.	F	Sig.
Controls	30	.30	.535	3.370	.000
Siblings	30	.37	.615		
Patients	30	.70	.750		
Total	90	.46	.656		

Significance P < 0.05

Chart 23: Means graph of Verbal n-back test,

1back errors among the three groups



There is a statistical difference between the three groups when they were compared with the mean scores of the verbal 1 back error test.

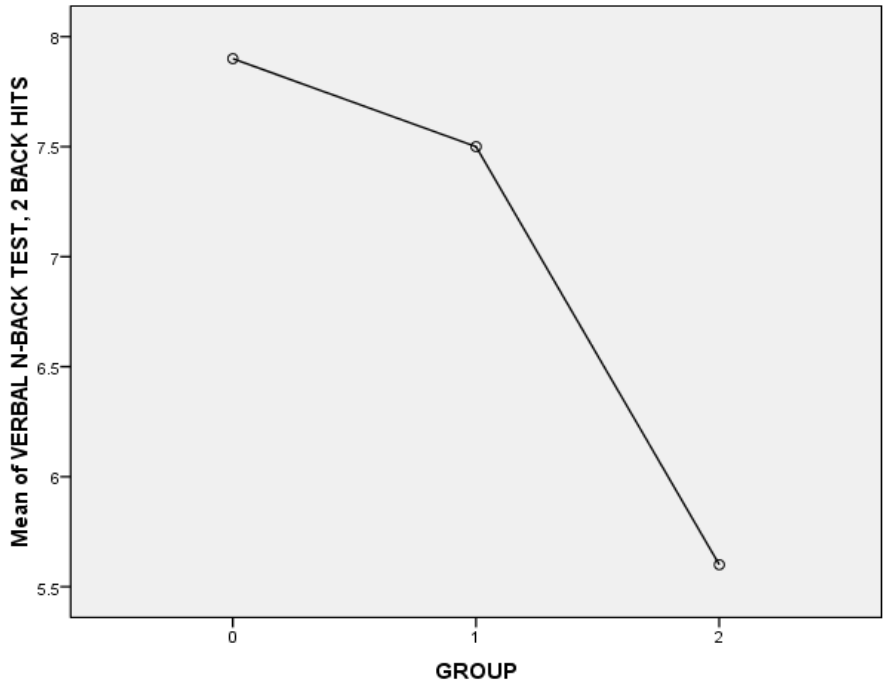
Verbal N-back test, 2 back hits:

Table 25: Comparison of Verbal N-back test, 2 back hits among the three groups

Group	N	Mean	S.D.	F	Sig.
Controls	30	7.90	.481	66.348	.000
Siblings	30	7.50	.731		
Patients	30	5.60	1.133		
Total	90	7.00	1.298		

Significance $P < 0.05$

Chart 24: Means graph of Verbal n-back test,
2 back errors among the three groups



The mean scores of the verbal 2 back hits in the patient group were lower when compared to the other groups of the siblings and the normal group. There is a statistical difference between the three groups with respect to this test

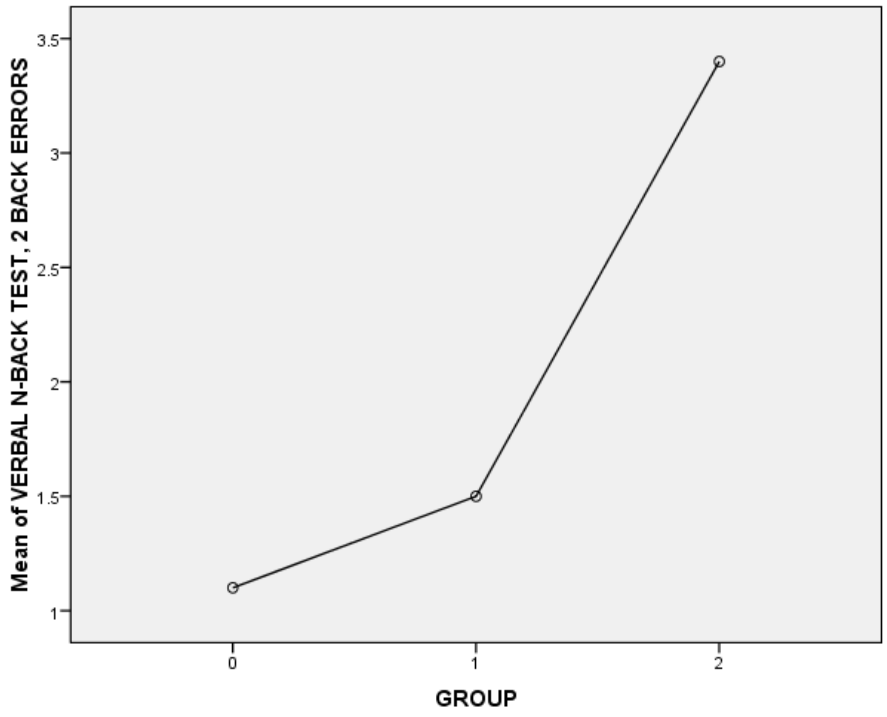
Verbal N-back test, 2 back errors:

Table 26: Comparison of Verbal N-back test, 2 back errors among the three groups

Group	N	Mean	S.D.	F	Sig.
Controls	30	1.10	.481	66.348	.000
Siblings	30	1.50	.731		
Patients	30	3.40	1.133		
Total	90	2.00	1.298		

Significance $P < 0.05$

Chart 25: Means graph of Verbal N-back test, 2 back errors among the three groups



There is a statistical difference between the three groups of the patients, siblings and the normal group.

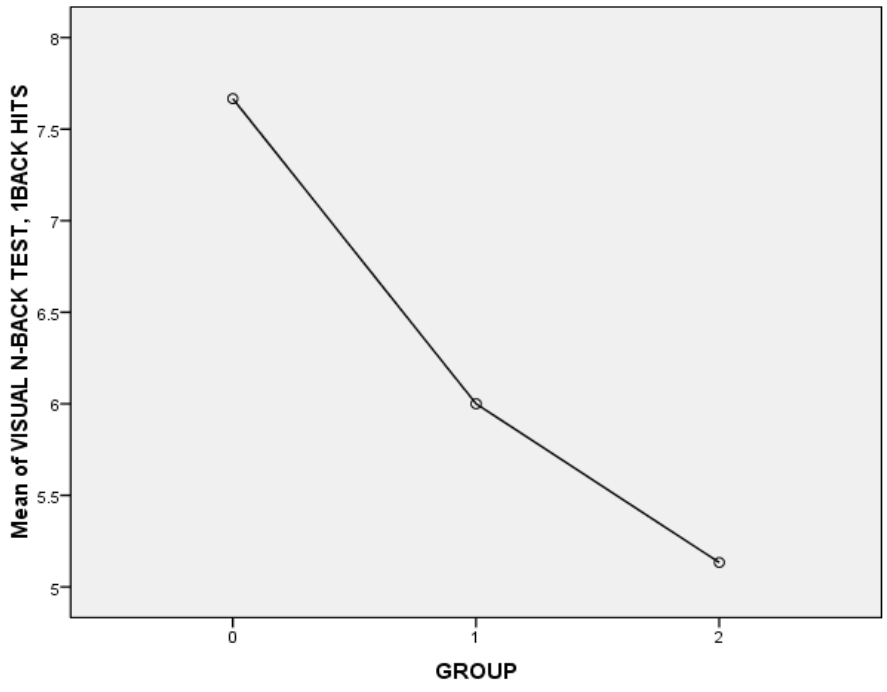
Visual N-back test, 1 back hits:

Table 27: Comparison of Visual N-back test, 1 back hits among the three groups

Group	N	Mean	S.D.	F	Sig.
Controls	30	7.67	.844	67.466	.000
Siblings	30	6.00	.910		
Patients	30	5.13	.819		
Total	90	6.27	1.356		

Significance $P < 0.05$

Chart 26: Means graph of Visual N-back test, 1 back hits among the three groups



The mean score of the patient group in the visual 1 back hits was lower when compared to the other groups. The sibling group was lower when compared with the normal group. There is a statistical difference between the three groups.

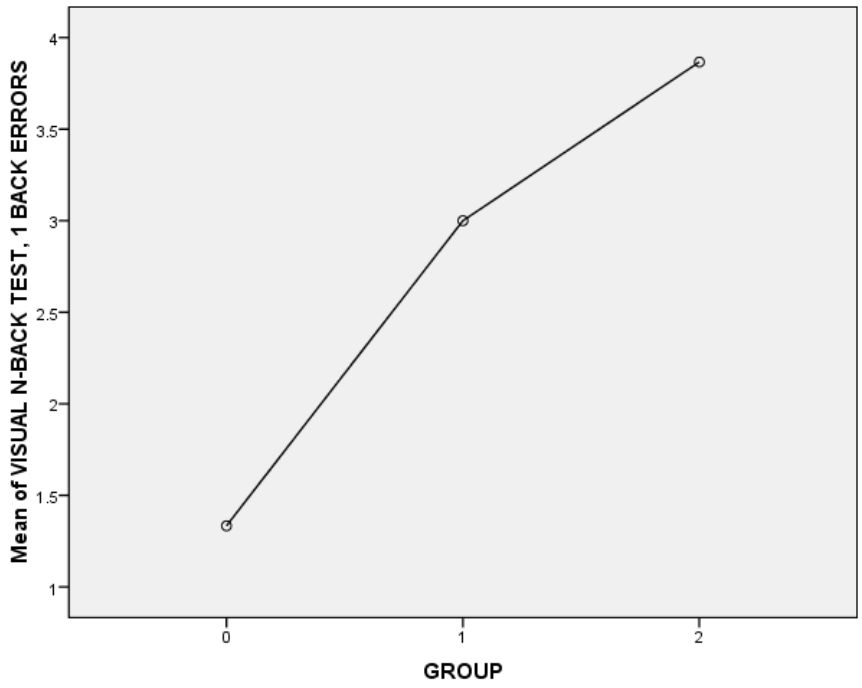
Visual N-back test, 1 back error:

Table 28: Comparison of Visual N-back test, 1 back error among the three groups

Group	N	Mean	S.D.	F	Sig.
Controls	30	1.33	.844	67.466	.000
Siblings	30	3.00	.910		
Patients	30	3.87	.819		
Total	90	2.73	1.356		

Significance $P < 0.05$

Chart 27: Means graph of Visual N-back test, 1 back errors among the three groups



There is a significant difference between the three groups when their mean scores in the above said test was compared. Patient group performed worst in the three groups while the sibling group was worse when compared with the normal group.

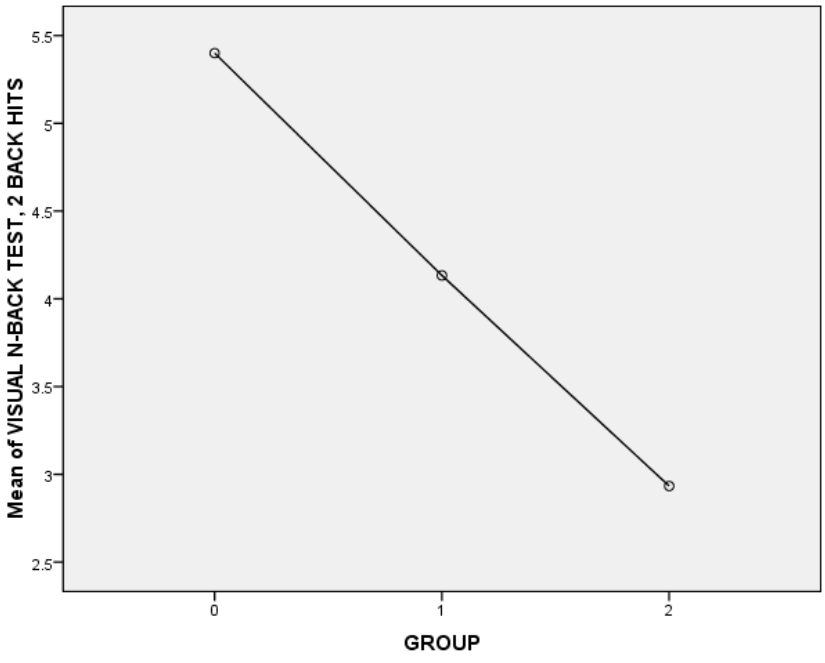
Visual N-back test, 2 back hits:

Table 29: Comparison of Visual N-back test, 2 back hits among the three groups

Group	N	Mean	S.D.	F	Sig.
Controls	30	5.40	.894	51.887	.000
Siblings	30	4.13	1.074		
Patients	30	2.93	.828		
Total	90	4.16	1.373		

Significance $P < 0.05$

Chart 28: Means graph of Visual N-back test, 2 back hits among the three groups



When the mean score in the visual 2 back hits were compared between the three groups, there is a statistical difference between the three groups.

Visual N-back test, 2 back errors:

Table 30: Comparison of Visual N-back test,

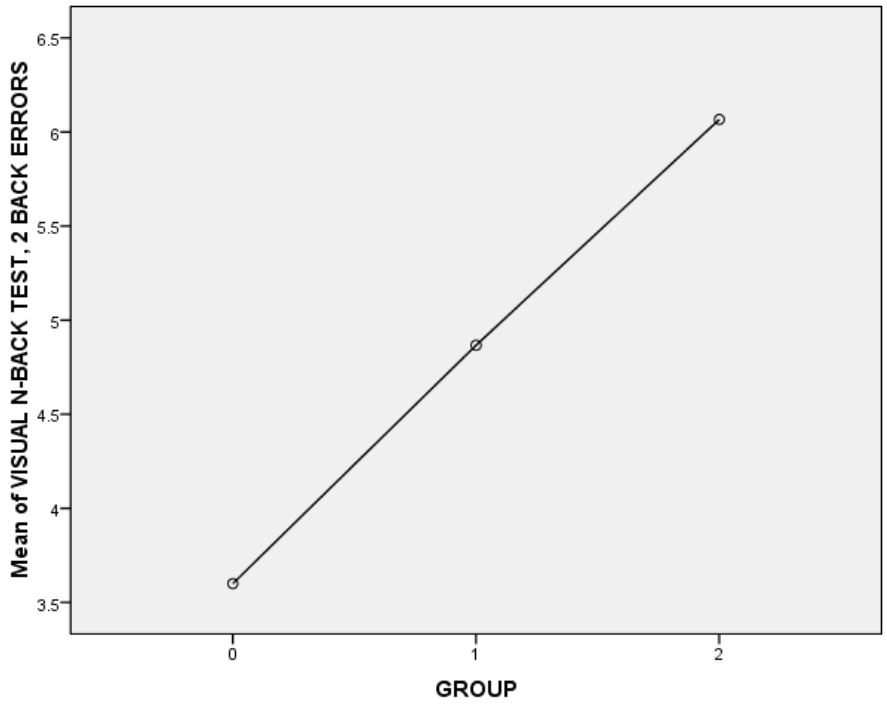
2 back errors among the three groups

Group	N	Mean	S.D.	F	Sig.
Controls	30	3.60	.894	51.887	.000
Siblings	30	4.87	1.074		
Patients	30	6.07	.828		
Total	90	4.84	1.373		

Significance P < 0.05

Chart 29: Means graph of Visual N-back test,

2 back errors among the three groups



There is a statistical difference between the three groups when they were compared by the scores of the visual 2 back error test.

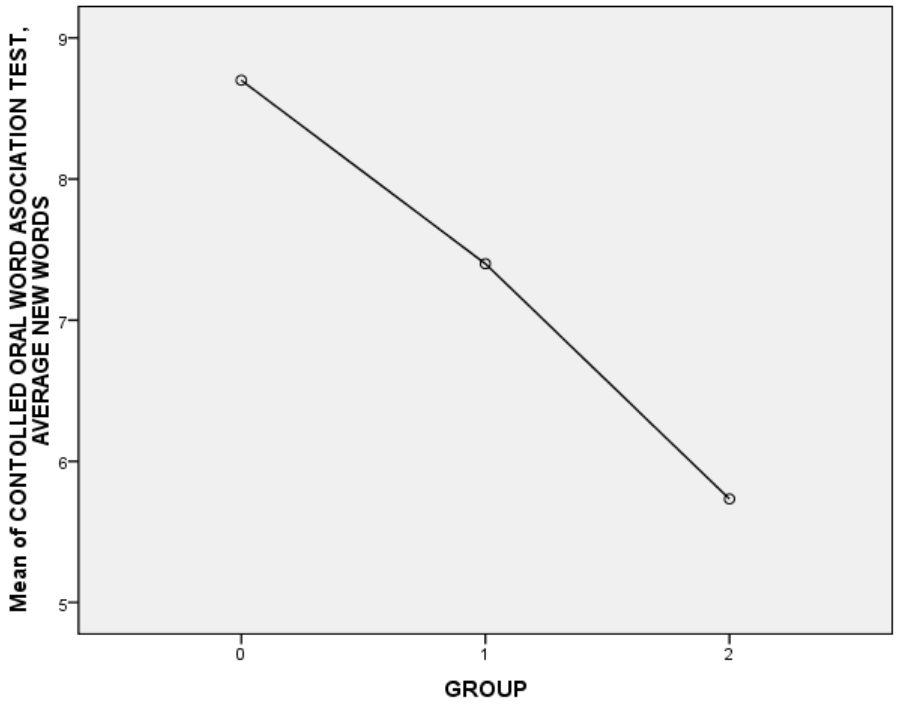
Controlled oral word association test, average new words:

Table 31: Comparison of Controlled oral word association test, average new words among the three groups

Group	N	Mean	S.D.	F	Sig.
Controls	30	8.70	2.136	20.086	.000
Siblings	30	7.40	1.831		
Patients	30	5.73	1.413		
Total	90	7.28	2.172		

Significance $P < 0.05$

Chart 30: Means graph of Controlled oral word association test, average new words among the three groups



There is statistical difference between the three groups compared with respect to this test. Patients and siblings scored lower when compared with the normal controls.

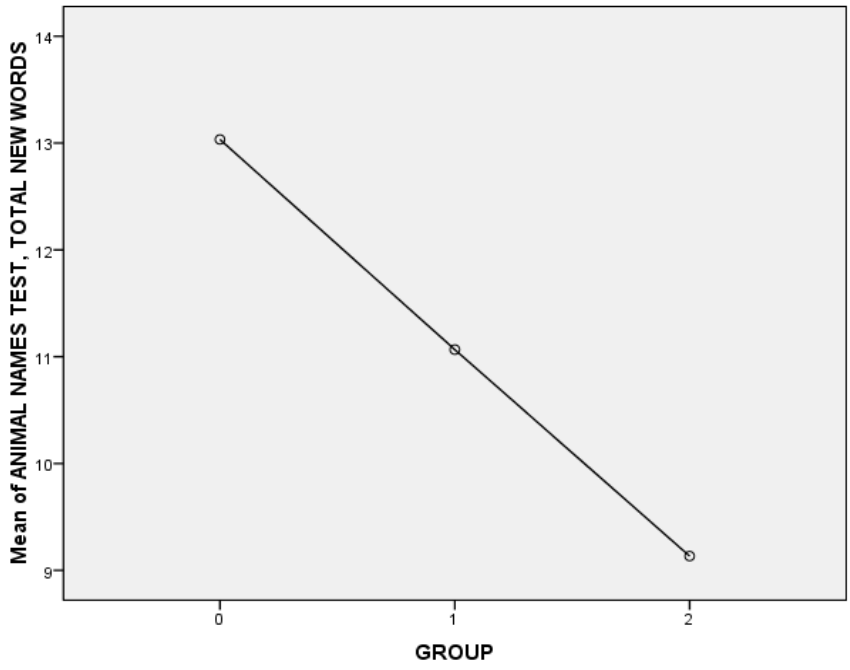
Animal names test, total new words:

Table 32: Comparison of Animal names test, total new words among the three groups

Group	N	Mean	S.D.	F	Sig.
Controls	30	13.03	1.691	42.001	.000
Siblings	30	11.07	1.639		
Patients	30	9.13	1.613		
Total	90	11.08	2.284		

Significance $P < 0.05$

Chart 31: Means graph of Animal names test, total new words among the three groups



The patient group performed worse when compared with the sibling and normal group and the sibling group performed well when compared with the patient group while worse when compared with the normal group. There is a statistical difference between the three groups

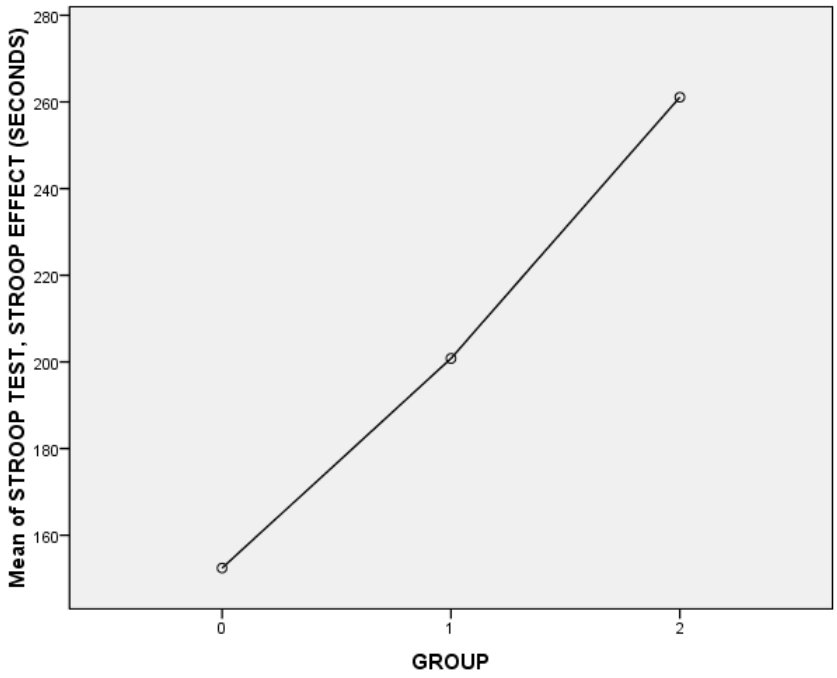
Stroop test, stroop effect (seconds):

Table 33: Comparison of Stroop test, stroop effect (seconds) among the three groups

Group	N	Mean	S.D.	F	Sig.
Controls	30	152.43	2.146	124.756	.000
Siblings	30	200.80	30.897		
Patients	30	261.10	23.479		
Total	90	204.78	51.913		

Significance $P < 0.05$

Chart 32: Means graph of Stroop test, stroop effect (seconds) among the three groups



There is a statistical difference between the three groups when they were compared using the stroop test.

Table 34: Correlation between the illness characteristics and P300 amplitude

Illness characteristics	Correlations	P300 amplitude Fz	P300 amplitude Cz	P300 amplitude Pz
Age of onset of illness (years)	Pearson correlation	.595**	.506	.610**
	Sig.	.001	.004	.000
Duration of illness (months)	Pearson correlation	-.403**	-.409**	-.506
	Sig.	.027	.025	.004
Lag period for treatment (months)	Pearson correlation	-.363	-.340**	-.374**
	Sig.	.049	.066	.042
Duration of treatment (months)	Pearson correlation	-.374**	-.400*	-.527**
	Sig.	.042	.029	.003
PANSS positive score	Pearson correlation	-.020	-.047	-.051
	Sig.	.917	.804	.789
PANSS negative score	Pearson correlation	-.175**	-.248	-.232**
	Sig.	.354	.186	.216
PANSS general psychopathology score	Pearson correlation	-.420**	-.384**	-.377**
	Sig.	.021	.036	.040
PANSS total score	Pearson correlation	-.353**	-.364**	-.353**
	Sig.	.056	.048	.055

From the correlation analysis, it is found that the P300 amplitude are having a strong correlation with the age of onset of the illness, duration of illness and the duration of treatment. There is a negative correlation between the P300 amplitude and the PANSS negative score and the PANSS general psychopathology score. Also, there is a negative correlation between the PANSS total score and the P300 amplitude

values. There is no correlation between the PANSS positive score and the P300 amplitude values.

Table 35: Correlation between the illness characteristics and P300 latency

Illness characteristics	Correlations	P300 latency Fz	P300 latency Cz	P300 latency Pz
Age of onset of illness (years)	Pearson correlation	-.484**	-.413	-.645**
	Sig.	.007	.023	.000
Duration of illness (months)	Pearson correlation	.297**	.301**	.278
	Sig.	.111	.106	.136
Lag period for treatment (months)	Pearson correlation	.220	.248**	.264**
	Sig.	.242	.186	.159
Duration of treatment (months)	Pearson correlation	.308**	.295*	.250**
	Sig.	.098	.114	.183
PANSS positive score	Pearson correlation	.099	.049	-.090
	Sig.	.604	.798	.637
PANSS negative score	Pearson correlation	.122**	.236	.073**
	Sig.	.520	.210	.702
PANSS general psychopathology score	Pearson correlation	.363**	.245**	.341**
	Sig.	.048	.191	.065
PANSS total score	Pearson correlation	.309**	.267**	.238**
	Sig.	.096	.153	.205

There is significant correlation between the age of onset of illness and the P300 latency values. Also, there is a significant correlation between the PANSS general psychopathology score and the P300 latency scores. There is no significant correlation between the other illness characteristics and the P300. In the case of

relationship between the P300 and the age of onset of illness, it has a negative correlation.

Table 36: Correlation between the illness characteristics, Digit symbol substitution test and Digit vigilance test

Illness characteristics	Correlations	Digit symbol substitution test, total time (seconds)	Digit vigilance test, total time (seconds)	Digit vigilance test, total errors
Age of onset of illness (years)	Pearson correlation	-.618	-.630**	-.587**
	Sig.	.000	.000	.001
Duration of illness (months)	Pearson correlation	.386**	.307	.466**
	Sig.	.035	.099	.009
Lag period for treatment (months)	Pearson correlation	.353**	.261**	.422
	Sig.	.056	.164	.020
Duration of treatment (months)	Pearson correlation	.354*	.296**	.431**
	Sig.	.055	.112	.017
PANSS positive score	Pearson correlation	.032	.075	.002
	Sig.	.867	.693	.990
PANSS negative score	Pearson correlation	.139	.141**	.214**
	Sig.	.465	.456	.256
PANSS general psychopathology score	Pearson correlation	.362**	.345**	.415**
	Sig.	.050	.062	.023
PANSS total score	Pearson correlation	.302**	.300**	.362**
	Sig.	.105	.107	.050

Digit vigilance test has a strong correlation with the age of onset of illness. These two variables have a negative correlation between them. Similarly, PANSS general psychopathology score has a significant correlation with the digit vigilance test. These is no significant correlation between the other test and the illness characteristics.

Table 37: Correlation between the illness characteristics and Trail making test, part A and part B

Illness characteristics	Correlations	Trail-making test, part A (seconds)	Trail-making test, part B (seconds)	Trail-making test, part B - part A (seconds)
Age of onset of illness (years)	Pearson correlation	-.587**	-.599	-.497**
	Sig.	.001	.000	.005
Duration of illness (months)	Pearson correlation	.466**	.545**	.523
	Sig.	.009	.002	.003
Lag period for treatment (months)	Pearson correlation	.422	.438**	.371**
	Sig.	.020	.016	.044
Duration of treatment (months)	Pearson correlation	.431**	.543*	.555**
	Sig.	.017	.002	.001
PANSS positive score	Pearson correlation	.002	.105	.192
	Sig.	.990	.579	.310
PANSS negative score	Pearson correlation	.214**	.355	.433**
	Sig.	.256	.054	.017
PANSS general psychopathology score	Pearson correlation	.415**	.477**	.450**
	Sig.	.023	.008	.013
PANSS total score	Pearson correlation	.362**	.480**	.510**
	Sig.	.050	.007	.004

Trail making test, both part A and part B has a significant correlation with all the illness characteristics except the PANSS positive and negative score. Trail making test show a significant correlation with the age of onset of illness and duration of illness.

Table 38: Correlation between the illness characteristics,

Triads test and Verbal 1-back test

Illness characteristics	Correlations	TRIADS TEST, TOTAL ERRORS	VERBAL N-BACK TEST, 1 BACK HITS	VERBAL N-BACK TEST, 1 BACK ERRORS
Age of onset of illness (years)	Pearson correlation	-.604**	.525	-.525**
	Sig.	.000	.003	.003
Duration of illness (months)	Pearson correlation	.553**	-.428**	.428
	Sig.	.002	.018	.018
Lag period for treatment (months)	Pearson correlation	.473	-.483**	.483**
	Sig.	.008	.007	.007
Duration of treatment (months)	Pearson correlation	.531**	-.331*	.331**
	Sig.	.003	.074	.074
PANSS positive score	Pearson correlation	-.032	-.049	.049
	Sig.	.867	.797	.797
PANSS negative score	Pearson correlation	.245**	-.196	.196**
	Sig.	.192	.299	.299
PANSS general psychopathology score	Pearson correlation	.485**	-.393**	.393**
	Sig.	.007	.032	.032
PANSS total score	Pearson correlation	.414**	-.349**	.349**
	Sig.	.023	.059	.059

Verbal and visual N-back tests have a significant correlation with all the illness characteristics of the patient group except the PANSS positive and negative scores.

Table 39: Correlation between the illness characteristics, Verbal 2-back test and Visual 1-back test

Illness characteristics	Correlations	VERBAL N-BACK TEST, 2 BACK HITS	VERBAL N-BACK TEST, 2 BACK ERRORS	VISUAL N-BACK TEST, 1BACK HITS
Age of onset of illness (years)	Pearson correlation	.472**	-.472**	.538**
	Sig.	.008	.008	.002
Duration of illness (months)	Pearson correlation	-.349**	.349**	-.447
	Sig.	.058	.058	.013
Lag period for treatment (months)	Pearson correlation	-.220	.220	-.408**
	Sig.	.242	.242	.025
Duration of treatment (months)	Pearson correlation	-.390**	.390**	-.412**
	Sig.	.033	.033	.024
PANSS positive score	Pearson correlation	-.049	.049	-.002
	Sig.	.795	.795	.991
PANSS negative score	Pearson correlation	-.256**	.256**	-.274**
	Sig.	.173	.173	.143
PANSS general psychopathology score	Pearson correlation	-.363**	.363**	-.426**
	Sig.	.049	.049	.019
PANSS total score	Pearson correlation	-.353**	.353**	-.393**
	Sig.	.055	.055	.032

Verbal and visual N-back tests have a significant correlation with all the illness characteristics of the patient group except the PANSS positive and negative scores.

Table 40: Correlation between the illness characteristics and visual N-back tests

Illness characteristics	Correlations	VISUAL N-BACK TEST, 1 BACK ERRORS	VISUAL N-BACK TEST, 2 BACK HITS	VISUAL N-BACK TEST, 2 BACK ERRORS
Age of onset of illness (years)	Pearson correlation	-.538**	.335	-.335**
	Sig.	.002	.070	.070
Duration of illness (months)	Pearson correlation	.447**	-.390**	.390
	Sig.	.013	.033	.033
Lag period for treatment (months)	Pearson correlation	.408	-.324**	.324**
	Sig.	.025	.081	.081
Duration of treatment (months)	Pearson correlation	.412**	-.381*	.381**
	Sig.	.024	.038	.038
PANSS positive score	Pearson correlation	.002	-.046	.046
	Sig.	.991	.807	.807
PANSS negative score	Pearson correlation	.274**	-.203	.203**
	Sig.	.143	.281	.281
PANSS general psychopathology score	Pearson correlation	.426**	-.301**	.301**
	Sig.	.019	.106	.106
PANSS total score	Pearson correlation	.393**	-.291**	.291**
	Sig.	.032	.119	.119

Verbal and visual N-back tests have a significant correlation with all the illness characteristics of the patient group except the PANSS positive and negative scores.

Table 41: Correlation between the illness characteristics, Controlled oral word association test, Animal names test and Stroop test

Illness characteristics	Correlations	CONTOLLED ORAL WORD ASOCIATION TEST, AVERAGE NEW WORDS	ANIMAL NAMES TEST, TOTAL NEW WORDS	STROOP TEST, STROOP EFFECT (SECONDS)
Age of onset of illness (years)	Pearson correlation	.596**	.402	-.625**
	Sig.	.001	.028	.000
Duration of illness (months)	Pearson correlation	-.327**	-.250**	.428
	Sig.	.078	.183	.018
Lag period for treatment (months)	Pearson correlation	-.302	-.180**	.443**
	Sig.	.105	.342	.014
Duration of treatment (months)	Pearson correlation	-.298**	-.263*	.358**
	Sig.	.110	.160	.052
PANSS positive score	Pearson correlation	.052	-.196	-.091
	Sig.	.785	.299	.631
PANSS negative score	Pearson correlation	-.228**	.024	.205**
	Sig.	.227	.898	.277
PANSS general psychopathology score	Pearson correlation	-.363**	-.182**	.433**
	Sig.	.048	.337	.017
PANSS total score	Pearson correlation	-.323**	-.148**	.352**
	Sig.	.082	.434	.056

Stroop test has a significant correlation with the age of onset of illness, duration of treatment and lag period of treatment. It also shows a strong correlation with the PANSS general psychopathology score and the total score.

Table 42: Correlation between neuropsychological tests and P300 amplitude

Neuropsychological tests	Correlations	P300 amplitude Fz	P300 amplitude Cz	P300 amplitude Pz
Digit symbol substitution test, total time (seconds)	Pearson correlation	-.784	-.794*	-.803*
	Sig.	.000	.000	.000
Digit vigilance test, total time (seconds)	Pearson correlation	-.888	-.811**	-.860*
	Sig.	.000	.000	.000
Digit vigilance test, total errors	Pearson correlation	-.758	-.723**	-.803
	Sig.	.000	.000	.000
Trail-making test, part A (seconds))	Pearson correlation	-.798	-.712	-.860
	Sig.	.000	.000	.000
Trail-making test, part B (seconds)	Pearson correlation	-.790	-.766	-.872
	Sig.	.000	.000	.000
Trail-making test, part B - part A (seconds)	Pearson correlation	-.632	-.676	-.718
	Sig.	.000	.000	.000
TRIADS TEST, TOTAL ERRORS	Pearson correlation	-.832	-.862	-.833
	Sig.	.000	.000	.000

Verbal and visual N-back tests have a significant correlation with all the illness characteristics of the patient group except the PANSS positive and negative scores. There is significant correlation between the digit vigilance test and the central and parietal electrode measurements. There is no significant correlation between the P300 amplitude Fz and the neuropsychological tests.

Table 43: Correlation between neuropsychological tests and P300 amplitude

Neuropsychological tests	Correlations	P300 amplitude Fz	P300 amplitude Cz	P300 amplitude Pz
VERBAL N-BACK TEST, 1 BACK HITS	Pearson correlation	.783	.738	.593
	Sig.	.000	.000	.001
VERBAL N-BACK TEST, 1 BACK ERRORS	Pearson correlation	-.783	-.738	-.593
	Sig.	.000	.000	.001
VERBAL N-BACK TEST, 2 BACK HITS	Pearson correlation	.753	.780	.694
	Sig.	.000	.000	.000
VERBAL N-BACK TEST, 2 BACK ERRORS	Pearson correlation	-.753	-.780	-.694
	Sig.	.000	.000	.000
VISUAL N-BACK TEST, 1BACK HITS	Pearson correlation	.731	.605	.769
	Sig.	.000	.000	.000
VISUAL N-BACK TEST, 1 BACK ERRORS	Pearson correlation	-.731	-.605	-.769
	Sig.	.000	.000	.000
VISUAL N-BACK TEST, 2 BACK HITS	Pearson correlation	.695	.674	.717
	Sig.	.000**	.000	.000**
VISUAL N-BACK TEST, 2 BACK ERRORS	Pearson correlation	-.695	-.674	-.717
	Sig.	.000**	.000**	.000

Verbal and visual N-back tests have a significant correlation with all the illness characteristics of the patient group except the PANSS positive and negative scores. Visual 2-back test shows a significant correlation with the P300 amplitude. Visual 2-back hits have a positive correlation with the P300 amplitude while the visual 2-back errors have a negative correlation with the P300 amplitude.

Table 44: Correlation between neuropsychological tests and P300 amplitude

Neuropsychological tests	Correlations	P300 amplitude Fz	P300 amplitude Cz	P300 amplitude Pz
CONTOLLED ORAL WORD ASOCIATION TEST, AVERAGE NEW WORDS	Pearson correlation	.772	.787	.675
	Sig.	.000	.000**	.000**
ANIMAL NAMES TEST, TOTAL NEW WORDS	Pearson correlation	.657	.546	.626
	Sig.	.000**	.002*	.000**
STROOP TEST, STROOP EFFECT (SECONDS)	Pearson correlation	-.783	-.722	-.768
	Sig.	.000	.000	.000

There is a significant correlation between the Animal names test and Controlled oral association test with the P300 amplitude scores. There is no significant correlation between the Stroop test and the P300 amplitude scores.

Table 45: Correlation between neuropsychological tests and P300 latency

Neuropsychological tests	Correlations	P300 latency Fz	P300 latency Cz	P300 latency Pz
Digit symbol substitution test, total time (seconds)	Pearson correlation	.844	.796*	.740*
	Sig.	.000	.000	.000
Digit vigilance test, total time (seconds)	Pearson correlation	.903	.864**	.911*
	Sig.	.000	.000	.000
Digit vigilance test, total errors	Pearson correlation	.846	.714**	.884
	Sig.	.000	.000	.000
Trail-making test, part A (seconds))	Pearson correlation	.889	.807	.836
	Sig.	.000	.000	.000
Trail-making test, part B (seconds)	Pearson correlation	.898	.835	.813
	Sig.	.000	.000	.000
Trail-making test, part B - part A (seconds)	Pearson correlation	.736	.706	.635
	Sig.	.000	.000	.000
TRIADS TEST, TOTAL ERRORS	Pearson correlation	.841	.779	.843
	Sig.	.000	.000	.000

There is a significant correlation between the digit vigilance test and the P300 latency. Particularly, there is a significant correlation between the P300 latency in the Cz and Pz electrode while there is no significant correlation with the Pz electrode. There is no correlation with the other neuropsychological tests and the P300 latency.

Table 46: Correlation between neuropsychological tests and P300 latency

Neuropsychological tests	Correlations	P300 latency Fz	P300 latency Cz	P300 latency Pz
VERBAL N-BACK TEST, 1 BACK HITS	Pearson correlation	-.654	-.652	-.640
	Sig.	.000	.000	.000
VERBAL N-BACK TEST, 1 BACK ERRORS	Pearson correlation	.654	.652	.640
	Sig.	.000	.000	.000
VERBAL N-BACK TEST, 2 BACK HITS	Pearson correlation	-.845	-.718	-.766
	Sig.	.000	.000	.000
VERBAL N-BACK TEST, 2 BACK ERRORS	Pearson correlation	.845	.718	.766
	Sig.	.000	.000	.000
VISUAL N-BACK TEST, 1BACK HITS	Pearson correlation	-.732	-.837	-.836
	Sig.	.000	.000	.000
VISUAL N-BACK TEST, 1 BACK ERRORS	Pearson correlation	.732	.837	.836
	Sig.	.000	.000	.000
VISUAL N-BACK TEST, 2 BACK HITS	Pearson correlation	-.737	-.724	-.692
	Sig.	.000**	.000	.000**
VISUAL N-BACK TEST, 2 BACK ERRORS	Pearson correlation	.737	.724	.692
	Sig.	.000**	.000**	.000

There is a significant correlation between the visual 2-back test and the P300 latency. The other neuropsychological tests are not having a significant correlation with the P300 latency.

Table 47: Correlation between neuropsychological tests and P300 latency

Neuropsychological tests	Correlations	P300 latency Fz	P300 latency Cz	P300 latency Pz
CONTOLLED ORAL WORD ASOCIATION TEST, AVERAGE NEW WORDS	Pearson correlation	-.844	-.724	-.843
	Sig.	.000	.000**	.000**
ANIMAL NAMES TEST, TOTAL NEW WORDS	Pearson correlation	-.620	-.595	-.723
	Sig.	.000**	.001*	.000**
STROOP TEST, STROOP EFFECT (SECONDS)	Pearson correlation	.832	.731	.858
	Sig.	.000	.000	.000

There is a significant correlation between the Animal names test and Controlled oral word association test and the P300 latency values. There is no significant correlation between the Stroop test and the P300 latency.

DISCUSSION

The aim of the study was to measure the event related potential, P300 and neuropsychological tests in patients with schizophrenia and their unaffected biological siblings and to compare the results with controls. The study was done after matching for age, sex and education among the three groups, namely the patients with schizophrenia, their unaffected biological siblings and controls.

The sample, patients with schizophrenia and their siblings, was taken from the psychiatry outpatient department, Institute of Mental Health. This sample consisted of 30 patients and 30 siblings. The patients with paranoid schizophrenia were selected according to ICD-10. The control group consisted of 30 subjects who were not having any family history of psychiatric illness. This sample was selected from the caregivers of patients in other departments excepting psychiatry. The confounding bias due to the age, sex and education in the measurement of electrophysiological and neuropsychological tests were reduced by matching the three groups for age, sex and education. The subjects, who were taking medications which can have an impact on the cognition, were excluded from the study. The mean age of the study population was 28.62±3.03.

Comparison of P300 among the three groups:

With respect toP300 amplitude measurements in the three groups of subjects, there was a significant difference between the three groups. The difference was more in the case of the amplitude measured in the central and parietal regions when compared with the frontal regions. The mean amplitude in the controls was 11.760±3.18, siblings 8.257±2.23 and patients 4.130±1.32. It showed a statistical significance between the groups (F = 77.587). Similar results were obtained in other

studies which investigated the comparison between the P300 amplitude between the patients with schizophrenia and their unaffected siblings. The current study showed a difference in the amplitude as well in the latency of P300 between the groups. The amplitude and latency were measured in three regions of the scalp namely the frontal, central and parietal areas. There was a significant difference between the groups in the individual parameters also. Kidogami et al. showed the amplitude of P300 in the patients with schizophrenia and the first degree relatives of patients with schizophrenia was of low amplitude when compared with the control group (162). But there was no significant difference between the first degree relatives and patients with schizophrenia with respect to P300 amplitude. This showed that the P300 could be taken as a trait marker for schizophrenia. In another study by Black et al. observed that 40% of patients with schizophrenia showed P300 abnormalities while only 10% of first degree relatives of patients with schizophrenia showed P300 abnormalities (11). Similar to these studies, the current study also showed that the P300 amplitude was smaller in patients with schizophrenia when compared to the controls and the siblings of patients with schizophrenia. In the case of the siblings, the P300 amplitude was reduced when compared to the control group.

The P300 latency showed significant difference between the groups. The latency was longer for the patients with schizophrenia while it was intermediate between the patients and controls in the case of the siblings. Araki et al in their study showed similar results that the latency was prolonged in the case of patients with schizophrenia when compared the controls (163). In the case of first degree relatives of patients with schizophrenia, the latency was prolonged when compared to the normal controls but they were comparable to the patient group. But a meta-analysis on the P300 abnormalities in the schizophrenia had showed that the changes in the

latency were an inconsistent finding while the changes in the amplitude showed robust results.

Digit symbol substitution test:

In this study, digit symbol substitution test was given to the subjects to assess the mental speed. It showed a significant difference between the groups regarding the mental speed. Siblings showed a slower rate of mental speed when compared with the control group while patients with schizophrenia had the worst performance in the test. In a study by Amaresha et al. it was showed that the patients with schizophrenia had a worse speed of processing when compared to the controls. Also, the speed of processing was dependent upon various clinical correlates like the negative score in PANSS (164). Similarly, Laurent et al showed that there was a decrease in the performance in the tests measuring speed of processing in the first degree relatives of patients with schizophrenia (165).

Continuous performance test:

Continuous performance test, which was applied to measure the sustained attention, showed a statistical difference between the three group of subjects. The patients with schizophrenia and their siblings performed poorly with errors when compared to the control group. Avila et al studied the continuous performance test in the schizophrenia spectrum disorders and reported that the patients with schizophrenia had severe impairments in the performance (166). This study showed a gradation in the performance with highest deficits in the patients with schizophrenia while lesser impairments in the patients with schizotypal personality disorder. In another study by Bove et al, which studied the continuous performance test in 24 first degree relatives of patients with schizophrenia, showed slight decrease in performance in the test

when compared with the control group. In this study, it was showed that the performance of the test in the first degree relatives was not dependent on the basic symptoms (167).

Trail-making test:

In this study, trail-making test showed that there was only slight difference between the groups when trail-making A test was compared between the groups. But these was a statistical difference between the groups was observed when trail-making B test was compared between the groups. This difference showed that the attention and set shifting deficits were the underlying problems in the case of patients with schizophrenia. The deficits were also evident in the siblings but not to the level of patients. This shows a gradation the scoring of trail-making B test with lowest in the patients with schizophrenia followed by the siblings and the controls. In a study by Fujiki et al. showed that the relatives of patients with schizophrenia show difference in the performance of trail making test. Contrary to the current study, the above said study showed a difference in the relatives in the trail-making A test also (168).

Triads test:

The triads test was used to measure the divided attention among the subjects. This test showed a significant difference between the groups. When compared with the normal control group, the patients with schizophrenia and siblings of patients with schizophrenia performed worse. No similar study could be found in the literature review using this test.

Working memory:

In this study, the working memory was measured by N-back tests. These tests measured the verbal and visual working memory separately. The results of the current study were there was a significant difference between the verbal and visual working memory between the groups. In this, the visual working memory showed a greater significance of difference between the groups when compared with the verbal working memory. In other study, Conklin et al., using the digit forward and digit backward method to measure the working memory, showed that there was impairment in both the digit forward and backward in the case of patients with schizophrenia (169). Conklin et al found out that the first degree relatives of patients with schizophrenia had deficits in working memory only when the task at hand required much of the reserves of the central executive functions (170).

Stroop test:

The stroop test was administered to measure the response inhibition in the three different groups. Response inhibition is a sub-test to measure the executive functions of the brain. The stroop effect was calculated from the test to measure the response inhibition. The mean scores in the three groups were 152.43, 200.8 and 261.1, for controls, siblings and patients, respectively. There was a significant difference between the three groups indicating that the response inhibition was affected in the sibling and patient group when compared to the controls. This indicates that the sibling group is having deficits in the function of response inhibition when compared to the controls. Similar findings were reported by other studies. In a study by Jameson et al. which studied the executive functions in the parents and siblings of patients with schizophrenia reported a significant difference between the

performances of the stroop test when compared with the controls (171). But in a study by Becker et al., the post-conflict related performance in stroop test had intact results comparable to the general population (172).

Controlled oral word association test:

The results from the current study showed that there is a statistical significance between the groups in regard to the phonemic fluency. This shows that the word production in the patients with schizophrenia is well below the controls. In the case of the siblings of patients with schizophrenia, the measurement is significantly different from the control group. This shows that there is a deficit in the siblings in the phonemic fluency. This is in relation with other studies, Keefe et al., and Dollfus et al., which showed that the relatives of patients with schizophrenia performed worse when compared with the control group (173-174).

Animal names test:

The mean number of new words produced by the control group was 13.03±1.69, siblings 11.07±1.63 and for the patients with schizophrenia was 9.13±1.61. There is a statistical difference between the groups. The worse performance in the animal names test represents the deficit in the category fluency. The patients with schizophrenia have a worse performance in the category fluency. Next in line was the siblings of patients with schizophrenia who have a worse performance when compared with the control group. These findings corroborate with resuts from other studies. Heinrichs and Zakzanis showed that the patients with schizophrenia had a low score in the category fluency and executive functioning (175). Another study by Laurent et al. showed that the patients with schizophrenia and their first degree siblings had impaired verbal fluency when compared with the age and sex matched controls (176).

Correlation between the P300, neuropsychological test and clinical variables:

In the current study, there was a significant correlation between the clinical variables in the patient with schizophrenia group and the electrophysiological and neuropsychological measures. There were significant correlation between the P300 and the neuropsychological test scores also. The age of onset of illness and the duration illness had a significant correlation with the P300 amplitude and latency. PANSS positive score did not have a significant correlation with the P300 amplitude and latency but PANSS general psychopathology score and total score had a significant correlation with them.

In the neuropsychological tests, digit vigilance test, visual 2-back test and stroop test had a significant correlation with the age of onset of illness and the duration of illness. They also had a significant correlation with the PANSS general psychopathology score and total score.

When the P300 amplitude and latency were correlated with the neuropsychological tests, they showed a significant correlation between the P300 amplitude an latency in the Cz and Pz electrodes while not much significant correlation with the Fz.

These findings were similar to other studies which have analyzed the correlation between P300, neuropsychological tests and symptoms in schizophrenia patients (177). Similar studies had shown that there is a reduction in the amplitude of the P300 in patients with schizophrenia with significant correlation to the negative PANSS scores while there is no significant relation with the PANSS positive scores (178).

CONCLUSION

1. The patients with schizophrenia and their unaffected biological siblings showed significant impairments in the event related potential P300 amplitude and latency when compared with the controls.

2. The patients with schizophrenia and their unaffected biological siblings showed significant impairments in the tests administered to measure the neuropsychological functioning when compared with the controls.

3. Except Trail-making A test and Verbal N-back working memory test, all other neuropsychological tests showed impairments in the patient and sibling group when compared with the controls.

4. Stroop test, Continuous performance test and visual N-back test showed very significant differences between the patients with schizophrenia and the unaffected biological siblings.

5. In patients with schizophrenia, clinical parameters correlated significantly with the event related potential P300amlitude and latency.

6. Strong correlation is evident between the P300 amplitude and the duration of illness and PANSS negative score.

7. Age of onset of illness, duration of untreated illness, duration of illness, PANSS negative score and PANSS general psychopathology score correlated significantly with the neuropsychological tests. Strong correlation is found between the stroop and continuous performance test and the clinical variables in patients with schizophrenia.

LIMITATIONS

1. A major limitation in the study was the sample size. A larger sample size would have thrown greater light on the analysis and might have revealed clear differences between the groups.

2. The patients with schizophrenia, at the time of evaluation, were on the antipsychotic medications. The presence of these drugs might have an effect on the cognitive function of the patients. But it was unethical to withdraw the drug during the study period as it can increase the chance of relapse.

3. The study was a cross-sectional one measuring the event related potentials and neuropsychological performances. This might bring about the individual variation the subjects during one assessment.

4. Halo effect would have affected the results as the assessor was not blinded to subjects from the three different groups.

FUTURE DIRECTION

1. The patients with schizophrenia could be followed up and periodic assessment of the event related potential P300 and neuropsychological tests could be done to measure the progress of the illness. This could also be done to see the improvement with the medications in the patients.

2. The unaffected biological siblings of patients with schizophrenia who have a high risk of developing the illness could be followed for early detection of symptoms and treatment. This might improve the prognosis of the illness

3. Specific cognitive remediation tests could be developed to improve specific neuropsychological functions which are very affected in the patients with schizophrenia. They could be used as an adjuvant to medications.

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APPENDIX

PROFORMA

Socio-demographic profile:

Serial number:

Name:

Age:

Sex:

1. Male
2. Female

Education:

1. Profession or Honours
2. Graduate or post graduate
3. Intermediate or post high school diploma
4. High school certificate
5. Middle school certificate
6. Primary school certificate
7. Illiterate

Occupation:

1. Profession
2. Semi-Profession
3. Clerical, Shop-owner, Farmer
4. Skilled worker
5. Semi-skilled worker
6. Unskilled worker
7. Unemployed

Income:

1. ≥32050
2. 16020 – 32049
3. 12020 – 16019
4. 8010 – 12019
5. 4810 – 8009
6. 1601 – 4809
7. ≤ 1600

Marital status:

1. Married
2. Divorcee
3. Single

Socio economic status:

1. Upper
2. Upper middle
3. Lower middle
4. Upper lower
5. Lower

Residence:

1. Urban
2. Semi urban
3. Rural

Type of family:

1. Joint
2. Nuclear

Religion:

1. Hindu
2. Christian
3. Muslim
4. Others

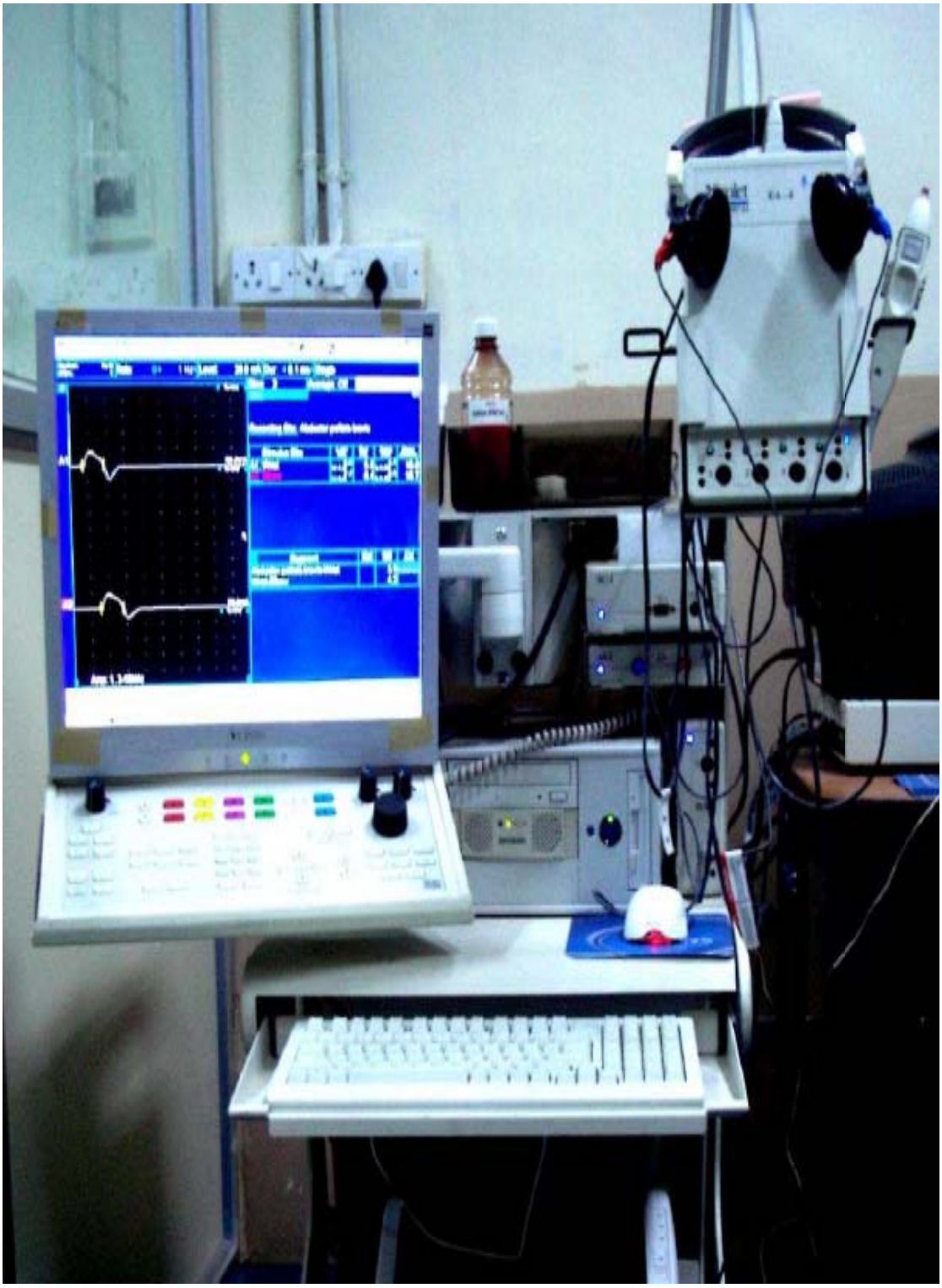
Illness characteristics:

Age of onset of illness (years):

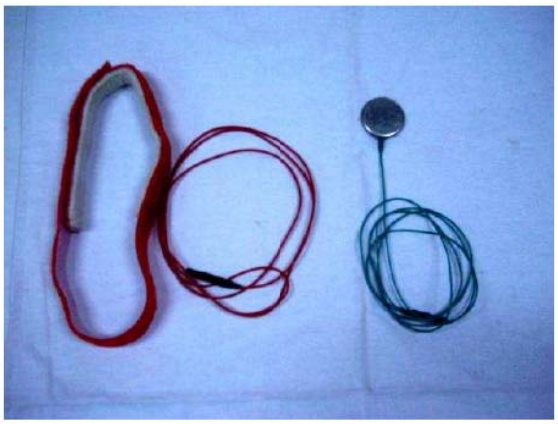
Duration of illness (months):

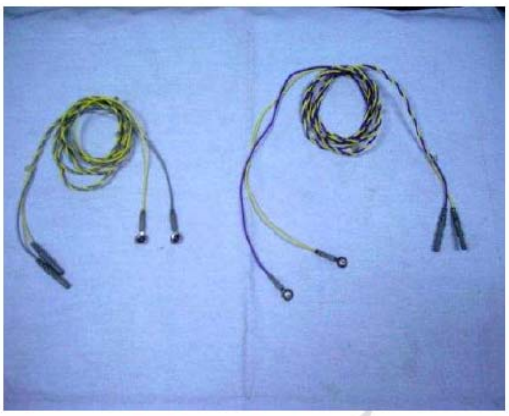
Lag period for treatment (months):

Duration of treatment (months):



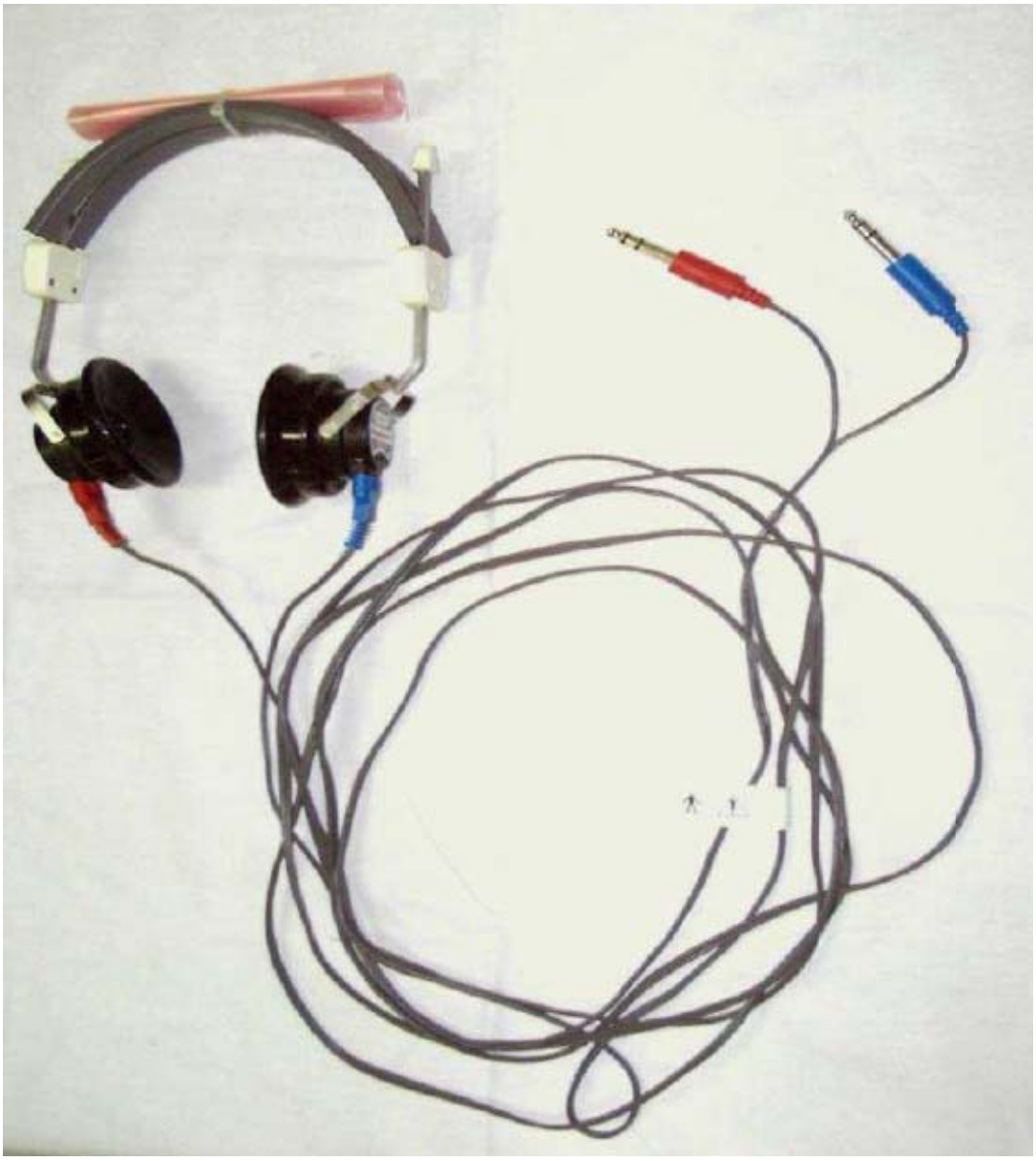
RMS NEURO DIAGNOSTIC SYSTEM TO MEASURE P300 EVENT RELATED POTENTIALS



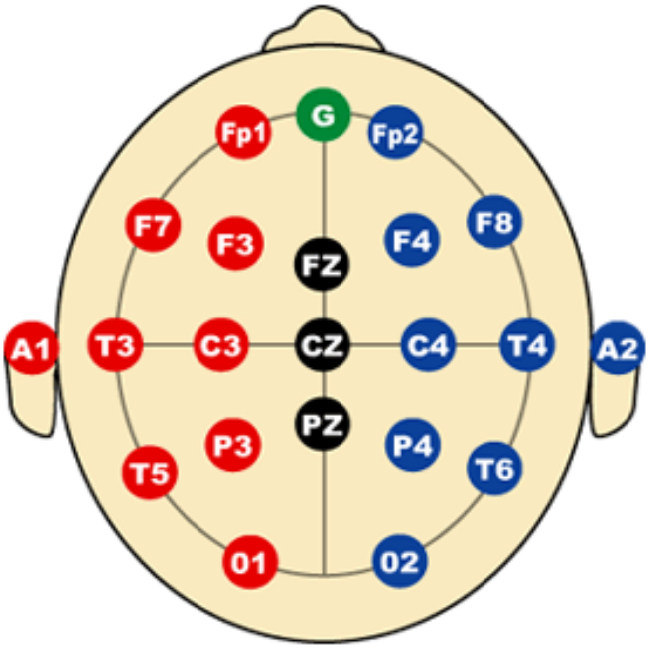


GROUND ELECTRODES AND SCALP ELECTRODES

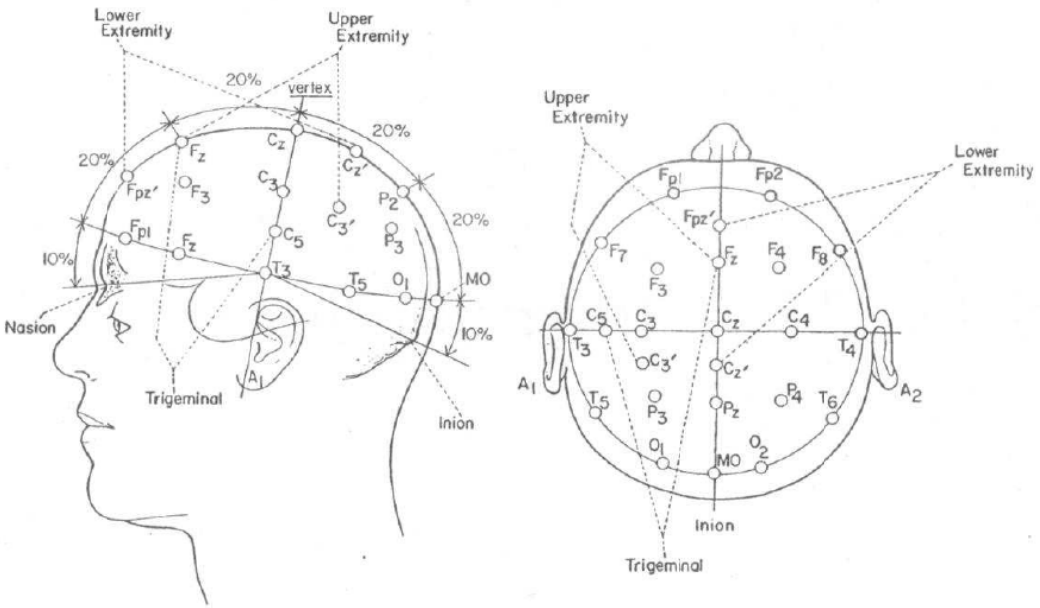
Electrode paste, adhesive tape, electrolyte jelly, skin preparation solution



Ear phone



10-20 INTERNATIONAL SYSTEM



ELECTRODE PLACEMENT SITE

DIGIT SYMBOL SUBSTITUTION TEST

1	2	3	4	5	6	7	8	9
⊢	⊥	⊐	L	U	O	∧	X	=

2	1	3	7	2	4	8	1	5	4	2	1	3	2	1	4	2	3	5	2	3	1	4	6	3

1	5	4	2	7	6	3	5	7	2	8	5	4	6	3	7	2	8	1	9	5	8	4	7	3

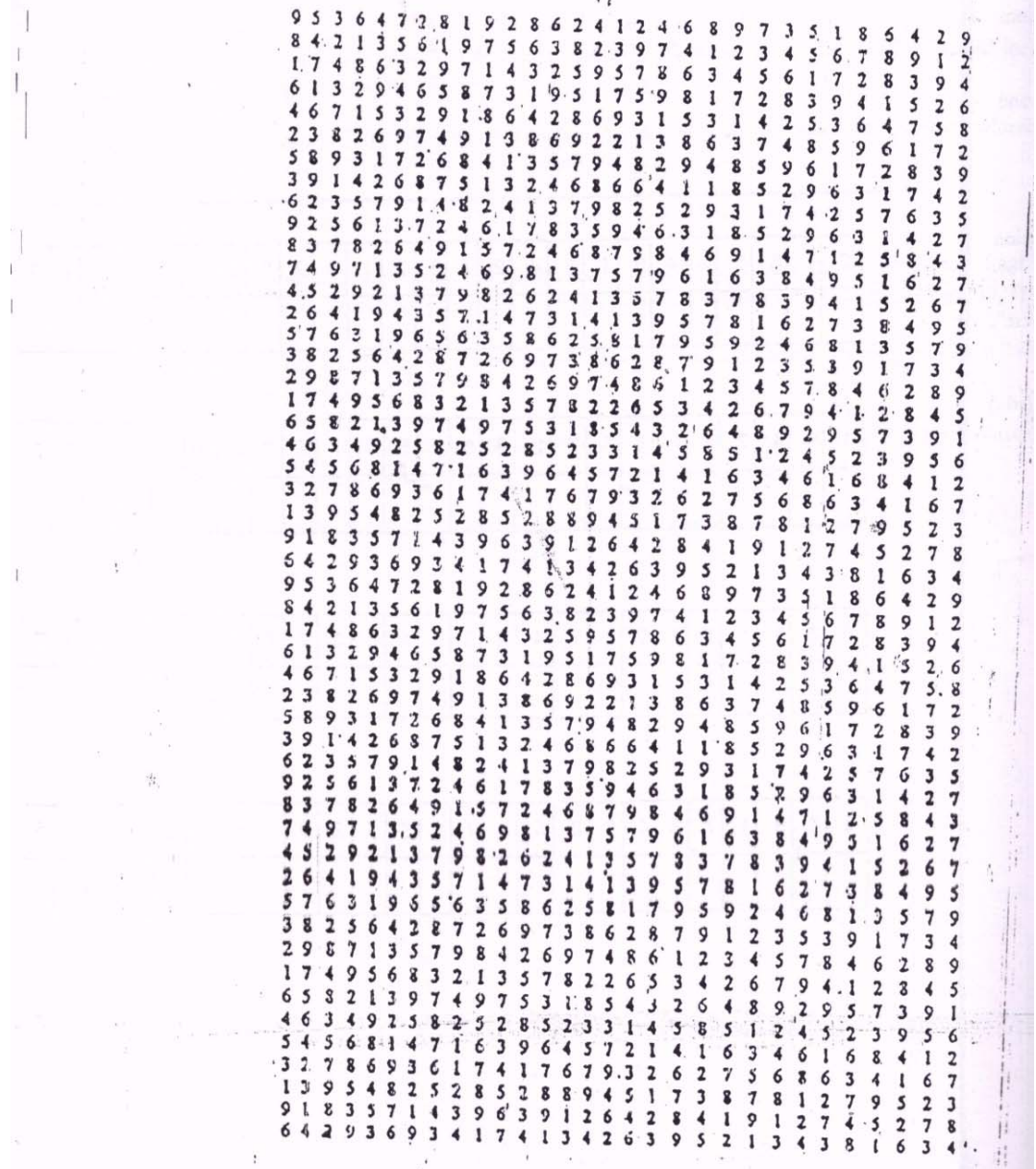
6	2	5	1	9	2	8	3	7	4	6	5	9	4	8	3	7	2	6	1	5	4	6	3	7

9	2	8	1	7	9	4	6	8	5	9	7	1	8	5	2	9	4	8	6	3	7	9	8	6

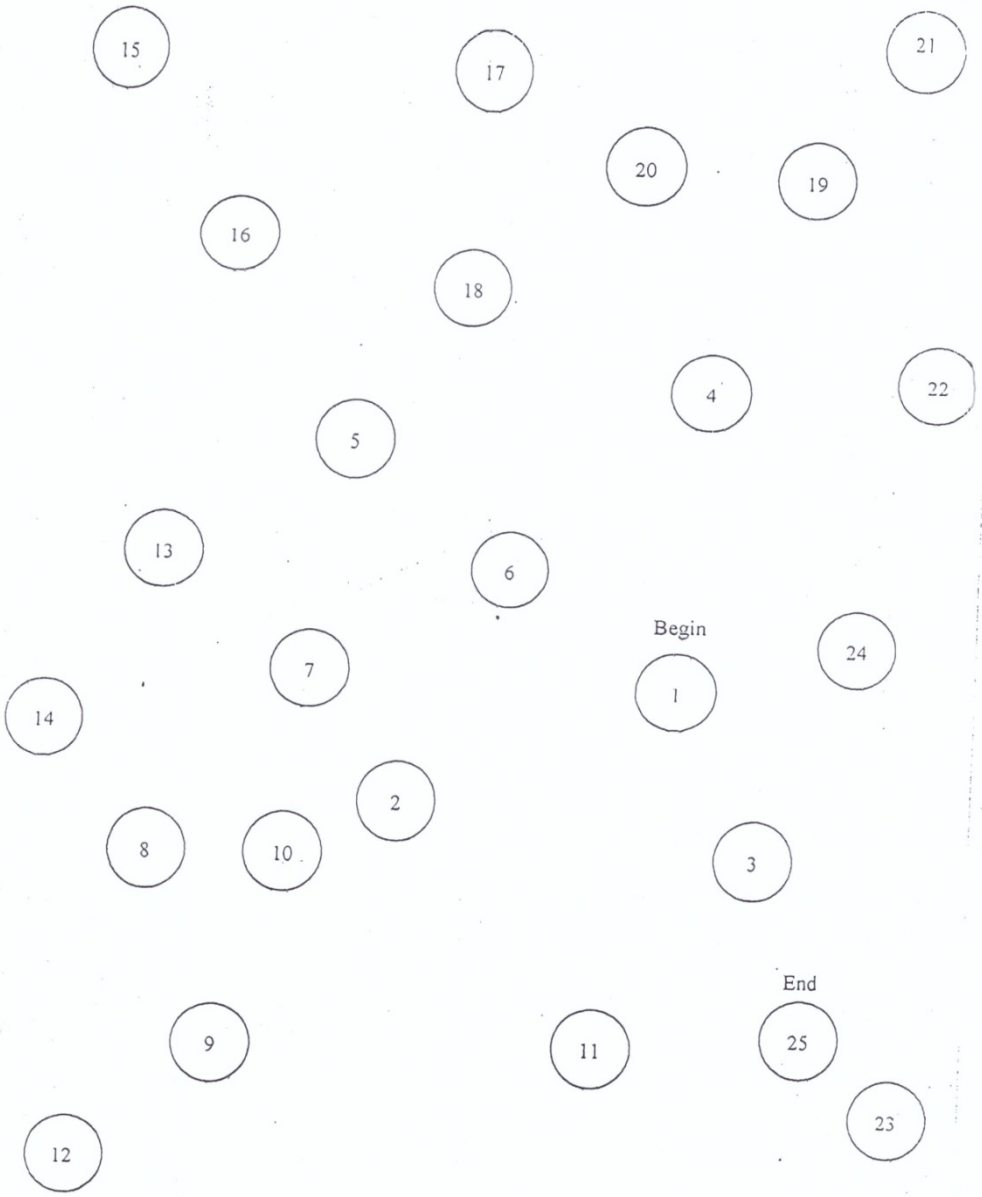
DIGIT VIGILANCE TEST

Serial No. : Name Age. Sex Date

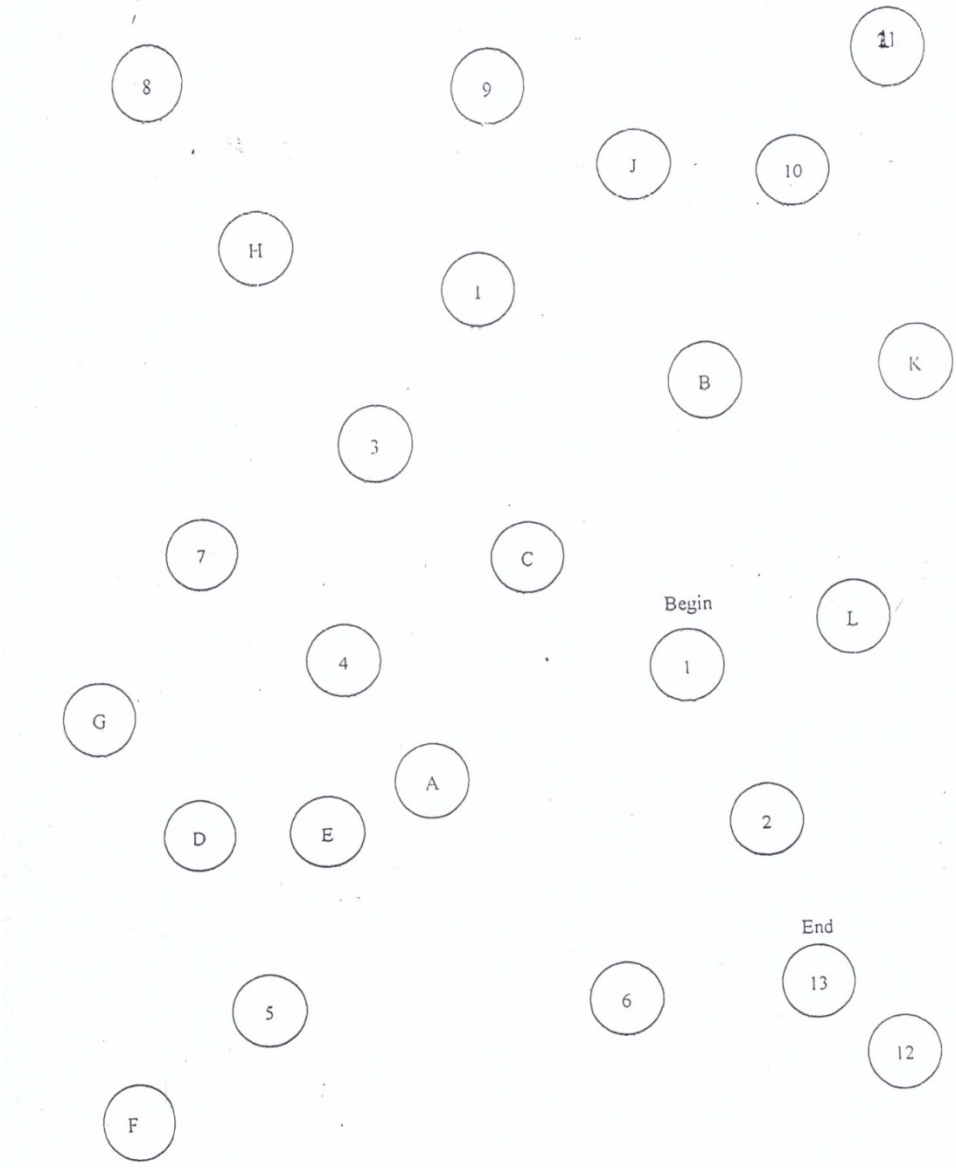
Total Time Errors O C



Trial Making Test -A



Trial Making Test -B



Appendix

VERBAL WORKING MEMORY

1 BACK

1	GA	
2	JA	
3	**JA**	
4	CHA	
5	HA	
6	**HA**	
7	SHA	
8	RA	
9	NA	
10	MA	
11	**MA**	
12	KA	
13	PA	
14	**PA**	
15	LA	
16	VA	
17	TA	
18	**TA**	
19	LA	
20	PA	
21	VA	
22	**VA**	
23	DA	
24	**DA**	
25	CHA	
26	SHA	
27	**SHA**	
28	GA	
29	YA	
30	**YA**	

2 BACK

1	NA	
2	GA	
3	**NA**	
4	MA	
5	LA	
6	JA	
7	LA	
8	MA	
9	KA	
10	LA	
11	**KA**	
12	JA	
13	YA	
14	MA	
15	**YA**	
16	DHA	
17	BHA	
18	**DHA**	
19	VA	
20	SHA	
21	**VA**	
22	GA	
23	**VA**	
24	**GA**	
25	DA	
26	NA	
27	**DA**	
28	CHA	
29	RA	
30	MA	

	H	O	C	ERROR (O + C)
1 BACK				
2 BACK				

RED	BLUE	GREEN	YELLOW	RED	BLUE	YELLOW	RED	BLUE	GREEN	YELLOW	GREEN	RED	BLUE	GREEN	YELLOW
YELLOW	RED	BLUE	GREEN	YELLOW	RED	BLUE	GREEN	YELLOW	RED	BLUE	GREEN	YELLOW	YELLOW	RED	BLUE
BLUE	GREEN	YELLOW	RED	BLUE	GREEN	YELLOW	RED	BLUE	GREEN	YELLOW	RED	BLUE	GREEN	YELLOW	RED
GREEN	YELLOW	RED	BLUE	GREEN	YELLOW	RED	BLUE	GREEN	YELLOW	RED	GREEN	YELLOW	RED	BLUE	GREEN
YELLOW	RED	BLUE	GREEN	YELLOW	RED	BLUE	GREEN	YELLOW	RED	BLUE	GREEN	BLUE	YELLOW	RED	BLUE
GREEN	YELLOW	RED	BLUE	GREEN	YELLOW	RED	BLUE	GREEN	YELLOW	YELLOW	RED	BLUE	GREEN	YELLOW	RED
RED	BLUE	GREEN	YELLOW	RED	BLUE	GREEN	YELLOW	RED	BLUE	GREEN	YELLOW	RED	RED	BLUE	GREEN
BLUE	GREEN	YELLOW	RED	BLUE	GREEN	YELLOW	RED	GREEN	YELLOW	RED	BLUE	GREEN	BLUE	GREEN	YELLOW
RED	GREEN	YELLOW	RED	BLUE	GREEN	YELLOW	RED	BLUE	GREEN	YELLOW	BLUE	GREEN	YELLOW	RED	BLUE
YELLOW	RED	BLUE	GREEN	YELLOW	RED	BLUE	GREEN	YELLOW	RED	RED	BLUE	GREEN	YELLOW	RED	BLUE
RED	BLUE	GREEN	YELLOW	RED	GREEN	YELLOW	RED	BLUE	GREEN	BLUE	GREEN	YELLOW	RED	BLUE	GREEN

ரெட்	புளு	கிரீன்	எல்லோ	புளு	கிரீன்	ரெட்	புளு	ரெட்	புளு	கிரீன்	எல்லோ	ரெட்	புளு	கிரீன்	புளு
எல்லோ	ரெட்	புளு	கிரீன்	ரெட்	ரெட்	புளு	கிரீன்	ரெட்	புளு	ரெட்	புளு	கிரீன்	எல்லோ	ரெட்	எல்லோ
புளு	கிரீன்	ரெட்	புளு	கிரீன்	எல்லோ	ரெட்	புளு	கிரீன்	எல்லோ	ரெட்	புளு	கிரீன்	ரெட்	புளு	கிரீன்
எல்லோ	ரெட்	புளு	கிரீன்	ரெட்	புளு	கிரீன்	எல்லோ	ரெட்	புளு	கிரீன்	எல்லோ	ரெட்	புளு	கிரீன்	எல்லோ
ரெட்	புளு	கிரீன்	எல்லோ	ரெட்	புளு	கிரீன்	ரெட்	புளு	கிரீன்	ரெட்	புளு	கிரீன்	எல்லோ	ரெட்	புளு
கிரீன்	ரெட்	புளு	கிரீன்	எல்லோ	ரெட்	புளு	கிரீன்	எல்லோ	புளு	கிரீன்	ரெட்	புளு	கிரீன்	எல்லோ	புளு
எல்லோ	ரெட்	புளு	கிரீன்	எல்லோ	கிரீன்	எல்லோ	ரெட்	புளு	ரெட்	புளு	கிரீன்	எல்லோ	ரெட்	புளு	கிரீன்
புளு	கிரீன்	ரெட்	புளு	கிரீன்	எல்லோ	கிரீன்	எல்லோ	ரெட்	புளு	கிரீன்	ரெட்	புளு	கிரீன்	எல்லோ	எல்லோ
கிரீன்	எல்லோ	ரெட்	ரெட்	புளு	கிரீன்	எல்லோ	ரெட்	புளு	கிரீன்	எல்லோ	ரெட்	புளு	கிரீன்	எல்லோ	ரெட்
புளு	கிரீன்	ரெட்	புளு	கிரீன்	ரெட்	புளு	கிரீன்	எல்லோ	ரெட்	புளு	கிரீன்	எல்லோ	ரெட்	புளு	கிரீன்
ரெட்	புளு	கிரீன்	எல்லோ	ரெட்	எல்லோ	ரெட்	புளு	கிரீன்	எல்லோ	ரெட்	புளு	ரெட்	புளு	கிரீன்	எல்லோ

INFORMATION TO PARTICIPANTS

TITLE: ELECTROPHYSIOLOGICAL AND NEUROPSYCHOLOGICAL MEASURES IN

PATIENTS WITH SCHIZOPHRENIA AND THEIR UNAFFECTED BIOLOGICAL SIBLINGS:

A FAMILY STUDY

Principal Investigator: VIJAYA RAGHAVAN D

Co-Investigator (if any):

Name of Participant:

Site: MADRAS MEDICAL COLLEGE, CHENNAI

You are invited to take part in this research/ study/procedures/tests. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

What is the purpose of research?

Schizophrenia is a common disorder characterized by cognitive, social and functional impairments. It usually presents as positive symptoms like delusions and hallucinations. These symptoms may last for a long time. Early identification of the disorder and screening tools for the disorder in the general population will be of immense help in finding the vulnerable people and following them up and treating them at the earliest. We want to test the efficacy and safety of a new lab tests this disease/condition.

We have obtained permission from the Institutional Ethics Committee.

The study design

All patients in the study will be divided into three groups. You will be assigned to either of the groups. The three groups will be patients with schizophrenia, unaffected biological siblings of patients with schizophrenia and normal controls who have no family history of any mental illness.

Study Procedures

The study involves evaluation of lab test for which we will be monitoring your EEG and neuropsychological tests. The planned scheduled visits involve visits at two days in a week initial visit. You will be required to visit the hospital two times during the study.

At each visit, the study physician will examine you. EEG or neuropsychological test measures will be collected at each visit. These tests are essential to monitor your condition, and to assess the safety and efficacy of the treatment given to you.

In addition, if you notice any physical or mental change(s), you must contact the persons listed at the end

of the document. You may have to come to the hospital (study site) for examination and investigations

apart from your scheduled visits, if required.

Women of childbearing potential

You must not participate if you are pregnant, breastfeeding a child, or if you are of childbearing potential and not practicing effective methods of contraception (for studies/procedures which may harm the fetus).

Possible risks to you – If any, Briefly mention: In this study, EEG electrode will be place in the scalp

of the participants and the event related potential will recorded, during the placement of the electrode gel

will be used to adhere the leads to the scalp for better conduction. It may rarely cause burning sensation

in the skin, which will subside by itself in few minutes.

Possible benefits to you - If any, Briefly mention: Since the tests in them has a screening potential for the disease, the persons with abnormal scores will be referred for appropriate medical services for further evaluation and treatment.

Possible benefits to other people

The results of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefit to future patients.

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, Institutional Ethics Committee and any person or agency required by law like the Drug Controller General of India to view your data, if required. The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution. You will be taken care of and you will not loose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons. However, it is advisable that you talk to the research team prior to stopping the treatment/discontinuing of procedures etc.

Signature of Investigator Signature of Participant

Date: Date:

Informed consent form

Title of the study - ELECTROPHYSIOLOGICAL AND NEUROPSYCHOLOGICAL MEASURES IN PATIENTS WITH SCHIZOPHRENIA AND THEIR UNAFFECTED BIOLOGICAL SIBLINGS: A FAMILY STUDY

Name of the participant: _____

Name of the Principal/Co-Investigator: VIJAYA RAGHAVAN D

Name of the Institution: MADRAS MEDICAL COLLEGE, CHENNAI

Name and address of the sponsor / agency (ie), if any:

I, _____, have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in the study titled "ELECTROPHYSIOLOGICAL AND NEUROPSYCHOLOGICAL MEASURES IN PATIENTS WITH SCHIZOPHRENIA AND THEIR UNAFFECTED BIOLOGICAL SIBLINGS: A FAMILY STUDY"

(1) I have read and understood this consent form and the information provided to me.

(2) I have had the consent document explained to me.

(3) I have been explained about the nature of the study.

(4) I have been explained about my rights and responsibilities by the investigator.

(5) I have informed the investigator of all the treatments I am taking or have taken in the past months/ years including any native (alternative) treatments.

(6) I have been advised about the risks associated with my participation in the study.✶

(7) I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms.✶

(8) I have not participated in any research study within the past _____ month(s).✶

(9) [I have not donated blood within the past _____months -- Add if the study involves extensive blood sampling]✶

(10) I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in the hospital.✶

(11) I am also aware that the investigators may terminate my participation in the study at any time, for any reason, without my consent.✶

(12) I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Government agencies, and ethics committee. I understand that they may inspect my original records.

(13) I understand that my identity will be kept confidential if my data are publicly presented.

(14) I have had my questions answered to my satisfaction.

(15) I consent voluntarily to participate as a participant in the research study.

I am aware, that if I have any questions during this study, I should contact the investigators. By signing this consent from, I attest that the information given in this document has been clearly explained to me and understood by me. I will be given a copy of this consent document.

For adult participants

Name and signature / thumb impression of the participant (or legal representative if participant incompetent):

(Name) _____(Signature)_____ Date: _____

Name and signature of impartial witness (required for illiterate patients):

(Name) _____ (Signature)_____ Date:_____

Address and contact number of the impartial witness: _____

Name and signature of the Investigator or his representative obtaining consent:

(Name) _____ (Signature)_____ (Date)_____

For children being enrolled in research

Whether child's assent was asked: Yes No (Tick one)

[If the answer to the above question is Yes, write the following phrase:

You agree with the manner in which assent was asked for from your child and given by your child.

You agree to have your child take part in this study.]

[If answer to the above question is No, give reason(s):_____

Although your child did not or could not give his or her assent, you agree to your child's participation in this study.]

Name and signature / thumb impression of the participant's parent(s) (or legal representative):

(Name) _____ (Signature)_____ Date: _____

(Name) _____ (Signature)_____ Date: _____

Name and signature of impartial witness (required if parents of participant child illiterate):

(Name) _____ (Signature)_____ Date:_____

Address and contact number of the impartial witness: _____

_____

Name and signature of the Investigator or his representative obtaining consent:

(Name) _____ (Signature) _____ (Date) _____

ஆராய்ச்சி தகவல் தாள்

தலைப்பு: ஸ்கிசோஃப்ரினியா நோயாளிகள் மற்றும் அவர்களது பாதிக்கப்படாத உடன்பிறப்பகளின் மின் உடலியங்கியல் மற்றும் நரம்பியஉளவியல் அளவுகள் பற்றிய குடும்ப ஆய்வு.

ஆராய்ச்சி செய்பவரின் பெயர்: மரு. விஜய ராகவன் .த

பங்குகொள்வரின் பெயர்:

இடம் : இராஜிவ் காந்தி அரசு பொது மருத்துவமனை, சென்னை- 600003.

ஆராய்ச்சியின் நோக்கம் : ஸ்கிசோஃப்ரினியா நோயாளிகள் மற்றும் அவர்களது பாதிக்கப்படாத உடன்பிறப்பகளின் மின் உடலியங்கியல் மற்றும் நரம்பியஉளவியல் அளவுகள் பற்றிய குடும்ப ஆய்வு நடைபெறுகிறது. நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க விரும்புகிறோம்.

முடிவுகளை அல்லது கருத்துக்களை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆய்வின் முடிவுகளை ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிக்கப்படும் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளரின் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

நாள் :_____

இடம் : _____

ஆராய்ச்சி ஒப்புதல் படிவம்

ஆராய்ச்சியின் தலைப்பு: ஸ்கிசோஃப்ரினியா நோயாளிகள் மற்றும் அவர்களது பாதிக்கப்படாத உடன்பிறப்பகளின் மின் உடலியங்கியல் மற்றும் நரம்பியஉளவியல் அளவுகள் பற்றிய குடும்ப ஆய்வு.

பங்குகொள்வரின் பெயர்:

ஆராய்ச்சி செய்பவரின் பெயர்: மரு. விஜய ராகவன் .த

இடம் : இராஜிவ் காந்தி அரசு பொது மருத்துவமனை, சென்னை- 600003.

_____ எனும் நான், எனக்கு கொடுக்கப்பட்ட தகவல் தாளினை படித்து புரிந்துகொண்டேன். நான் **18** வயதை கடந்திருப்பதால் என்னுடைய சுய நினைவுடனும் மற்றும் முழு சுதந்திரத்துடனும் இந்த ஆராய்ச்சியில் என்னைச் சேர்த்துக்கொள்ள சம்மதிக்கிறேன்.

நான் எனக்கு கொடுக்கப்பட்ட தகவல் தாளினை படித்து புரிந்துகொண்டேன்.

எனக்கு இந்த ஆராய்ச்சியின் ஒப்புதல் படிவம் விளக்கப்பட்டது.

எனக்கு இந்த ஆராய்ச்சியின் நோக்கமும், விவரங்களும் விளக்கப்பட்டது.

எனக்கு என்னுடைய உரிமைகளை பற்றி விளக்கப்பட்டது.

நான் இதுவரை எடுத்துக்கொண்ட அணைத்து மருத்துவ முறைகளைப் பற்றி தெரிவித்திருக்கிறேன்.

இந்த ஆராய்ச்சியில் இருந்து நான் எந்நேரமும் பின் வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் எற்படாது என்பதையும் நான் புரிந்துகொண்டேன்.

என்னை பற்றிய எந்த தகவல்களும் அடையாளமும் வெளியிடபட மாட்டாது என்பதை நான் புரிந்துகொண்டேன்.

என்னுடைய முழு சுதந்திரத்துடனும் இந்த ஆராய்ச்சியில் என்னைச் சேர்த்துக்கொள்ள சம்மதிக்கிறேன்.

பங்கேற்பாளர் கையொப்பம் **ஆராய்ச்சியாளரின் கையொப்பம்**

நாள் : _____

இடம் : _____

S.NO	AGE	SEX	EDUCATION (IN YEARS)	OCCUPATION	INCOME	SOCIOECONOMIC STATUS	MARITAL STATUS	GROUP	RELIGION	LOCALITY	FAMILY TYPE	AGE AT ONSET OF ILLNESS (YEARS)	DURATION OF ILLNESS (MONTHS)	LAG PERIOD FOR TREATMENT (MONTHS)	DURATION OF TREATMENT (MONTHS)	PANSS POSITIVE	PANSS NEGATIVE	PANSS GENERAL PSYCHOPATHOLOGY	PANSS TOTAL	P300 AMPLITUDE Fz (µV)	P300 AMPLITUDE Cz (µV)	P300 AMPLITUDE Pz (µV)	P300 LATENCY Fz (ms)	P300 LATENCY Cz (ms)	P300 LATENCY Pz (ms)	DIGIT SYMBOL SUBSTITUTION TEST, TOTAL TIME (SECONDS)	DIGIT VIGILANCE TEST, TOTAL TIME (SECONDS)	DIGIT VIGILANCE TEST, TOTAL ERRORS	TRAIL-MAKING TEST, PART A (SECONDS)	TRAIL-MAKING TEST, PART B (SECONDS)	TRAIL-MAKING TEST, PART B - PART A (SECONDS)	TRIADS TEST, TOTAL ERRORS	VERBAL N-BACK TEST , 1 BACK HITS	VERBAL N-BACK TEST , 1 BACK ERRORS	VERBAL N-BACK TEST , 2 BACK HITS	VERBAL N-BACK TEST , 2 BACK ERRORS	VISUAL N-BACK TEST , 1BACK HITS	VISUAL N-BACK TEST, 1 BACK ERRORS	VISUAL N-BACK TEST, 2 BACK HITS	VISUAL N-BACK TEST, 2 BACK ERRORS	CONTOLLED ORAL WORD ASSOCIATION TEST, AVERAGE NEW WORDS	ANIMAL NAMES TEST, TOTAL NEW WORDS	STROOP TEST, STROOP EFFECT (SECONDS)
1	25	1	8	4	5	4	1	0	1	3	1									11.5	9.2	7.3	348	381	356	375	636	15	55	118	63	5	8	1	7	2	6	3	4	5	8	13	175
2	25	2	10	4	5	4	1	0	3	1	1									11.6	14.3	10.6	330	336	332	275	548	11	41	81	40	4	9	0	8	1	8	1	5	4	9	15	158
3	27	2	8	7	7	4	1	0	1	1	2									8.3	10.1	8.3	364	371	360	358	618	14	58	120	62	4	9	0	7	2	7	2	4	5	7	12	181
4	35	1	9	6	6	4	1	0	1	1	1									10.2	12.4	9.8	362	355	348	298	579	13	51	108	57	5	9	0	8	1	8	1	4	5	7	12	168
5	33	1	8	6	6	4	1	0	1	2	1									6.4	10.9	9.1	349	376	349	335	607	15	56	111	55	6	8	1	8	1	7	2	4	5	6	16	192
6	27	2	9	7	7	5	1	0	2	1	1									10.1	12.8	10.2	351	358	338	318	598	14	49	100	51	5	9	0	8	1	8	1	5	4	8	11	159
7	26	1	12	5	5	4	1	0	1	1	2									15.8	16.6	11.6	295	296	311	193	397	6	23	52	29	2	9	0	9	0	9	0	7	2	12	16	128
8	30	2	8	7	7	4	1	0	1	1	1									8.9	10.2	8.1	369	385	349	368	626	11	58	98	40	6	7	2	8	1	7	2	4	5	9	10	187
9	30	1	12	5	5	4	1	0	1	2	1									16.4	15.6	12.5	302	295	308	218	518	8	25	51	26	1	9	0	8	1	9	0	6	3	11	12	118
10	26	1	9	6	6	4	1	0	1	1	1									11.3	11.3	10.3	308	348	331	288	583	15	46	86	40	5	8	1	8	1	8	1	5	4	7	14	161
11	31	2	8	7	7	4	1	0	1	1	2									9.6	9.9	8.6	352	371	342	317	667	15	53	108	55	5	9	0	7	2	6	3	5	4	7	13	173
12	25	1	12	4	4	3	5	0	2	1	1									14.8	18.6	10.5	299	286	317	234	435	7	27	56	29	2	9	0	8	1	9	0	6	3	12	10	118
13	28	2	10	5	5	4	1	0	1	1	1									12.1	15.3	10.9	319	330	331	281	531	10	43	84	41	3	9	0	8	1	8	1	6	3	9	12	155
14	34	1	8	5	5	4	3	0	1	1	1									8.1	12.1	6.5	348	369	346	358	627	13	49	118	77	5	9	0	8	1	7	2	5	4	6	12	179
15	25	2	11	4	4	4	5	0	3	2	1									13.8	15.6	10.1	318	318	328	251	592	9	38	68	30	3	9	0	8	1	8	1	6	3	10	14	142
16	28	2	9	5	5	4	1	0	1	1	1									10.4	12.2	9.8	368	345	335	309	617	11	46	89	43	4	8	1	8	1	8	1	6	3	8	14	166
17	26	1	8	7	7	5	1	0	2	1	2									7.6	11.5	8.6	337	381	350	363	673	14	58	102	44	5	8	1	7	2	7	2	5	4	8	16	171
18	26	1	11	5	5	4	5	0	1	1	1									11.9	14.9	10.5	326	215	328	238	498	9	29	81	52	2	9	0	8	1	8	1	6	3	12	12	134
19	31	2	10	7	7	4	1	0	1	1	1									12.1	15.1	11.2	334	338	334	279	539	10	38	85	47	3	9	0	8	1	8	1	6	3	10	16	151
20	27	1	12	5	5	4	1	0	2	3	1									17.2	18.3	12.6	312	281	321	191	445	7	24	66	42	1	9	0	8	1	8	1	7	2	11	13	108
21	32	2	9	6	6	4	1	0	1	1	1									10.4	10.6	9.2	352	358	346	289	617	10	47	89	42	5	9	0	8	1	8	1	6	3	7	15	151
22	32	1	13	4	4	3	5	0	1	2	1									19.1	19.3	12.7	285	275	300	179	397	6	20	50	30	1	9	0	9	0	9	0	7	2	13	13	100
23	28	1	9	6	6	4	1	0	2	1	1									10.5	13.1	10.2	318	343	336	317	583	11	48	106	58	4	9	0	8	1	8	1	5	4	7	12	160
24	32	2	13	4	4	3	3	0	3	1	1									18.9	19.6	13.1	289	278	304	174	385	6	21	55	34	1	9	0	8	1	8	1	6	3	12	13	103
25	27	2	10	7	7	5	1	0	1	1	1									11.5	14.8	10.4	325	318	335	271	553	11	40	88	44	4	9	0	8	1	7	2	6	3	9	12	149
26	31	1	9	7	7	4	1	0	2	3	1									9.9	13.1	10.8	329	344	349	329	591	12	49	96	47	5	9	0	8	1	8	1	5	4	6	13	158
27	33	1	11	5	5	4	1	0	1	1	2									13.2	15.6	11.2	317	327	321	248	437	8	30	76	46	3	9	0	8	1	8	1	6	3	9	12	128
28	28	1	8	6	6	4	1	0	1	1	1									9.3	10.5	8.8	376	366	358	363	611	13	60	104	44	5	8	1	7	2	6	3	5	4	5	13	170
29	26	2	10	5	5	4	1	0	1	3	1									11.6	14.6	9.8	330	309	330	274	548	10	41	80	39	3	9	0	8	1	7	2	5	4	8	14	153
30	26	1	9	6	6	4	5	0	1	1	1									10.3	12.8	9.5	365	349	343	334	579	12	46	91	45	6	8	1	8	1	7	2	5	4	8	11	177
31	31	1	8	6	6	4	1	1	1	1	2									4.1	8.3	4.6	364	400	368	369	728	16	55	112	57	9	8	1	6	3	5	4	3	6	5	9	218
32	31	2	13	7	7	5	1	1	2	2	1									12.9	14.7	11.5	328	300	331	223	450	9	35	81	46	2	9	0	9	0	8	1	6	3	11	15	145
33	29	1	9	5	5	4	1	1	1	1	2									7.1	9.2	9.5	351	376	368	325	693	16	49	108	59	8	8	1	8	1	6	3	4	5	6	10	201
34	25	1	13	5	5	4	5	1	1	3	1									13	13.8	12.9	336	418	339	229	468	12	36	86	50	2	9	0	8	1	7	2	5	4	12	13	150
35	27	1	8	6	6	4	5	1	1	1	2									5.6	6.7	6.2	361	398	365	368	704	19	51	118	67	8	8	1	8	1	5	4	3	6	7	9	223
36	25	2	13	3	4	3	5	1	1	1	1									12.4	14.6	11.9	333	426	369	239	495	11	38	82	44	2	9	0	8	1	8	1	6	3	10	14	148
37	29	1	9	6	6	4	1	1	2	1	2									7.2	10.1	9.2	351	376	352	328	675	16	49	106	57	7	9	0	8	1	5	4	5	4	6	11	216
38	30	1	9	7	7	5	1	1	1	1	1									7.6	9.8	9.6	358	381	361	241	688	15	51	102	51	8	9	0	8	1	6	3	4	5	7	11	222
39	32	2	10	7	7	4	1	1	3	3	1									8.4	10.6	10.2	341	342	355	294	618	15	45	98	53	7	9	0	8	1	6	3	4	5	8	12	198
40	32	1	8	6	6	4	1	1	1	1	2									6.8	7.5	8.2	362	376	359	368	728	17	53	111	78	8	9	0	7	2	6	3	3	6	9	10	211
41	25	2	12	4	4	3	1	1	1	1	2									11.5	13.2	11.9	321	318	362	265	498	13	39	91	52	5	9	0	8	1	7	2	5	4	9	13	156
42	26	1	9	5	5	4	1	1	2	2	1									7.1	10.1	8.4	356	368	354	348	698	16	52	106	54	8	8	1	7	2	6	3	3	6	5	11	210
43	25	2	10	6	6	4	1	1	1	1	2									8.4	10.8	9.3	338	346	361	286	609	14	41	101	60	6	9	0	8	1	6	3	4	5	7	12	200
44	26	1	8	7	7	4	1	1	1	1	1									6.3	7.8	7.5	359	369	342	361	714	17	52	114	62	9	7	2	7	2	5	4	3	6	5	9	234
45	29	2	9	7	7	5	1	1	1	1	2									6.9	9.6	9.5	347	366	349	318	706	16	49	99	50	8	8	1	7	2	5	4	3	6	7	10	228
46	29	2	11	7	7	4	1	1	2	1	1									8.9	11.2	10.6	342	332	345	286	567	12	37	88	51	5	9	0	8	1	7	2	4	5	8	12	183
47	29	1	8	6	6	4	1	1	1	1	2									5.4	6.5	5.7	355	301	370	361	735	19	54	120	66	7	7	2	8	1	6	3	3	6	6	10	244
48	31	2	10	7	7	4	1	1	1	1	1									7.9	10.9	9.6	338	342	352	279	600	16	45	100	55	5	9	0	7	2	6	3	5	4	7	12	181
49	25	2	9	6	6	4	1	1	3	1	2									6.3	9.6	8.5	349	347	359	308	675	16	51	110	59	7	9	0	7	2	5	4	3	6	6	11	202
50	33	1	8	6	6	4	1	1	1	1	1									6.7	8.4	8.1	350	327	361	366	718	17	54	109	55	8	9	0	8	1	5	4	4	5	6	9	231
51	25	2	9	6	6	4	3	1	1	3	2									7.9	10.3	9.2	356	361	362	341	651	15	49	101	52	9	8	1	7	2	5	4	4	5	6	10	206
52	35	2	10	6	6	4	1	1	2	1	1									7.9	10.9	9.9	346	336	320	283	589	15	43	96	53	7	9	0	7	2	6	3	5	4	8	11	195
53	26	1	9	5	5	4	5	1	1	2	2									8.4	9.9	8.5	353	376	363	298	661	14	52	98	46	8	9	0	8	1	6	3	4	5	7	9	221
54	26	2	8	5	5	4	1	1	1	1	1									7.1	9.1	7.4	365	323	369	339	702	15	50	111	61	8	9	0	8	1	5	4	3	6	7	10	252
55	34	2	12	7	7	5	1	1	1	1	1									10.4	12.1	10.9	335	315	331	236	492	11	41	83	42	5	9	0	8	1	7	2	6	3	8	13	169
56	27	1	11	4	4	3	1	1	1	1	2									9.8	12.4	10.1	346	330	342	267	516	13	45	89	44	6	9	0	7	2	7	2	6	3	9	12	187

57	33	2	8	7	7	4	1	1	1	1	1									7.6	6.2	4.8	358	345	351	318	703	16	49	106	57	9	8	1	6	3	5	4	3	6	5	10	223
58	26	2	12	4	4	4	1	1	1	1	2									11.4	10.5	11.8	337	308	343	239	507	13	39	85	46	5	9	0	8	1	7	2	5	4	9	13	158
59	29	2	11	7	7	4	1	1	2	2	1									9.5	11.9	10.2	344	345	349	276	521	13	42	93	51	6	9	0	7	2	6	3	5	4	10	12	164
60	27	1	8	5	5	4	1	1	1	1	1									7.2	7.6	9.1	357	362	368	345	729	16	53	118	65	8	9	0	6	3	6	3	3	6	6	9	248
61	25	2	9	7	7	5	1	2	1	1	1	22	36	12	24	20	14	38	72	3.4	6.8	5.9	381	377	382	356	721	20	60	141	81	9	8	1	5	4	5	4	2	7	6	7	273
62	25	1	9	7	7	4	1	2	1	3	2	21	48	24	24	24	18	46	88	4.1	6.1	6.2	392	381	389	361	734	22	63	138	75	10	8	1	4	5	4	5	3	6	5	6	281
63	25	1	8	7	7	4	5	2	2	1	1	18	84	48	36	23	21	69	113	2.5	5.4	3.2	400	392	395	380	765	23	69	150	81	11	7	2	5	4	4	5	3	6	4	7	296
64	26	2	10	7	7	4	1	2	1	1	1	22	48	12	36	14	19	58	91	4.3	7.8	6.8	365	365	370	326	645	17	54	126	72	9	9	0	5	4	5	4	4	5	7	9	251
65	27	1	11	6	6	4	1	2	1	2	1	23	48	12	36	18	31	33	82	4.9	7.6	7.3	352	358	368	307	618	14	50	116	66	7	9	0	6	3	6	3	4	5	7	10	246
66	35	2	8	7	7	4	2	2	2	1	2	19	192	72	120	21	29	68	118	1.6	6.2	1.5	389	383	381	378	751	19	70	148	78	12	7	2	5	4	4	5	2	7	6	7	294
67	33	1	10	7	7	5	3	2	1	1	1	24	108	36	72	21	28	71	120	4.2	8.1	6.6	368	369	378	321	652	18	55	129	74	9	9	0	5	4	5	4	3	6	6	10	250
68	25	1	9	6	6	4	5	2	1	3	1	20	60	24	36	17	18	47	82	2.9	7.5	5.2	388	377	385	366	701	20	59	138	79	9	9	0	6	3	5	4	3	6	5	9	274
69	25	2	10	5	5	4	5	2	1	1	2	21	48	24	24	19	21	56	96	3.6	7.6	6.8	371	351	371	331	667	19	53	118	65	8	8	1	6	3	6	3	3	6	5	11	255
70	26	1	10	5	5	4	5	2	1	1	1	22	48	12	36	15	23	44	82	5.1	7.1	7.5	356	366	364	338	658	17	55	121	66	8	9	0	6	3	6	3	3	6	6	11	248
71	26	1	9	5	5	4	1	2	1	1	1	22	48	24	24	17	11	44	72	4.2	6.9	6.3	378	379	383	357	749	19	59	136	77	10	8	1	6	3	5	4	2	7	5	8	263
72	31	2	8	6	6	4	3	2	1	1	2	18	156	60	96	19	36	58	113	3.3	6.1	3.4	381	393	389	369	753	22	64	149	85	11	8	1	5	4	4	5	2	7	4	8	289
73	34	1	10	6	6	4	4	2	3	2	1	23	132	36	96	22	27	54	103	5.9	7.5	6.7	366	338	361	346	631	19	58	131	73	9	9	0	6	3	6	3	3	6	6	9	259
74	31	1	9	6	6	4	1	2	1	1	1	22	108	36	72	24	35	76	135	4.5	7	5.2	389	361	374	373	676	20	61	146	85	9	9	0	6	3	5	4	2	7	6	10	273
75	26	2	12	7	7	4	5	2	1	1	1	24	24	6	18	16	14	33	63	6.2	9.6	7.7	341	334	355	298	572	14	46	112	66	7	9	0	8	1	6	3	4	5	9	11	218
76	31	1	10	6	6	5	3	2	2	1	2	26	60	12	48	23	24	35	82	5.5	8.4	7.2	356	371	359	375	618	15	51	128	77	8	9	0	7	2	5	4	3	6	7	10	238
77	33	2	9	7	7	4	3	2	1	3	1	27	72	24	48	28	28	43	99	3.7	6.5	6.2	382	386	363	367	691	17	58	136	78	8	8	1	5	4	5	4	2	7	6	9	256
78	26	1	8	7	7	5	1	2	1	1	1	19	84	12	72	18	32	58	108	2.9	5.4	2.5	391	389	392	371	732	26	61	150	89	10	8	1	4	5	4	5	2	7	4	7	273
79	27	2	13	5	5	4	1	2	3	1	1	25	24	8	16	18	18	38	74	6.9	11.5	11.2	330	330	345	280	526	11	40	108	68	4	9	0	8	1	7	2	5	4	8	12	212
80	28	2	8	4	4	3	1	2	1	2	2	23	60	24	36	24	24	43	91	3.7	7.2	4.7	376	398	386	361	727	22	66	141	75	10	8	1	6	3	4	5	2	7	5	8	288
81	32	1	9	7	7	4	2	2	1	1	1	17	180	84	96	23	39	71	133	3.9	6.6	5.7	368	366	371	346	698	20	61	145	84	9	8	1	5	4	5	4	3	6	5	10	263
82	28	2	12	7	7	4	1	2	1	1	1	23	60	24	36	24	34	54	112	5.6	10.5	10.2	346	348	352	302	583	16	47	119	72	6	9	0	7	2	6	3	4	5	7	11	228
83	32	1	8	7	7	4	1	2	3	1	1	21	132	36	96	24	38	68	130	2.8	3.5	4.3	396	400	376	378	734	19	59	149	90	12	7	2	4	5	5	4	3	6	5	8	251
84	29	2	11	4	4	3	1	2	1	1	2	23	72	36	36	31	14	33	78	5.1	7.9	6.8	355	351	368	313	619	18	46	122	76	8	9	0	6	3	6	3	4	5	7	9	223
85	27	1	9	6	6	4	1	2	1	2	1	22	60	24	36	22	21	48	91	4.3	5.4	5.1	384	369	372	341	678	19	58	138	80	9	9	0	5	4	6	3	3	6	5	12	276
86	30	1	13	4	4	3	5	2	2	1	2	23	84	48	36	23	24	59	106	6.6	10.5	10.5	330	332	349	291	553	11	42	103	61	6	9	0	8	1	6	3	4	5	9	10	233
87	30	2	9	7	7	5	1	2	1	3	1	21	108	24	84	21	32	68	121	2.7	4.5	6.3	375	355	384	368	708	19	55	134	79	10	8	1	5	4	5	4	3	6	5	7	266
88	27	1	8	6	6	5	5	2	1	1	2	22	60	36	24	23	14	46	83	1.9	2.8	5.9	388	371	383	373	725	22	61	138	77	11	7	2	5	4	5	4	2	7	4	8	281
89	32	1	8	6	6	4	1	2	1	1	1	19	156	72	84	14	39	75	128	3.4	3.9	6.1	376	386	386	368	701	20	62	145	83	12	7	2	5	4	4	5	2	7	4	10	298
90	27	2	9	7	7	5	1	2	2	2	2	23	48	12	36	18	21	42	81	4.2	7.5	6.8	392	368	379	333	673	19	62	137	75	10	8	1	4	5	5	4	3	6	4	10	277