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Differences in visual attention processing: An event-related potential comparative analysis within psychotic disorders

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Abstract

Introduction: Sustained attention is known to be dysfunctional in psychotic disorders. Sustained attention is the ability to remain focused on a specific time-locked stimulus within a task. We aimed to determine whether there are specific group differences between CON and three psychotic disorders: SCZ, MPD and BPD, then to determine differences between these psychotic disorders. This included differences in behavioural performance and prominent electrophysiological event-related potential (ERP) wave components during cueing and target processing of a visual sustained attention task. Further we aimed to characterize ERP waveform component relationships across and within these groups for demographics, substance use, behavioural performance, and clinical variables, the last limited to the psychotic groups. Lastly, we investigated the effects of prescribed medications on ERP wave components within the psychotic groups.

Methodology: 103 participants (29 schizophrenia (SCZ), 28 bipolar disorder with a history of psychosis (BPD), 21 methamphetamine-induced psychotic disorder (MPD), and 30 controls (CON)) underwent electroencephalography (EEG) record while completing a visual continuous performance task. Participants were presented with 60 trials with three consecutive S's, the presentation of the third S required a behavioural response. Prominent ERP waveform components were extracted from cues and target stimulus. Group differences were determined by ANOVA with Bonferroni post-hoc correction or multivariate Kruskal-Wallis test dependent on data distribution. Relationships between ERP wave components were determined appropriate with Spearman's Rank order correlation analyses.

Results: (1) MPD reported higher use of substances compared to CON, SCZ and BPD. SCZ behavioural performance was poorer compared to CON which was shown by their longer response times, reduced accuracy and increased errors of omission. Clinically, MPD was found to have a shorter duration of illness compared to SCZ. Then SCZ was found to have more positive symptoms compared to BPD whereas BPD had more negative symptoms compared to SCZ. For the first cue, wave component differences were found only over the left hemisphere, for P100 amplitude over the frontal cortex, P300 amplitude over the central cortex, and N170 amplitude over the parietal cortex. For the presentation of the second cue, differences noted for all groups were localised to the frontal and central brain regions, for P100 and N170 ERP waveforms. For the target stimulus wave component differences were found over the prefrontal, frontal and parietal brain regions, within CON, SCZ, BPD and MPD. (2) For the first cue, education positively correlated with the N170 left parietal amplitude in CON and P300 right parietal amplitude in MPD. During the second cue, the left parietal N170 latency in SCZ correlated positively with education and the left central P300 latency correlated negatively with education in MPD. The age on the day of testing correlated positively with the target left frontal P300 latency in MPD. For the first cue, substance use positively correlated with the left and right parietal P300 latency and negatively for the right parietal P100 amplitude in SCZ. In MPD, a negative correlation was noted across left and right prefrontal N170 and P300 amplitudes, and positive correlation for the left prefrontal P300 latency in MPD. For the target stimulus, correlations were evident for the left and right parietal N70, N170 amplitudes, P300 latency, the right parietal P100 amplitude and left central P300 latency in SCZ. For the first cue, in SCZ PANSS total score correlated positively with left and right central P300 amplitudes and the left parietal P300 amplitude. For the second cue; in MPD, the PANSS negative symptom score, positively correlated with the P100 and N170 left parietal amplitude, left and right parietal P150 amplitude, left central and right parietal P300 amplitude. For the target, the Hamilton depression rating scale correlated positively with the left and right frontal P300 amplitude in MPD and then negatively with the right parietal P300 amplitude in SCZ. Behavioural performance in CON, positively correlated with the left parietal N70, P100, P150 and N170 amplitude the number of correct responses, and left central N170 amplitude. While the number of impulsive responses correlated negatively with the left parietal N70, P100, P150 and N170 and the left central N170 amplitude of CON. For the second cue, behavioural

performance was related to the fronto-parietal relationship across all groups. For the target stimulus, impulsive responses positively correlated with the left parietal N70 latency in SCZ. Overall response time negatively correlated with the right parietal P300 latency for SCZ. (3) Medication was found to affect ERP wave components during the sustained visual attention task. For the first cue FGA's increased the left central P100 amplitude in both SCZ and BPD and decreased the left parietal P100 amplitude in SCZ only. The use of antipsychotics increased the right parietal N70 and left central P100 amplitudes in BPD, specifically the right prefrontal N170 amplitude was increased with the use of SGA's. Then clozapine use increased the left frontal P100 amplitude in SCZ. For the second cue, SGA's decreased the right parietal P150 amplitude in SCZ but in MPD the right parietal P150 amplitude was increased with haloperidol use, and FGA. SGA's increased the left parietal P300 latency in BPD and sodium valproate decreased the left prefrontal P300 latency. For the target stimulus, SGA's decreased the right parietal P100, P150 and left parietal P150 amplitudes and increased the left central P300 latency in BPD.

Conclusion: (1) sustained attentional performance is poorer in SCZ. Our study adds to previous studies showing attention processing deficits in SCZ, are evident during cueing of a sustained attention tasks; (2) substance use was found to slow cognitive processing, education improved executive function and information processing, and symptom severity was associated with dysfunction of prefrontal and frontal cortices; (3) antipsychotic medication was related to improved processing of salient information. These data support the current literature and provide novel insights to the attentional processing deficits during cueing in the psychotic disorders

Table of Contents

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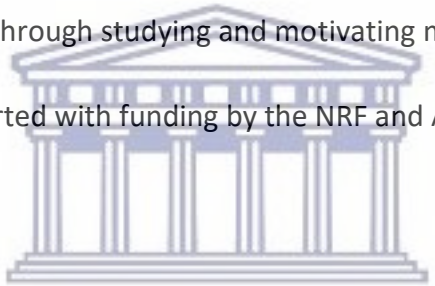


Abbreviations

cm	Centimeters
Hz	Hertz
µV	Microvolts
mm	Millimeters
msec	milliseconds
Ag-AgCl	Silver- silver chloride
Fp_1	Left pre-frontal cortex electrode
Fp_2	Right pre-frontal cortex electrode
F_7	Left temporal cortex electrode
F_8	Right temporal cortex electrode
C_3	Left central cortex electrode
C_4	Right central cortex electrode
P_3	Left parietal cortex electrode
P_4	Right parietal cortex electrode
BPD	Bipolar I disorder with a significant history of psychosis
BMI	Body mass index
CDS	Calgary depression scale
CP	Chlorpromazine
CGI-S	Clinical Global impression severity scale
CPT	Continuous performance task
CON	Controls
DSM	Diagnostic statistical manual of mental disorders
DA	Dopamine
DAT	Dopamine transporter
ECI	Electrode Cap International
EEG	electroencephalography
EMG	Electromyography
EOG	Electrooculography
ERPs	Event- related potentials
FGA	First generation antipsychotics

GAF	Global assessment of functioning
HAM-D	Hamilton depression rating scale
HREC	Health Sciences Research Ethics Committee
HIV	Human- immuno deficiency virus
ICA	Independent component analysis
MA	Methamphetamine
MPD	Methamphetamine-induced psychotic disorder
N	Negative
ANOVA	One- way measures analysis of variance
P	Positive
PANSS	Positive and negative syndrome scale
SCZ	Schizophrenia
SGA	Second generation antipsychotics
GUI	Simple graphical user interface
SCID-DSM-IV	Structured Clinical Interview for Diagnostic Systematic Manual- IV
ASSIST	The Alcohol, Smoking and Substance Involvement Screening Test
TSI	Total substance involvement
YMRS	Young Mania Rating scale

List of figures

Figure 3.3 Grand mean event-related potentials of the target stimulus for the continuous performance task (-200 msec prior and 800 msec post presentation) for bilateral pre-frontal (Fp1 and Fp2), frontal (F3 and F4), central (C3 and C4), and parietal (P3 and P4), left and right electrodes respectively. *Differences in P100 waveform (50-150msec) left frontal P100 amplitude (F3) in SCZ > CON and SCZ > BPD. however, post hoc analysis did not show any specific group differences for right frontal N70 latency (F4). @Differences were found for N170 waveform (100-250msec) latency and amplitude; the left prefrontal latency (Fp1) and CON < MPD. The right prefrontal (Fp2) amplitude in SCZ > CON, SCZ > BPD and SCZ > MPD. The left frontal amplitude (F3) in CON < SCZ; right frontal amplitude (F4) in CON < SCZ.# Differences were found for P300 waveform (200-400msec) right prefrontal P300 latency (Fp2) was specifically shorter for CON < SCZ and CON < MPD. CON – control; SCZ-schizophrenia; BPD- bipolar with a history of psychosis; MPD- methamphetamine-induced psychotic disorder. Significance P<0.05.....52

List of tables

Chapter 1 Literature review

1.1 Background

Mental illnesses have been around for centuries; however it was not until the nineteenth century that they were contextualised and characterised by symptom(s) and course (Farreras, I. G, 2017). By the twentieth century research into the etiology of psychiatric disorders became increasingly important (Kessler 2000). There have been continual improvements in the clinical diagnostics as can be seen in the revisions of the diagnostic statistical manual of mental disorders (DSM) (American Psychiatric Association 2013b), and are seen to aid treatment approaches (Saddichha et al. 2008). Current psychiatric medications serve to manage symptoms, e.g. antipsychotic medication in the treatment of psychosis, rather than a cure thereof (Perez et al. 2016). This limitation has led to new approach to psychiatric disorders where we search for biological mechanisms, with the hope of improving treatment regimens and development of new drug treatments, to ultimately improve patient prognosis (The National Institute of Mental Health 2015).

Schizophrenia spectrum disorders, i.e. psychotic disorders (Trotman et al. 2013), are known to affect 1% of the world's population (Mandelli et al. 2014; Rudolph et al. 2015). Psychosis is the active state of a psychotic disorder whereby the person undergoes an episode of severe behavioural changes, impaired cognitive functioning and a distorted sense of reality (Quach et al. 2016). Psychosis significantly reduces individuals' ability to make good judgements, alters the ability to think clearly, behave appropriately and function (Serper & Berenbaum 2008). The typical characteristic symptoms of psychosis experienced are hallucinations and/ or delusions which they believe are real (Quach et al. 2016). Importantly psychosis are not only symptoms related to hallucinations/delusions, referred to as positive symptoms, but these individuals also experience negative symptoms, e.g. social withdrawal, and cognitive symptoms which greatly impact daily activities and are a burden to the individual and family members involved (Perez et al. 2016). Approximately 21 million individuals are diagnosed with schizophrenia (SCZ) (World Health Organization 2008). SCZ does not affect a specific race or nationality (Chong et al. 2016), and occurs equally in men and females. However the peak age of onset in females occurs 5- 7 years later than males; 10–25 years in males and 25–35 years in females (Tandon et al. 2013; Hu

et al. 2016). The exact reason to why this occurs is not completely certain (Hu et al. 2016). Some hypothesize that the later onset of SCZ in females is due to the hormones present in women during puberty, and protective effect of the hormone estrogen (Erick Messias, Chuan-Yu Chen 2009; Kirkbride et al. 2012; Perez et al. 2016).

Patients diagnosed with SCZ can be hospitalized several times in their lifetime (Erick Messias, Chuan-Yu Chen 2009). A drop in re- hospitalisation has been seen with good clinical management and support from family (Mccormick et al. 2015). It is reported that up to 10% of patients diagnosed with SCZ commit suicide (Rössler et al. 2005), the development of persecutory delusions and use of substances of abuse, e.g. cannabis, have been shown to increase violence in SCZ (Spitzer et al. 1978).

The presentation of psychosis is not limited to the schizophrenia spectrum of disorders, and can also be apparent in Bipolar disorder (BPD) and methamphetamine-induced psychotic disorder (MPD) (Grant et al. 2012; Soh et al. 2015). Like SCZ, BPD is a challenge and a lifelong struggle which affects the individual as well as their family (Hall et al. 2014). BPD, previously known as manic- depressive illness is a psychiatric disorder which classically presents with polarity of mood, i.e. mania and depression (Laxman et al. 2008). Individuals with BPD may also present with both mood polarities at one time and this is referred to as a mixed episode (Johnson & Leahy 2003). The presentation of psychosis in BPD can present in any mood state or episode, or when euthymic, i.e. stable mood state (Park et al. 2004). There are no restrictions to the race, nationality, social or educational class of an individual (Young & Grunze 2013). BPD affects 60 million individuals worldwide (World Health Organization 2017), it is expected that individuals with a diagnosis of severe BPD will spend 20-50% of their lifetime in care (Young & Grunze 2013), due to cyclical nature of the disorder (0.4 episodes per year) (Ayano 2016), with episodes typically lasting between 2 to 7 months (Young & Grunze 2013). A higher incidence of suicide, greater than 10%, is reported for BPD (Price & Marzani-Nissen 2012; Ayano 2016). Patients diagnosed with BPD are typically between the ages of 17 and 21 years old (Ayano 2016), and generally chronic, i.e. lifelong (Mccormick et al. 2015). There are some cases where BPD starts in childhood but the diagnosis is difficult as the symptoms can present as attention deficit hyperactivity disorder or as other developmental disorders (Johnson & Leahy 2003). There is no bias to whether more men or women are being diagnosed with BPD (Price & Marzani-Nissen

2012). However, it was found that more women experience a higher number of depressive episodes and men experience a higher number of manic episodes (Ayano 2016).

With respect to methamphetamine (MA), in the Western Cape of South Africa 33% of individuals are reported to have used methamphetamine, and 15% of psychiatric hospital admission are a result of MA psychosis (Corrigall et al. 2007; Lategan et al. 2016). MPD in the Western Cape exceeds reports from Asia, reported to be 10% (Farrell et al. 2002), worldwide 16 million people are reported to use MA (Bousman et al. 2009). One out of every four individuals using MA are female (Bousman et al. 2009; Zarrabi et al. 2016). The high incidence of MA abuse has been related to its recreational use or individuals testing the product and ultimately enjoying the high and eventually becoming addicted to the drug. The high levels of MA can cause; pulmonary oedema and congestion, heart failure and cerebrovascular haemorrhage, ultimately leading to death (Petit et al. 2012). The clinical presentation of psychosis in MPD is very similar to that of SCZ (Glasner-Edwards & Mooney 2014).

1.2 Diagnostic criteria for schizophrenia, bipolar disorder and methamphetamine induced psychotic disorder

Diagnostically the psychotic disorder spectre comprises of: schizophrenia, brief psychotic disorder, schizotypal personality disorder, delusional disorder, schizophreniform disorder, schizoaffective disorder, catatonic, substance or medication induced psychotic disorder and psychosis due to a general medical condition (Mandelli et al. 2014). An example of substance -induced psychosis is MPD (Rusyniak 2012). Further, Bipolar I disorder may present with psychosis or psychotic symptoms, and some view Bipolar I as a psychotic disorder (Craddock et al. 2005).

1.2.1 Schizophrenia diagnosis

SCZ has an array of symptoms linked to it which are divided into three categories: positive, negative, and cognitive disturbances (Hill et al. 2010). The positive symptoms include: (1) delusions which can present as religiosity, paranoia, ideas of reference, thought disorder, thought control, or grandiosity; (2) hallucinations which can be present via any sense, predominantly visual and auditory, however patients may present with tactile, olfactory, or

gustatory. The negative symptoms include: apathy, absent, blunted or incongruous emotional responses, reductions in speech, social withdrawal, impaired attention, anhedonia, and sexual problems (American Psychiatric Association 1994). According to the DSM IV, if the patient presents with auditory hallucinations or bizarre delusions they will likely receive a diagnosis of SCZ (American Psychiatric Association 1994). Prior to the onset of symptoms, social and occupational dysfunction can occur, these are referred to as prodromal symptoms. Prodromal symptoms generally appear 1-6 months prior to psychotic episode, however this period can also be longer. The onset occurs between the age of 15 and 45 years of age (Tandon et al. 2009), onset beyond 45 years old has been linked to neurodegeneration and aging (Chan 2017).

1.2.2 Bipolar disorder

BPD is a mental illness characterized by severe depression along with elevated or irritable mood states, i.e. mania (Anticevic et al. 2015). BPD was first known as a mood disorder as individuals presented with alterations in mood whereby periods of euphoria is achieved with a sudden change to major depression (Young & Grunze 2013). BPD is separated into two diagnostic categories; bipolar disorder type I and bipolar disorder type II. BPD type I is the more severe of the two. BPD type I patients display full mania alternating between periods of depression (Khaleghi et al. 2015). BPD type II differs to BPD type I due to the absence of a full manic episode, as they experience hypomanic episode which are not as severe (Ayano 2016), and do not necessarily require hospitalization (Mccormick et al. 2015). Manic states are accompanied by pressured speech, altered sleeping patterns due to a decreased need for sleep, increased libido, grandiosity, reckless behaviour and severe thought disturbances with the presence or absence of psychosis (Mccormick et al. 2015).

1.2.3 Methamphetamine- induced psychotic disorder

Methamphetamine (MA) also known by its many street names; speed, ice, kryptonite and crystal meth, is a drug which stimulates the central nervous system (Buxton & Dove 2008; Petit et al. 2012). It was originally synthesized as an ephedrine in the early 1900's. It was only in the late 1960's that the drug become heavily abused in California through backyard MA laboratory production. The drug is presented as a powder or liquid and a more potent form of the drug was developed which was in the form of crystals (Petit et al. 2012). MA

can be ingested orally, through nasal insufflation/ snorting, vaginally and rectally, through intravenous injection, and via the inhalation of smoke vapours (Allerton & Blake 2008). Users of MA also describe to feel increased libido, endless energy, and increased productivity. Tweaking can be experienced, which refers to hallucinating crawling insects on the skin, which can result in scratching and picking skin resulting in scabs and scarring (Petit et al. 2012). Tweaking is more noticeable in long term MA users where dose of use has been escalated to achieve the desired effect of the drug (Buxton & Dove 2008). When the effects of MA wear off, feelings of anxiety and depression kick in (Scott et al. 2007).

As per DSM-IV, after intoxication and withdrawal if psychotic symptoms persist between 1 and 4 weeks the diagnosis MPD may be given (American Psychiatric Association 1994). The presentation of psychosis has been linked to heavy drug use however can also be present with low MA abuse, and is suggested to stimulate an underlying psychotic disorder (Perry & Juhl 1977; Hermens et al. 2009; Shariat & Elahi 2010; Zarrabi et al. 2016).

Individuals admitted to psychiatric hospitals for MPD tend to be re- diagnosed with SCZ if they present with another psychotic episode that cannot be related to the use of MA, after 6 months of having their first psychotic episode (American Psychiatric Association 1994). This change in diagnosis is largely due to the similarity of symptoms between SCZ and MPD (American Psychiatric Association 1994). Bell, conducted a clinical study which involved fourteen cases of patients diagnosed with SCZ who were actively using MA at regular intervals for years. It was found that after years of MA use, similarities in presentation between MPD and SCZ were evident (Bell 1965). The symptoms of psychosis lasted for months following the initial diagnosis. After observation, Bell concluded that MPD produces a model of psychosis similar to SCZ than that produced by any other hallucinogenic drug (Bell 1965). In the recent years many other studies have investigated the similarities between MPD and SCZ. Supporting Bell, several studies report similarities between positive symptoms of SCZ in MPD (Hermens et al. 2009; Shariat & Elahi 2010; Bramness et al. 2012; Medhus et al. 2015; Barnhorst 2015; Zarrabi et al. 2016; Paulus 2017). An interesting caveat, is the reported similarity between BPD and MPD, as delusions of grandeur and aggression are often reported in both (Zarrabi et al. 2016).

1.3 Dopamine in psychotic disorders

In psychiatric disorders, neurotransmission is dysfunctional, medication prescribed aims to improve neurotransmission (Mikkelsen et al. 1987; Gil-da-Costa et al. 2013). In psychosis and psychotic illnesses, the dopamine systems are strongly suggested to be the primary neurotransmitter system that is dysfunctional (Mikkelsen et al. 1987), and primary drugs, antipsychotics which act on the dopamine systems are prescribed.

The dopamine (DA) system is important in the control of muscle movement, cognitive function and reward mechanisms (Gurevicha et al. 2016). DA, a monoamine, is synthesized within dopaminergic neurons. Once the neuron is excited DA is released from the neuronal terminal via exocytosis into the synapse and acts by; binding to the post-synaptic DA receptors (D_1 receptor), then regulated by pre-synaptic neuron DA auto-receptors (D_2 receptor), and recycled by re-uptake at pre-synaptic neuron via dopamine transporter (DAT) (Jan 2013). Methamphetamine stimulates the dopaminergic systems in four ways: (1) directly stimulates dopamine receptors and with higher affinity; (2) increases the release of dopamine; (3) prevents and reverses dopamine reuptake; (4) reduces the breakdown of DA and MA by reduction of monoamine oxidase (Jaber et al. 1996; Paulus 2017).

The DA system consists of four different pathways; mesolimbic, mesocortical, nigrostriatal and tuberoinfundibular. Both mesolimbic and mesocortical pathways originate from the ventral tegmental area in the brainstem and are important in cognitive regulation and function (Emilien et al. 1999). Positive symptoms in schizophrenia are thought to be caused by increased dopamine in the mesolimbic pathway (Guzman & Farinde 2016). The dysfunction of the mesocortical pathway is associated with cognitive decline and negative symptoms in schizophrenia (Guzman & Farinde 2016). The onset of negative symptoms and cognitive decline is said to be from the reduced activation of the D_1 receptor in the prefrontal cortex (Brisch 2014). The nigrostriatal pathway is involved in controlling muscle movement by regulating the release of dopamine to the neostriatum (Jibson 2017). The process occurs from the transport of DA from the substantia nigra to the neostriatum. By stopping the release of DA to the neostriatum with DA antagonists, extrapyramidal symptoms especially Parkinsonism become apparent. Within the tuberoinfundibular pathway DA inhibits the production of prolactin inhibiting factor. The DA produced within

the hypothalamus and transported to the pituitary gland via the tuberoinfundibular pathway. Therefore, the blocking of the D_2 receptors results in an increase in the production of prolactin from the pituitary gland, causing hyperprolactinemia (Guzman & Farinde 2016).

A primary theory which addresses the development of schizophrenia states that symptoms of schizophrenia are caused by overactive neuronal activity which is highly dependent on dopamine – the dopamine hypothesis of schizophrenia (Spitzer et al. 1978; Basset et al. 2014). This theory suggests that elevated dopamine activating the D_2 receptors results in more positive symptoms in SCZ and decreased activation of D_1 receptors results in more negative symptoms and cognitive dysfunction (Spitzer et al. 1978; Zacher & Holmes 2012; Brisch 2014).

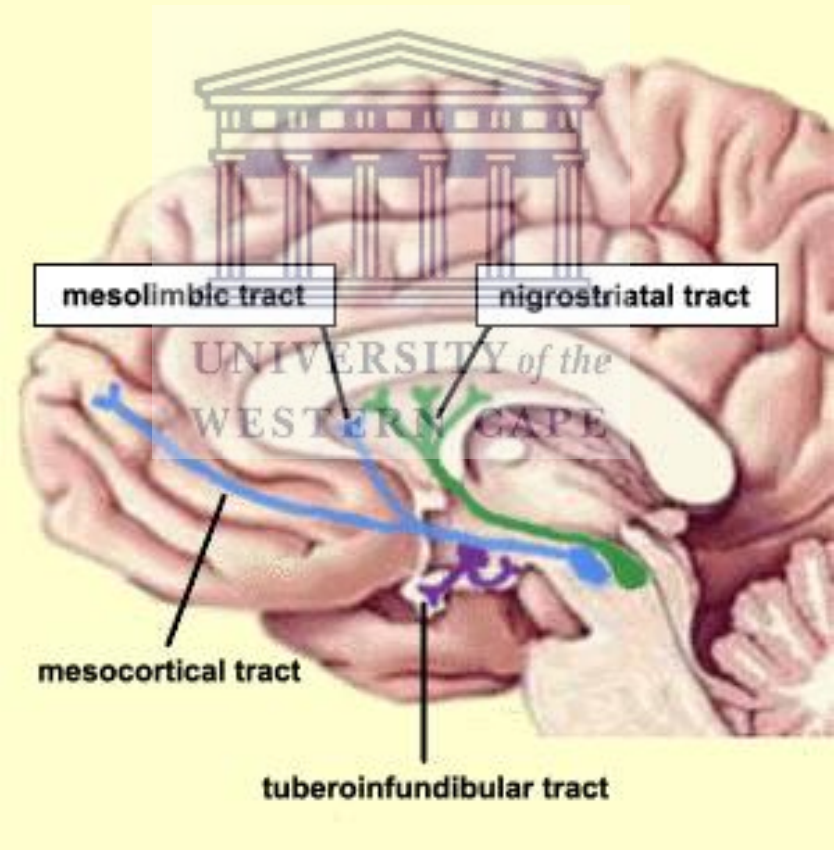


Figure 1.1 Dopaminergic pathways. Dopamine is produced and released via four different pathways: mesolimbic tract, mesocortical tract, tuberoinfundibular tract and the nigrostriatal tract. Source of image from (S. M. Stahl 2008).

DA has two families of receptors; D_1- like dopamine receptor family and D_2- like dopamine receptor family (Shin & Chung 2012). The D_1-like dopamine receptor family consists of D_1

and D_5 receptors whereas the D_2-like dopamine receptor family consists of D_2, D_3, and D_4 receptors (Gurevicha et al. 2016). Both D_1 and D_2 receptors are the most abundant DA receptors (Jaber et al. 1996; Gurevicha et al. 2016). D_1 receptors have been linked to cognitive impairment when too much DA is release (Stigge-Kaufman 2005). It is known that cognitive dysfunction is a core feature in patients diagnosed with SCZ (Li et al. 2016). A relationship between increased DA binding to the prefrontal cortex D_1 receptors and cognitive dysfunction has been found in patients diagnosed with SCZ (Brisch 2014).

The D_2 receptors are G protein family receptors which functions in intracellular signal transduction to regulate DA concentration within the neuron (Emilien et al. 1999; Zhen et al. 2015). Dysfunction of the D_2 receptor has been found to increase dopamine concentration in psychiatric disorders such as SCZ and depression (Schwalbe et al. 2017). This is supported by the remission of psychotic symptoms with administration of first generation antipsychotics (FGA, also referred to as typical antipsychotics) and second generation antipsychotics (SGA, also referred to as atypical antipsychotics) (Saddichha et al. 2008), which primarily and selectively block the dopamine D_2 post synaptic receptors in the brain (Sampaio et al. 2017). Most FGA prescriptions are for the blocking of D_2 receptors to effectively target the positive symptoms of SCZ. However the blocking of D_2 receptors by FGA's can cause too little DA to be taken up thus resulting in negative symptoms (Li et al. 2016).

1.4 Pharmacological treatment of psychosis

The first antipsychotic medication, chlorpromazine (CP) (Drake & Mueser 2002; Gowda et al. 2017), a typical antipsychotic (FGA), was developed in the 1950's, aside serving as a chronic medication it is effective in emergency situations and upon admission to calm actively psychotic patients (Abou-Setta et al. 2012; Campillo et al. 2015). Specifically, CP attenuates acute psychotic symptoms including agitation and excitement, as well as attenuating positive symptoms, i.e. hallucinations and delusions (Ban 2007). CP is considered to be a low- potency FGA as it has a lower risk of side effects compared to other FGA's, e.g. haloperidol (Jibson 2015). FGA's such as CP and haloperidol act by inhibiting the Cytochrome P450 2D6 enzyme interrupting DAT, thus calming an agitated patient (Campillo et al. 2015; Jibson 2015). Cytochrome P450 2D6 is an enzyme which metabolizes both m-

tyramine and p- tyramine, hydroxytryptamines and neurosteroids into dopamine in the brain and liver (Wang et al. 2009).

FGAs have been shown to suppress the positive symptoms (i.e. hallucinations, delusions and disorganization) of SCZ (Hill et al. 2010). However, studies have shown that high doses of FGA's i.e. chlorpromazine can also worsen cognitive performance (Weickert & Goldberg 2005; Hill et al. 2010). Aside the mode of action in antagonizing the D_2 receptors, chlorpromazine is also a potent muscarinic receptor antagonist (Jibson 2015). The action of chlorpromazine antagonizing the muscarinic receptors and D_2 receptors, can cause potential cognition slowing (Weiss et al. 2002). Psychiatric patients who were prescribed lower dosages of FGA showed mild to moderate cognitive improvement, a reduction in speed and motor performance was still noted (Weickert & Goldberg 2005).

Treatment with FGA can result in the development of extrapyramidal side effects (Divac et al. 2014). *In vitro* studies conducted to understand the mechanisms of FGA's showed that when more than 80% of the D_2 receptors are blocked with antipsychotic medications, extrapyramidal side effects are present (Ananth et al. 2001). These extrapyramidal side effects in FGA can include; rigidity, bradykinesia, tremor, akathisia and tardive dyskinesia (Jibson 2015). The understanding of how extrapyramidal side effects are caused was found by conducting *in vivo* animal studies, by injecting with a D_2 receptor antagonist, which induced the rats to catalepsy state (Ananth et al. 2001).

Anticholinergics (i.e. orphenadrine) help to counter or reduce the extrapyramidal side effects (Hill et al. 2010). This occurs by the blocking of muscarinic receptors with anticholinergic drugs, thus preventing the acetylcholine activity and decreasing muscle rigidity and tremor (Rehse et al. 2016). It has also been used in the treatment of parkinsonism due to the muscle relaxant properties (Campillo et al. 2015; Lertxundi et al. 2017). Parkinsonism occurs as a result of substantia nigra striatal dopamine degeneration resulting in the bradykinesia, tremor and rigidity seen in some patients suffering from this side effect (Emilien et al. 1999; Shin & Chung 2012). Even though anticholinergics help counter the side effects of FGA's, it has its' own disadvantages. Anticholinergics can cause side effects which include; dry or sticky lips, pale and cool dry skin, urinary disorders, increased anxiety, rapid breathing, cardiac arrhythmia, tachycardia and shallow breathing

(Mintzer & Burns 2000; Hu et al. 2016). Then the use of anticholinergics in combination with FGA's have been shown to cause adverse effects on cognitive function (Hill et al. 2010). Further, high doses of FGA's can be fatal which stimulated the development of a new line of antipsychotics, atypical antipsychotics (SGAs) having reduced extrapyramidal side effects (Jibson 2015; Jibson 2017; Sampaio et al. 2017).

SGA's are atypical antipsychotics which were modelled from the FGA chlorpromazine (Divac et al. 2014). SGA's were developed in the 1980's, e.g. risperidone and olanzapine (Watanabe et al. 2010; Abou-Setta et al. 2012) which are effective in the treatment of positive and negative symptoms within SCZ, bipolar mania, acute agitation and other psychiatric conditions such as major depression (Zhang et al. 2013; Jibson 2017). SGA's function by acting as a serotonin- dopamine antagonist (targeting the 5-HT_{2A} receptor) and a D_2 receptor antagonist (Hill et al. 2010; Mauri et al. 2014; Guzman & Farinde 2016). Compared to FGA's, SGA's bind with lower affinity to the D_2 receptors (Ananth et al. 2001). In a situation where hallucinogens (i.e. lysergic acid diethylamide or LSD) is used, psychotic symptoms can present and persist (Geyer & Vollenweider 2008). In the case where a patient is presenting with psychosis as the result of 5- HT_{2A} hallucinogen, serotonin antagonists can be prescribed to reduce the presence of psychotic symptoms (Pytliak et al. 2011). Of the current SGA's available, risperidone was found to have a higher risk of extrapyramidal side effects (Jibson 2017). Other SGA's such as clozapine, and quetiapine are known to have anticholinergic properties (Jibson 2017). Quetiapine is used as a first line treatment in BPD and SCZ (Gianfrancesco et al. 2005; Calabrese et al. 2017) and has a high affinity for muscarinic receptors and low affinity for D_2 receptors (Nielsen et al. 2015). Quetiapine was found to decrease stress induced cell proliferation in the hippocampal region in the brain of patients suffering from a psychiatric disorder (Rief et al. 2016). Clozapine, compared to quetiapine, is generally used as a last choice antipsychotic treatment especially for patients who are not responding to first line treatments (Marder et al. 1991). The side effects of clozapine extend even further; induced ocular blindness is a side effect of clozapine which can fortunately be reversed through treatment with risperidone (Gowda et al. 2017). However, cardiometabolic adverse effects and weight gain, remain a concern for SGAs (Jibson 2017). The cardiovascular diseases associated with psychiatric disorders are caused by the induction of vasodilation and natriuresis (Emilien et

al. 1999). When increased levels of DA are released into the blood stream, stimulation of the α-adrenergic receptors occurs causing a rise in blood pressure. Due to the increase in cardiovascular diseases and obesity in individuals with a psychiatric disorder, methods and other medications need to be developed to reduce the side effects of SGA medication (Saddichha et al. 2008).

Both FGA's and SGA's have their pros and cons, and all might not work due to the patient having drug resistance (Abou-Setta et al. 2012; Leucht et al. 2013). However, even though SGA's are more efficient, they can be quite costly compared to FGA's (Leucht et al. 2013). Also, the long term use of FGA's and SGA's can cause the development of metabolic syndrome, which is currently affecting most prescribed antipsychotic medications for long periods of time (De Hert et al. 2008; Seow et al. 2017). Metabolic syndrome causes the individual to have increased risk for diabetes and cardiovascular disease which can essentially lead to death (Graham et al. 2008).

There are currently different treatment guidelines for the management of manic and depressive episodes. These treatment guidelines help by reducing the reoccurrence or frequency of acute episodes (Rief et al. 2016). Currently to prevent both manic and depressive episodes in patients diagnosed with BPD, monotherapy with first-line treatments, including SGAs are administered (Ketter et al. 2016). There is currently ongoing research into the reduction of hospital admissions through the use of long- acting injections (Kisely et al. 2015). The production of long- acting injections (i.e. risperidone and olanzapine) is highly recommended for the prevention of mania (Abou-Setta et al. 2012). Depot injections are also seen as a treatment option in the psychotic disorders, due to severity of illness or non-compliance to medication (Wingård et al. 2017). Depot antipsychotic medications are administered intramuscular to psychiatric patients (Roberts & Geppert 2004). Theoretically, depot antipsychotics have a greater effectiveness compared to oral antipsychotic medications as it does not go through the harsh acids in the stomach (Citrome et al. 2010). With increasing the effectiveness of treatment, costs involved in the management of the psychiatric disorders can be reduced (Kisely et al. 2015). Examples of depot antipsychotic medications include Flupentixol, Zuclopenthixol and Fluphenazine which are typical antipsychotics (Guzman & Farinde 2016).

1.5 Gene and environmental interaction

Genetic and environmental factors influence whether an individual will develop psychosis (Olvet & Hajcak 2009; Perez et al. 2016). Previous genetic studies have shown there is an increased risk in developing a mental illness if there is a family history of psychotic disorders (Ayano 2016). SCZ is known to be highly heritable, evidenced by genetic twin and family history studies (Mandelli et al. 2014). Individuals from parents with diagnosis of SCZ and monozygotic twins have a 40% chance of inheriting the mental disorder. A similar effect was seen in patients diagnosed with BPD (Juli et al. 2012). BPD genetic studies in siblings and twins have shown that children from parents with diagnosis of BPD are more susceptible to developing BPD or unipolar disorder. Monozygotic twins are at a higher risk (40-70%) of developing BPD compared to dizygotic twins (Craddock et al. 2005). Children born from a parent diagnosed with BPD has a 10% chance of developing BPD themselves or another psychotic disorder (Juli et al. 2012; Ayano 2016). However, the development of other psychotic disorders does not follow the Mendelian pattern of inheritance. Genetic twin studies have revealed insight into the strong genetic components to developing BPD. The twin studies have shown that monozygotic twins have a 75% concordance compared to dizygotic twins (10.5% concordance) in developing BPD (Juli et al. 2012). Adoption studies have shown that the child of a BPD parent still has the risk of developing BPD even though they are not living with their biological parents (Ayano 2016). This shows that an individual who carries the susceptibility genes is still at risk of developing BPD irrespective of their environment (Juli et al. 2012). However, this does not mean that environmental influences can't increase the risk of developing a psychiatric disorder.

A prime example of the environmental interaction crossed with genetic vulnerability is the abuse of methamphetamine, which causes overstimulation of the DA systems. Psychosis due to MA abuse, is suggested to result from hereditary pre-disposition to psychiatric disorders and drug use (Perry & Juhl 1977; Hermens et al. 2009; Shariat & Elahi 2010; Zarrabi et al. 2016). Other environmental risk factors may seem less direct and include adverse psychosocial influences, e.g. childhood trauma, including physical and sexual trauma (Tsuang et al. 2004; Perez et al. 2016) or dysfunctional relationship pattern through development, which can also promote the use and abuse of substances (Schmidt 2007;

Adzic 2012; National Institute of Health and Clinical Excellence 2014; Quach et al. 2016). Other environmental influences can include: access to good nutrition and stress during the mothers' pregnancy (Mansur et al. 2012), e.g. malnutrition of the mother can starve the baby in utero, potentially causing hormone and chemical imbalances as well as underdevelopment of the brain and other organs (Schmidt 2007). Also, mothers who use substances during pregnancy can increase their child's risk for developing serious neurodevelopmental disorders (American Psychiatric Association 2013a).

Another gene- environmental interaction, which continues to increase is social adversity, e.g. refugee or asylum seekers, and urbanisation (LaPorte et al. 1994; Hermens et al. 2009; Tandon et al. 2009; Adzic 2012; Mandelli et al. 2014; Basset et al. 2014; Tsuang et al. 2004; Seredenina et al. 2017; Kirkbride et al. 2012). Social adversity mechanisms have been found to be the link between genetic and environmental interaction which aid in the development of psychosis. In addition, it has been noted in both men and women that have moved from rural to urban areas show greater susceptibility to the impact of the high prevalence and availability of drugs, and high levels of substance- induced psychosis have been reported (Kirkbride et al. 2012; Perez et al. 2016).

Prognosis related environmental risk factors for those with diagnosis of SCZ are also apparent. Patients may go untreated, e.g. limited infrastructure within health care system or family are unable to pay costs of treatment or therapy, or stop taking their medication as they feel better or do not want to be controlled by taking medication, particularly apparent in paranoid patients with a psychotic disorder (Hyman et al. 2001; Chong et al. 2016).

1.6 Cognitive deficits in schizophrenia, bipolar I disorder, and methamphetamine induced psychotic disorder

Areas of the brain associated with cognitive deficits are generally the frontal and parietal lobes. The frontal lobe is associated with cognitive functioning, and not limited to, attention, reasoning, planning and problem solving. Deficits within the frontal lobe can lead impaired cognitive function (Dias et al. 2011). The parietal lobe is associated with, but not limited to, orientation, recognition, perception of stimuli, and their association. Deficits within the parietal lobe can lead to the inability to recognize salient stimuli such as faces,

letters and patterns. It is known that mental disorders are characterised by cognitive dysfunctions (Rief et al. 2016). Cognitive deficits are seen as the primary limitation to integration of individuals with a diagnosis of SCZ into society (Hill et al. 2010). Specific cognitive deficits highlighted include delayed memory recall, reduced processing speed, poor attention and concentration and impaired executive functioning (Harvey 2011). Negative symptoms associated with SCZ have been found to correlate with the cognitive decline of the affected individuals over time (Nielsen et al. 2015). This correlation can however be influenced by age, predisposition due to genetics, and environmental influences.

Cognitive dysfunction are also seen in patients with mood disorders i.e. BPD and depression (Harvey 2011). However, the severity of cognitive impairment is greater in SCZ compared to BPD (Trivedi 2006). Within BPD, cognitive dysfunctions include attention, executive function, learning, memory, and psychomotor speed (Martínez-Arán et al. 2004; Reddy et al. 2014). These cognitive dysfunctions are found to be worse in patients presenting with active BPD symptoms of depression, mania and residual dysthymia compared to BPD patients in a period of euthymia (Harvey 2011). Impulsivity associated with sustained attention deficits, are comparable in BPD and SCZ (Dickman 2000; Camelo et al. 2013). Specific neurotransmitter systems (i.e. dopamine and serotonin) have been related to impulse behaviour (Atmaca 2014), it has also been suggested that impulsivity in SCZ and BPD are influenced by antipsychotic medications (Reddy et al. 2014).

There are many debates on the effect that MA has on neurocognitive function however, many studies reveal contradictory results regarding cognitive dysfunction in MPD (Scott et al. 2007; Hart et al. 2012; Paulus 2017). Psychostimulants, e.g. MA, have been shown to displace DA at receptor level due to its' higher affinity at DA receptors. The high affinity of MA decreases the function of DA, from over activation of the DA system (Breier et al. 1997; Rusyniak 2012). As the individual uses higher doses of MA, the production of DA is decreased, in an attempt to attenuate over activation of the DA system (Jan 2013). Methamphetamine has been noted to affect executive function (Rusyniak 2012). Impairments in executive functioning affect strategic planning, behavioural initiation, and goal- directed behaviour (Mahurin et al. 1998). These traits along with impulsivity, are often described in SCZ and BPD (Koob & Volkow 2010). Koob and Volkow, (2010) stated drug

addiction is associated with impulsivity and compulsive behaviour. Sensitisation of the dopaminergic system has been suggested to underlie behavioural and drug addictions (Carter et al. 2011). In MPD cognitive deficits were found to persist long after methamphetamine use (Scott et al. 2007), and this is apparent within frontostriatal and frontolimbic systems (Petit et al. 2012).

We do not fully understand the biological mechanisms which lead to the cognitive symptoms apparent in psychosis. Attempts to understand the underlying mechanisms of cognitive dysfunction in the psychotic disorders is continual, in the clinical research setting and by use of animal models (Emilien et al. 1999; Weiss et al. 2002; Harvey 2011). Sadly, cognitive dysfunction in psychotic illnesses is not treated with current medication regimes (Featherstone et al. 2007). And the duration of antipsychotic treatment and high doses of antipsychotic medication have been shown to aid in the decline of cognitive function (Rehse et al. 2016), albeit more apparent for FGA's versus SGA's (Hill et al. 2010). With the development of SGA's, the dosage of antipsychotic medication was lower, and is more efficient in helping treat negative symptoms and cognitive impairment (Sampaio et al. 2017), apparent for olanzapine and risperidone (Weiss et al. 2002; Weickert & Goldberg 2005). It is purported that most SCZ patients who are receiving managed treatment can live a productive life if their cognitive impairment is not severe (Harvey 2011).

1.7 Sustained attention deficits in schizophrenia, bipolar I disorder, and methamphetamine induced psychotic disorder

Attention is a key cognitive function that has been shown to be dysfunctional in SCZ and other psychotic disorders (Rief et al. 2016). Attention is a resource demanding process in which the brain decides what to process, i.e. salient versus non-relevant information (Shipp 2004). It is accepted that there are four different types of attention: sustained attention, divided attention, selective attention, and alternating attention. Sustained attention determines the efficiency of divided and selective attention (Sarter et al. 2001). As an example, sustained attention can be seen as the ability to maintain focus on a specific time locked stimulus within a task (Featherstone et al. 2007). The theory of sustained attention, is currently suggested to be reliant on the mindfulness theory stating that errors created with sustained attentional tasks are related to mind wondering causing a shift in focus on

internal thoughts (Helton et al. 2009). There are four neurotransmitter systems which are involved in sustaining attentional processes: the primary system involved is the locus coeruleus norepinephrine system, however the raphe serotonin system, acetylcholine system, and mesocortical and mesolimbic dopamine systems are also involved (Okena et al. 2006; Javitt 2009).

Of particular relevance, in the psychotic disorders, is the role of dopaminergic dysfunction that underlies attentional deficits. (Hart et al. 2012). Dopaminergic dysfunction was found to be related to the efficiency of D_2 receptors (Cohen et al., 1998) and the functioning of the basal ganglia (Sotoyama et al., 2011). The basal ganglia are the globus pallidus, dorsal and ventral striatum, ventral pallidum, corpus striatum, the substantia nigra and the subthalamic nucleus striatum. The basal ganglia is involved in voluntary movement, cognition, reaction time and emotion (Gruendler et al. 2011). The basal ganglia has a limbic sector (mesolimbic pathway) which is involved in reward learning and interacts with the prefrontal cortex to control attentional processing (Van Schouwenburg et al. 2015). Ikuta et al., (2014) conducted a study which addressed sustained attention and the basal ganglia region in first episode psychosis. The study revealed hyperactivation of the globus pallidus during attentional tasks prior to the onset of psychosis (Ikuta et al. 2014). Antipsychotic medication has been shown to improve attentional processing in psychotic disorders (McGurk et al. 2004). An example of tasks which test for sustained and selective attentional processing deficits include the continuous performance task (CPT) (Perlstein et al. 1998; Filbey et al. 2008), which can be presented visually or auditory (Huang et al. 2007). The visual system consist of two pathways, the magnocellular and parvocellular system, which processes the visual environment (Johnson et al. 2005). In patients with SCZ, cortical visual processing is impaired causing difficulties in object recognition, reading and motion detection (Javitt 2009). Event- related potentials (ERPs) have been used to determine and understand visual processing impairments. Furthermore, ERPs have been used to study attention more specifically the neural circuitry involved in attention (Luck et al. 2000).

1.8 What is Event related potential (ERP)?

It is possible to investigate cortical processing of task stimuli via record ERPs (Luck et al. 2000; Saavedra & Bougrain 2012). An ERP is the electrophysiological response to a time-

locked stimulus, recorded during electroencephalography (EEG) (Huang et al. 2007; Dufau et al. 2009). The ERP refers to a specific window of time immediately before (-200ms) the stimulus of interest and shortly thereafter (+800ms). Within the ERP there are positive and negative deflections. These positive and negative deflections represent wave components of the ERP. The time at which they occur (latency reported in msec) and the size of the deflection (amplitude reported in Hz) are measures extracted from the ERP and are related to specific cognitive processes (Saavedra & Bougrain 2012). There have been many studies conducted focusing on the ERPs for visual related tasks (Mangun & Hillyard 1991; Van Der Lubbe & Woestenburg 1997; Hillyard & Anllo-Vento 1998; Luck 1998; De Pascalis & Speranza 2000; Radin 2004; Pourtois et al. 2008; Takeda et al. 2008; Nemrodov et al. 2011; Huang et al. 2011; Saavedra & Bougrain 2012; Howells et al. 2014; Dundas et al. 2014; Vareka et al. 2014; Oribe et al. 2015; Frey et al. 2016; San Martín et al. 2016; Luck et al. 2000). Within these studies, typical wave components include: P100, P150, N170 and P300 (Onitsuka et al. 2013), e.g. the P100 waveform is a positive (P) wave component that occurs approximately 100 msecs after the presentation of the stimulus To produce a reliable ERP for a specific stimulus a grand mean average is obtained (an average of at least 20 ERPs which are overlaid), this is to remove artefact, i.e. cortical activity, which is not related to the stimulus of the task being completed. There are several prominent wave components related to visual attention processes.

The N70 ERP waveform reflects somatosensory processing which occurs before the occurrence of the visual P150 ERP (Adams et al. 2017). The N70 ERP waveform is of small-amplitude with a negative (N) deflection that occurs approximately 70 msec after the visual presentation of a stimulus. The standard window in which the peak occurs is between 60 and 110 msec (Antal et al. 2004; Heimrath et al. 2012; Chapman et al. 2013). The N70 is associated with the activation of the striatal cortex and also reflects the extrastriata activity, which is posterior to the visual cortex (Saint-Amour et al. 2005). The N70 ERP waveform has been studied in somatosensory based tasks (Saint-Amour et al. 2005; Arnfred et al. 2000; Bolton & Staines 2011; Arnfred 2005), effects of medication on ERPs in Alzheimer's disease (Chapman et al. 2013), and in EEG studies using transcranial magnetic stimulation (Heimrath et al. 2012; Antal et al. 2004). There are very few studies which have addressed the N70 ERP in SCZ, BPD and MPD. In one study frontal (EEG ERPs recorded from

electrodes positioned over the frontal cortex) N70 amplitude was observed to be greater in SCZ compared to controls during the presentation of a primed stimulus (Arnfred et al. 2006). The N70 has been shown to be integrally involved in visual- spatial attention (Balslev et al. 2013; Adams et al. 2017), further research is required to understand the potential differences between the psychotic disorders.

The second waveform of interest is the P100 ERP waveform which is a small-amplitude, positive deflection that occurs approximately 100 msec after the presentation of the target (Burra et al. 2017). The P100 is also noted as the first positive peak after the N70 ERP waveform (Antal et al. 2004), or as an early P150 which starts a few milliseconds before the initial start of the P150 (Coch & Mitra 2010). The P100 is associated with attention-demanding tasks (Bolton & Staines 2011), yet the exact link to cognitive process(es) remain unknown (Campanella et al. 2006). The P100 has been hypothesized to reflect facial processing while the later N170 is related to the structural coding of the face (Hileman et al. 2011). The initial processing by the P100 followed by the N170 indicates that the P100 is involved in cueing. An attention based study showed that the right central P100 amplitude is greater when an individual attended to a specific stimuli compared to when a stimuli was ignored (Bolton & Staines 2011). This same result was repeated within another visual attention based task involving a sequential string of letters and distractor (Biehl et al. 2013).

Studies on the P100 in SCZ report attenuated P100 amplitude while in BPD it is enhanced (Campanella et al. 2006; Earls et al. 2016). The P100 amplitude and latency deficits in SCZ were linked to the parietal cortex (Johnson et al. 2005). These P100 differences in patients with SCZ are sensory processing deficits, that are likely to impact attentional processes (Sulejmanpašić et al. 2017). Sensory processing deficits include the brain not processing; sight, smell, hearing, touch and taste (Campanella et al. 2006). More frequently, visual tasks use facial emotion- based tasks to determine global processing of visual perception. Overall SCZ was found to have an attenuated P100 amplitude for non- facial and facial cues compared to healthy controls (Onitsuka et al. 2013), suggesting deficits in the absence of specific types of stimuli. In BPD the P100 amplitude was shown to be increased compared to controls (CON) based on the data collected from a visual based task involving faces exerting emotion, and this has been related to emotional dysregulation in BPD and impairment of prefrontal cortical processing (Berchio et al. 2017). How the P100 amplitude

is related to attentional processing that does not carry emotional valence in BPD needs further investigation. Patients having decreased concentration and impaired sensory processing have been noted to have attenuated P100 amplitude and lengthened latency (Wahlstrom 2014). Even though very little research has been conducted on MPD, EEG analysis of MA users were shown to have slower and poorer performance in attentional tasks compared to controls (Ceballos et al. 2009). The P100 may be a useful marker in distinguishing sensory processing deficits that affect attentional processing in SCZ and BPD. It would further be interesting to see if MPD P100 amplitude was attenuated or greater, and if P100 latency is lengthened or decreased, to see if the P100 plays a role in attentional dysfunction seen in MPD.

The N170 was first discovered upon the visual presentation of faces (Luck 2005; Dundas et al. 2014). It was later found that the N170 appeared after the presentation of known words (Luck 2005). The N170 ERP waveform is a negative deflection that occurs approximately 170 msec after stimulus presentation (Feuerriegel et al. 2015). The N170 was found to be right lateralized (Hileman et al. 2011) however, there are instances where the N170 amplitude was found bilaterally in relation to expert or executive functioning. Tanaka et al. (2001) showed that the amplitude does remain slightly attenuated in the left hemisphere compared to the right hemisphere. Furthermore, studies involving emotional based tasks in the form of faces have shown that within BPD the amplitude for happy faces were larger than that of sad faces (Feuerriegel et al. 2015; Minami et al. 2015). Deficits in facial processing have been linked to underlying decision or semantic processing (Campanella et al. 2006). In healthy individuals with typical development, the N170 latency is delayed and the amplitude is increased (Hileman et al. 2011). The N170 has been previously found to have an attenuated amplitude in patients with SCZ during the presentation of neutral and emotional facial images (Onitsuka et al. 2013; Feuerriegel et al. 2015; Cao et al. 2015; Maher et al. 2016). Further studies in SCZ revealed that there are reductions in N170 amplitudes which was not apparent in their first- degree family members (Onitsuka et al. 2013). In early onset SCZ transient visual evoked potential studies addressed the P100 and N170 early visual cortical responses and found attenuated amplitudes (Butler & Javitt 2005). Studies conducted between BPD and SCZ revealed the N170 latency was delayed compared to CON during word and facial processing (Wynn et al. 2013). Then in a different

study looking at word processing, the N170 latency was shortened indicating deficits/absence of earlier sensory processing (Strelets et al. 2015). Currently the knowledge available within the N170 ERP waveform mostly covers facial and emotion processing within CON, SCZ and BPD, very few address attentional processing (Okumura et al. 2015). Decreased N170 amplitudes in SCZ and BPD support deficits in understanding or processing of emotions. Okumura et al, (2015) found that the same results collected for letter and word coding are consistent with left lateral N170 amplitude and latency in early visual processing. Then, more research is needed to investigate N170 differences within MPD, and to see whether N170 amplitude and latency are similar in SCZ and BPD when processing non- emotional stimuli

The P300 event-related potential waveform is thought to represent cortical updating processes (Sur & Sinha 2009). The P300 ERP waveform is a large- amplitude, positive deflection that occurs approximately 300 msec post stimulus presentation. The P300 waveform has been studied in a mix of visual and auditory tasks in healthy control and in individuals with various mental disorders. The P300 has been widely studied in SCZ (Roth et al. 2007; Oribe et al. 2015; Dufau et al. 2009). These studies show that the P300 waveform in SCZ is usually attenuated (small amplitude) and delayed (longer latency) in response to target stimuli (Ethridge et al. 2015; VanMeerten et al. 2016). Both Ethridge et al (2015) and VanMeerten et al, (2016) suggest that P300 attenuated amplitude and delayed latency provides insight into the potential mechanisms involved in attentional processing within SCZ and BPD.

P300 studies within BPD are few. However, from the few studies conducted a reduction in P300 amplitude has been reported in patients diagnosed with BPD (Turetsky et al. 2007; Ethridge et al. 2015). Both studies revealed that attentional processing is altered, as seen by the P300 waveform differentially in BPD and SCZ (Tekok-Kilic et al. 2001; Kuperberg 2004; Johannesen et al. 2013; Ethridge et al. 2015), finding P300 amplitude is globally reduced in SCZ, then BPD show reduced parietal P300 amplitudes, when compared with controls, then no P300 latency differences were reported. Reduced P300 amplitude is associated with the visual and attention processing within SCZ and BPD. In SCZ and BPD, the reduced amplitudes, and at different cortical regions, frontal vs. parietal, are suggested to reflect primary cognitive deficit related to these psychotic disorders (Turetsky et al. 2007; Roth et

al. 2007; Chun et al. 2013). To date no studies have been conducted in MPD and it would be interesting to see if they too show deficits in their P300 waveform.

To address the limited literature on attentional processing deficits across the psychotic disorders, and clear absence of studies in MPD, we developed a visual continuous performance task to investigate voluntary sustained attention (Helton et al. 2009). First, to address response to target stimuli and prominent ERP wave components, as described above. Second, to address the potential role of cueing ERP wave components in attentional dysfunction, which has not been formally addressed across the psychotic disorders, this was based on previous work by our laboratory (Howells et al. 2012), which found significant differences in how BPD processed cueing information.

Sustained attention is known to be dysfunctional in psychotic disorders (Rief et al. 2016). Sustained attention is the ability to remain focussed on a specific time- locked stimulus within a task (Featherstone et al. 2007). Many studies have looked at sustained attention in SCZ (Johnson et al. 2005; Campanella et al. 2006; Earls et al. 2016; Sulejmanpašić et al. 2017) and BPD (Martínez-Arán et al. 2004; Harvey 2011). However, very few studies have investigated sustained attention in MPD (Yvonne 2006; Fassbender et al. 2015). Through using a visual sustained attention focused continuous performance task (CPT), we aimed to: (1) determine whether there are specific group differences between CON, SCZ, MPD and BPD. This included differences in (a) behavioural performance while completing the task and (b) prominent electrophysiological event- related potential (ERP) wave components during cueing and target processing.

(2) Few studies have investigated the relationship between ERP waveform components with demographic, drug use, clinical variables, and behavioural performance. In this study we aimed to characterize relationships that are apparent across groups and determine whether there are unique relationships with specific psychotic disorders. Due to the limited studies addressing the potential interaction of demographics, drug use and clinical variables, this study strictly characterized these relationships.

(3) Despite the current knowledge to the positive and negative effects of psychotropic medication, very few studies have addressed the effects they have on behavioural performance and ERP wave components. In a review conducted by (Amato et al. 2017) it

was evident that effects of medication on neurological systems within psychotic disorders are unclear. This limitation is due to most studies only focusing on a single psychotic disorder and comparing it to a healthy control group. By incorporating more than one psychotic group, effects of medication can be investigated across the psychotic disorders to distinguish whether there are differences. With this study we aim to investigate medication use and its' potential effect, by grouping those 'on' compared them to those 'off' a specific psychotropic medication, this was made possible by including three psychotic disorders.

Chapter 2 Methodology

2.1 Participants

A total of 103 participants were recruited for this study. This included the recruitment of participant with diagnosed psychotic disorders: schizophrenia (SCZ, N= 27), bipolar I disorder with a significant history of psychosis (BPD, N= 28), methamphetamine induced psychotic disorder (MPD, N= 21), and socio-demographic matched controls (CON, N= 27).

2.2 Inclusion of participants

All participants were between the ages of 18 and 40. All participants were interviewed, using the Structured Clinical Interview for Diagnostic Systematic Manual- IV (SCID-DSM-IV) (American Psychiatric Association 1994). For the psychiatric groups, only outpatients were recruited. Individuals recruited for SCZ group had clear diagnosis of schizophrenia as other disorders from the schizophrenia spectrum were excluded, e.g. schizoaffective and schizophreniform (American Psychiatric Association 1994). Individuals recruited for BPD group had clear diagnosis of Bipolar I disorder with a significant history of psychosis (American Psychiatric Association 1994), and currently euthymic (e.g. no presentation of mood polarity) (Mccormick et al. 2015). Individuals recruited for MPD group were included if it was clear that the cause of the psychosis was a result of methamphetamine use (American Psychiatric Association 2013a). Individuals recruited for CON group were included if there was an absence of mental illness, including psychosis or psychotic symptoms (DSM Axis I disorders) (American Psychiatric Association 1994). Further, participants were not recruited if they presented with an active mood state, e.g. depression or anxiety, to reduce potential interference on ERP waveforms (Stigge-Kaufman 2005).

2.3 Exclusion of participants

Participants were excluded if they reported a history of: electroconvulsive shock therapy; transcranial magnetic stimulation; epilepsy, including childhood epilepsy or known family history; major brain trauma or brain surgery including stroke or brain aneurism; any chronic medical illness that required medical care or prescription medication, e.g. fibromyalgia, diabetes, known HIV positive status; history of psychosis as a result of a general medical condition; females that were pregnant or breastfeeding; and any individual who presented with clinically apparent mental dysfunction.

Further exclusion criterion were applied as the research participants also underwent magnetic resonance imaging as a separate part of the umbrella project, these additional exclusion criteria are as follows: physiological implant (e.g. pacemaker, cochlear implant, aneurism clip); extensive tattoos on upper body; piercings that could not be removed; possible shrapnel or bullets in the body; any form of severe motoric disturbances above a very minimal tremor, e.g. no tardive dyskinesia, akathisia, etc.

2.4 Ethical considerations

Ethical clearance for the research study was obtained from the University of Cape Town's Health Sciences Research Ethics Committee (HREC Ref No: 192/2010) and was conducted in accordance with the Declaration of Helsinki. Furthermore, approval was obtained from the Western Cape Provincial Government and respective hospitals (appendix B). Importantly, this was a multimodal imaging study, of which the EEG and ERPs were collected during a sustained attention task. For this thesis, only the ERPs was analysed.

Participation in the current study was voluntary and participants were allowed to exit the study at any time during their participation. Prior to participating in the study participants were required to sign informed consent (appendix A).

2.5 Study procedures

Participants were required to present at 08h00. This study included several brain imaging modalities, including EEG recordings and MRI scan. The focus of my study was the ERP

analysis from the EEG recording. All ERP recordings were collected between 11h00- 12h00 during a working week day. In addition, participants completed several subjective questionnaires during the day and if from a psychotic group they also completed several clinical scales with a clinician after the battery of brain imaging modalities.

2.6 Demographic information, clinical scales, and subjective questionnaires

The following demographic information was collected: gender, date of birth, education, and handedness. The clinical demographic information related to psychotic groups included: age of onset of the disease, duration of illness, and current medication regime.

The Psychotic symptom related clinical scale included the Positive and negative syndrome scale (PANSS)– which is an operationalised and drug- sensitive instrument used to assess positive and negative symptoms in schizophrenia (Kay et al. 1982). The positive symptom subscale includes delusions, conceptual disorganization, hallucinatory behaviour, excitement, grandiosity, suspiciousness, and hostility. The negative symptom subscale addresses emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking and assesses for blunted affect. Lastly, the general psychopathology subscale assesses somatic concern, tension, mannerisms and posturing, anxiety, feelings of guilt, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance. The PANSS scale uses a rating of 1 to 7 to score an individual for each section. The rating scale meaning is as follows; 1 = absent, 2 = minimal, 3 = mild, 4 = moderate, 5 = moderate- severe, 6 = severe, and 7 = extreme. For the results of the PANSS scale, a score of the ratings across items are between 7- 49 for the Positive and Negative Scales and 16-112 for the general psychopathology scales.

Then three mood related clinical scales were included; the Calgary depression scale (CDS) which is a scale used to measure the level of depression in schizophrenia (Addington et al. 1990), the Hamilton depression rating scale (HAM-D)– a clinical scale used to assess symptoms of depression (Hamilton 1960) and the Young Mania Rating scale (YMRS)– used

to determine the severity of manic symptoms (Young et al. 1978). The CDS scale was found to be more specific to depression in SCZ compared to the HAM-D scale, as it helps distinguish depression from negative symptoms of SCZ (Grover et al. 2017). The CDS scale comprises of 9 items to which if a patient describes 6 or more, the patient is said to have a major depressive disorder. The HAM-D scale consists of 17 items, of which each item is rated on either a 5- point scale (0−4) or 3- point scale (0−2). A score of more than 7 indicates the presence of depression. The severity of the depression is graded as mild (score of 8–13), moderate (score of 14– 18), severe (score of 19–22) and very severe (score of > 23). Lastly, the young mania rating scale comprises of 11 items which are divided into four questions scored (0-8) and 7 items scored (0-4). The final scoring of the scale is; mania (YMRS = 12), depression (YMRS = 3), or euthymia (YMRS = 2).

Further, the Clinical Global impression severity scale (CGI-S) was used to determine illness severity in psychiatry (Aas 2011). The scale is rated 1-7; 1=normal, not at all ill, 2=borderline mentally ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill, 7=among the most extremely ill patients. Lastly the Global assessment of functioning (GAF) was used. The GAF is a scoring system used to briefly assesses the patients' global functioning by also considering the patient's history, psychosocial circumstances, symptoms, behaviour, and the impact of the symptoms on the patient's ability to function (Busner & Targum 2007). The scale is scored out of 100; a score of 1-30 is a possible patient for inpatient care, an individual with a score of 31-69 is a potential candidate for outpatient care, and a patient with a score of 70 and higher may be a patient who is functioning too well for the need of any treatment (Aas 2011) (Appendix C).

2.7 Electroencephalography hardware

EEG data was recorded using the Biopac MP150 data acquisition system with ten 100C biopotential amplifiers attached (Biopac Systems Incorporated 2012). The 100C amplifiers are biopotential transducers used to amplify voltages smaller than 0.01 volts (10 microvolts), i.e. electrical brain signals measured in microvolts (µV) collected via the EEG electrodes of the EEG cap (Biopac Systems Incorporated 2012). The EEG lycra cap used to collect the EEG recordings had a standard 10/20 system containing recessed pure tin electrodes (Electro-cap international inc n.d.). A referential linked ear referencing montage

was incorporated using a pair of 9mm Electro-Cap Tin Ear Electrodes. The Electrodes contained a plastic covered spring clip back to hold the electrodes in place. The ten 100C EEG amplifiers were connected using jumper cables for referencing to linked ear electrodes. EEG channels recorded from included: pre-frontal (Fp_1, Fp_2), frontal (F_3, F_4), temporal (F_7, F_8), central (C_3, C_4) and parietal (P_3, and P_4).

Then an electrooculography (EOG) 100C amplifier was also attached to the Biopac MP150 system, to permit the removal of eye related activity from the EEG recordings. Similarly to the EEG 100C amplifier, the EOG 100C amplifier is used to amplify voltages smaller than 0.01 volts (10 microvolts). Electrooculography (EOG) is a technique used to measure the resting state of the retina (Siddiqui & Shaikh 2013). Two 4 mm Ag-AgCl lead shielded electrodes which was placed 1 cm below and 1 cm to the outer edge of the right eye.

Lastly, participants were grounded using electromyography (EMG) positioned on the forearm. Grounding the participants through EMG recording, prevents the loss of the signal of interest by reducing powerline noise interference as well as static energy (Costa et al. 2016). This set-up was defined by the overarching research project which incorporated additional electrophysiological measurements, Cortical Inhibition and Attentional modulation: A study of Psychosis (CIAM – HREC/192). The setup for CIAM – HREC/192 consisted of magnetic resonance spectroscopy (MRS) to assess the level of brain chemicals, electroencephalography to assess electrical activity, and using electroencephalography with transcranial magnetic stimulation to assess changes in electrical activity.

2.8 Electroencephalography software

The MP150 system data were collected using Biopac software Acqknowledge 4.1 data acquisition and analysis software (Figure 2.1). The software allows for instant viewing, measure, replay and transforming and analysis of the EEG data recorded (Biopac Systems Incorporated 2012). The ten 100 C biopotential amplifiers attached to the Biopac MP150 system included an electrooculography amplifier (EOG= channel A12), electromyography (EMG= channel A11) and ten EEG 100C amplifiers connected to collect data for the prefrontal (Fp_1 = channel A1, Fp_2 = channel A2), frontal (F_3 = channel A3, F_4 = channel A4), temporal (F_7 = channel A5, F_8 = channel A6), central (C_3 = channel A7, C_4 = channel A8) and

parietal (P_3 = channel A9 and P_4 = channel A10). All the channels were run at a sampling rate of 500Hz.

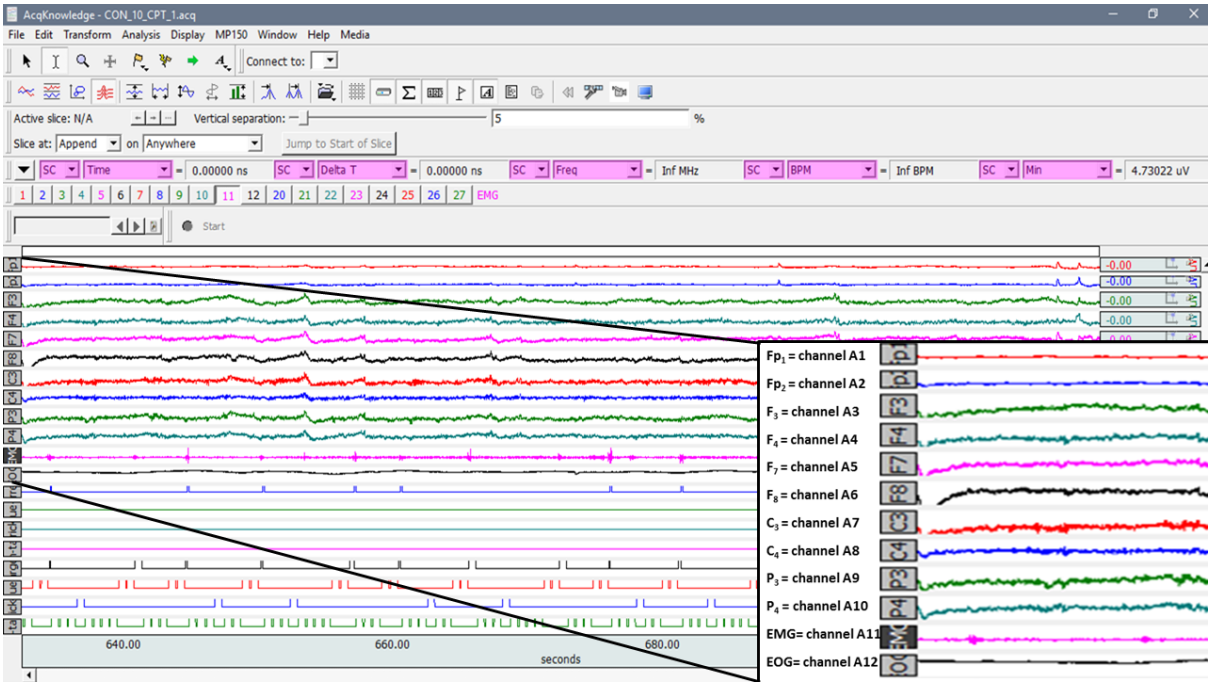


Figure 2.1 Acqknowledge electroencephalography channels of interest. The data collected for EEG analysis included twelve different channels; pre-frontal (Fp_1 = channel A1, Fp_2 = channel A2), frontal (F_3 = channel A3, F_4 = channel A4), temporal (F_7 = channel A5, F_8 = channel A6), central (C_3 = channel A7, C_4 = channel A8) and parietal (P_3 = channel A9 and P_4 = channel A10), electromyography (EMG=channel A11) channel which served as ground, and electrooculography (EOG= channel A12). Acqknowledge 4.1 software was used to collect the data. Electrodes F_7 and F_8 were not analysed during the final analysis.

2.9 Behavioural task software

Eprime 2.0 is software, used to design behavioural tasks, collect behavioural performance, and conduct behavioural analyses. E- Studio, the design tool within Eprime, was used to design the visual continuous performance task used. Eprime records data in milliseconds (msec) and was designed to send digital inputs of stimuli to Acqknowledge 4.1 (Figure 2.2) (Schnieder *et al,* 2012).

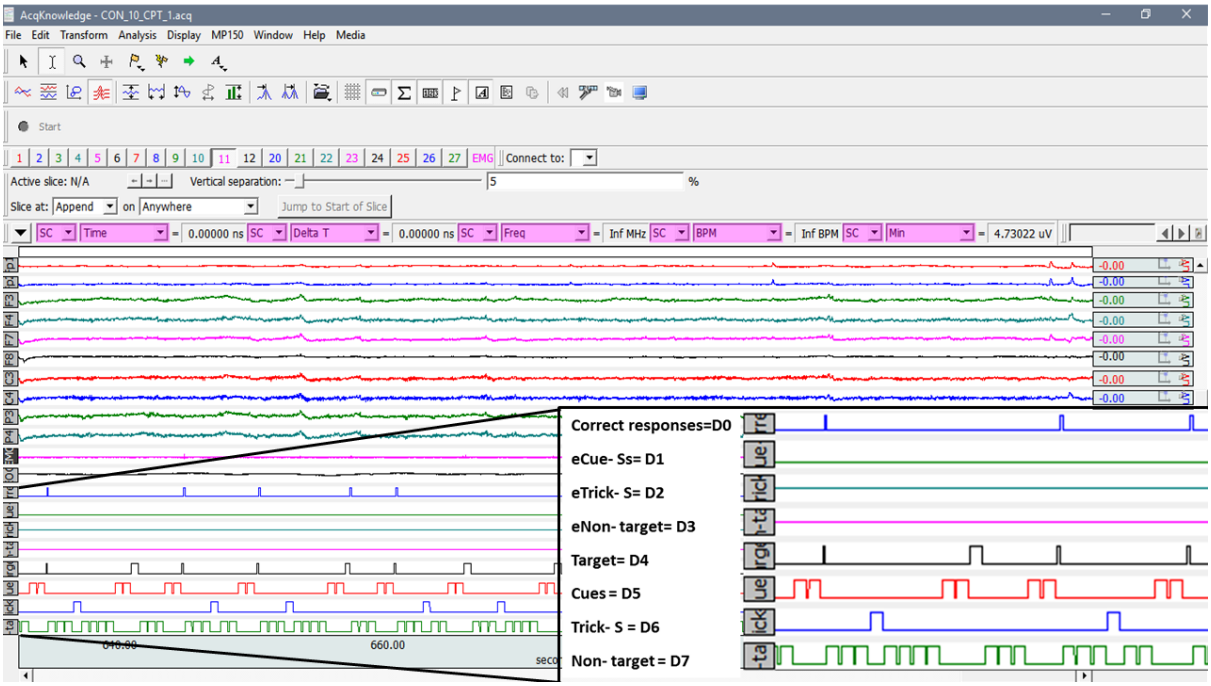
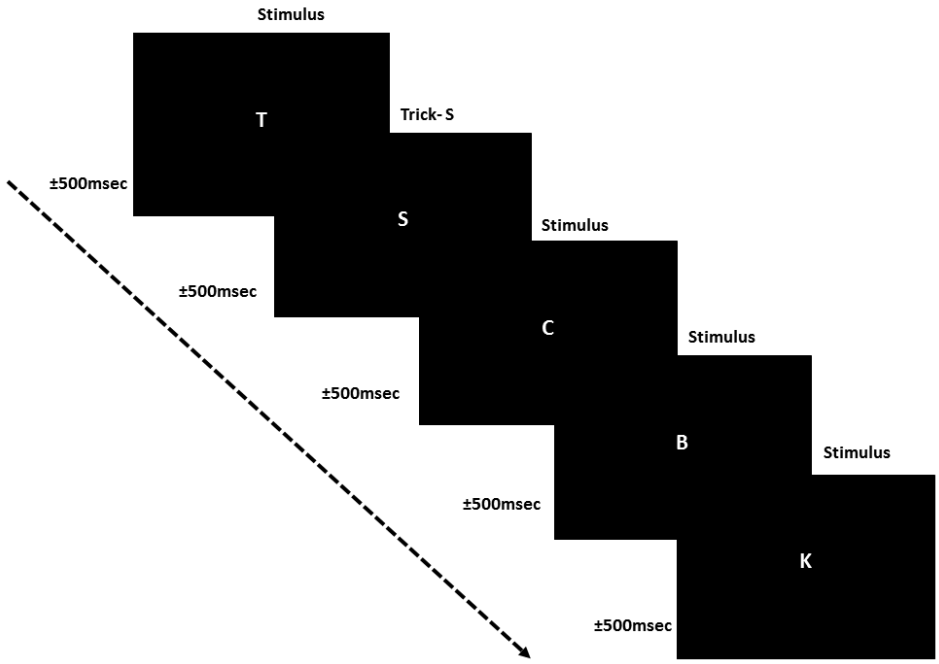


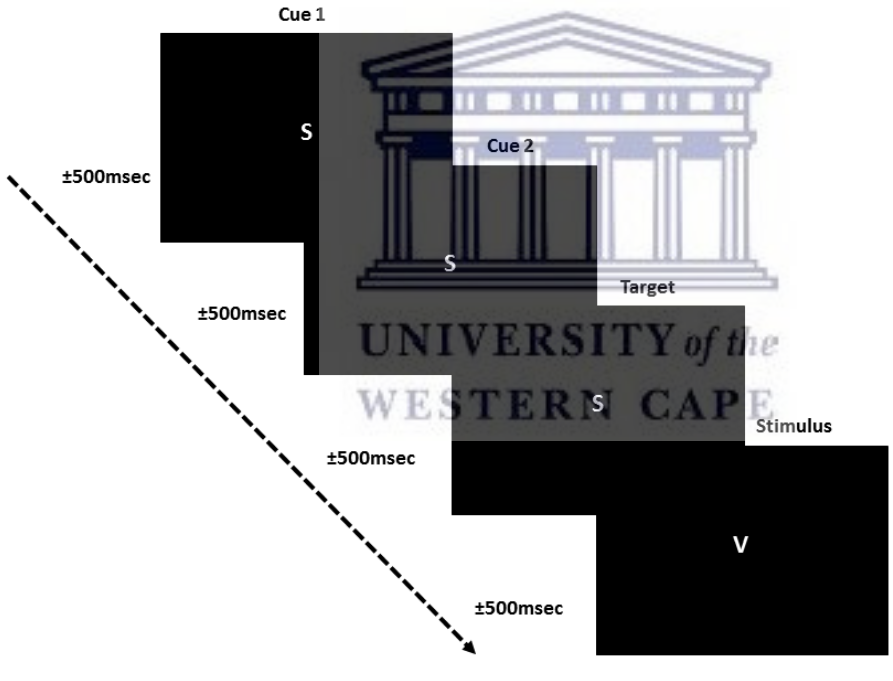
Figure 2.2 Representation of the cues in the Continuous Performance task. The digital channels for trigger collection included eight different channels; correct responses (digital channel D0), eCue- Ss (digital channel D1), eTrick- S (digital channel D2), eNon- ta target (digital channel D3) target (digital channel D4), cues (digital channel D5), trick- S (digital channel D6) and non- target (digital channel D7). All channels were collected at 500Hz.

2.10 Voluntary sustained attention task: a visual continuous performance task (S-S-S)

The continuous performance task (CPT) involves the presentation of three consecutive S's within a series of randomized letters of the alphabet. The purpose of the CPT task is to measure the participants' ability to sustain attention during the completion of a task which contains a cueing process, target and non- stimuli. Participants were presented with 60 trials with three consecutive S's, the presentation of the third S required a behavioural response. In addition, 40 single S's or trick S's were embedded in the task with inter-stimuli letters. The task contained 20 letters of the alphabet and excluded the vowels, A, E, I, O, U as well as the letter X. Each letter was presented for 500 msec with a 100 msec inter-stimulus interval before the next stimulus (Figure 2.3). However, the participant was able to shorten the presentation of the third S if a response was given before the 500 msec time limit (Figure 2.2, channel D4).



(a)



(b)

Figure 2.3 Representation of the visual Continuous Performance task. The continuous performance task was designed as a time- locked response task, where the letters appeared in a randomized order. Each letter was presented individually, appearing for 500 msec and disappearing for 100 msec before the next stimulus. (a) The trick stimulus was presented to distract the participant from the presentation of the three consecutive S's. (b) The presentation of the three consecutive S's occurred as cue 1, cue 2 and the target S. The participant was able to shorten the presentation of the third S if a response was given before the 500 msec time limit.

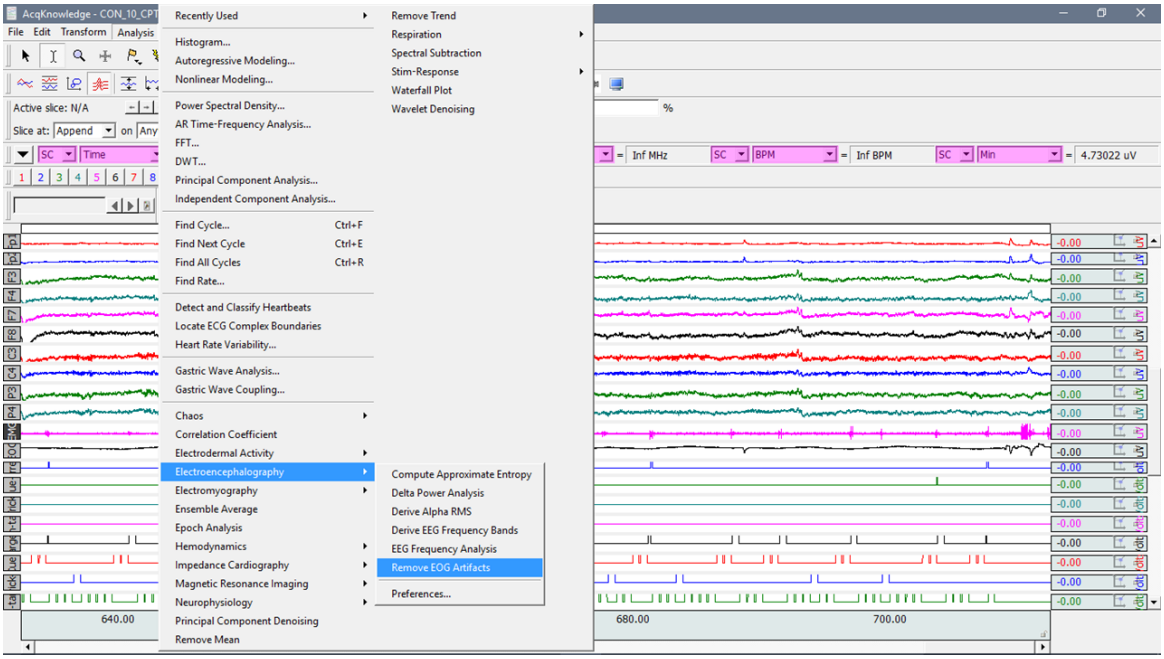
2.11 Electroencephalography set up

Prior to starting the EEG, the placement of the electrodes and CPT task was re-explained to ensure that the participant knew what the EEG consisted of. The participant was asked to sit at a desk with a desktop computer screen in front of them. An alcohol swab was used to clean natural oils and loose skin cells of from the forehead and on the side and below the right eye. Two sponge discs, used to support the Electrode Cap International (ECI) electrode lycra cap, were positioned on the forehead. Earrings were asked to be removed prior to attachment of the earlobe reference electrodes. An electrode gel was placed inside the 4mm EOG electrodes prior to attaching the electrodes with a double- sided adhesive disk on the side and 1cm below the right eye. The ECI electrode lycra cap was pulled onto the participants head and positioned, electrode gel was inserted into the hollow EEG electrodes using a blunt needle and syringe. Lastly, the EMG electrode was placed on the participant's forearm.

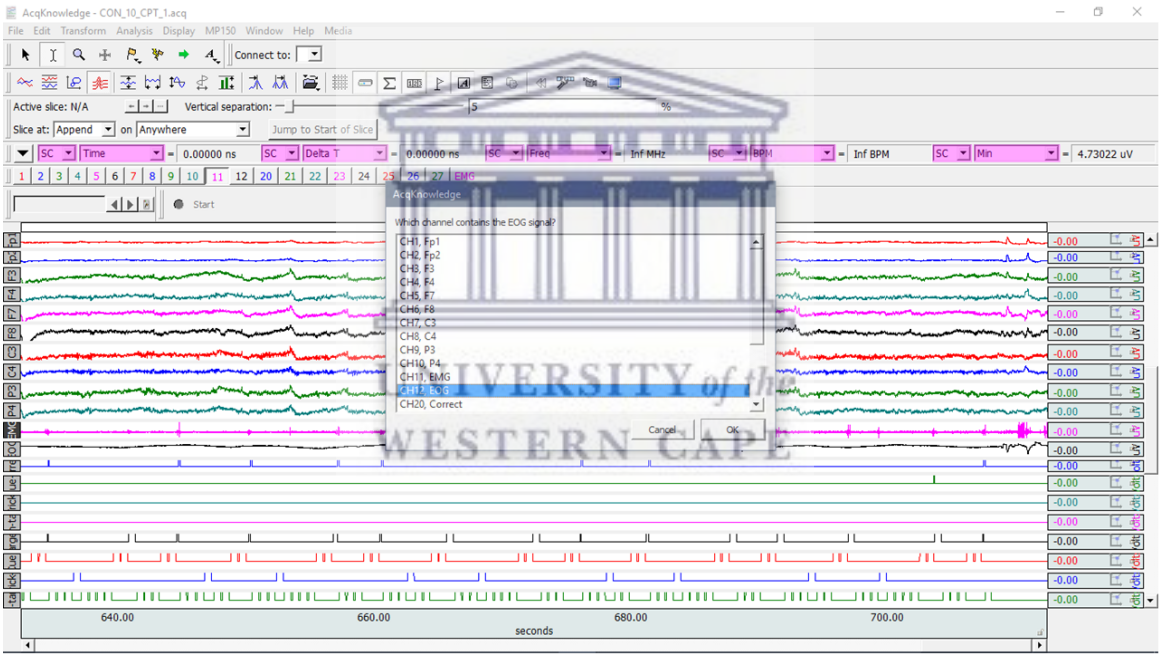
After completion of the EEG setup, the Acqknowledge 4.1 software was opened and the E-prime experiment file was loaded. The participant was asked to relax while the researcher observed the electrode channels. The channels were observed for any flat lined signals or channels with a lot of activity ("noisy" channels). If any noisy channels were present; the electrodes were checked for any bubbles in the electrode gel, hair which could be obstructing the connection from electrode to scalp or more gel was applied. Once all electrodes were producing excellent signal the EEG record was initiated, and participant completed the visual CPT.

2.12 Electroencephalography analysis

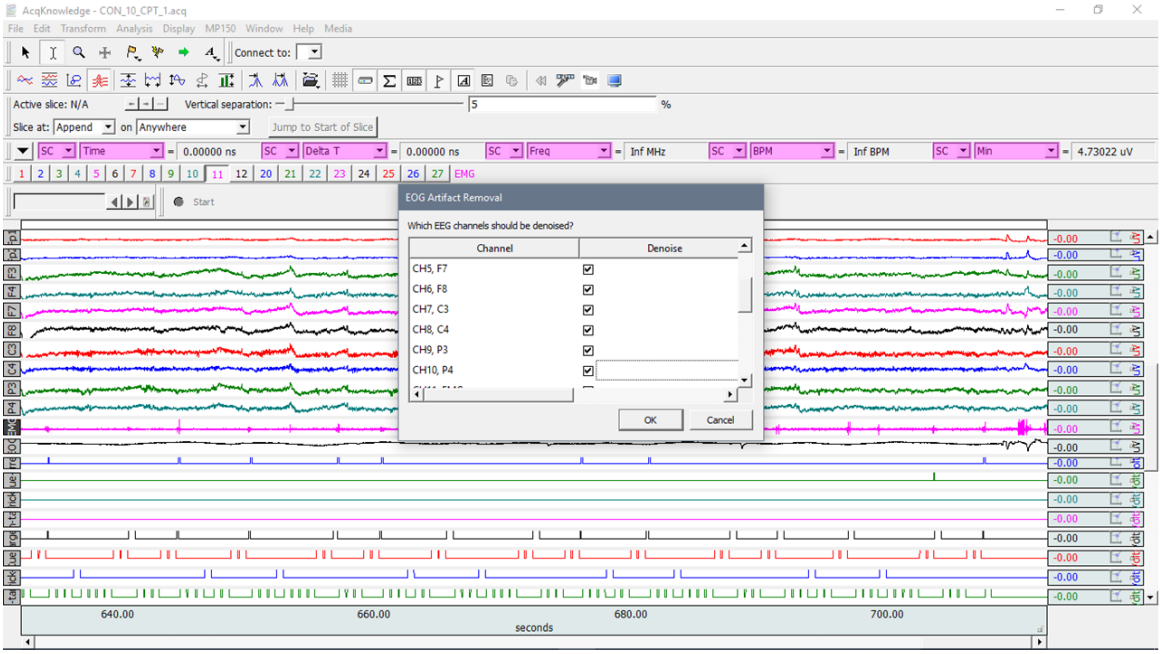
Preceding frequency and ERP extraction, the raw EEG data were corrected for EOG artefact using an automated independent component analysis (ICA) within the data collection software package, Acqknowledge 4.1 (Figure 2.4). It is important to apply ICA for EOG artefact removal when extracting ERPs from a data set, due to eye blinking emitting a positive peak at 300 msec (previously discussed in section 1.8) (Bonfiglio et al. 2009). All files which were EOG corrected were saved as Matlab coded file (extension .mat).



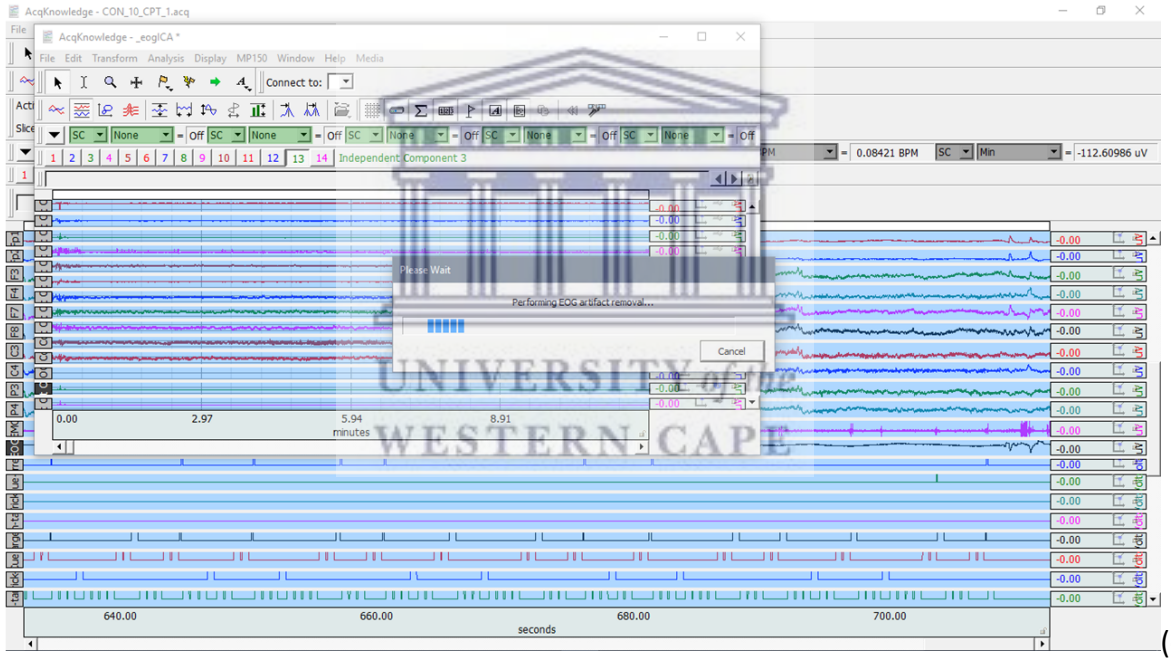
(a)



(b)



(c)



(d)

Figure 2.4 Acqknowledge EOG removal. The raw electroencephalography data collected during completion of the continuous performance task was EOG corrected through the Acqknowledge 4.1 software to remove eye movement from the data which could false results when analysing the ERPs. (a) Electrooculography removal was conducted by clicking the analysis tab in Acqknowledge 4.1 – scrolling to electrooculography- then clicking remove EOG artefacts. (b) The EOG channel was selected from the command box to select the channel which recorded electrooculography. (c) The channels (pre-frontal (Fp_1 = channel A1, Fp_2 = channel A2), frontal (F_3 = channel A3, F_4 = channel A4), temporal (F_7 = channel A5, F_8 = channel A6), central (C_3 = channel A7, C_4 = channel A8) and parietal (P_3 = channel A9 and P_4 = channel A10)) to be denoised from EOG were selected from the command box. (d) The process of EOG artefact removal was initiated.

2.13 Event Related Potential extraction

The ERP waveforms extracted were from the pre- frontal (Fp_1, Fp_2) frontal (F_3 and F_4), central (C_3 and C_4), and parietal lobes (P_3 and P_4). The ERPs were extracted using an ERP extraction Matlab tool with simple graphical user interface (GUI) (Matlab, Mathworks, MA, USA, developed in-house) (Figure 2.5). Setting for ERP window: 1000 msec epoch; 200 msec before and 800 msec after, target stimulus. An artefact rejection limit of ±100µV was set to each extraction. This ensured that there was removal of an ERP with substantial distortion or artefact that may reduce the signal to noise ratio of the ERP waveform.

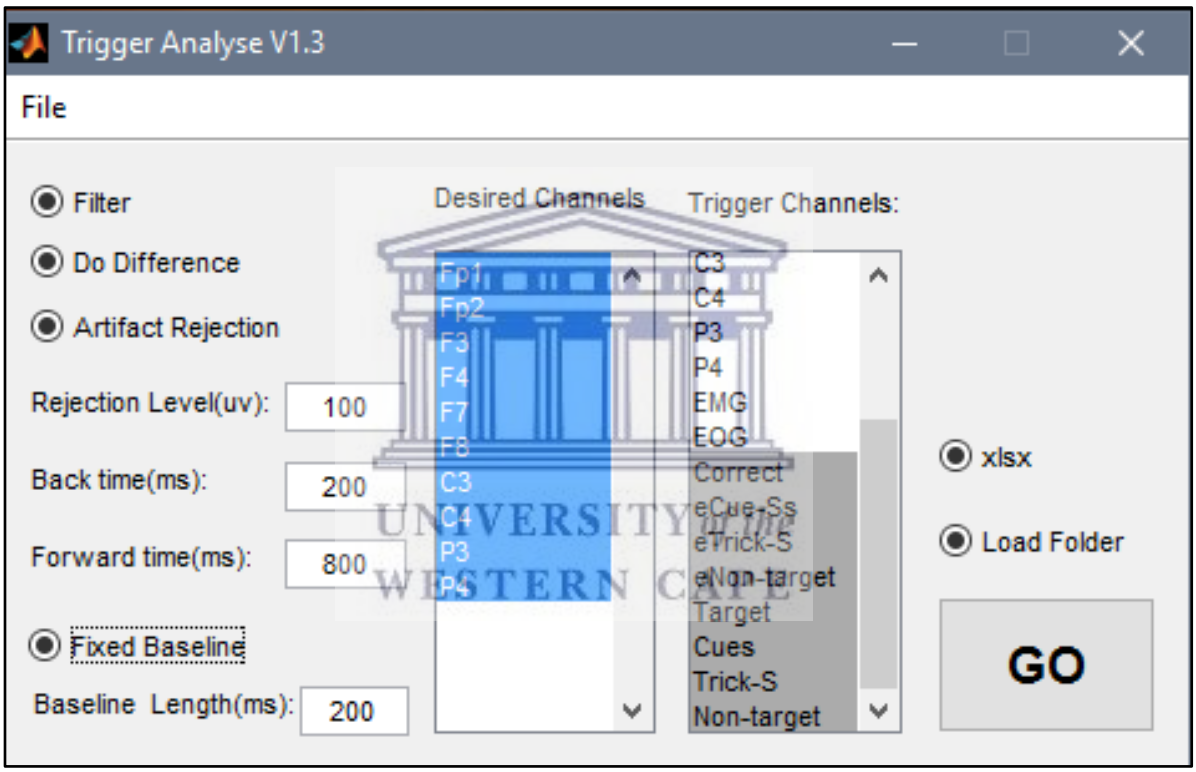


Figure 2.5 Event related potential Matlab Graphical User Interface. The program was specifically made to extract the ERP data from EOG corrected data. A 100µV artefact rejection limit and a fixed baseline length of 200 msec was used for the ERP analysis. The time was set to 200 msec backward and 800 msec forward to capture a 1000 msec epoch. The cues and target were analysed separately.

To identify robust ERP waveform components from the data collected, grand averages ERP waveforms were created for each group and plotted on an XY lined scatter plot. The amplitude (µV) and latency (msec) values were extracted for each robustly identified ERP wave component. The windows used to extract the ERP waveforms from each channel are presented in **table 2.1**.

Table 2.1 Epochs used for the extraction of ERP waveforms from each channel for all four stimuli; first cue, second cue, and target stimulus.

Target	*Fp_1*	*Fp_2*	*F_3*	*F_4*	*C_3*	*C_4*	*P_3*	*P_4*
N70							20-150	20-150
P150							70-200	70-200
P100			50-150	50-150	50-150	50-150	50-150	50-150
N170	100-200	100-200	100-200	100-200	100-250	100-250	100-250	100-250
P300	200-400	200-400	200-400	200-400	300-500	300-500	250-500	250-500

The ERP waveforms extracted from the first cue, second cue, and target stimulus included the N70 (20-150 msec window) and early positive P150 (70-200 msec window) for the parietal electrodes (P_3 and P_4). The N70 is a small-amplitude, positive deflection that occurs approximately 70 msec after each cue, and target. The P150 is a small-amplitude, positive deflection that occurs approximately 150 msec after each cue, and target. The P100 (50-150 msec window) was extracted for the frontal (F_3 and F_4), central (C_3 and C_4) and parietal (P_3 and P_4) electrodes. The P100 is a small-amplitude, positive deflection that occurs approximately 100 msec after each cue, and target. The early N150 (100- 200 msec window- Fp_1, Fp_2, F_3 and F_4; 100-250 msec window- C_3, C_4, P_3 and P_4) was extracted for the frontal, central and parietal electrodes. The N150 is a small-amplitude, positive deflection that occurs approximately 150 msec after each cue, and target. The P300 ERP waveform was extracted for the frontal (200-400 msec window- Fp_1, Fp_2, F_3 and F_4), central (300-500 msec window- C_3 and C_4) and the parietal (250-500 msec window- P_3 and P_4) electrodes. The P300 is a small-amplitude, positive deflection that occurs approximately 300 msec after each cue, and target.

A further visual inspection was conducted by plotting the participant data for each stimulus separately on a μV vs msec line graph (Figure 2.6). The visual inspection consisted of looking at each participants' data throughout the stimuli data extracted, to exclude participants with results which contained more than two sets of arbitrary data within each channel.

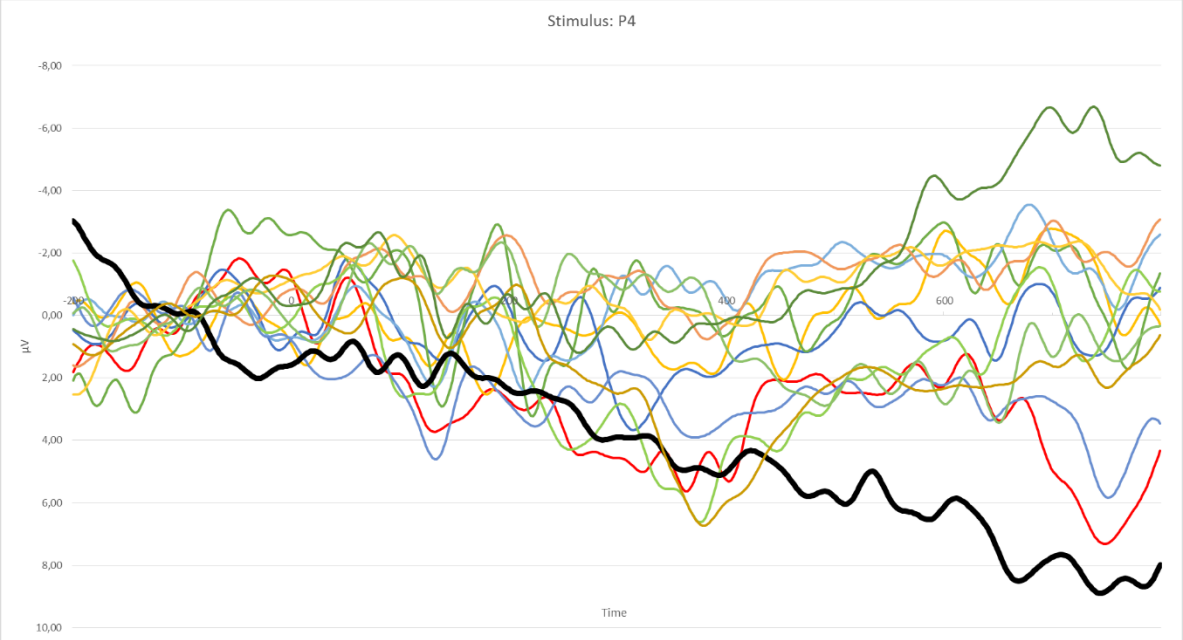


Figure 2.6 Exclusion of data. Event- related potential data was analysed using visualization through a "microvolt vs time" line graph to exclude data which did not conform to the averaged event- related potential waveforms. In this case, the event-related potential data moved at a steady decline and had no form. An example is seen by the bold black line.

2.14 Statistical analysis

Statistica (Dell, 2016) was used to conduct the statistical analysis on the data collected. A descriptive statistical analysis was applied to the data to determine normality using the Shapiro Wilks W test. Analysis of the Shapiro Wilks W test, the parametric and non-parametric data was determined using a P- value less than 0.05 as the limit for parametric data ($P<0.05$). The data obtained were both parametric and non-parametric.

To characterize our population, group differences in demographics (age on the day of testing, duration at school, tertiary education, total years of education, weight, height, BMI and handedness), drug use (total substance use and individual drug use of tobacco, alcohol, cannabis, cocaine, methamphetamine, inhalants, sedatives, hallucinogen, opioids, and mandrax), and behavioural performance (correct responses, overall response time, errors of commission, errors of omission, and responses to distractor stimuli, i.e. trick S responses) are reported between the four groups.

Then differences in clinical scale scores Positive and Negative Symptom Scale for Schizophrenia (PANSS) total score, PANSS positive symptom subscale, PANSS negative symptom subscale, PANSS general psychopathology subscale, Calgary depression rating scale, Hamilton depression rating scale, Young mania rating scale, clinical global impression of illness severity scale, global assessment of functioning scale, and the Simpson angus scale for parkinsonism), duration of illness, and medication variables where statistical analysis was viable, i.e. n was sufficient to perform sound statistical analysis, (chlorpromazine equivalents, use of any antipsychotic, 1st generation antipsychotics (FGA), prominently used FGAs (haloperidol), 2nd generation antipsychotics (SGA), prominently used SGAs (clozapine, risperidone), mood stabilizers, lithium, sodium valproate, serotonin/norepinephrine reuptake inhibitors, and anticholinergics) are reported for the three psychotic groups.

Then three different analyses were conducted to determine the aims of the current thesis:

(1) A group analysis across the four groups (CON, SCZ, BPD and MPD) to determine whether group differences in (a) behavioural performance and (b) event related potential wave components amplitudes and latencies. This was achieved by first conducting an analysis of distribution for each variable, using Shapiro-Wilks test. That data which was of normal distribution underwent univariate one- way analysis of variance (ANOVA). When the ANOVA yielded significance, these variables underwent post-hoc testing with Bonferroni correction to determine whether there were specific group differences ($p < 0.05$). That data which was not of normal distribution underwent multiple independent Kruskal-Wallis ANOVA, which provided the overall ANOVA test result and between group differences. These differences are reported where the ANOVA yielded significance ($p < 0.05$).

(2) ERP wave-component amplitude and latency correlation analyses were performed for (a) all four groups (CON, SCZ, BPD, MPD) with demographics, drug use, and behavioural performance data, and (b) within the psychotic groups (SCZ, BPD, MPD) for clinical variables (clinical scales, duration of illness and chlorpromazine equivalent). Due to the data distribution non-parametric correlation analysis was performed, using Spearman's, rank order (Rho > ±0.5 and p-value < 0.01). Due to the correlation analysis taking an exploratory approach, with limited event-related potential studies in these disorders investigating the

interaction of demographics and clinical variables, we applied greater stringency in reporting. The strength of relationship was increased to ±0.5 (Rho; (Mukaka 2012)) and increased the probability of the relationship being repeated by lowering the P- value to 0.01 (Dahiru 2008). Caution is still needed when these data are interpreted as the sample size is limited, however do provide insight to future studies and more complex statistical analysis. Further, the statistical package used, Statistica, does not have the function to permit co-variate analysis within non-parametric ANOVAs.

(3) The last analysis was performed to determine the potential difference 'on' or 'off' psychotropic medications by grouping all the psychotic groups and comparing those 'on' a specific medication to those 'off' that specific medication. The analysis included medication which was prescribed to at least 8 of the 76 participants with a diagnosis of a psychotic disorder. This permitted us to determine group differences by those on a medication and off a medication (number on: number off). The following medications were investigated: any antipsychotic prescribed (62:14); 1st generation antipsychotics prescribed (35:41); haloperidol (22:54); 2nd generation antipsychotics prescribed (33:43); clozapine (10:66); risperidone (15:61); mood stabilizers (33:44); lithium (14:62); sodium valproate (22:54); and anticholinergic (orphenadrine; 15:61), refer to **Table 3.5**.

The group difference 'on' and 'off' a specific medication was also determined within an individual psychotic group when at least 8 of the individuals were either off or on a medication. This permitted us to determine differences within SCZ for 1st generation antipsychotic prescribed (9:18), 2nd generation antipsychotic prescribed (18:9), and clozapine (9:18). Then within BPD for any antipsychotic prescribed (20:8), 1st generation antipsychotic prescribed (10:18), 2nd generation antipsychotic prescribed (10:18), lithium (13:15), and sodium valproate (15:13). And within MPD for haloperidol (13:8), and anticholinergics (8:13). Univariate analysis was applied to the parametric data by one- way analysis of variance (ANOVA), and non- parametric data Mann- Whitney U testing was applied.

Chapter 3 Results

3.1 Participant demographics

To characterize our population, group differences in demographics, drug use, and behavioural performance are reported between the four groups (CON, SCZ, BPD, MPD). Then differences in clinical scale scores, duration of illness, and medication variables where statistical analysis was viable, i.e. n was sufficient to perform sound statistical analysis, are reported for the three psychotic groups (SCZ, BPD, MPD).

3.1.1 Participant characteristics

A total of 103 participants between the ages of 19 and 40 were recruited for the present study. The individuals diagnosed with a psychiatric disorder consisted of 27 (females n=11, males n=16) participants diagnosed with schizophrenia (SCZ), 28 (females n=12, males n= 16) participants diagnosed with bipolar I mood disorder with a history of psychosis and 21 (females n=9, males n=12) participants diagnosed with methamphetamine induced psychotic disorder (MPD). Then 27 (females n=15, males n=12) controls (CON) were recruited.

An attempt was made to balance the demographic information across groups, however the following demographic differences were found CON ($H_{3,103}$=12.96, P=0.004) were younger in age compared to SCZ (P=0.041) and BPD (P=0.036). MPD ($H_{3,103}$=11.50, P=0.009) reported fewer years at school compared to CON (P=0.043). Then MPD ($H_{3,103}$=10.96, P=0.011) reported shorter total duration at school going compared to CON (P=0.017) and BPD (P=0.041). No significant group difference was noted for time spent at a tertiary institution. There were differences in weight ($H_{3,103}$=18.88, P<0.001), SCZ weighed more than MPD (P=0.049) and CON (P=0.019), then BPD weighed more than MPD (P=0.010) and CON (P=0.003). Differences in BMI were also found ($H_{3,103}$=24.18, P<0.001), where SCZ BMI was greater than MPD (P=0.010) and CON (P=0.006), then BPD BMI was greater than MPD (P=0.001) and CON (P<0.001), **Table 3.1**.

3.1.2 Drug use

The ASSIST, a public health tool to assess drug use, was performed across all groups. The total substance involvement (TSI) score ($H_{3,103}=34.83$, $P<0.001$) was higher in MPD compared to CON ($P<0.001$), SCZ ($P<0.001$) and BPD ($P<0.001$). Tobacco ASSIST score ($H_{3,103}=24.74$, $P<0.001$) was higher in MPD compared to CON ($P<0.001$), SCZ ($P=0.021$) and BPD ($P=0.028$). Cannabis ASSIST score ($H_{3,103}=16.94$, $P<0.001$) was higher in MPD compared to CON ($P=0.005$), SCZ ($P=0.002$) and BPD ($P=0.012$). Methamphetamine ASSIST score ($H_{3,103}=63.31$, $P<0.001$) was higher in MPD compared to CON ($P<0.001$), SCZ ($P<0.001$) and BPD ($P<0.001$). Differences were found for the opioid ASSIST score ($H_{3,103}=16.16$, $P=0.001$), specific group differences were not evident. Mandrax ASSIST score ($H_{3,103}=36.49$, $P<0.001$) was higher in MPD compared to CON ($P<0.001$), SCZ ($P=0.012$) and BPD ($P<0.001$). No significant differences were evident for the alcohol ASSIST, cocaine ASSIST, inhalant ASSIST, sedative ASSIST and hallucinogen ASSIST scores, **Table3.4.**

Table 3.1 Demographic information

		Control n = 27 15 females/12 males			Schizophrenia n = 27 11 females/16 males			Bipolar I disorder n = 28 12 females/16 males			Methamphetamine induced psychosis n = 21 9 females/12 males		Kruskal Wallis (H-test)	Post hoc analysis
		Median	Range		Median	Range		Median	Range		Median	Range		
Age on day of imaging (yrs)	*	25,00	19-33		29,00	20-39		30.5	21-40		26,05	19-35	$H_{3,\ 103}$=12,96; P=0,004	CON vs SCZ P=0,041; CON vs BPD P=0,036
Duration at school (yrs)		12,00	8-14		12,00	7-14		12,00	9-12	#	10,24	7-12	$H_{3,\ 103}$=11,50; P=0,009	MPD vs CON P=0,043
Tertiary education (yrs)		0,00	0-10		0,00	0-6		1.5	0-8		0,57	0-4,5	**ns**	
Total duration of education (yrs)		12,00	8-12		12,00	7-18		13.5	9-20	@	10,80	7-16,5	$H_{3,\ 103}$=10,96; P=0,011	MPD vs CON P=0,017; MPD vs BPD P=0,041
Weight (kg)	*	68,40	55-84		80,00	50-136		83,85	52,7-110	&	68,77	47,5-98	$H_{3,\ 103}$=18,88; P<0,001	CON vs SCZ P=0,019; CON vs BPD P=0,003; MPD vs SCZ P=0,049; MPD vs BPD P=0,010
BMI	*	23,19	18,16-30,85		28,07	17,30-47,46		29,26	19,35-39,17	&	23,34	18,5-30,6	$H_{3,\ 103}$=24,18; P<0,001	CON vs SCZ P=0,006; CON vs BPD P<0,001; MPD vs SCZ P=0,010; MPD vs BPD P=0,001
Handedness (left:right)		1:26			3:24			2:26			3:19			

** CON vs SCZ and BPD; # CON vs MPD; @ MPD vs CON and BPD & MPD vs SCZ and BPD. ns Non- significant. Non- parametric Kruskal Wallis (H- test), Significance P<0,05.*

Table 3.2 Behavioural performance

		Control n = 27 15 females/12 males			Schizophrenia n = 27 11 females/16 males		Bipolar I disorder n = 28 12 females/16 males			Methamphetamine induced psychosis n = 21 9 females/12 males		Kruskal Wallis (H-test)	Post hoc analysis
		Median	Range		Median	Range	Median	Range		Median	Range		
Continuous Performance Task													
Correct responses (x/60)		59,00	18-60	*	48,50	15-60	58,00	13-60		50,00	16-60	$H_{3,\ 102}$=13,81; P=0,003	CON vs SCZ P=0,003
Overall response time (msec)		209,00	84-533	*	465,50	57-1044	302,50	134-674		283,00	105-677	$H_{3,\ 102}$=18,93; P<0,001	CON vs SCZ P<0,001
Errors of commission		0,00	0-28		5,00	0-33	1,00	0-46		5,00	0-44	**ns**	
Total number of omissions		0,00	0-24	#	3,00	0-45	0,00	0-18		0,00	0-12	$H_{3,\ 102}$=17,12;P<0,001	CON vs SCZ P=0,002; SCZ vs BPD P=0,014
Total number of trick S responses		0,00	0-13		0,00	0-11	0,00	0-4		0,00	0-5	**ns**	

** CON vs SCZ # SCZ vs CON and BPD. ns Non- significant. Non- parametric Kruskal Wallis (H- test), Significance P<0,05.*

3.1.3 Clinical scales

Clinical scales were only performed in the psychotic groups to analyse differences in clinical symptoms. The PANSS scale scores were assessed, as a total score, and its subscale scores: positive, negative and general psychopathology. PANSS total score ($H_{2,76}$=13.28, P=0.001) was attenuated (lower) in BPD compared to SCZ (P=0.013) and MPD (P=0.041). PANSS positive score ($H_{2,76}$=10.06, P=0.006) was poorer (higher) in SCZ compared to BPD (P=0.015). PANSS negative score ($H_{2,76}$=23.53, P<0.001) was attenuated (lower) in BPD compared to SCZ (P<0.001) and MPD (P<0.001). The general psychopathology score ($H_{2,76}$=7.14, P=0.028) was poorer (higher) in SCZ compared to BPD (P=0.028). Clinical global impression score ($H_{2,76}$=10.69, P=0.004) was poorer (higher) in SCZ compared to BPD (P=0.006). Global assessment of function scores ($H_{2,76}$=6.72, P=0.034) was poorer (lower) in SCZ compared to BPD (P=0.031). Extrapyramidal side effects score, using the Simpson Angus scale for Parkinsonism, ($H_{2,76}$=14.24, P<0.001) was higher in SCZ compared to BPD (P=0.006). No significant differences were found between groups for mood scales (Young Mania Rating Scale, Hamilton Depression Rating Scale, and Calgary Depression Rating Scale for Schizophrenia), **Table 3.3**.

Table 3.3 Clinical scales performed in psychotic disorders

	Psychotic groups combined n=76			Schizophrenia n=27			Bipolar I disorder n=28		Methamphetamine induced psychosis n=21		Kruskal Wallis (H-test)	Post Hoc Analysis
	Median	Range		Median	Range		Median	Range	Median	Range		
Positive & Negative Syndrome Scale												
Total score	43	30-100		48	30-100	*	35	30-73	45	30-77	$H_{2,76}$=13,28; P=0,001	BPD vs SCZ P=0,001; BPD vs MPD P=0,041
Positive symptoms	8	7-25	#	12	7-24		7	7-25	7	7-19	$H_{2,76}$=10,06; P=0,006	BPD vs SCZ P=0,015
Negative symptoms	11	7-30		13	7-30	*	9	7-20	12	7-27	$H_{2,76}$=23,53; P<00,01	BPD vs SCZ P<0,001; BPD vs MPD P<0,001
General psychopathology	22	16-50	#	23	16-50		19	16-37	22	16-38	$H_{2,76}$=7,14; P=0,028	BPD vs SCZ P=0,028
Calgary depression for schizophrenia	1	0-13		2	0-8		0	0-13	1	0-9	**ns**	
Hamilton depression rating scale	1	0-20		2	0-10		0	0-20	2	0-5	**ns**	
Young mania rating scale	2	0-16		3	0-15		1	0-16	2	0-12	**ns**	
Clinical global impression of illness severity	2	1-4	#	3	1-4		2	1-4	2	1-4	$H_{2,76}$=10,69; P=0,004	BPD vs SCZ P=0,006
Global assessment of functioning scale	65	5-90	#	60	30-85		71	5-85	65	31-90	$H_{2,76}$=6,72; P=0,034	BPD vs SCZ P=0,031
Simpson Angus scale for parkinsonism	0	0-16	#	1	0-16		0	0-1	0	0-9	$H_{2,76}$=14,24; P<0,001	BPD vs SCZ P=0,006

* BPD vs SCZ, and MPD ;# SCZ vs BPD. ns Non- significant. Non- parametric Kruskal Wallis (H- test), Significance P<0,05.

Table 3.4 Drug use

	Controls n=27		Schizophrenia n=27		Bipolar I disorder n=28			Methamphetamine induced psychosis n=21		Kruskal Wallis (H-test)	Post Hoc Analysis
	Median	Range	Median	Range	Median	Range		Median	Range		
Total substance involvement score	16	0-49	26	0-121	22	0-80	*	54	0-139	$H_{3,103}$=34,83; P<0,001	MPD vs CON P<0,001; MPD vs SCZ P<0,001; MPD vs BPD P<0,001
Tobacco score	3,00	0-31	9,00	0-38	9,00	0-39	*	21,00	0-34	$H_{3,103}$=24,74; P<0,001	MPD vs CON P<0,001; MPD vs SCZ P=0,021; MPD vs BPD P=0,028
Alcohol score	5,00	0-22	3,00	0-29	6,50	0-24		6,00	0-24	**ns**	
Cannabis score	3	0-9	3	0-20	3	0-24	*	9	0-28	$H_{3,103}$=16,94; P<0,001	MPD vs CON P=0,005; MPD vs SCZ P=0,002; MPD vs BPD P=0,021
Cocaine score	0	0-6	0	0-1	0	0-3		0	0-9	**ns**	
Methamphetamine score	0	0-3	0	0-29	0	0-3	*	11	0-41	$H_{3,103}$=63,31; P<0,001	MPD vs CON P<0,001; MPD vs SCZ P<0,001; MPD vs BPD P<0,001
Inhalants score	0	0-3	0	0-6	0	0-0		0	0-3	**ns**	
Sedatives sleeping pill score	0	0-3	0	0-6	0	0-16		0	0-6	**ns**	
Hallucinogens score	0	0-5	0	0-3	0	0-8		0	0-3	**ns**	
Opioids score	0	0-3	0	0-6	0	0-3		0	0-3	$H_{3,103}$=16,16; P=0,001	%
Mandrax score	0	0-3	0	0-6	0	0-3	*	3	0-15	$H_{3,103}$=36,49; P<0,001	MPD vs CON P<0,001; MPD vs SCZ P=0,012; MPD vs BPD P<0,001

** MPD vs all other groups; % Denotes significant differences but not between groups. ns Non- significant. Non- parametric Kruskal Wallis (H- test), Significance P<0,05.*

3.1.4Illness duration and medication

Analysis was conducted on the medication used within psychotic groups to determine whether medication effects were specific to clinical diagnosis. Within the psychotic group's, differences were found for years with clinical diagnosis: years with diagnosis ($H_{2,76}$=13.77, P=0.001) was shorter in MPD compared to SCZ (P=0.004) and BPD (P=0.002). Few studies have addressed illness duration across psychotic disorders. However, our results supports literature in that age, illness duration and medication can alter brain function (Tan et al. 2016).

First generation antipsychotics (FGAs; $H_{2,76}$=10.50, P=0.005) were prescribed more in MPD compared to SCZ (P=0.033) and BPD (P=0.047). The FGA haloperidol ($H_{2,76}$=15.82, P<0.001) was prescribed more in MPD compared to SCZ (P=0.007) and BPD (P=0.047). Second generation antipsychotics (SGAs; $H_{2,76}$=9.77, P=0.007) were prescribed more for SCZ compared to MPD (P=0.033). Differences were found for clozapine ($H_{2,76}$=14.85, P<0.001), however specific group differences were not evident.

Mood stabilizers ($H_{2,76}$=38.22, P<0.001) were prescribed more in BPD compared to MPD (P<0.001) and SCZ (P<0.001). The mood stabilizer lithium ($H_{2,76}$=22.94, P<0.001) was prescribed more in BPD compared to SCZ (P=0.019) and MPD (P=0.016). Then sodium valproate ($H_{2,76}$=13.35, P=0.001) was prescribed more to BPD compared to MPD (P=0.025).

Differences were found in anticholinergic's (i.e. orphenadrine) prescription ($H_{2,76}$=7.20, P=0.027) however specific group differences were not evident. Furthermore, no differences were found for the chlorpromazine equivalent, i.e. antipsychotic dose, **Table 3.5**.

3.2 Group differences in behavioural performance and event-related potential wave components

To address the first aim, a group analysis across the four groups (CON, SCZ, BPD and MPD) to determine whether group differences in (a) behavioural performance and (b) event related potential wave components amplitudes and latencies, this included prominent wave components during the cueing process and target stimulus.

3.2.1Behavioural performance group differences

The participants were asked to complete the Continuous Performance Task (CPT) where the behavioural performance data revealed several group differences, **Table 3.2**. For number of correct responses, i.e. accuracy, ($H_{3,102}$=13.81, P=0.003) SCZ made fewer correct responses than CON (P=0.003). Response times ($H_{3,102}$=18.93, P<0.001) were longer in SCZ than CON (P<0.001). Errors of omission ($H_{3,102}$=17.12, P<0.001) SCZ made more compared to CON (P=0.002) and BPD (P=0.014).

3.2.2Continuous performance event-related potential group differences

Several significant group differences in ERP wave components were found during the CPT. These differences were apparent for the cueing stimuli (first cue the first S presented and second cue the second S presented) and target stimulus (third S presented), **figure 2.3**.

3.2.2.1 First cue event-related potential wave component group differences

During the presentation of the first cue significant differences were found for the left frontal P100 amplitude (F_3($H_{3,103}$)=8.78, P=0.024) and left central P300 amplitude (C_3($H_{3,103}$)=9.18, P=0.026) however with post hoc analysis no significant group differences were evident. Then left parietal N170 amplitude (P_3($H_{3,103}$)=9.83, P=0.020) was smaller for SCZ compared to MPD (P=0.019), **Figure 3.1**.

Table 3.5 Medication

	Psychotic groups combined n=76		Schizophrenia n=27		Bipolar I disorder n=28			Methamphetamine induced psychosis n=21		Kruskal Wallis (H-test)	Post Hoc Analysis
	Median	Range	Median	Range	Median	Range		Median	Range		
Duration of psychotic disorders (yrs)	5	0,25-20	6	1-20	6	0,60-16	*	1	0,25-13	$H_{2,76}$=13,77; P=0,001	MPD vs SCZ P=0,004; MPD vs BPD P=0,002
Chlorpromazine equivalents	100	0-1500	200	0-1500	87,5	0-600		100	0-450		
Prescribed medications											
Any antipsychotic	62		22		20			20		**ns**	
1st generation antipsychotics	35		9		10		*	16		$H_{2,76}$=10,50; P=0,005	MPD vs SCZ P=0,033; MPD vs BPD P=0,047
Haloperidol	22		3		6		*	13		$H_{2,76}$=15,82; P<0,001	MPD vs SCZ P=0,007; MPD vs BPD P=0,047
Chlorporomazine	4		0		2			2		**ns**	
Sulpiride	2		2		0			0		**ns**	
Depot (Flupentixol:Zuclopenthixol: Fluphenazine)	5:5:1		2:3:1		1:1:0			2:2:1		**ns**	
2nd generation antipsychotics	33	#	18		10			5		$H_{2,76}$=9,77; P=0,007	MPD vs SCZ P=0,033
Clozapine	10		9		1			0		$H_{2,76}$=14,85; P<0,001	**%**
Olanzapine	2		2		0			0		**ns**	
Risperidone	15		5		5			5		**ns**	
Quetiapine	6		2		4			0		**ns**	
Moodstabilizers	33		6		25			2		**ns**	
Lithium	14		1	&	13			0		$H_{2,76}$=38,22; P<0,001	BPD vs SCZ P<0,001; BPD vs MPD P<0,001
Sodium valproate	22		5	&	15			2		$H_{2,76}$=22,94; P<0,001	BPD vs SCZ P=0,019; BPD vs MPD P=0,016
Lamotrigine	2		0	$	2			0		$H_{2,76}$=13,35; P=0,001	BPD vs MPD P=0,025
Serotonin/Norepinephrine reuptake inhibitors (Fluoxetine:Citalopram:Amitriptyline)	4:1:2		1:1:1		2:0:0			1:0:1		**ns**	
Anticholinergics - Orphenadrine	15		5		2			8		$H_{2,76}$=7,20; P=0,027	**%**

* MPD vs SCZ, and BPD; # SCZ vs MPD ; % Denotes significant differences but not between groups; & BPD vs SCZ, and MPD ; $ BPD vs MPD. ns Non- significant. Non- parametric Kruskal Wallis (H- test), Significance P<0,05.

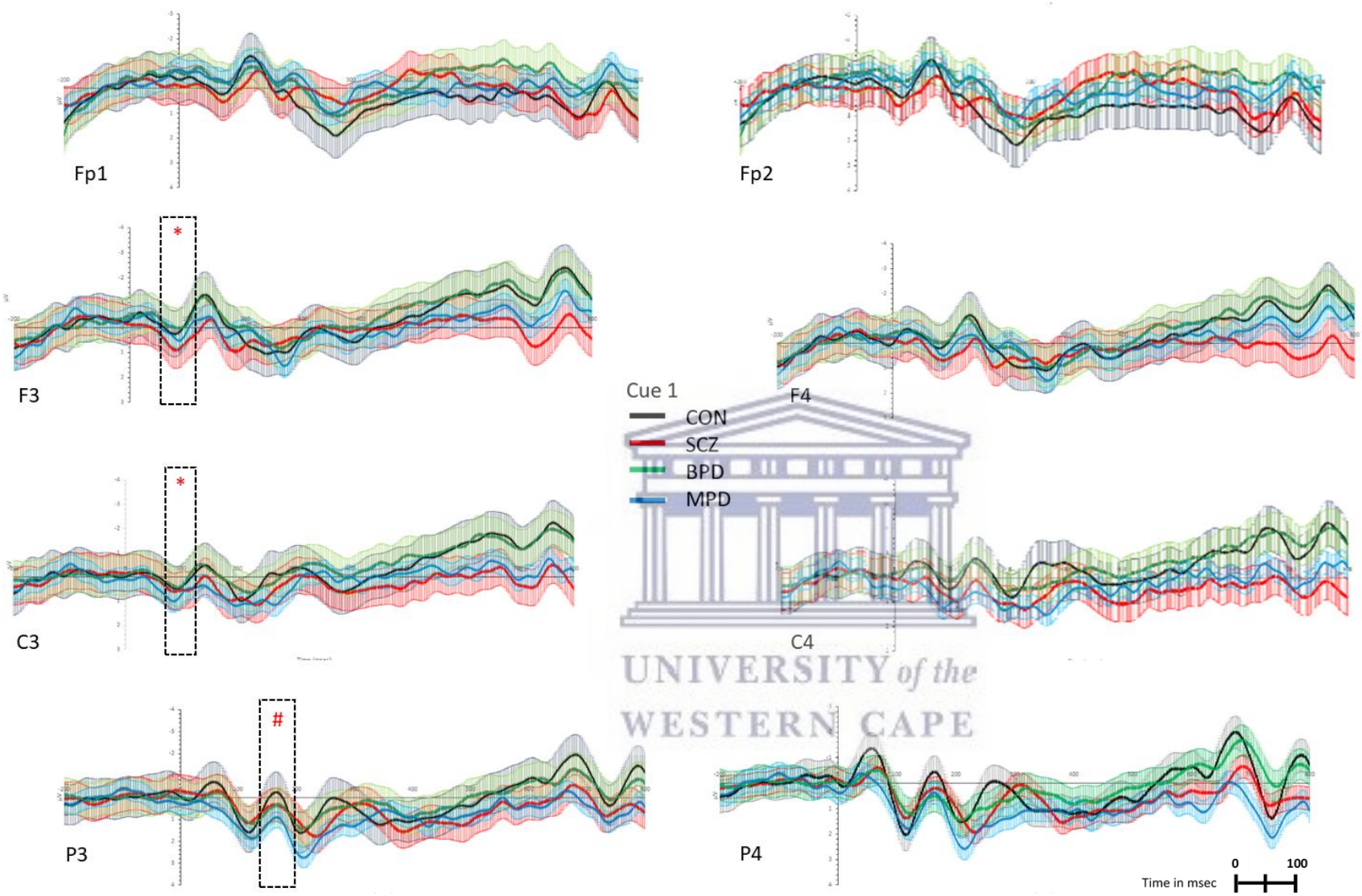


Figure 3.1 Grand mean event-related potentials of the first cue for the continuous performance task (-200 msec prior and 800 msec post cue presentation) for bilateral pre-frontal (Fp1 and Fp2), frontal (F3 and F4), central (C3 and C4), and parietal (P3 and P4), left and right electrodes respectively. *Differences in P100 waveform (50-150msec) amplitude were found for however post hoc analysis did not show any specific group differences for left frontal (F3) and left central (C3) electrode. #Left parietal (P_3) N170 waveform (100-250msec) amplitude was smaller for SCZ compared to MPD (P= 0.019). CON – control; SCZ- schizophrenia; BPD- bipolar with a history of psychosis; MPD- methamphetamine-induced psychotic disorder. Data represent the median with range of group grand mean average ERPs, Significance P<0.05

3.2.2.2 Second cue event-related potential wave component group differences

Several differences in amplitude were found for the second cue P100 wave component; left frontal amplitude ($F_3(F_{3,102})$=4.22; P=0.007) in SCZ was greater compared to CON (P=0.020) and BPD (P=0.045), right frontal amplitude ($F_4(F_{3,102})$=4.10; P=0.008) in SCZ was greater compared to CON (P=0.030) and BPD (P=0.025), left central amplitude ($C_3(H_{3,103})$=8.71; P=0.033) in SCZ was greater compared to CON (P=0.045), and the right central amplitude ($C_4(H_{3,103})$=11.53; P=0.009) in SCZ was greater compared to CON (P=0.022).

Several differences were found for N170 latency and amplitude; left pre-frontal latency ($Fp_1(H_{3,103})$=12.60; P=0.005) was shorter in CON compared to SCZ (P=0.008) and MPD (P=0.024). Then right central amplitude ($C_4(F_{3,102})$=2.93, P=0.037) in CON was smaller compared to SCZ (P=0.042). Then differences were found between groups for the right pre-frontal latency ($Fp_2(H_{3,103})$=8.55; P=0.035) and right frontal amplitude ($F_4(F_{3,102})$=2.90, P=0.038) however with post-hoc analysis specific group differences were not evident, **Figure 3.2**.

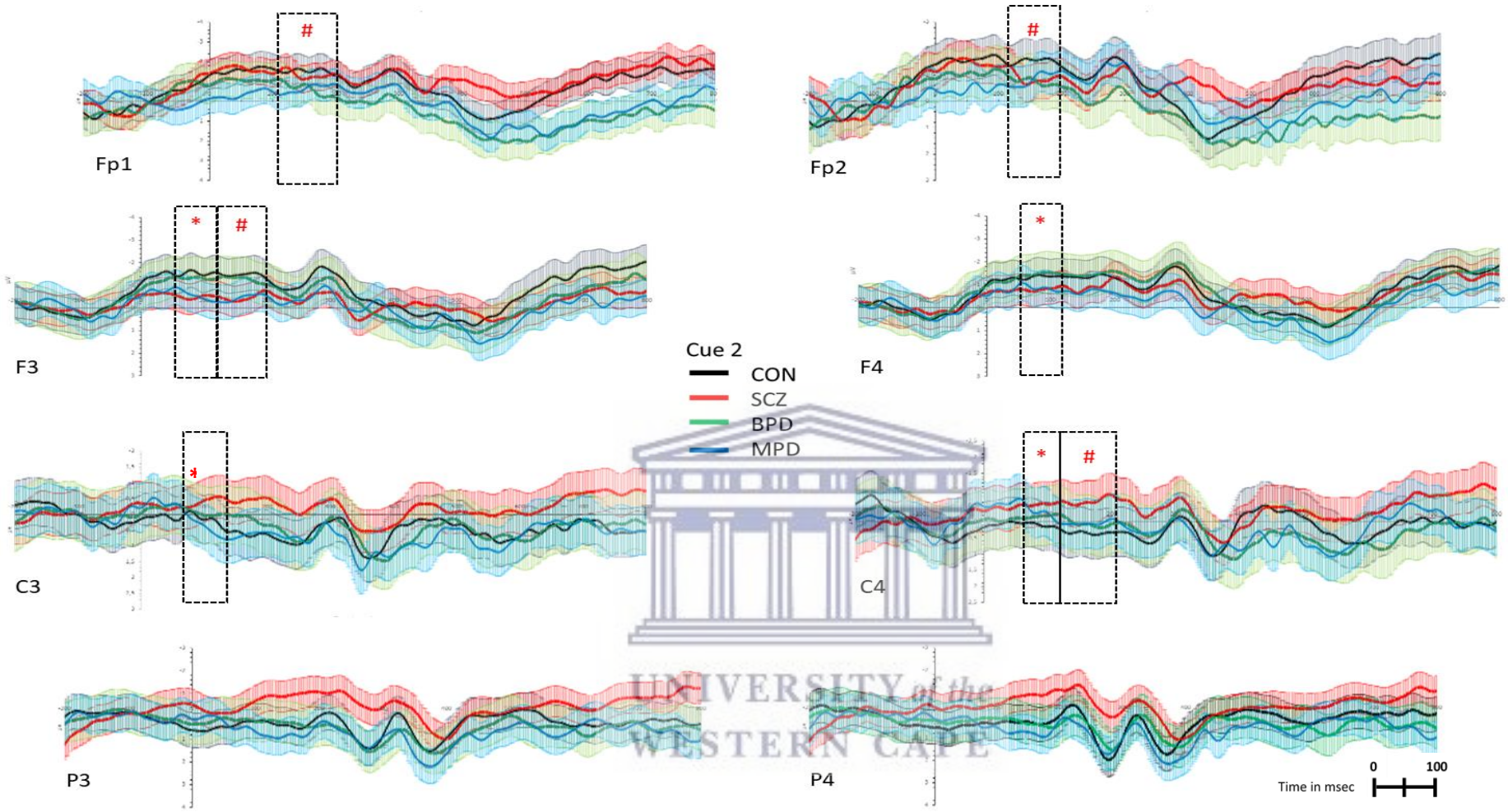


Figure 3.2 Grand mean event-related potentials of the second cue for the continuous performance task (-200 msec prior and 800 msec post presentation) for bilateral pre-frontal (Fp1 and Fp2), frontal (F3 and F4), central (C3 and C4), and parietal (P3 and P4), left and right electrodes respectively. #Differences in P100 waveform (50-150msec) amplitude were found for; left frontal (F3) in SCZ > CON and SCZ > BPD, right frontal (F4) in SCZ > CON and SCZ > BPD, left central (C3) in SCZ > CON, and the right central (C4) in SCZ > CON. *Differences were found for N170 waveform (100-250msec) latency and amplitude; left pre-frontal latency (Fp1) CON < SCZ and CON < MPD. Then right central amplitude (C4) in CON < SCZ. After post hoc analysis, no significant differences were found between groups in the right pre- frontal (Fp2) and left frontal (F3). CON – control; SCZ- schizophrenia; BPD- bipolar with a history of psychosis; MPD- methamphetamine-induced psychotic disorder. Data represent the median with range of group grand mean average ERPs, Significance P<0.05.

3.2.2.3 Target stimulus event-related potential wave component group differences

For the target stimulus, significant differences ERP wave components were found. For N70 wave component: right parietal N70 latency differed ($F_4(H_{3,103})=8.19$; P=0.042), no specific group differences were found with post hoc analysis. Left frontal P100 amplitude ($F_3(H_{3,103})=11.68$; P=0.008) in SCZ was greater than CON (P=0.005). Right frontal P100 amplitude ($F_4(H_{3,103})=14.99$; P=0.001) in SCZ was greater than CON (P=0.001) and BPD (P=0.022).

The left prefrontal N170 latency ($Fp_1(H_{3,103})=11.60$; P=0.008) was shorter for CON compared to SCZ (P=0.034) and MPD (P=0.041). The right prefrontal N170 amplitude ($Fp_2(F_{3,102})=3.77$; P=0.013) in SCZ was greater than CON (P=0.046), BPD (P=0.043) and MPD (P=0.044). The left frontal N170 amplitude ($F_3(F_{3,102})=2.81$; P=0.043) in SCZ was greater than CON (P=0.027); right frontal N170 amplitude ($F_4(F_{3,102})=4.18$; P=0.007) in SCZ was greater than CON (P=0.006).

Then right prefrontal P300 latency ($Fp_2(H_{3,103})=12.34$; P=0.006) was shorter for CON compared to SCZ (P=0.038) and MPD (P=0.017), **Figure 3.3**.

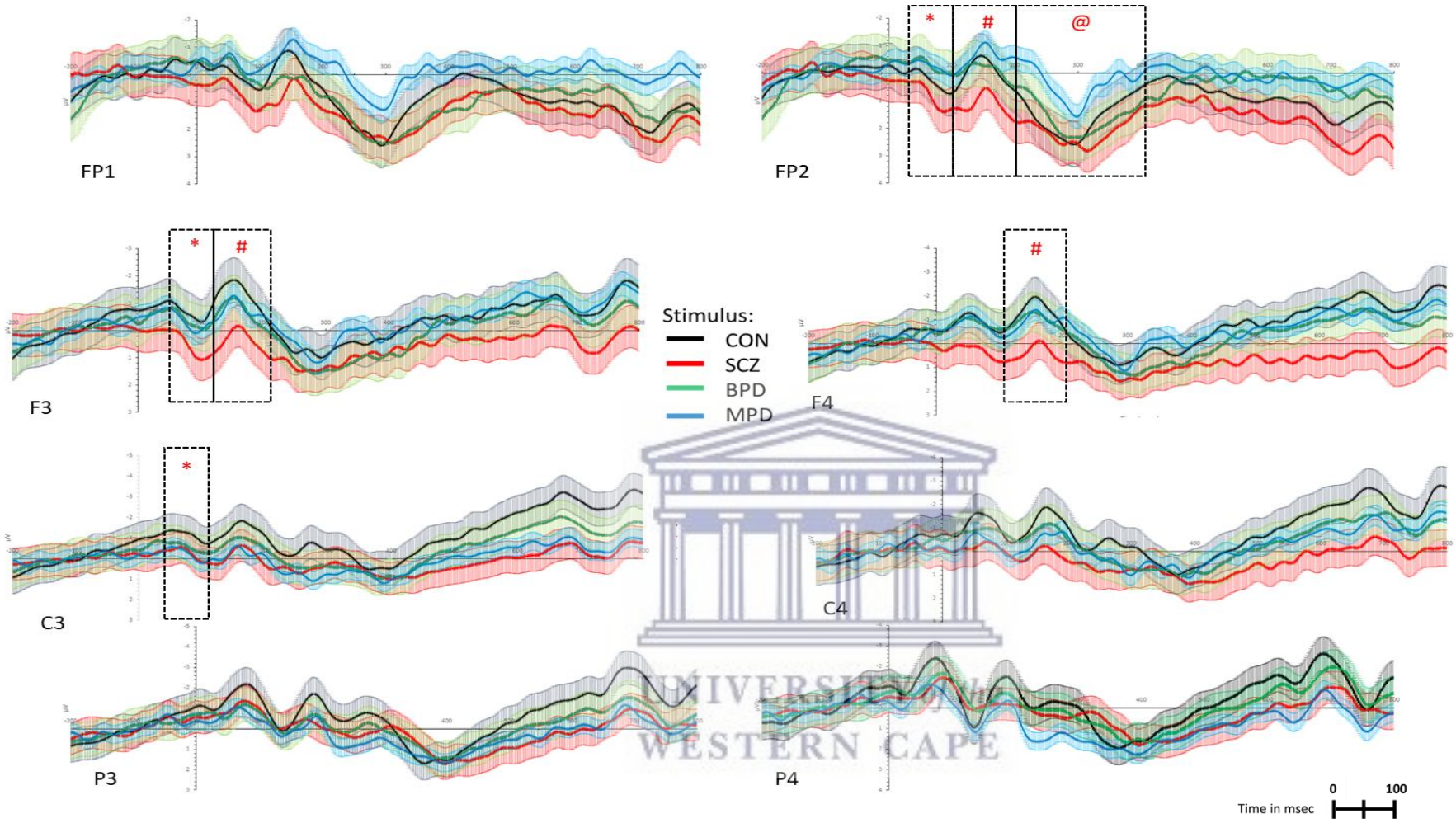


Figure 3.3 Grand mean event-related potentials of the target stimulus for the continuous performance task (-200 msec prior and 800 msec post presentation) for bilateral pre-frontal (Fp1 and Fp2), frontal (F3 and F4), central (C3 and C4), and parietal (P3 and P4), left and right electrodes respectively. *Differences in P100 waveform (50-150msec) left frontal P100 amplitude (F3) in SCZ > CON and SCZ > BPD. however, post hoc analysis did not show any specific group differences for right frontal N70 latency (F4). @Differences were found for N170 waveform (100-250msec) latency and amplitude; the left prefrontal latency (Fp1) and CON < MPD. The right prefrontal (Fp2) amplitude in SCZ > CON, SCZ > BPD and SCZ > MPD. The left frontal amplitude (F3) in CON < SCZ; right frontal amplitude (F4) in CON < SCZ.# Differences were found for P300 waveform (200-400msec) right prefrontal P300 latency (Fp2) was specifically shorter for CON < SCZ and CON < MPD. CON – control; SCZ- schizophrenia; BPD- bipolar with a history of psychosis; MPD- methamphetamine-induced psychotic disorder. Data represent the median with range of group grand mean average ERPs, Significance P<0.05.

3.3 Event related potential wave component correlation analysis

To address the second aim, to characterize event related potential wave component amplitude and latency relationships, correlation analyses were performed on (a) all four groups (CON, SCZ, BPD, MPD) with demographics, drug use, and behavioural performance data, and (b) within the psychotic groups (SCZ, BPD, MPD) for clinical variables (clinical scales, duration of illness, and medication prescribed).

3.3.1 Event-related potential wave component correlates with demographics

When group demographics were combined several correlations were found with ERP wave components of the CPT, significance $P<0.01$. The first of the spearman's rank correlation between ERPs and demographics was over all groups combined. Then the same analysis was looked at within each group (appendix E and appendix F).

Within CON for education, duration at school correlated with the first cue left parietal N170 amplitude ($P_3R_{Spearman's}$=0.51, p=0.005). Then tertiary education correlated with the first cue left parietal N170 amplitude ($P_3R_{Spearman's}$=0.53, p=0.003). For physical characteristics, weight correlated with the first cue left central P300 latency ($C_3R_{Spearman's}$=0.55, p=0.002).

Within SCZ for education, duration at school correlated with: target stimulus left parietal N170 latency ($P_3R_{Spearman's}$=0.56, p=0.002). The total years at school and total duration of education correlated with the second cue left parietal N170 latency ($P_3R_{Spearman's}$=0.58, p=0.001), and second cue left parietal N170 latency ($P_3R_{Spearman's}$=0.57, p=0.001).

Within MPD for age, the age on day of testing correlated with: target stimulus left frontal P300 latency ($F_3R_{Spearman's}$=-0.56, p=0.008), first cue right parietal N70 latency ($P_4R_{Spearman's}$=0.55, p=0.009), and first cue right parietal P300 amplitude ($P_4R_{Spearman's}$=0.72, p=0.001). For education, the duration of education correlated with: the second cue left central P300 latency ($C_3R_{Spearman's}$=-0.55, p=0.009). Tertiary education correlated with: target stimulus right central P100 latency ($C_4R_{Spearman's}$=0.60, p=0.003) and first cue right parietal P300 amplitude ($P_4R_{Spearman's}$=0.68, p=0.006). For physical characteristics, BMI correlated with the second cue right frontal P100 latency ($F_4R_{Spearman's}$=-0.55, p=0.009).

3.3.2 Event-related potential wave component correlates with drug use

Within CON for ASSIST scores i.e. measure of drug use, total substance involvement correlated with: first cue left parietal N170 latency ($P_3R_{Spearman's}$=-0.50, p=0.007), and target stimulus left parietal P300 ($P_3R_{Spearman's}$=-0.54, p=0.003). Tobacco ASSIST correlated with: first cue left prefrontal N170 latency ($Fp_1R_{Spearman's}$=-0.50, p=0.007), and target stimulus left parietal P300 amplitude ($P_3R_{Spearman's}$=-0.58, p=0.001). Alcohol ASSIST correlated with: second cue left parietal N170 amplitude ($P_3R_{Spearman's}$=0.55, p=0.002), and target stimulus right prefrontal P300 amplitude ($Fp_2R_{Spearman's}$=-0.51, p=0.006). Cannabis ASSIST correlated with: target stimulus right frontal P100 latency ($F_4R_{Spearman's}$=-0.55, p=0.002), second cue right frontal P100 latency ($F_4R_{Spearman's}$=-0.54, p=0.003), second cue right parietal N70 amplitude ($P_4R_{Spearman's}$=0.50, p=0.007), first cue left central N170 latency ($C_3R_{Spearman's}$=-0.52, p=0.004); second cue right parietal N170 amplitude ($P_4R_{Spearman's}$=0.53, p=0.003), and target stimulus right frontal P300 amplitude ($F_4R_{Spearman's}$=-0.50, p=0.007). Cocaine ASSIST correlated with and first cue right prefrontal N170 amplitude ($Fp_2R_{Spearman's}$=0.50, p=0.007). Methamphetamine ASSIST correlated with the second cue left central N170 amplitude ($C_3R_{Spearman's}$=0.52, p=0.004). Hallucinogen ASSIST correlated with the second cue: left parietal N70 amplitude ($P_3R_{Spearman's}$=-0.50, p=0.007), left parietal P100 amplitude ($P_3R_{Spearman's}$=0.52, p=0.004); right parietal P100 amplitude ($P_4R_{Spearman's}$=0.49, p=0.008), and left parietal P150 amplitude ($P_3R_{Spearman's}$=-0.52, p=0.004).

Within SCZ for ASSIST scores, total substance involvement correlated with: target stimulus left parietal N70 amplitude ($P_3R_{Spearman's}$=-0.61, p<0.001), target stimulus right parietal N70 amplitude ($P_4R_{Spearman's}$= -0.55, p=0.002), target stimulus right parietal P100 amplitude ($P_3R_{Spearman's}$=-0.57, p=0.001), first cue left parietal P100 latency ($P_3R_{Spearman's}$=-0.50, p=0.007), target stimulus left parietal N170 amplitude ($P_3R_{Spearman's}$=-0.56, p=0.002), target stimulus right parietal N170 amplitude ($P_4R_{Spearman's}$=-0.55, p=0.002), second cue left parietal P300 latency ($P_3R_{Spearman's}$=0.53, p=0.004), second cue right parietal P300 latency ($P_4R_{Spearman's}$=0.50, p=0.007), target stimulus left parietal P300 latency ($P_3R_{Spearman's}$=0.55, p=0.002), and target stimulus right parietal P300 latency ($P_4R_{Spearman's}$= 0.56, p=0.002). Tobacco ASSIST correlated with: target stimulus left parietal N70 amplitude ($P_3R_{Spearman's}$=-0.56, p=0.002), target stimulus right parietal N70 amplitude ($P_4R_{Spearman's}$=-0.51, p=0.005), first cue left frontal P100 amplitude ($F_3R_{Spearman's}$=0.50, p=0.007), first cue left parietal P100

amplitude ($P_3R_{Spearman's}$=0.61, p<0.001), first cue left parietal P100 latency ($P_3R_{Spearman's}$=-0.51, p=0.006); target stimulus right parietal P100 amplitude ($P_3R_{Spearman's}$= -0.57, p=0.001), right frontal P100 amplitude ($F_4R_{Spearman's}$=0.61, p<0.001), first cue left frontal N170 latency ($F_3R_{Spearman's}$=0.54, p=0.003), target stimulus left central P300 latency ($C_3R_{Spearman's}$=0.61, p<0.001), second cue right parietal P300 latency ($P_4R_{Spearman's}$=0.54, p=0.003), target stimulus right parietal P300 latency ($P_4R_{Spearman's}$=0.58, p=0.001), and target stimulus left parietal P300 latency ($P_3R_{Spearman's}$=0.60, p<0.001). Cannabis ASSIST correlated with the second cue right parietal P100 amplitude ($P_4R_{Spearman's}$=-0.50, p=0.007). Alcohol ASSIST correlated with the target stimulus left frontal N170 amplitude ($F_3R_{Spearman's}$=0.55, p=0.002).

Within BPD for ASSIST scores, total substance involvement correlated with the second cue left frontal N170 amplitude ($F_3R_{Spearman's}$=0.52, p=0.004). Tobacco ASSIST correlated with the first cue right central N170 amplitude ($C_4R_{Spearman's}$=0.50, p=0.005).

Within MPD for ASSIST scores, total substance involvement correlated with: second cue left prefrontal P300 latency ($Fp_1R_{Spearman's}$=0.55, p=0.008). Tobacco ASSIST correlated with: first cue right central P300 latency ($C_4R_{Spearman's}$=0.62, p=0.002). Alcohol ASSIST correlated with: first cue right frontal N170 amplitude ($F_4R_{Spearman's}$=0.58, p=0.004), second cue left prefrontal N170 amplitude ($Fp_1R_{Spearman's}$=0.76, p<0.001), second cue right prefrontal N170 amplitude ($Fp_2R_{Spearman's}$=-0.63, p=0.002), second cue left prefrontal P300 amplitude ($Fp_1R_{Spearman's}$=-0.72, p<0.001), and second cue right prefrontal P300 amplitude ($Fp_2R_{Spearman's}$=-0.66, p=0.001). Methamphetamine ASSIST correlated with the target stimulus left parietal N170 amplitude ($P_3R_{Spearman's}$=-0.56, p=0.007).

3.3.3 Event- related potential wave component correlates with behavioural performance

Within CON for behavioural performance, number of correct responses correlated with: first cue left parietal N70 amplitude ($P_3R_{Spearman's}$=0.65, p<0.001), first cue left parietal P100 amplitude ($P_3R_{Spearman's}$=0.56, p=0.002), first cue left parietal P150 amplitude ($P_3R_{Spearman's}$=0.61, p<0.001), first cue left central N170 amplitude ($C_3R_{Spearman's}$=0.51, p=0.006), and first cue left parietal N170 amplitude ($P_3R_{Spearman's}$=0.67, p<0.001). The total number of omissions correlated with: first cue left parietal cortex N70 amplitude ($P_3R_{Spearman's}$=-0.53, p<0.001) and target stimulus left parietal N170 amplitude ($P_3R_{Spearman's}$=-0.52, p=0.005). The total number of impulsive responses correlated with: first cue left

parietal N70 amplitude ($P_3R_{Spearman's}$=-0.65, p<0.001), first cue left parietal P100 amplitude ($P_3R_{Spearman's}$=-0.56, p=0.002), first cue left parietal P150 amplitude ($P_3R_{Spearman's}$=-0.61, p= p<0.001), first cue left central N170 amplitude ($C_3R_{Spearman's}$=-0.53, p=0.004), second cue left central N170 amplitude ($C_3R_{Spearman's}$=-0.52, p=0.005), target stimulus left central N170 amplitude ($C_3R_{Spearman's}$=-0.50, p=0.007), and first cue left parietal N170 amplitude ($P_3R_{Spearman's}$=-0.70, p<0.001).

Within the SCZ for behavioural performance, number of correct responses correlated with the first cue left parietal P150 latency ($P_3R_{Spearman's}$=0.50, p=0.008). Response time correlated with: target stimulus left central P300 latency ($C_3R_{Spearman's}$=-0.57, p=0.002), target stimulus right central P300 amplitude ($C_4R_{Spearman's}$=-0.54, p=0.004), target stimulus right parietal P300 latency ($P_4R_{Spearman's}$=-0.51, p=0.006), second cue right central P300 latency ($C_4R_{Spearman's}$=-0.53, p=0.005), and second cue right parietal P300 latency ($P_4R_{Spearman's}$=-0.52, p=0.006). The number of omissions correlated with the second cue right frontal P100 amplitude ($F_4R_{Spearman's}$=-0.57, p=0.001). Then number of impulsive responses correlated with: target stimulus left parietal N70 latency ($P_3R_{Spearman's}$=0.60, p=0.001) and second cue left parietal N70 latency ($P_3R_{Spearman's}$=0.60, p<0.001).

Within the MPD for behavioural performance, the number of omissions correlated with: first cue left frontal, P100 amplitude ($F_3R_{Spearman's}$=0.66, p= p<0.001), first cue left central, P100 amplitude ($C_3R_{Spearman's}$=0.62, p=0.002), first cue left parietal P100 amplitude ($P_3R_{Spearman's}$=0.61, p=0.002), second cue right parietal P100 amplitude ($P_4R_{Spearman's}$=0.55, p=0.008), and second cue right parietal P150 amplitude ($P_4R_{Spearman's}$=0.57, p=0.005).

3.3.4Event- related potential wave component correlates with clinical scales

Within SCZ for clinical scale scores, PANSS total correlated with the first cue: left central P300 amplitude ($C_3R_{Spearman's}$=0.52, p=0.005), right central P300 amplitude ($C_4R_{Spearman's}$=0.53, p=0.003), and left parietal P300 amplitude ($P_3R_{Spearman's}$=0.62, p<0.001). PANSS negative subscale correlated with the first cue left parietal P300 amplitude ($P_3R_{Spearman's}$=0.58, p=0.001). PANSS general psychopathology subscale correlated with: target stimulus right parietal P150 latency ($P_4R_{Spearman's}$=-0.53, p=0.003), second cue right parietal P150 latency ($P_4R_{Spearman's}$=-0.52, p=0.004), and first cue left parietal P300 amplitude ($P_3R_{Spearman's}$=0.56, p=0.002). Hamilton Depression Rating Scale correlated with:

first cue right frontal N170 latency ($F_4R_{Spearman's}$=-0.51, p=0.006), first cue left parietal N170 amplitude ($P_3R_{Spearman's}$=0.60, p<0.001), first cue right parietal P300 latency ($P_4R_{Spearman's}$=-0.52, p=0.004), and target stimulus right parietal P300 amplitude ($P_4R_{Spearman's}$=-0.52, p=0.004). Young Mania Rating Scale correlated with the first cue right central P100 latency ($C_4R_{Spearman's}$=-0.61, p=0.006). Then Clinical Global Impression correlated with the first cue left parietal N170 latency ($P_3R_{Spearman's}$=-0.50, p=0.006).

Within BPD for clinical scale scores, PANSS total correlated with the first cue: left central P100 amplitude ($C_3R_{Spearman's}$=0.54, p=0.002) and right central P100 amplitude ($C_4R_{Spearman's}$=0.50, p=0.006). PANSS positive subscale correlated with the second cue right parietal N170 amplitude was ($P_4R_{Spearman's}$=-0.50, p=0.005). PANSS negative subscale correlated with the first cue right parietal P300 amplitude ($P_4R_{Spearman's}$=0.50, p=0.006). Calgary Depression Rating Scale correlated with the target stimulus right central N170 amplitude ($C_4R_{Spearman's}$=0.50, p=0.005). General Assessment of Function correlated with the target stimulus left prefrontal N170 amplitude ($Fp_1R_{Spearman's}$=0.50, p=0.006), target stimulus right prefrontal N170 amplitude ($Fp_2R_{Spearman's}$=0.55, p=0.002), second cue left prefrontal N170 amplitude ($Fp_1R_{Spearman's}$=0.50, p=0.006), and second cue right prefrontal N170 amplitude ($Fp_2R_{Spearman's}$=0.51, p=0.005).

Within MPD for clinical scale scores, PANSS negative subscale correlated with: second cue left parietal P100 amplitude ($P_3R_{Spearman's}$=0.55, p=0.009), second cue left parietal P150 amplitude ($P_3R_{Spearman's}$=0.61, p=0.003), second cue right parietal P150 amplitude ($P_4R_{Spearman's}$=0.57, p=0.006), second cue left parietal N170 amplitude ($P_3R_{Spearman's}$=0.57, p=0.006), target stimulus right parietal P300 amplitude ($P_4R_{Spearman's}$=0.61, p=0.003), second cue left central P300 amplitude ($C_3R_{Spearman's}$=0.56, p=0.007), and second cue right parietal P300 amplitude ($P_4R_{Spearman's}$=0.56, p=0.007). Calgary Depression Rating Scale correlated with: target stimulus left central P100 latency ($C_3R_{Spearman's}$=-0.56, p=0.007), first cue left frontal N170 amplitude ($F_3R_{Spearman's}$=-0.56, p=0.008), first cue left frontal P300 amplitude ($F_3R_{Spearman's}$=-0.65, p=0.001), first cue right frontal P300 amplitude ($F_4R_{Spearman's}$=-0.62, p=0.0026), and target stimulus left frontal P300 latency ($F_3R_{Spearman's}$=0.56, p=0.007). Hamilton Depression Rating Scale correlated with: target stimulus left frontal P300 latency ($F_3R_{Spearman's}$=0.55, p=0.008), and target stimulus right frontal P300 latency

($F_4R_{Spearman's}$=0.58, p=0.005). Clinical Global Impression correlated with the second cue right frontal P100 latency ($F_4R_{Spearman's}$=-0.56, p=0.007).

3.3.5 Event-related potential wave component correlated with illness duration and chlorpromazine equivalents

There were no significant differences noted for chlorpromazine equivalent across groups however, differences were evident for illness duration within MPD. Within MPD duration of illness correlated with: target stimulus left frontal P100 latency ($F_3R_{Spearman's}$=-0.56, p<0.001), first cue left parietal P100 latency ($P_3R_{Spearman's}$=0.56, p=0.007), second cue the left frontal P100 latency ($F_3R_{Spearman's}$=-0.57, p=0.006), and first cue left parietal P150 latency ($P_3R_{Spearman's}$=0.70, p<0.001).

3.4 Event-related potential wave component differences by medication

To address the third aim, event-related potential wave component differences '*on*' and '*off*' a specific medication was determined by group the psychotic groups together. Then within each psychotic group '*on*' and '*off*' a medication where it was possible statistically (appendix D).

3.4.1 First cue event-related potential wave component medication differences

For the first cue ERP medication differences were found within all psychotic groups and then within SCZ and BPD only.

In all psychotic groups prescription of FGAs increased left central P100 amplitude (z=3,14;p=0,001, $on_{1.42(-1.07-7.26)}$ $off_{0.34(-4.19-3.04)}$), lengthened left central P100 latency (z=2,60;p=0,009, $on_{134(50-150)}$ $off_{98(50-150)}$), increased right central P100 amplitude (z=2,58;p=0,009, $on_{0.94(-1.20-4.21)}$ $off_{0.42(-5.88-4.20)}$), increased left parietal P100 amplitude (z=2,54;p=0,010, $on_{1.38(-0.86-5.92)}$ $off_{0.48(-2.95-4.69)}$), increased right parietal P100 amplitude (z=2,26;p=0,023, $on_{1.44(-0.87-4.69)}$ $off_{0.61(-4.42-5.38)}$), and lengthened right parietal N170 latency ($F_{1,76}$=4,49;p=0,037, $on_{220(100-250)}$ $off_{178(100-250)}$). In all psychotic groups prescription of SGAs shortened the left central P100 latency (z=2,88;p=0,003, $on_{88(50-150)}$ $off_{122(50-150)}$), shortened the left parietal P100 latency (z=1,97;p=0,048, $on_{92(50-150)}$ $off_{114(50-150)}$), increased the right prefrontal N170 amplitude (z=-2,63;p=0,008, $on_{-1.27(-5.45-6.46)}$ $off_{-2.28(-14.34-2.05)}$), and increased

the right central N170 latency (z=-2,29;p=0,021, $on_{190(100-250)}$ $off_{144(100-250)}$). In all psychotic groups prescription of mood stabilizers increased the left prefrontal P300 amplitude ($F_{1,76}$=4,53;p=0,036, $on_{2.29(2.68)}$ $off_{0.93(2.81)}$). In all psychotic groups prescription of anticholinergics increased the left prefrontal N170 amplitude (z=-2,25;p=0,023, $on_{-1.38(-3.89-3.29)}$ $off_{-2.20(-14.74-1.05)}$). In all psychotic groups prescription of any antipsychotic increased the right parietal N70 amplitude (z=2,08;p=0,037, $on_{-0.71(-5.97-2.87)}$ $off_{-1.93(-6.52-2.45)}$), increased the left central P100 amplitude (z=2,35;p=0,018, $on_{0.81(-4.19-7.26)}$ $off_{0.09(-3.39-2.53)}$), and increased the left parietal P100 amplitude (z=2,16;p=0,030, $on_{1.09(-2.95-5.92)}$ $off_{0.35(-2.35-2.26)}$). In all psychotic groups prescription of clozapine reduced the right parietal N170 amplitude ($F_{1,76}$=13,71;p<0,001, $on_{-1.06(2.01)}$ $off_{-3.68(2.54)}$), increased the left frontal P300 amplitude ($F_{1,76}$=4,09;p=0,046, $on_{2.36(1.19)}$ $off_{1.19(-1.69)}$). In all psychotic groups prescription of risperidone increased the right prefrontal N170 amplitude (z=-1,98;p=0,047, $on_{-1.21(-4.00-6.46)}$ $off_{-1.82(-14.34-2.05)}$) and shortened the right parietal N170 latency (z=2,46;p=0,013, $on_{158(108-216)}$ $off_{214(100-250)}$). In all psychotic groups prescription of haloperidol lengthened the left central P100 latency (z=-2,39;p=0,016, $on_{134(56-150)}$ $off_{101(50-150)}$), lengthened the right frontal N170 latency (z=2,25;p=0,024, $on_{118(100-200)}$ $off_{165(100-200)}$), lengthened the right parietal N170 latency (z=-2,02;p=0,043, $on_{225(100-250)}$ $off_{190(100-250)}$), lengthened the left prefrontal P300 latency (z=-2,07;p=0,037, $on_{378(218-400)}$ $off_{342(200-400)}$), lengthened the right frontal P300 latency (z=-2,06;p=0,038, $on_{370(228-400)}$ $off_{344(200-400)}$), and reduced the left central P300 latency (z=1,96;p=0,049, $on_{361(300-400)}$ $off_{390(300-500)}$). In all psychotic groups prescription of lithium increased the left prefrontal P300 amplitude ($F_{1,76}$=5,92;p=0,017, $on_{3.20(-1.62-10.14)}$ $off_{1.68(-6.32-6.36)}$).

In SCZ prescription of FGAs increased left central P100 amplitude (z=2.13; P=0.032, $on_{0.85(0.047)}$ $off_{0.32(-4.19-2.23)}$) and reduced left parietal P100 amplitude (z=2.44; P=0.014, $on_{1.82(0.064-3.54)}$ $off_{0.24(-2.95-4.44)}$). In SCZ, clozapine lengthened left frontal P100 amplitude (z=-2,75;p=0,005, $on_{1.50(0.25-7.02)}$ $off_{-0.08(-3.75-3.10)}$).

In BPD prescription of any antipsychotic medication increased right parietal N70 amplitude (z=2.49; P=0.012, $on_{-0.69(-2.39-2.87)}$ $off_{-2.10(-6.52-0.30)}$) and increased left central P100 amplitude (z=1.98; P=0.047, $on_{0.70(-1.21-2.82)}$ $off_{-0.33(-3.38-2.21)}$). Prescription of FGAs in BPD increased left central P100 amplitude (z=1.98; P=0.046, $on_{1.76(-0.66-2.82)}$ $off_{0.30(-3.38-2.39)}$), while prescription of

SGAs in BPD increased right prefrontal N170 amplitude (z=2.03; P=0.020, $on_{-1.42(-3.99-6.46)}$ $off_{-2.93(-9.97-0.78)}$).

3.4.2Second cue event-related potential wave component medication differences

For the second cue ERP medication differences were found when all three psychotic groups were combined and within each of the psychotic disorders.

In all psychotic groups prescription of FGAs increased the left prefrontal P300 latency ($F_{1,76}$=5,43;p=0,022, $on_{316.11(42.45)}$ $off_{298(202-388)}$). In all psychotic groups prescription of SGAs reduced the right parietal P150 amplitude (z=2,30;p=0,021, $on_{1.13(-2.52-5.36)}$ $off_{2.12(-7.96-16.25)}$), increased the right central P300 latency (z=-2,87;p=0,004, $on_{404(300-500)}$ $off_{368(300-484)}$), and increased the left parietal P300 latency (z=-2,59;p=0,009, $on_{400(250-500)}$ $off_{374(250-500}$). In all psychotic groups prescription of mood stabilizers shortened the right prefrontal N170 latency (z=2,64;p=0,008, $on_{140(100-200)}$ $off_{156(100-200)}$). In all psychotic groups prescription of anticholinergics increased the left prefrontal N170 amplitude ($F_{1,76}$=4,39;p=0,039, $on_{0.35(2.39)}$ $off_{-1.46(2.67)}$). In all psychotic groups prescription of clozapine increased the right frontal P100 amplitude ($F_{1,76}$=7,91;p=0,006, $on_{2.36(1.91)}$ $off_{0.09(2.44)}$), increased the left prefrontal N170 amplitude ($F_{1,76}$=4,31;p=0,041, $on_{0.68(2.97)}$ $off_{-1.17(2.56)}$), increased the right frontal N170 amplitude ($F_{1,76}$=7,01;p=0,009, $on_{-0.11(1.53)}$ $off_{-2.26(2.46)}$), increased the left prefrontal P300 amplitude ($F_{1,76}$=4,06;p=0,047, $on_{4.99(3.77)}$ $off_{2.81(3.09)}$). In all psychotic groups prescription of risperidone lengthened the right central P300 latency (z=-2,98;p=0,002, $on_{4.26(352-500)}$ $off_{372(300-500)}$). In all psychotic groups prescription of haloperidol increased the right parietal P100 amplitude (z=-2,13;p=0,032, $on_{2.14(-7.96-13.39)}$ $off_{1.14(-3.07-7.11)}$), increased the right parietal P150 amplitude (z=-2,51;p=0,011, $on_{3.35(-7.96-16.25)}$ $off_{1.51(-3.37-8.54)}$), shortened the left central P300 latency (z=2,44;p=0,014, $on_{357(300-500)}$ $off_{396(300-500)}$), and shortened the right central P300 latency (z=2,11;p=0,034, $on_{336(300-484)}$ $off_{385(300-500)}$). In all psychotic groups prescription of sodium valproate increased the right parietal N70 latency (z=-2,13;p=0,032, $on_{85(20-150)}$ $off_{72(20-150)}$), and increased the left prefrontal P300 latency ($F_{1,76}$=4,10;p=0,046, $on_{319.73(41.49)}$ $off_{295.67(202-398)}$).

In SCZ, SGAs reduced right parietal P150 amplitude (z=2.03; P=0.042, $on_{1.22(-2.19-5.35)}$ $off_{2.11(1.44-8.53)}$).

In BPD, SGAs lengthened left parietal P300 latency (z= -2.13; P=0.032, $on_{439(312\text{-}500)}$ $off_{373(250\text{-}452)}$). In BPD sodium valproate shortened left prefrontal P300 latency ($F_{1.26}$=5,19; P=0.031, $on_{316.93(41.67)}$ $off_{276.61(51.95)}$).

In MPD, haloperidol increased right parietal P150 amplitude (z=-1.99; P=0.046, $on_{5.20(-7.96\text{-}16.25)}$ $off_{1.18(-2.51\text{-}4.86)}$).

3.4.3Target event-related potential wave component medication differences

For the target stimulus ERP medication differences were found when all three psychotic groups were combined and within BPD only.

In all psychotic groups prescription of SGAs reduced the right parietal P100 amplitude (z=3,01;p=0,002, $on_{-1.10(-230\text{-}8.54)}$ $off_{1.27(-2.94\text{-}5.20)}$), reduced the left parietal P150 amplitude (z=2,47;p=0,013, $on_{0.54(-4.35\text{-}7.53)}$ $off_{1.61(-3.11\text{-}6.60)}$), reduced the right parietal P150 amplitude (z=2,96;p=0,003, $on_{0.43(-2.30\text{-}8.54)}$ $off_{2.11(-3.278.27)}$), lengthened the left central P300 latency (z=-2,71;p=0,006, $on_{404(300\text{-}500)}$ $off_{364(300\text{-}500)}$), lengthened the right central P300 latency (z=-2,43;p=0,014, $on_{406(300\text{-}500)}$ $off_{372(300\text{-}480)}$), and lengthened the left parietal P300 latency (z=-3,25;p=0,001, $on_{406(250\text{-}500)}$ $off_{37(250\text{-}500)}$). In all psychotic groups prescription of clozapine reduced the left parietal N70 amplitude ($F_{1,76}$=4,42;p=0,038, $on_{-3.10(2.23)}$ $off_{-1.75(1.83)}$), reduced the left parietal P100 amplitude ($F_{1,76}$=4,47;p=0,037, $on_{-0.32(2.02)}$ $off_{0.97(1.76)}$), increased the right prefrontal N170 amplitude ($F_{1,76}$=6,74;p=0,011, $on_{0.61(1.52)}$ $off_{-1.07(1.94)}$), increased the right frontal N170 amplitude ($F_{1,76}$=4,41;p=0,039, $on_{-0.51(1.38)}$ $off_{-1.77(1.81)}$). In all psychotic groups prescription of risperidone, lengthened the left central P300 latency (z=-3,07;p=0,002, $on_{4.26(362\text{-}500)}$ $off_{370(300\text{-}500)}$), lengthened the right central P300 latency (z=-2,35;p=0,018, $on_{408(352\text{-}500)}$ $off_{374(300\text{-}500)}$), and lengthened the left parietal P300 latency (z=-2,46;p=0,013, $on_{408(250\text{-}500)}$ $off_{378(250\text{-}500)}$). In all psychotic groups prescription of haloperidol increased the right parietal P100 amplitude (z=-2,19;p=0,028, $on_{2.19(-2.88\text{-}5.20)}$ $off_{0.25(-2.94\text{-}8.58)}$), increased the right parietal P150 amplitude (z=-2,11;p=0,034, $on_{2.33(-2.88\text{-}8.27)}$ $off_{0.88(-3.27\text{-}8.58)}$), and shortened the left central P300 latency (z=1,99;p=0,045, $on_{357(300\text{-}500)}$ $off_{392(300\text{-}500)}$). In all psychotic groups prescription of lithium increased the left central N170 latency (z=-2,19;p=0,028, $on_{182(138\text{-}250)}$ $off_{159(100\text{-}250)}$), and increased the left parietal N170 latency (z=-1,99;p=0,045, $on_{188(100\text{-}250)}$ $off_{159(100\text{-}246)}$). In all psychotic groups prescription of sodium valproate shortened the left central P100 latency (z=2,10;p=0,035, $on_{97(50\text{-}138)}$ $off_{113(50\text{-}150)}$),

and lengthened the left prefrontal P300 latency ($F_{1,76}$=4,44;p=0,038, $on_{324.55(35.70)}$ $off_{300(49.53)}$).

In BPD, SGAs: reduced right parietal P100 amplitude (z=2.22; P=0.025, $on_{-0.50(-182-2.17)}$ $off_{1.49(-2.94-4.11)}$), reduced left parietal P150 amplitude (z=1.98; P=0.046, $on_{0.10(-2.14-3.04)}$ $off_{1.70(-2.89-4.53)}$), reduced right parietal P150 amplitude (z=2.46; P=0.010, $on_{-0.04(-2.06-2.17)}$ $off_{2.09(-3.264.11)}$), lengthened left central P300 latency (z= -2.01; P=0.044, $on_{431(300-500)}$ $off_{345(300-458)}$), and lengthened left parietal P300 latency (z= -2.85; P=0.004, $on_{445(344-500)}$ $off_{373(250-450)}$). Then lithium in BPD lengthened left central N170 latency (z= -2.09; P=0.030, $on_{182(138-250)}$ $off_{158(114-220)}$).

Chapter 4 Discussion

Our main findings for each of our aims are as follows: (1) sustained attentional performance is poorer in SCZ. Our study adds to previous studies showing attention processing deficits in SCZ are evident during cueing of a sustained attention tasks; (2) substance use was found to slow cognitive processing, education improved executive function and information processing, and symptom severity was associated with dysfunction of prefrontal and frontal cortices; (3) antipsychotic medication was related to improved processing of salient information.

The study included 103 participants (27 CON, 27 SCZ, 28 BPD and 21 MPD). Although our intent was to match demographics across groups, we found CON were younger in age compared to SCZ and BPD. MPD reported fewer years at school compared to CON, and MPD reported shorter total duration at school going compared to CON and BPD, reduced education in methamphetamine users has previously been reported (O'Brien & Anthony 2009; Paulus 2017). Furthermore, SCZ weighed more than MPD and CON, then BPD weighed more than MPD and CON. Lastly SCZ BMI was greater than MPD and CON, and BPD BMI was greater than MPD and CON. These significant weight differences are likely due to psychotropic medication and their duration of use (Jibson 2017). The total substance involvement (TSI) score was higher in MPD compared to CON, SCZ and BPD. Tobacco ASSIST score was higher in MPD compared to CON, SCZ and BPD. Cannabis ASSIST score was higher in MPD compared to CON, SCZ and BPD. Methamphetamine use score was higher in MPD compared to CON, SCZ and BPD. It was expected that MPD would report high use of methamphetamine and other substances when compared to our other groups (McKetin et al. 2013).

Clinically, SCZ and MPD reported higher positive and negative symptom scores compared with BPD. Then SCZ reported greater general psychopathology on the PANSS scale compared to BPD. These data suggest severity of illness, not only psychotic symptoms, was greater in SCZ when compared to BPD. This was supported by general clinical assessment of mental health, using the clinical global impression and global assessment of function scales, where scores were worse for SCZ compared with BPD. Extrapyramidal side effects score, using the Simpson Angus scale for Parkinsonism, was higher in SCZ compared to BPD. This is

likely due to clozapine being prescribed more in SCZ compared to BPD (Johnsen & Kroken 2012). SGA's generally have fewer extrapyramidal side effects as compared to FGA's except for clozapine, olanzapine, and risperidone (Leucht et al. 2009). MPD reported shorter duration of illness when compared with SCZ and BPD. We suggest this difference is related to the transition in diagnosis from MPD to SCZ with time, this study however excluded participants with either a diagnosis of SCZ or BPD which may have had a causal link to the methamphetamine abuse. First generation antipsychotics, ergo haloperidol, were prescribed more in MPD compared to SCZ and BPD. This is due to the effectiveness of haloperidol in treating the effects of methamphetamine (Glasner-Edwards & Mooney 2014). Second generation antipsychotics were prescribed more for SCZ compared to MPD. SCZ has longer duration of illness compared to MPD and therefore are given FGA's for initial symptoms of psychosis and thereafter are given SGA's for management of symptoms (Abou-Setta et al. 2012; Johnsen & Kroken 2012). Differences were found for clozapine; however specific group differences were not evident. Our results show that cognitive deficits in SCZ, are slightly improved with SGA's. Mood stabilizers in general and lithium were prescribed more in BPD compared to MPD and SCZ. Then sodium valproate was prescribed more to BPD compared to MPD. This was to be expected as BPD is primarily a disorder of mood and medications prescribed are to improve mood stability (Malhi et al. 2017).

4.1 Groups differences in behavioural performance and event-related potential wave components

Behaviourally, performance of the CPT task, SCZ performed poorer than the other groups. This included poorer accuracy, a greater number of incorrect responses, longer response times, and more errors of omission compared to CON, they also made more errors of omission than BPD. SCZ is known to have cognitive deficits compared to CON (Onitsuka et al. 2013). Increased N170 and P300 amplitudes along with lengthened latencies have previously been noted in SCZ (Onitsuka et al. 2013; Feuerriegel et al. 2015). The increased amplitudes and lengthened latencies in SCZ indicate that cueing and processing of sustained attention is different in SCZ when compared with CON. Albeit that it is known that SCZ present with cognitive deficits and deficits in processing target stimuli, this study

provides ERP evidence to cognitive differences during cue processing. The lack of difference in BPD and MPD compared with CON suggests that cueing and processing of the sustained attentional task applied in this study are not affected (**Table 4.1**).

Table 4.1:Groups differences in behavioural performance and event-related potential wave components

	Group differences	Schizophrenia	Methamphetamine induced psychosis
Continuous Performance Task			
Behavioural performance	SCZ had fewer correct responses compared to CON SCZ response times were longer compared to CON SCZ errors of ommission were more compared to CON and BPD		
Cue 1	left frontal P100 amplitude left central P300 amplitude		left parietal N170 amplitude was < compared to MPD
Cue 2	right pre-frontal N170 latency right frontal N170 amplitude	left frontal P100 amplitude was > compared to CON and BPD right frontal P100 amplitude was > compared to CON and BPD left central P100 amplitude was > compared to CON right central P100 amplitude was > compared to CON right central N170 amplitude was > compared to CON left pre-frontal N170 latency was > compared to CON	left pre-frontal N170 latency was > compared to CON
Target	right parietal N70 latency	left frontal P100 amplitude was > compared to CON right frontal P100 amplitude was > compared to CON and BPD right prefrontal N170 amplitude was > compared to CON, BPD and MPD left frontal N170 amplitude was > compared to CON right frontal N170 amplitude was > compared to CON left pre-frontal N170 latency was > compared to CON right pre-frontal P300 latency was > compared to CON	right pre-frontal P300 latency was > compared to CON

The table denotes significant ANOVA, parametric (F-test) and non-parametric (H-test) ERP differences across all groups with further ERP differences noted within CON, SCZ, BPD and MPD. Significance P<0,05

4.1.1 First cue event- related potential wave component group differences

For the first cue, wave component differences were found only over the left hemisphere, for the P100 amplitude over frontal, P300 amplitude over the central cortex, and N170 amplitude over the parietal cortex. The task our participants performed included repetition of stimuli to improve the signal to noise ratio of neural activity, task repetition is known to activate the left hemisphere, the inability to maintain processing has been related to the inability to maintain engagement of the left hemisphere during repetitive tasks (Nemrodov et al. 2011). The P100 amplitude differences were not linked to specific group differences, i.e. the overall test found a significant difference, and post-hoc test did not yield specific

group differences. Extraction of this wave component was supported by the literature, which states that the P100 is integrally involved in cognitive processes, however the exact neural mechanism during cognitive processing remain unknown (Campanella et al. 2006). It has been suggested that P100 amplitude decreases when the individual does not attend to a task (Bolton & Staines 2011). Due to the presence of an extractable P100 during early cueing, first cue, it suggests that our participants were engaged with the task while they were performing it and there were differences in the ability of participants to maintain early cognitive processes related to repetition.

The N170 amplitude over the left parietal cortex was smaller in SCZ when compared to MPD during the first cue only. Previous studies have shown that N170 amplitude is reduced when the working memory capacity is at a max point (Morgan et al. 2008). This suggests that SCZ, compared to MPD, are unable to recruit working memory sufficiently and therefore have reduced ability to concentrate or maintain attention during the task. It has been noted in SCZ, that the N170 is attenuated when processing emotional stimuli (Lynn & Salisbury 2008; Feuerriegel et al. 2015; Cao et al. 2015; Maher et al. 2016). The N170 usually shows dominance over the right hemisphere during a task which involves the presentation of faces showing different emotions (Tso et al. 2017). However our study did not involve face processing, but N170 related to letter processing (Stevens et al. 2013). In healthy adults a greater amplitude has been noted for the N170 in single letter processing. Our findings for the our first cue support these previous studies (Stevens et al. 2013; Begum et al. 2014). Taking this literature into consideration our findings suggest that individuals with SCZ and MPD have differences in the initiation of cue processing during a sustained attention task.

4.1.2 Second cue event- related potential wave component group differences

For the presentation of the second cue, differences noted for all groups were localised to the frontal and central brain regions and for P100 and N170 ERP waveforms. Left and right frontal and central P100 amplitude in SCZ was greater compared to CON. SCZ had greater left and right frontal P100 amplitude compared to BPD. Bolton and Steines (2011) suggested a decrease in P100 amplitude in the dorsal lateral prefrontal cortex contributes to processing and filtering of irrelevant information (Bolton & Staines 2011), with poorer

behavioural performance in SCZ and increased P100 amplitude during the second cue this may suggest that are reported in the literature SCZ that they have a reduced ability to filter and process relevant stimuli compared to CON and BPD. Then CON had a shorter left pre-frontal N170 latency when compared to SCZ and MPD. This suggests that visual processing is slower in SCZ and MPD. The lack of difference found for BPD suggests that deficits in cue processing is limited to SCZ (Heimrath et al. 2012; Stevens et al. 2013) and MPD. Lastly, SCZ N170 amplitude was greater when compared to CON These results indicate that there are possible sensory deficits which can influence target stimuli selection(Okena et al. 2006)

4.1.3 Target stimulus event- related potential wave component group differences

For the target stimulus wave component differences were found over the prefrontal, frontal and parietal brain regions. SCZ had a greater left and right frontal P100 amplitude compared to CON. SCZ had a greater right frontal P100 amplitude compared to BPD. The P100, involved in basic visual processing (Wynn et al. 2008), was found to be greater in SCZ compared to CON and BPD. As previously mentioned, the presence of the P100 during a cued task implies that the individual was engaged in the task. Also, the greater P100 amplitude in SCZ for the presentation of target stimuli is indicative of differentiating between the target stimulus and potential distractors (Lynn et al. 2016), this suggests that SCZ requires enhanced processing of the P100 which may be related to ineffective filtering of what is relevant and what is not.

SCZ N170 was found to differ, they reported greater right prefrontal N170 amplitude compared to CON, BPD and MPD, and greater left and right frontal N170 amplitude compared to CON. Then SCZ and MPD N170 latency was longer than reported in. For the first and second cue an increase in N170 amplitude and delayed latency was noted over the prefrontal and frontal cortex in SCZ. In a study conducted by Wynn et al, (2008) the N170 showed delayed latency and increased amplitude in SCZ, supporting our findings. While, Campanella et al, (2006), and Morgan et al, (2008) reported delayed latency and decreased N170 amplitude, contrasting our current findings. Our results show that SCZ recognized the series of cues preceding the target but had a delay in responding to the target stimuli when it was presented. The enhanced amplitudes of P100 and N170 show that SCZ were engaged in the task and were applying significant effort. Campanella et al, (2006) suggested that

deficits in early (P100 and N170) visual processing underlies further dysfunction of the P300 in SCZ. However, our data suggests that the cognitive deficits are more strongly related to later (P300) cognitive processing, following increased amplitude in P100 and N170 waveforms which reflects the poor cognitive performance reported in SCZ.

To support this, SCZ and MPD reported longer P300 latency over their right prefrontal cortex when compared with CON. The longer latency in SCZ and MPD suggests a longer temporality to completing cortical updating and orientating, supported by SCZ's poorer behavioural performance (Sur & Sinha 2009). The differences found over the prefrontal and frontal regions indicate that there are impaired executive function in SCZ (Krishnadas et al. 2014). Finding the P300 difference in MPD too, suggests that MPD share in part the executive function deficits seen in SCZ, and are related to later cognitive processing, further research is required to contrast the similarities reported in MPD with SCZ.

4.2 Event- related potential wave component relationships

Many relationships were found between demographics, drug use, and clinical variables and ERP wave components during the sustained visual attention task. Overall, for the first cue, education positively correlated with the N170 left parietal amplitude in CON and P300 right parietal amplitude in MPD. During the second cue, the left parietal N170 latency in SCZ correlated positively with education and the left central P300 latency correlated negatively with education in MPD. The age on the day of testing correlated negatively with the first cue right parietal N70 latency and correlated positively with the target left frontal P300 latency in MPD (**Table 4.2**).

Table 4.2: Event related wave component correlates with demographics

	Control	Schizophrenia	Methamphetamine induced psychosis
Cue 1: Demographics			
Age on day of imaging (yrs)			- right parietal N70 latency
			+ right parietal P300 amplitude
Duration at school (yrs)	+ left parietal N170 amplitude		
Tertiary education (yrs)	+ left parietal N170 amplitude		+ right parietal P300 amplitude
Cue 2: Demographics			
Duration at school (yrs)		+ left parietal N170 latency	- left central P300 latency
Total duration of education (yrs)		+ left parietal N170 latency	
Target: Demographics			
Age on day of imaging (yrs)			+ left frontal P300 latency
Duration at school (yrs)		+ left parietal N170 latency	

Correlation differences across all four groups and further across psychotic groups (SCZ, BPD, MPD), in demographics, behavioural performance, and drug use. + positive correlation - negative correlation. Spearman's rank order Rho ±0,5 Significance P< 0,01

A summary of these relationships are as follows: for the first cue, drug use negatively correlated with the CON left prefrontal, central and parietal N170 latencies and positively correlated with the right central N170 amplitude in BPD. In SCZ, correlations were noted for the P100 left frontal and parietal amplitude and latencies and the N170 frontal latency. In MPD there was a positive correlation with the right frontal N170 amplitude and right central P300 latency. For the second cue, drug use correlated positively with the right parietal N70, right prefrontal N170 and left frontal N170 amplitudes, and negatively correlated with the right frontal P100 latency in CON. A positive correlation was noted across left and right parietal P300 latency and negatively for the right parietal P100 amplitude in SCZ. A positive correlation was noted for the left frontal N170 amplitude in BPD. In MPD, a negative correlation was noted across left and right prefrontal N170 and P300 amplitudes, and positive correlation for the left prefrontal P300 latency in MPD. For the target stimulus, correlations were evident for the right frontal P100 latency and P300 amplitude and the left parietal P300 amplitude in CON. Left and right parietal N70, N170 amplitudes, P300 latency, the right parietal P100 amplitude and left central P300 latency in SCZ correlated with drug use. Lastly the left parietal N170 amplitude in MPD correlated positively with drug use (**Table 4.3**).

Table 4.3: Event related wave component correlates with drug use

	Control	Schizophrenia	Bipolar I disorder	Methamphetamine induced psychosis
Cue 1: Drug use				
TSI	- left parietal N170 latency	- left parietal P100 latency		
Tobacco	- left prefrontal N170 latency	+ left frontal P100 amplitude	+ right central N170 amplitude	+ right central P300 latency
		+ left parietal P100 latency		
		- left frontal N170 latency		
Cannabis	- left central N170 latency			
Alcohol				+ right frontal N170 amplitude
Cue 2: Drug use				
TSI		+ left parietal P300 latency	+ left frontal N170 amplitude	+ left prefrontal P300 latency
		+ right parietal P300 latency		
Cannabis	- right frontal P100 latency	- right parietal P100 amplitude		
	+ right parietal N70 amplitude			
Alcohol	+ right prefrontal N170 amplitude			- left prefrontal N170 amplitude
	+ left frontal N170 amplitude			- right prefrontal N170 amplitude
				- left prefrontal P300 amplitude
				- right prefrontal P300 amplitude
Target: Drug use				
TSI	- left parietal P300 amplitude	- left parietal N70 amplitude		
		- right parietal N70 amplitude		
		- right parietal P100 amplitude		
		- left parietal N170 amplitude		
		- right parietal N170 amplitude		
		+ left parietal P300 latency		
		+ right parietal P300 latency		
Tobacco	left parietal P300 amplitude	- left parietal N70 amplitude		
		- right parietal N70 amplitude		
		- righ parietal P100 amplitude		
		+ left central P300 latency		
		+ right parietal P300 latency		
		+ left parietal P300 latency		
Cannabis	- right frontal P100 latency			
	- right frontal P300 amplitude			
Methamphetamine				+ left parietal N170 amplitude
Alcohol	+ right frontal P300 amplitude			

Correlation differences across all four groups and further across psychotic groups (SCZ, BPD, MPD), in demographics, behavioural performance, and drug use. + positive correlation - negative correlation. Spearman's rank order Rho ±0,5 Significance P<0,01

A summary of these relationships which pertained only to the psychotic groups are as follows: for the presentation of the first cue, the PANSS total correlated with the left and right central and parietal P300 amplitude in SCZ. The SCZ left parietal and right central P300 amplitude correlated with the PANSS general. PANSS total correlated with the left and right central P100 amplitude and PANSS general correlated with the left parietal P100 amplitude in BPD. Then the BPD right parietal P300 amplitude correlated with the PANSS negative (**Table 4.4, Table 4.5, Table 4.6**).

Table 4.4: Event related wave component correlates with clinical scales for the first cue

	Schizophrenia	Bipolar I disorder	Methamphetamine induced psychosis
	ERP wave form	**ERP wave form**	**ERP wave form**
Positive & Negative Syndrome Scale			
Total score	+ left central P300 A	+ left central P100 A	
	+ right central P300 A	+ right central P100 A	
	+ left parietal P300 A		
Negative symptoms	+ left parietal P300 A	+ right parietal P300 A	
General psychopathology	+ right central P300 A	+ left parietal P100 A	
	+ left parietal P300 A		
Calgary depression for schizophrenia			- left frontal P300 A
			- right frontal P300 A
			- left frontal N170 A
Hamilton depression rating scale	- right parietal P300 T		
	- right frontal N170 T		
	+ left parietal N170 A		
	+ right parietal N170 A		
Young mania rating scale	- right central P100 T		
Clinical global impression of illness severity	left parietal N170 T		
Global assessment of functioning scale		left prefrontal N170 A	
		right prefrontal N170 A	

Correlation differences across all four groups and further across psychotic groups (SCZ, BPD, MPD), in demographics, behavioural performance, and drug use. + positive correlation - negative correlation. Spearman's rank order Rho ± 0,5 Significance P< 0,01

Table 4.5: Event related wave component correlates with clinical scales for the second cue

	Schizophrenia		Bipolar I disorder		Methamphetamine induced psychosis
	ERP wave form		ERP wave form		ERP wave form
Positive & Negative Syndrome Scale					
Positive symptoms		-	right parietal N170 A		
Negative symptoms				+	left central P300 A
				+	right parietal P300 A
				+	left parietal N170 A
				+	left parietal P100 A
				+	left parietal P150 A
				+	right parietal P150 A
General psychopathology	- right parietal P150 T				
Clinical global impression of illness severity				-	right frontal P100 T
Global assessment of functioning scale		+	left prefrontal N170 A		
		+	right prefrontal N170 A		

Correlation differences across all four groups and further across psychotic groups (SCZ, BPD, MPD), in demographics, behavioural performance, and drug use. + positive correlation - negative correlation. Spearman's rank order Rho ± 0,5 Significance P< 0,01

Table 4.6: Event related wave component correlates with clinical scales for the target stimulus

	Schizophrenia		Bipolar I disorder		Methamphetamine induced psychosis
	ERP wave form		ERP wave form		ERP wave form
Positive & Negative Syndrome Scale					
Negative symptoms				+	right parietal P300 A
General psychopathology	- right parietal P150 T				
Calgary depression for schizophrenia		+	right central N170 A	+	left frontal P300 T
				+	left central P100 T
Hamilton depression rating scale	- right parietal P300 A			+	left frontal P300 T
				+	right frontal P300 T
Global assessment of functioning scale		+	left prefrontal N170 A		
		+	right prefrontal N170 A		

Correlation differences across all four groups and further across psychotic groups (SCZ, BPD, MPD), in demographics, behavioural performance, and drug use. + positive correlation - negative correlation. Spearman's rank order Rho ± 0,5 Significance P< 0,01

4.2.1 Event- related wave component correlates with demographics

Education was related to the first cue's N170 and P300. The N170 and P300 waveforms have been shown to be affected by level of education (Begum et al. 2014). Within CON, years of tertiary education and number of years at school were positively correlated with

left parietal N170 amplitude, supporting the findings of Begum et al (2014). These findings suggest that CON with higher levels of education, showed recognition and attention that the cueing process has been initiated by the presentation of the first cue. Then MPD right parietal P300 amplitude positively correlated with level of tertiary education, suggesting that in MPD tertiary education was advantageous to cortical updating at this early cueing stage. Our study follows previous results conducted by (Begum et al. 2014) showing that education does indeed influence the N170 and P300 ERP waveforms. Further, increased education to be related with increased P300 amplitude during the cueing process suggests that individuals are more strongly involved in early frontal executive processes when in the cueing stages of the task versus cortical updating (Sur & Sinha 2009), this finding requires further investigation as there is an absence of cueing P300 research in MPD to contrast this finding.

Duration of education was related to left hemisphere N170 latency in SCZ and MPD for the second cue. The total duration at school positively correlated with the left parietal N170 latency in SCZ. Delayed N170 latency was previously found in SCZ indicating deficits in executive function and visual processing deficits. The N170 latency has been linked to damage of the prefrontal and frontal cortex, resulting in delayed processing of visual stimuli (Adams et al. 2017). Scott et al, (2007) found that SCZ and MPD have damage to the prefrontal and frontal cortices (Scott et al. 2007; Bonilha et al. 2008; Hazlett et al. 2008; Petit et al. 2012). The duration at school negatively correlated with the left central P300 latency within MPD, also a positive correlation was noted with the left parietal N170 latency in SCZ. As with the first cue, education influenced the N170 and the P300 waveforms of the second cue.

For the target stimulus; the left parietal N170 latency positively correlated with the duration at school in SCZ, low education level in SCZ has previously been reported to affect behavioural performance (Erick Messias, Chuan-Yu Chen 2009). The left frontal P300 latency positively correlated with the age on the day of testing in MPD. These results indicate that age of MA use can influence cognition. These data suggest neural circuitry for the N170 to P300 are not only related to SCZ but are related to education and this association is apparent in SCZ and MPD.

4.2.2 Event- related wave component correlates with drug use

Early cognitive processing was affected by substance involvement across all groups. For the first cue; total substance involvement correlated positively with the right central P100 amplitude within BPD. A negative correlation was found for the left parietal N170 latency in CON, along with the left parietal P100 latency in SCZ with the total substance involvement. Slowed cognitive processing has previously been shown in substance abuse, this has been shown in CON and SCZ, and includes attentional processing and loading of working memory use (D'Souza et al. 2012; Petit et al. 2012; Thames et al. 2014), e.g. slowed P300 and reduce P300 latency (D'Souza et al. 2012). There is limited data reporting on early cognitive processing ERP waveforms, and further study is required to fully elucidate the relationships found with total substance use during the cueing process.

Tobacco use has previously been shown to improve cognition and patient recovery at mental health institutions despite the adverse effects tobacco has on the human body (Weinberger & Sofuoglu 2009). Tobacco use positively correlated with the left frontal P100 amplitude, left parietal P100 latency, and negatively correlated with the frontal N170 latency in SCZ. The right central N170 amplitude in BPD, and right central P300 latency in MPD correlated positively with tobacco use. Tobacco use in SCZ has previously been positively related to negative symptoms within SCZ (Patkar et al. 2002). Despite the strong correlation to negative symptoms in SCZ, amplitude reduction following tobacco use has shown an enhanced ability in individuals to ignore irrelevant stimuli as well as follow habituation (Veltri et al. 2017). This enhancement has been shown in previous studies which added alertness, verbal working memory and attention accuracy to the list of enhancements (Wesnes & Warburton 1983; Heishman et al. 2010; Kleykamp et al. 2011).

Alcohol use correlated positively with the right central N170 amplitude in MPD only. A previous study reported a similar finding in detoxified alcoholics (Matheus-Roth et al. 2016), a second found delayed latency of the N170 (Zhang et al. 2017). It is known that the abuse of alcohol affects frontal and more severely the subcortical brain structures (Moselhy et al. 2001; Brumback et al. 2007). Our finding support's the reported literature and likely addresses the damage in of gating neural activity, a result of alcohol abuse. Cannabis use correlated negatively with the left central N170 latency in CON. Van Tricht et al, (2013) and

Troup et al (2016) reported attenuated amplitudes and longer latencies in cannabis users (van Tricht et al. 2013; Troup et al. 2016). The current findings in part support the literature, however finding increased P100 and N170 amplitude contradict previous studies. Winton- Brown et al, (2015) indicated cannabis use in high psychosis risk patients have reduced sensory gating and overall reduced cortical function. Alcohol, tobacco and cannabis use reduced early sensory gating which therefore indicates a reduced ability to filter irrelevant information with use of these substances.

The second cue revealed substance involvement affected early and late cognitive processing across all groups. Total substance involvement scores positively correlated with the left and right parietal P300 latency in SCZ, the left frontal N170 amplitude in BPD and the left prefrontal P300 latency in MPD. Cannabis use correlated positively with the right parietal N70 latency and negatively with the right frontal P100 latency within CON, and right parietal P100 amplitude in SCZ. Cannabis use affected executive functioning along with movement and speech (D'Souza et al. 2009). These relationships suggest that cannabis use affected cue processing in CON, and minimally affected cue processing in psychotic disorders. Alcohol positively correlated with the left frontal N170 amplitude and right prefrontal N170 amplitude in CON, the left and right prefrontal N170 and P300 amplitude in MPD. Alcohol is known to affect the prefrontal and frontal cortex function (Moselhy et al. 2001). There is a single study which has addressed the effects of alcohol on N170 latency, however this study investigated hazardous drinkers and found longer N170 latencies in facial processing (Zhang et al. 2017). Further study is required to understand the mechanisms in which alcohol shortens the N170 latency during early cueing processes.

During target processing, substance use strongly correlated with wave components over parietal regions across all groups, then unique relationships within CON, SCZ and MPD were found. Total substance involvement correlated negatively with the right parietal P100 amplitude, negatively with both the left and right parietal N70 amplitude and N170 parietal amplitude in SCZ, as well as negatively with the left parietal P300 amplitude in CON. The total substance involvement correlated positively with left and right parietal P300 latency in SCZ. Methamphetamine use positively correlated with the left parietal N170 amplitude in MPD. MA has previously been shown to have an attenuated P300 amplitude during early MA abstinence (Berman et al. 2009). This reduction in amplitude is from the disruption of

catecholaminergic neurotransmission in individual with chronic MA use (Nordahl et al. 2003). Tobacco use correlated negatively with the left parietal P300 amplitude in CON, then negatively with both the left and right parietal N70 amplitude and positively with the left and right parietal P300 latency, then positively correlated with the left central P300 latency and negatively with the right parietal P100 amplitude in SCZ. Our result adds to a previous study conducted on the effects of tobacco use in SCZ which has been shown to enhance parietal cognitive processing (Giessing et al. 2006). Our data extend these findings as we report a link between tobacco use and reliability of cue updating during attentional processing. Alcohol use correlated positively with the right parietal N170 latency across all groups and negatively with the right prefrontal P300 amplitude in CON. Cannabis use correlated negatively with the left frontal P100 latency and right frontal P300 amplitude in CON. Troup et al, (2016) explained that delayed latency and was noted when attention was directed at the emotional cues. Also, a reduction in amplitude was noted with an increase in cannabis dose (Troup et al. 2016). These results support the current literature, that with substance use recognition and perception of target stimuli, and attentional deficits are apparent and more strongly affect parietal cortices function (Kleykamp et al. 2011; Troup et al. 2016; Troup et al. 2017; Ehlers et al. 2003).

4.2.3 Event- related wave component correlates with behavioural performance

Behavioural performance was related to the early wave components of the first cue's ERP. By accessing the number of correct responses, impulsive responses, omissions and commissions, a record of attention can be recorded. Omissions assess the attention given to the task at hand whereas commission assesses impulsive behaviour (**Table 4.7**).

Table 4.7: Event related wave component correlates with behavioural performance

	Control	Schizophrenia	Methamphetamine induced psychosis
Cue 1: Behavioural performance			
Correct responses	+ left parietal N70 amplitude	+ left parietal P150 latency	
	+ left parietal P100 amplitude		
	+ left parietal P150 amplitude		
	+ left central N170 amplitude		
	+ left parietal N170 amplitude		
Total number of omissions	- left parietal N70 amplitude		+ left frontal P100 amplitude
			+ left central P100 amplitude
			+ left parietal P100 amplitude
Total number of impulsive responses	- left parietal N70 amplitude		
	- left parietal P100 amplitude		
	- left parietal P150 amplitude		
	- left central N170 amplitude		
	- left parietal N170 amplitude		
Cue 2:Behavioural performance			
Response time		- right central P100 latency	
		- right parietal P300 latency	
Total number of omissions		- right frontal P100 amplitude	+ right parietal P100 amplitude
			+ right parietal P150 amplitude
Total number of impulsive responses	- left central N170 amplitude	+ left parietal N70 latency	
Target: Behavioural performance			
Response time		- left central P300 latency	
		- right central P300 amplitude	
		- right parietal P300 latency	
Trick stimulus responses		+ left frontal P100 latency	
Total number of omissions	- left parietal N170 amplitude		
Total number of impulsive responses	- left central N170 amplitude	+ left parietal N70 latency	

Correlation differences across all four groups and further across psychotic groups (SCZ, BPD, MPD), in demographics, behavioural performance, and drug use. + positive correlation - negative correlation. Spearman's rank order Rho ±0,5 Significance P<0,01

In CON, the number of correct responses positively correlated with the left parietal N70, P100, P150 and N170 amplitude, and left central N170 amplitude. While the number of impulsive responses correlated negatively with the left parietal N70, P100, P150 and N170 and the left central N170 amplitude of CON. Then the number of omissions negatively correlated with CON left parietal N70 amplitude. These relationships suggest that during early processing of initial cueing, increased amplitudes are related to improved behavioural performance, while decreased amplitudes are related to impulsive behavioural response. In SCZ, the number of correct responses positively correlated with left parietal P150 latency and SCZ performed significantly worse than the CON. This relationship suggests that with slower P150 processing, behavioural performance in SCZ may improve. The P150 in SCZ has previously been noted to potentially underlie severity of negative symptoms (Higashima et al. 2004). However, further research is required to fully understand the role the P150 has in SCZ behavioural performance.

Lastly, in MPD the number of omissions positively correlated with left frontal P100 amplitude, and left parietal P100 amplitude in BPD, suggesting omissions in MPD and BPD are related to P100 processes however in relation to different cortical brain area functioning. Behavioural performance was related to the early wave components of the first cue's ERP, further research is required to elucidate these findings.

For the second cue, behavioural performance was related to the fronto-parietal relationship across all groups. The number of impulsive responses negatively correlated with the left central N170 amplitude in CON and positively correlated with the left parietal N70 latency in SCZ. The number of omissions negatively correlated with the right frontal P100 amplitude in SCZ and positively correlated with the right parietal P100 and P150 amplitude in MPD. Featherstone et al, (2007) suggested there are deficits in attentional performance with increased omissions, and reduced response accuracy. These relationships with poor behavioural performance suggest that during the cueing process, attentional processes related to the P100 and P150 were attenuated in SCZ and MPD, i.e. reduced engagement at this stage of cueing (Bolton & Staines 2011). Overall, response time negatively correlated with the right central P100 and right parietal P300 latency in SCZ. The P300 reflects cortical updating which is generally attenuated in SCZ (Ethridge et al. 2015). Overall response time reflected shortened cortical processing (i.e. early visual and attentional) over the right hemisphere central and parietal regions. This shows that the second cue ERP wave form is partially impaired in SCZ and that there is a slight preparative measure before the arrival of the target stimulus (Dufau et al. 2009; Ethridge et al. 2015). Together, the ERP wave component findings for the second cue suggest a disengagement of attentional processes in SCZ, while MPD only showed early processing deficits.

For the target stimulus, the total number of impulsive responses positively correlated with the left parietal N70 latency in SCZ. Hoptman et, (2015) and Reddy et al, (2014) suggested that impulsivity in SCZ leads to attentional deficits, however no relationships between impulsive responses and ERP wave components were found in SCZ. In CON the total number of impulsive responses negatively correlated with the left central N170 latency and the number of omissions negatively correlated with the left parietal N170 latency of CON. Increased omissions and incorrect responses leads to a decrease in response time, indicating that errors are more likely due to impulsive responses in individuals with

cognitive deficits (Hebert 2015). The overall response time negatively correlated with the right central P300 amplitude and the left central P300 latency for CON, and the right parietal P300 latency for SCZ. A previous study with similar results indicated a negative frontocentral ERP waveform occurred after an error of omission (Garofalo et al. 2014). These data suggest increased N170 amplitudes may impact the P300 wave form and attentional processing in SCZ, i.e. the shift from early to late cognitive processing needs further investigation as the neural connectivity from N170 to P300 is dysfunctional in SCZ and may underlie impulsive responding.

4.2.4 Event- related wave component correlates with clinical scales

The clinical scales scores revealed correlations with the first cue's wave components in the psychotic groups. For the Positive and Negative Syndrome Scale (PANSS) BPD showed relationships with early cognitive processing and cortical updating over parietal cortex, while SCZ showed relationships with cortical updating over central and parietal cortex. In BPD PANSS total score correlated positively with left and right central P100 amplitudes; then its subscale, PANSS general psychopathology correlated positively with left parietal P100 amplitude; and PANSS negative symptom subscale correlated positively with right parietal P300 amplitude. In SCZ PANSS total score correlated positively with left and right central P300 amplitudes and the left parietal P300 amplitude; then its subscale, PANSS general psychopathology score correlated positively with right central and left parietal P300 amplitude; and PANSS negative symptom subscale correlated positively with the left parietal P300 amplitude. Increased PANSS scores have been strongly related to poor attentional performance including the reduction in amplitude of early (P100) and late (P300) event- related wave components during target processing (Chang et al. 2014; Campanella et al. 2006; Iwanami et al. 1995). Finding these relationships during cueing may suggest that cognitive resources are being inappropriately applied, i.e. increased amplitudes over central and parietal cortices reflect good performance during the presentation of the stimulus and not cueing processes.

The remaining clinical scales showed relationships predominantly with latency of wave components of the first cue's ERP. Latency is the time it takes for a specific wave component to reach its maximal amplitude, latency therefore addresses the speed of

processing (Clayson et al. 2013; Polich 1992). Longer latencies were related to severity of clinical symptoms across the psychotic groups for right central P100 (Young mania rating scale) and P300 (Calgary depression rating scale; Hamilton depression rating scale) wave components. Within SCZ longer latencies were also related to severity of clinical symptoms for right central P100 (Young mania rating scale), right frontal N170 (Hamilton depression rating scale), left parietal N170 (Clinical global impressions scale), right parietal P300 (Hamilton depression rating scale). However shorter latencies were also found with increased severity of clinical symptoms, within SCZ right parietal P150 (Hamilton depression rating scale). It has been noted in the literature that more severe clinical symptoms are associated with delayed cognitive processing, i.e. longer latencies (Zamani et al. 2014; Tripathi et al. 2015), and the majority of our findings support these, further study is required to understand the shorter latency of the P150, but it may be related to bypassing P100 which led to greater activation of circuitry related to P150. And within MPD decreased amplitudes were related to severity of depression scores as they were negatively correlated with left and right frontal P300 amplitudes. Tripathi *et al*. (2015) showed similar results indicating that attenuated amplitudes are associated with more severe symptoms of depression. Then damage to reward systems with use of MA has been related to depressive symptoms (Petit et al. 2012). A result of MA preventing and reversing DA reuptake causing a reduction in DA production, this has previously been related to negative symptoms in SCZ and depression (Spitzer et al. 1978; Volkow et al. 2001; Zacher & Holmes 2012). In SCZ left and right parietal N170 amplitude was positively related to the Hamilton depression rating scale. The parietal region in SCZ has been linked to emotional expression (Onitsuka et al. 2013) and further emotional interference (García-Pacios et al. 2015). Emotional interference is the body's predisposition to mentally block out emotion in order to focus on relevant information (García-Pacios et al. 2015). This last finding suggests that negative and depressive symptoms, i.e. emotional interference, impacts early cognitive processing in SCZ (Kim et al. 2013). Our cohort were stable outpatients, these correlates suggest that even with low clinical scale scores the first cue wave components are affected.

With the second cue, clinical scales scores were correlated with wave components across the psychotic groups. In MPD, the PANSS negative symptom score, positively correlated with left parietal P100 amplitude, left parietal N170 amplitude, left and right parietal P150

amplitude, left central P300 amplitude, and right parietal P300 amplitude. This array of relationships in MPD, suggest that the presentation of negative symptoms in MPD bear a significant role in cue recognition and cognitive interference (Kim et al. 2013). These results also suggest that negative symptoms not only affect later cognitive processing but early cognitive processing in MPD. PANSS positive symptom score negatively correlated with the right parietal N170 amplitude within BPD. The N170 amplitude, as mentioned previously, has been found to increase with attentional based dysconnectivity in BPD (Kraguljac et al. 2016). Lastly, the clinical global impression scale negatively correlated with the right frontal P100 latency in MPD. These results support the idea suggesting a deficit in early visual processing within BPD and MPD (Earls et al. 2016; Campanella et al. 2006).

The global assessment of functioning scale positively correlated with left and right N170 amplitude, which supports the findings in MPD with respect to the PANSS correlations, where symptom severity is related to deficits in early visual processing and early cognitive processing.

Psychotic symptom severity was related to wave components of target stimulus. For the PANSS, PANSS negative symptom score correlated positively with the right parietal P300 amplitude in MPD. Negative symptoms have been shown to influence cognitive deficits (Trotman et al. 2013). PANSS general psychopathology score negatively correlated with the right parietal P150 latency in SCZ. As seen during the cueing ERP wave components group difference and relationships with symptom severity strongly related to early cognitive processes, including early visual processing being specifically related to negative symptoms, then later wave component P300 psychosis symptom relationships are restricted to MPD group, suggesting symptom severity more strongly affects MPD orientating and cortical updating.

The target stimulus wave components showed relationships with mood- related clinical scales, specifically scores from depression scales. The Hamilton depression rating scale correlated positively with the left and right frontal P300 amplitude in MPD and then negatively with the right parietal P300 amplitude in SCZ. It was previously found that depression was associated with cognitive deficits (Ravnkilde et al. 2002). The Calgary depression rating scale correlated positively with the right central N170 amplitude in BPD,

and the left frontal P300 latency and negatively with the left central P100 latency in MPD. These results indicate cognitive deficits can be related to nominal presentation of depressive symptoms, more so in BPD compared to MPD, which may be due to BPD being a mood disorder (Harvey 2011). An additional relationship found for N170 wave form, where the global assessment of functioning scale, a measure of general symptom severity within an affected individual (Aas 2011), was positively correlated with left and right prefrontal N170 latency in BPD. In a previous study, the global assessment of functioning scale relationship with the N170 suggested that early visual processing deficits were present in patients with SCZ (Ibáñez et al. 2012). In SCZ, recognition of the target was affected due to cortical processing being delayed in affected individuals (Rehse et al. 2016). From our results we can conclude that depressive symptoms in psychotic disorders are associated with dysfunction in the prefrontal and frontal cortices (Hoshino et al. 2005).

4.3 Event-related potential wave component differences by medication

Medication was found to affect ERP wave components during the sustained visual attention task. For the first cue FGA's increased the left central P100 amplitude in both SCZ and BPD and decreased the left parietal P100 amplitude in SCZ only. The use of antipsychotics increased the right parietal N70 and left central P100 amplitudes in BPD, specifically the right prefrontal N170 amplitude was increased with the use of SGA's. Then clozapine use increased the left frontal P100 amplitude in SCZ. These results suggest improved early cognitive processing in SCZ and BPD with the use of antipsychotics. For the second cue, SGA's decreased the right parietal P150 amplitude in SCZ but in MPD the right parietal P150 amplitude was increased with haloperidol use, and FGA. The opposing results for the P150 amplitude in SCZ and MPD suggests that haloperidol improved symptom severity and cognitive functioning in MPD but not in SCZ. SGA's increased the left parietal P300 latency in BPD and sodium valproate decreased the left prefrontal P300 latency. For the target stimulus, SGA's decreased the right parietal P100, P150 and left parietal P150 amplitudes and increased the left central P300 latency in BPD. These results indicate that SGA's improved visual processing in BPD but decreased attention.

4.3.1 First cue event- related potential wave component medication differences

For the first cue, prescription of antipsychotic medication increased the right parietal N70 amplitude across the psychotic groups and within BPD. Increased N70 amplitude and delayed latency was previously reported in a study conducted on patients diagnosed with SCZ (Arnfred et al. 2006)**.** Another study involving a flashing pattern task, suggested the N70 relates to late processing and sensory focus (Saint-Amour et al. 2005). This suggests early visual processing in SCZ and BPD is improved with antipsychotic medication use (Adams et al. 2017), refer to **section 1.8**. Across psychotic groups the left central and left parietal P100 amplitude was also increased with the prescription of antipsychotic medication, and the left central finding was also found within BPD. Very few studies have focused on medication effects on the P100 ERP waveform. An attenuated P100 ERP waveform depicts deficits early visual processing (Campanella et al. 2006). Degabriele et al (2011) found the P100 amplitude is increased in BPD, during the presence of the target cue. However various studies have used emotional cues (i.e. happy and sad faces) to determine differences in the P100 ERP waveform (Earls et al. 2016). The data presented suggests that the use of any antipsychotic medication enhances early visual processing, and this was more evident in BPD (**Table 4.8**).

Table 4.8: First cue event- related potential wave component medication differences

	All Psychotic Groups n = 76 32 females/44 males	Schizophrenia n = 27 11 females/16 males	Bipolar I disorder n = 28 12 females/16 males
Medication			
First generation antipsychotics	^ left central P100 amplitude	^ left central P100 amplitude	^ left central P100 amplitude
	^ left central P100 latency	v left parietal P100 amplitude	
	^ right central P100 amplitude		
	^ left parietal P100 amplitude		
	^ right parietal P100 amplitude		
	^ right parietal P100 latency		
Second generation antipsychotics	v left parietal P100 latency		^ right prefrontal N170 amplitude
	v left central P100 latency		
	^ right central N170 amplitude		
	^ right prefrontal N170 amplitude		
Mood stabilizers	^ left prefrontal P300 amplitude		
Anticholinergics	^ left prefrontal N170 amplitude		
any antipsychotic	^ right parietal N70 amplitude		^ right parietal N70 amplitude
	^ left parietal P100 amplitude		^ left central P100 amplitude
	^ left central P100 amplitude		
Clozapine	v right parietal N170 amplitude	^ left frontal P100 amplitude	
	^ left prefrontal N170 amplitude		
Risperidone	^ right prefrontal N170 amplitude		
	v right parietal N170 latency		
Haloperidol	^ left central P100 latency		
	^ right parietal N170 latency		
	^ right frontal N170 latency		
	^ right frontal P300 latency		
	^ right prefrontal P300 latency		
	v left central P300 latency		
Lithium	^ left prefrontal P300 amplitude		

Medication differences analysis was conducted on whether participants were "on" or "off" a specific medication. ^ increased amplitude/lengthened latency v decreased amplitude/reduced latency. Mann- Whitney U testing was applied. Significance P<0,05

Prescription of FGA's for the presentation of the first cue showed similar effects to the prescription of any antipsychotic medication however, both the left and right central and parietal regions reported differences in amplitudes and latencies across all psychotic groups and within SCZ. Individuals prescribed FGA's left central P100 amplitudes were greater, this increase was also apparent within SCZ and BPD. FGA's also increased the left parietal P100 amplitude across all groups, however within SCZ the left parietal P100 amplitude was slightly decreased. Lastly, FGA's increased the left and right central P100 amplitude, left central P100 latency, left and right parietal P100 amplitude and right parietal P100 latency across all psychotic groups. Barch and Sheffield (2014) described various studies showing deficits in cognitive performance as opposed to BPD and other depressive disorders (Barch & Sheffield 2014). These differences suggest that FGA's also improved early cognitive processing during the cueing process (Goff et al. 2011). Across all group's haloperidol an

FGA, lengthened the latencies over right parietal N170, right frontal N170, right frontal P300, right prefrontal P300, and the left central P100 and shortened the left central P300 latency. These findings in part contrast FGAs overall. Haloperidol was previous found to reduce metabolism in the prefrontal and frontal cortex (Oranje et al. 2009). Suggesting haloperidol use decreased cue processing speed, and slowed neuronal activity in the brain may be the reason why (Yael et al. 2013).

During the first cue SGA's shortened the left central and left parietal P100 latencies across all psychotic groups. Furthermore, SGA's increased the right central N170 and right prefrontal N170 amplitudes across all groups, then the right prefrontal N170 amplitude was increased in BPD. In a study conducted on FGA's verses SGA's, SGA's outperformed FGA's in cognition (including attention). The use of SGA's decreased the latency over the left hemisphere indicating possible improvement in working memory and executive function (Zhang et al. 2013; Bombaci 2016).

An SGA, clozapine, often prescribed to treat resistant psychosis (Marder et al. 1991; Jibson 2015), decreased the right parietal N170 amplitude and increased the left prefrontal N170 amplitude across all psychotic groups. Further, the left frontal P100 amplitude in SCZ was increased after clozapine use. According to previous studies conducted, SCZ has attenuated amplitudes in the parietal regions (Johnson et al. 2005; Campanella et al. 2006; Earls et al. 2016). These findings suggest that there may be dysfunctional connectivity across the parietal cortex resulting in cognitive impairment in SCZ. Our results follow previous studies which showed early visual processing which affected later processing in parietal regions after clozapine administration in SCZ (Micoulaud-Franchi et al. 2015; Campanella et al. 2006). An FGA, risperidone, increased the right prefrontal N170 amplitude and decreased the right parietal N170 latency across all groups. Kraguljac et al, (2016) found increased amplitude and latency across the fronto-parietal region to be a characteristic of executive and attentional based dysconnectivity. Contradicting results were observed in the present study indicating after risperidone use, attention and processing speed enhanced (Umbricht et al. 1999).

Mood stabilizers were associated with increased left prefrontal P300 amplitude and then the use of lithium, a mood stabilizer, showed increased left prefrontal P300 amplitude

across all groups. Chun et al, (2003) conducted a study in SCZ and BPD and found the P300 latency was delayed in BPD and the amplitude in SCZ was increased. Our findings indicate that mood stabilizers improved cognitive performance in BPD (Polich & Herbst 2000).

Lastly, anticholinergics prescribed to reduce extrapyramidal side effects, were found to increase the left prefrontal N170 amplitude across the psychotic disorders. A study conducted on the effects of anticholinergic use found that cognitive function improved with the use of antipsychotics across psychotic disorders (Rehse et al. 2016). Our findings suggest that high dose antipsychotics should try to be avoided to reduce the need for anticholinergics, and thereby reduce potential negative effects of chronic antipsychotic medications (Rehse et al. 2016).

Overall antipsychotics, FGA's and SGA's improved the cueing processing across the psychotic groups, and this was pronounced in SCZ. It is evident that prescribed medication for the management of psychotic symptoms can improve the processing of salient information, this is particularly noted during the first cue of our sustained performance task.

4.3.2 Second cue event- related potential wave component medication differences

When all antipsychotic medication was grouped no effects on the second cue ERP wave components were found, however FGA's and SGA's in isolation did. Prescription of FGA's increased the left prefrontal P300 latency across all groups, suggesting improved cue loading, i.e. activation of working memory improved after the use of FGA's (Lencer et al. 2008). The P150 has been related to processing spatial information and a decrease in the amplitude and latency can result in early visual processing deficits (Van Der Lubbe & Woestenburg 1997). Haloperidol, an FGA, increased the right parietal P150 amplitude across groups, specifically in MPD. Further haloperidol increased the right parietal P100 amplitude and decreased the left and right central P300 latency across all groups. These results suggest haloperidol improved cue processing. As was found with FGA's in general, haloperidol improved early cognitive processing, and improved cortical updating over central brain areas (**Table 4.9**).

Table 4.9: Second cue event- related potential wave component medication differences

	All Psychotic Groups	Schizophrenia	Bipolar I disorder	Methamphetamine induced psychosis
	n = 76	n = 27	n = 28	n = 21
	32 females/44 males	11 females/16 males	12 females/16 males	9 females/12 males
Medication				
First generation antipsychotics	^ left prefrontal P300 latency			
Second generation antipsychotics	v right parietal P150 amplitude	v right parietal P150 amplitude	^ left parietal P300 latency	
	^ left parietal P300 latency			
Mood stabilizers	v right prefrontal N170 latency			
Anticholinergics	^ left prefrontal N170 amplitude			
Clozapine	^ right frontal P100 amplitude			
	^ right frontal N170 amplitude			
	^ left prefrontal N170 amplitude			
	^ left prefrontal P300 amplitude			
Risperidone	^ right central P300 latency			
Haloperidol	^ right parietal P100 amplitude			^ right parietal P150 amplitude
	^ right parietal P150 amplitude			
	v left central P300 latency			
	v right central P300 latency			
Sodium valproate	^ right parietal N70 latency		v left prefrontal P300 latency	
	^ left prefrontal P300 latency			

Medication differences analysis was conducted on whether participants were "on" or "off" a specific medication. ^ increased amplitude/lengthened latency ˅ decreased amplitude/reduced latency. Mann-Whitney U testing was applied. Significance P<0,05

The prescription of SGA's increased the left parietal P300 latency across all groups and within BPD. The right parietal P150 amplitude was decreased across all groups, more so in SCZ with the use of SGA's, suggesting that with SGA's cue updating is enhanced in SCZ over parietal cortices while delayed cortical updating in BPD is over the parietal cortices (Lencer et al. 2008). The use of clozapine, an SGA, increased the right frontal P100 amplitude, left prefrontal and right frontal N170 amplitude, left prefrontal P300 amplitude across all groups. An increase in electrical brain activity after clozapine use has previously been noted by Purkayastha et al, (2012). Our data supports this as increased amplitudes are reflective of increase or stronger activation of neural circuitry that is recruited for a cognitive task. The use of risperidone, also an SGA, increased the right central P300 latency across all groups, suggesting a delay in the activation of P300 neural circuitry activation. A previous study found P300 amplitude to decrease with risperidone in SCZ and related this to reduced ability to cortically update task information. They did not report a difference in P300 latency (Nieman et al. 2002). Further study is needed as this study is the first to interrogate the role of medications during the sustained attentional cueing. Antipsychotic medication possibly helped in the processing of the second cue by activating working memory in preparation of the target stimulus and this was more strongly supported in SCZ (Luck et al. 2014).

During the second cue mood stabilizers decreased the right prefrontal N170 latency across the psychotic disorders. Across all groups sodium valproate, used as a mood stabilizer, increased the right parietal N70 latency and the left prefrontal P300 latency, while the left prefrontal P300 latency was decreased in BPD. The decrease in latency indicates that attentional processing was efficiently processed by the use of mood stabilizers (Hileman et al. 2011). Then prescription of risperidone and sodium valproate increased the latency of the P300 causing a delay in cortical updating and this may potentially be related to reduced assessment in predicting a target stimuli (Lencer et al. 2008). Overall, mood stabilizers have been shown to decrease mania in BPD but also enhances executive function and emotional control (Altinay et al. 2018). These data suggest that in BPD the impact of emotional interference is reduced by administration of mood stabilizers. Lastly, anticholinergics increased the left prefrontal N170 amplitude across the psychotic disorders. This result follows from previous studies showing reductions in working memory (Zhou et al. 2011; Kocsis et al. 2014).

Overall antipsychotics, FGA's and SGA's improved the cueing processing across the psychotic groups, as shown from the first cue. From these results it is evident that cue processing was enhanced by prescribing medication for the management of psychotic symptoms.

4.3.3 Target stimulus event- related potential wave component medication differences

Antipsychotic medications and mood stabilizers were related to wave components of the target stimulus, these relationships were evident across the psychotic groups and within BPD. The only FGA which showed relationships with target ERP wave components was haloperidol. Haloperidol increased the right parietal P100 and right prefrontal P150 amplitude and decreased the left P300 latency across all groups. As noted previously, increased amplitude in early ERP waveforms shows haloperidol improving cortical updating and working memory. Further, these results indicate that improved cue processing. SGA's decreased the right parietal P100 amplitude and left and right parietal P150 amplitude of all groups, and within BPD. SGA's also increased the left parietal P300 latency and left and right central P300 latency was noted across all groups, however only the left central P300 latency was decreased in BPD. Very few studies were found with the link between

antipsychotic medication and the effects on ERP wave components in BPD, further research is needed (**Table 4.10**)

Table 4.10: Target stimulus event- related potential wave component medication differences

	All Psychotic Groups n = 76 32 females/44 males	Bipolar I disorder n = 28 12 females/16 males
Medication		
Second generation antipsychotics	v right parietal P100 amplitude	v right parietal P100 amplitude
	v left parietal P150 amplitude	v left parietal P150 amplitude
	v right parietal P150 amplitude	v right parietal P150 amplitude
	^ left parietal P300 latency	^ left central P300 latency
	^ left central P300 latency	^ left central P300 latency
	^ left central P300 latency	
	^ right central P300 latency	
Clozapine	v left parietal N70 amplitude	
	v left parietal P100 amplitude	
	^ right prefrontal N170 amplitude	
	^ right frontal N170 amplitude	
Risperidone	^ left central P300 latency	
	^ right central P300 latency	
	^ left parietal P300 latency	
Haloperidol	^ right parietal P100 amplitude	
	^ right parietal P150 amplitude	
	v left central P300 latency	
Lithium	^ left central N170 latency	^ left central N170 latency
	^ left parietal N170 latency	
Sodium valproate	v left central P100 latency	
	^ left prefrontal P300 latency	

Medication differences analysis was conducted on whether participants were "on" or "off" a specific medication. ^ increased amplitude/lengthened latency ˅ decreased amplitude/reduced latency. Mann- Whitney U testing was applied. Significance P<0.05

Clozapine, an FGA, decreased the left parietal N70 and P100 amplitude across all groups. These results indicate that early visual processing is altered with the use of clozapine. However, increases in the right prefrontal N170 and frontal N170 amplitude were evident, indicating that there is potential improvement in attention- dependent information processing and reduced interference of emotion after clozapine use (Umbricht et al. 1998). Then, risperidone, an SGA, increased the left parietal P300 latency and both the left and right central P300 latency in all psychotic groups. Risperidone delayed information

processing as shown by increased latencies. Our results contrast with previous studies showing decreased latencies after risperidone use (Umbricht et al. 1999).

A mood stabilizer, lithium, increased the left central N170 latency across all groups and within BPD, and left parietal N170 latency was increased across groups. Importantly, lithium was primarily prescribed to BPD (see table 4.14). Previously, it has been reported that lithium use enhances the N170 ERP waveform in BPD resulting in dysfunction to the cognitive networks (Ilhan Atagün et al. 2015). Therefore, lithium should only be prescribed in emergency cases for psychotic episodes and not as a daily maintenance regime. Then sodium valproate, also mood stabilizer, increased the left prefrontal P300 latency and shortened the left central P100 latency. It is important to note that subtle changes by a slight decrease in amplitude or increase in latency were found to differ across the scalp from posterior to anterior, further research is needed to fully appreciate the effects of these mood stabilizers in cognitive processing.

Overall, information processing was improved after haloperidol and sodium valproate use for the target. It was also found that clozapine, risperidone and lithium resulted in reduced information processing and reduced emotion interference.

Chapter 5 Conclusion

The aim of this study was to determine whether there are specific group differences between CON and three psychotic disorders: SCZ, MPD and BPD, then to determine differences between these psychotic disorders. This included differences in behavioural performance and prominent electrophysiological event- related potential (ERP) wave components during cueing and target processing of a visual sustained attention task. Further we aimed to characterize ERP waveform component relationships across and within these groups for demographics, drug use, behavioural performance, and clinical variables, the last limited to the psychotic groups. Lastly, we investigated the effects of prescribed medications on ERP wave components within the psychotic groups.

Behaviourally, performance of the CPT task, SCZ performed poorer than the other groups. SCZ is known to have cognitive deficits compared to CON (Onitsuka et al. 2013). The increased amplitudes and lengthened latencies in SCZ indicated that cueing and processing of sustained attention is different in SCZ when compared with CON. The lack of difference in BPD and MPD compared with CON suggests that cueing and processing of the sustained attentional task applied in this study are not affected

Substance use was shown to slowed cognition in CON and SCZ, this includes attentional processing and loading of working memory use (D'Souza et al. 2012; Petit et al. 2012; Thames et al. 2014), e.g. slowed P300 and reduce P300 latency (D'Souza et al. 2012). Furthermore, across psychotic groups symptom severity was shown to negatively affect cognitive performance. There is limited data reporting on early cognitive processing ERP waveforms, and further study is required to fully elucidate the relationships found with total substance use during the cueing process.

Also, an outcome of the study showed that SCZ, MPD and BPD differentiated by medication as well. This research is important in understanding the adverse effects antipsychotic medications can have on an individual, and to further help the patient manage their disease better. The results of our study help in understanding behavioural and electrophysiological event- related differences across SCZ, BPD and MPD. Further studies looking into specific electrophysiological differences in MPD with comparison to SCZ is warranted. The inclusion of other biological markers, e.g. genetics and neuro-immunology of SCZ and MPD may

provide the missing links to understanding the deficits and differences in the ERP wave components. These studies will support elucidating what underlies dysfunctional neural networks identified in SCZ and MPD cortical functioning.

Several limitations are apparent in the current study. First, the number of individuals recruited for the study could have been more case matched. However, despite the low MPD numbers, significant differences were still found. This indicates that inclusion of more MPD individuals could have made the results stronger.

Using the information obtained in the present study, further research can be conducted to develop a panel of electrophysiological and neuroimmune markers for each of the psychotic disorders (Upthegrove et al. 2014; Dimitrov et al. 2014). Dimitrov et al, (2014) explained that IL-6 is increased in individuals who are at risk in developing psychosis. Similarly, Upthegrove et al, (2014) found increased inflammatory markers in individuals with SCZ. The discovery of specific neuroimmune markers along with the electrophysiological markers can be useful for diagnostic and treatment of the specific psychotic disorders. Furthermore, it was found that antipsychotic medication can influence the cytokine levels within an individual (Drzyzga et al. 2006). By conducting studies on the medication used for each psychotic disorder, relationships between medication use and EEG frequency and ERPs can be conducted in MPD as very few information is available. Lastly, a metanalysis can be conducted in SCZ and MPD, comparing neuroimmune markers, EEG frequency, ERP waveforms. As noted in the current study, the metanalysis will be informative as to the differences underlying the two disorders.

There is currently a lack of literature which has investigated the cueing process via the use of ERP waveforms, this is apparent in CON and within each of the psychotic disorders investigated. Our findings show that there are prominent differences in early cueing and target ERP waveforms which are unique to specific psychotic disorders. Relationships with demographics and clinical variables, including medication, do influence these early cueing and target ERP waveforms. The results presented show that further ERP studies are sorely needed to address these differences and relationships found, to distinguish differences in cognitive processing which may serve to provide a clearer understanding to which neural circuitry is uniquely dysfunctional in each of these psychotic disorders. This study provides

new insights to early processing deficits during the cueing and processing of a visual sustained attention task in the psychotic disorders and addresses the effects of medication through ERP wave component analysis.

Appendices

Appendix A Participant information sheet and consent form

The participant was supplied with an information sheet containing details of the research study and the tests they will undergo. A consent form was asked to be filled in and signed if the participant was willing to partake in the research study.

Cortical inhibition and attentional modulation a study of psychosis

University of Cape Town Human Ethics reference number: 192/2010

Participant information sheet

Attention is when you are able to focus on information. Like when you think of what you are going to wear, needs a level of attention. A person may find this difficult if they have other thoughts that don't allow them to pay attention. This is only one example, but applies to feelings as well. Like if you are worried about something, you cannot pay attention to something that may really need your attention. The ability to pay attention is different for everyone and may be more difficult for some.

The present study is not clinical. This study would like to understand how interfering or too many thoughts lower a person's ability to pay attention. This will be done through brain imaging techniques that allow us to record electrical activity (electroencephalography), the level of brain chemicals (magnetic resonance spectroscopy, MRS), and changes in electrical activity (electroencephalography with transcranial magnetic stimulation).

Recruitment into the present study will occur through referral from a medical practitioner who is informed as to your psychiatric illness. Participants without a history of psychosis will also be recruited as controls to compare findings. The control participants will be interviewed by a psychiatrist to determine inclusion (can participate). The controls will not undergo the brief repetitive transcranial magnetic stimulation (brTMS) but will have a 'fake' treatment referred to as sham TMS treatment.

Basic exclusion (cannot participate) criteria for the present study are as follows. Individuals who: are under the age of 18, or older than 40; have a history of, or have first-degree relatives (father, mother, brothers and/or sisters) with a history of, epilepsy or seizures; have a history of stroke or brain aneurism; have a chronic medical condition, including Parkinson's disease, Huntington's chorea, multiple sclerosis, and dementia; have cardiac devices, implanted medication pumps, intracardial lines, or cardiac disease; have apparent mental retardation; have a history of treatment with TMS therapy; have extensive tattoos on their face; or have orthodontic braces, will not be included in the study. Woman who are known or suspected to be pregnant or who are breast feeding will also be excluded from the study. Each participant will be checked off against a set of criterion from the TMS adult safety screen (Keel et al., 2000) by the researcher involved, and a magnetic resonance imaging (MRI) safety screen by a radiographer at the Cross-University Brain Imaging Centre (CUBIC).

Individuals who are suitable and willing to participate in the present study will need to be available for one working day from 08h30 to 17h30. Each participant will receive shopping vouchers for food to the value of R200, and will receive R50 toward travel expenses. Lunch will be provided on the day of participation.

Each participant is free to withdraw from the present study at any time. This study is for research purposes only and is not funded by a pharmaceutical (drug) company. Participant's details will be anonymous, as each participant will be assigned a participant number on the day of the recording session.

If you have any questions with respect to the present study do not hesitate to contact the principal investigator, Dr Fleur Howells at fleur.howells@uct.ac.za

If you would like to participate in the present study please contact us through any of the following:

Email: participant.CIAM@gmail.com, Cell number: 082 749 5223, Landline number: 021 404 5488

Please see the next page for further information of the brain imaging modalities that will be used in the present study.

Additional information for participant:

Fig 1

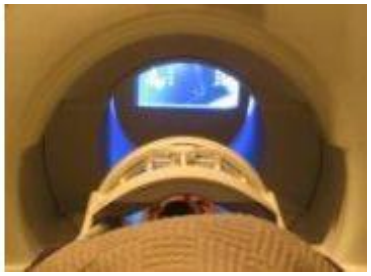


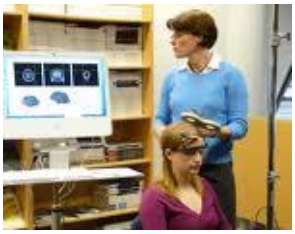
Fig 2

Magnetic Resonance Imaging (MRI) is a form of medical imaging that needs you lie on a scanner bed and be placed into a short tunnel (open at both ends) in line with a strong magnetic field (Fig 1). A device is placed over your head with a mirror system attached (Fig 2). You can relax during the scanning session by watching a movie or taking a nap, but you do need to keep as still as possible. The magnetic field attracts (pulls) metal objects. Therefore an MRI safety checklist is required to prevent cancellation of the scan once scheduled. These precautions are for your safety and to ensure optimal image data. Prior to entering the scan room the Radiographer will go through a checklist to ensure your safety. There are no known side effects of undergoing an MRI if you are seen as suitable by a Radiographer.

In addition, should you pass the first checkpoint, we will ask that you remove all metal objects for the period of scanning: no jewelry, watches, metal piercing (this includes all forms of piercing), pens, coins, cell phones etc. lockable change rooms and hospital gowns will be available, but we suggest you wear more suitable clothing such as a t-shirt & track pants that are preferably not nylon (with no zips, buckles etc). Any clothing that contains metal wire, buttons, and zips will need to be removed.

Once the scan commences you will hear a continuous loud noise for the duration of the sequence and each sequence lasts about 6-9 minutes each. Each of the sequences will make a different set of noises. You will be provided with earplugs and headphones to protect your ears from this noise. You will be under constant supervision verbally and visually for the duration of the entire scan (± 1hour in total).

The MRI scanning will be done at the Cross-University Brain Imaging Centre (CUBIC), Tygerberg hospital. You (the participant) will be transported to Tygerberg and back by a research assistant.



Transmagnetic cranial stimulation (TMS), works by placing a magnet next to the brain (over the scalp). When the magnetic coil is charged it changes the electrical activity of the surface area of the brain that is targeted. After one pulse from the magnetic coil the brain area is briefly inactive and this is a measure of the brain's ability to inhibit activity (cortical inhibition). This inhibition of activity is decreased in individuals with a history of psychosis. All participants with and without a history of psychosis will undergo the cortical inhibition protocol.

Brief repetitive transmagnetic cranial stimulation (brTMS) is used to increase communication between neurons. In doing this, we aim to improve attentional information processing. brTMS has been associated with brief headaches, which is as a result of nerves and muscles on the scalp. In addition the participant may show symptoms of temporary mania or depression, but this is very very rare. Only the participants with a history of psychosis will have brTMS as we would like to see whether we can improve their attention. The TMS machine makes a clicking noise, but not as loud at the MRI scanner. Earplugs will be provided to reduce the noise. The results from this study are for research purposes only and not a form of therapy.

During the cortical inhibition protocol and the brTMS continuous electroencephalographic (EEG) data will be collected. EEG records brain wave activity by placement of an electrode cap (similar to a swimming cap) that records electrical activity from the scalp. The participants' will complete computerized tasks of attention with breaks between the different protocols.

The EEG, cortical inhibition and brTMS will take place in the EEG suite of the educational center at Valkenberg Hospital, Observatory.

Participant Name _____ Participant Number _____

Cortical inhibition and attentional modulation a study of psychosis

University of Cape Town Human Ethics reference number: 192/2010

CONSENT FORM

I voluntarily agree to participate in the present study: Cortical inhibition and attentional modulation a study of psychosis, which includes magnetic resonance imaging (MRI), cortical inhibition protocol through transmagnetic cranial stimulation (TMS) pulses, and electroencephalography (EEG).

YES NO

In addition I voluntarily agree to undergo brief repetitive transmagnetic cranial stimulation (bRTMS) for research purposes only. (Only participants with a history of psychosis.)

YES NO

I am aware that brief repetitive transmagnetic cranial stimulation (brTMS) may lead to a brief headache as a result of stimulating nerves and muscles on the scalp and/or short-term symptoms of mania or depression.

YES NO

I have been informed of the procedures and have a copy of the study's information sheet (attached).

YES NO

I have been allowed the opportunity to ask questions that relate to the present study and they have been answered (else please ask these questions of the researcher before you sign this consent form).

YES NO

I …….. (Participant's full name) am voluntarily participating in the present study and am aware that at any point I may stop participating in the present study. If I stop participating there will be no impact (effect) on my current or future medical treatment.

Participant's signature: …… date: DAY / MONTH / YEAR

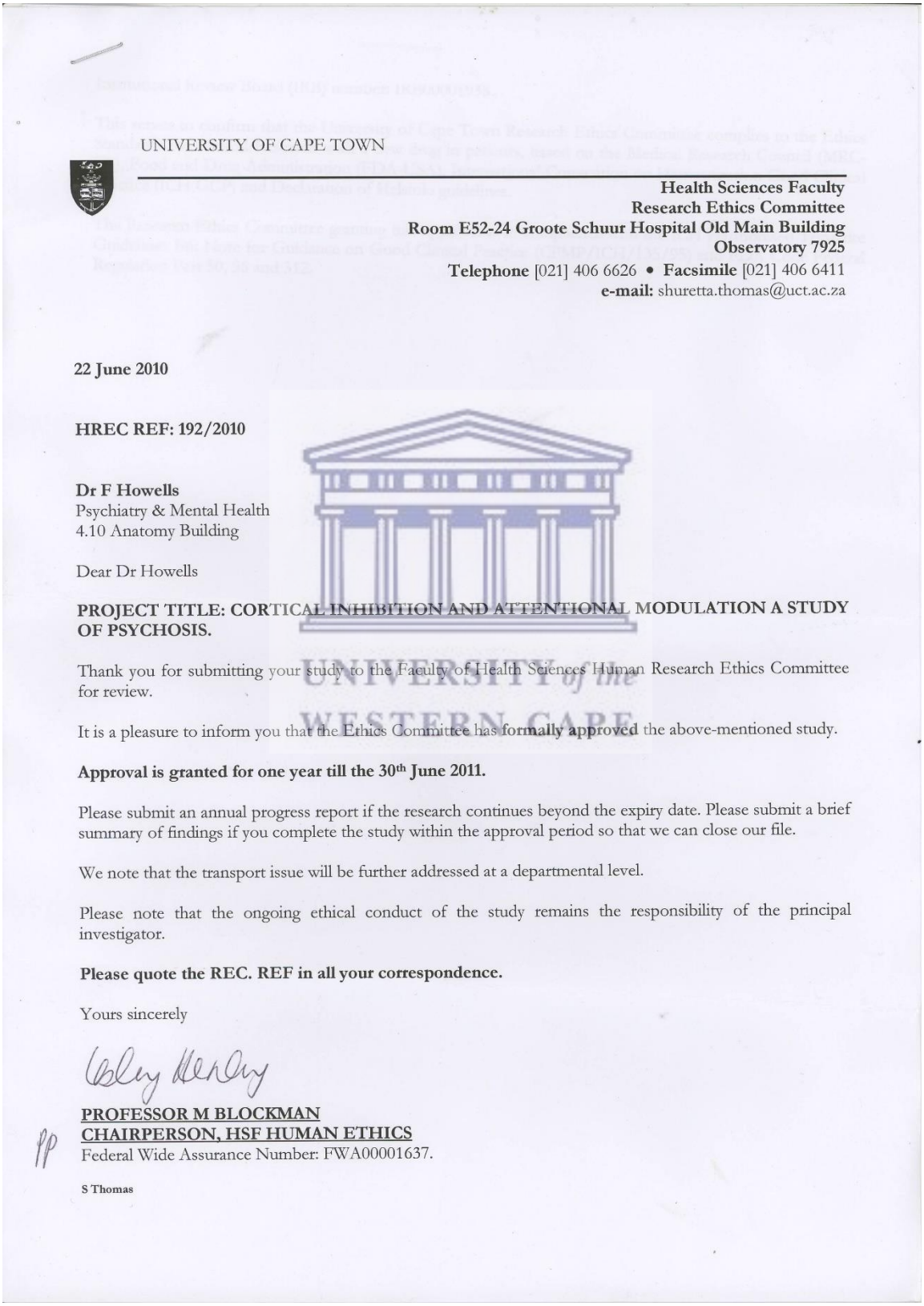
Participant's email and/or contact number: ……

I ……..(researcher's full name) have gone through the consent form and answered any questions that the participant has asked

Researcher's signature …… date: DAY / MONTH / YEAR

Appendix B Ethical clearance

Ethical clearance document for the conducting of the study was approved by the Human research ethical council (HREC/192).



UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
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Telephone [021] 406 6626 • **Facsimile** [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za

22 June 2010

HREC REF: 192/2010

Dr F Howells
Psychiatry & Mental Health
4.10 Anatomy Building

Dear Dr Howells

PROJECT TITLE: CORTICAL INHIBITION AND ATTENTIONAL MODULATION A STUDY OF PSYCHOSIS.

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the Ethics Committee has **formally approved** the above-mentioned study.

Approval is granted for one year till the 30th June 2011.

Please submit an annual progress report if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file.

We note that the transport issue will be further addressed at a departmental level.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.

pp

S Thomas

C 1. PANSS questionnaire

Positive and negative syndrome scale (PANSS) - Rating Form

Kay SR, Opler LA, Lindenmayer J-P (1988). Reliability and validity of the positive and negative syndrome scale for schizophrenics. Psychiatry research, 23:99-110

Instructions: Circle the appropriate rating for each dimension following the specified clinical interview. Refer to the rating manual for item definitions, description of anchoring points, and scoring procedure

	Absent	Minimal	Mild	Moderate	Moderate-severe	Severe	Extreme
Positive scale							
P1 Delusions	1	2	3	4	5	6	7
P2 Conceptual disorganization	1	2	3	4	5	6	7
P3 Hallucinatory behaviour	1	2	3	4	5	6	7
P4 Excitement	1	2	3	4	5	6	7
P5 Grandiosity	1	2	3	4	5	6	7
P6 Suspiciousness	1	2	3	4	5	6	7
P7 Hostility	1	2	3	4	5	6	7
Negative scale							
N1 Blunted effect	1	2	3	4	5	6	7
N2 Emotional withdrawal	1	2	3	4	5	6	7
N3 Poor rapport	1	2	3	4	5	6	7
N4 Passive/apathetic social withdrawal	1	2	3	4	5	6	7
N5 Difficulty in abstract thinking	1	2	3	4	5	6	7
N6 Lack of spontaneity & flow of convers	1	2	3	4	5	6	7
N7 Stereotyped thinking	1	2	3	4	5	6	7

	Absent	Minimal	Mild	Moderate	Moderate-severe	Severe	Extreme
General psychopathology scale							
G1 Somatic concern	1	2	3	4	5	6	7
G2 Anxiety	1	2	3	4	5	6	7
G3 Guilt feelings	1	2	3	4	5	6	7
G4 Tension	1	2	3	4	5	6	7
G5 Mannerisms & posturing	1	2	3	4	5	6	7
G6 Depression	1	2	3	4	5	6	7
G7 Motor retardation	1	2	3	4	5	6	7
G8 Uncooperativeness	1	2	3	4	5	6	7
G9 Unusual thought content	1	2	3	4	5	6	7
G10 Disorientation	1	2	3	4	5	6	7
G11 Poor attention	1	2	3	4	5	6	7
G12 Lack of judgment & insight	1	2	3	4	5	6	7
G13 Disturbance of volition	1	2	3	4	5	6	7
G14 Poor impulse control	1	2	3	4	5	6	7
G15 Preoccupation	1	2	3	4	5	6	7
G16 Active social avoidance	1	2	3	4	5	6	7

Scale	Total	Percentile	Range
Positive scale			
Negative scale			
General psychopathology			
Number of symptoms rated > 3:	Positive		Negative	
Typological classification			

Participant number Date of completion

C 2. Calgary depression rating scale

Calgary depression rating scale

Addington D, Addington J, Maticka-Tyndale E, Joyce J (1992). Reliability and validity of a depression rating scale for schizophrenics. Schizophrenia Research, 6:201-208

Interviewer: Ask the first question as written. Use follow up probes or qualifiers at your discretion. Time frame refers to last 2 weeks unless stipulated. N.B. the last item, #9, is based on observations of the entire review

1 Depression

How would you describe your mood over the last 2 weeks: Do you keep reasonably cheerful or have you been very depressed or low spirited recently? In the last 2 weeks how often have you (own words) every day? All day?

0	Absent	
1	Mild	Expresses some sadness or discouragement on questioning
2	Moderate	Distinct depressed mood persisting up to half the time over last 2 weeks; present daily
3	Severe	Markedly depressed mood persisitng daily over half the time interfering with normal motor and social functioning

2 Hopeless ness

How do you see the future for youself? Can you see any future? - or has life seemed quite hopeless? Have you given up or does there still seem some reason for trying?

0	Absent	
1	Mild	Has at times felt hopeless over the last week but still has some degree of hope for the future
2	Moderate	Persistent, moderate sense of hopelessness over last week. Can be persuaded to acknowledge possibility of things being better
3	Severe	Persisting and distressing sense of hopelessness

3 Self depreciation

What is your opinion of yourself compared to other people? Do you feel better or not as good or about the same as most? Do you feel inferior or even worthless?

0	Absent	
1	Mild	Some inferiority; not amounting to feeling of worthlessness.
2	Moderate	Subject feels worthless, but less than 50% of the time
3	Severe	Subject feels worthless more than 50% of the time. May be challenged to acknowledge otherwise

4 Guilty ideas of reference

Do you have the feeling that you are being blamed for something or even wrongly accused? What about? (Do not include justifiable blame or accusation. Exclude delusions of guilt.)

0	Absent	
1	Mild	Subject feels blamed but not accused less than 50% of the time
2	Moderate	Persisting sense of being blamed, and/or occasional sense of being acused.
3	Severe	Persitent sense of being accused. When challenged acknowledges that it is not so

5 Pathological guilt

Do you tend to blame youself for little things you may have done in the past? Do you think you deserve to be so concerned about this?

0	Absent	
1	Mild	Subject sometimes feels over guilty about some minor peccadillo, but less than 50% of time
2	Moderate	Subject usually (over 50% of time) feels guilty about past actions the significance of which s/he exaggerates
3	Severe	Subject usually feels s/he is to blame for everything that has gone wrong, even when not his/her fault

6 Morning depression

When you have felt depressed over the last 2 weeks have you noticed the depression being worse at any particular time of day?

0	Absent	No depression
1	Mild	Depression present but no diurnal variation
2	Moderate	Depression spontaneously mentioned to be worse in the a.m.
3	Severe	Depression markedly worse in a.m., with impared functioning which improves in p.m.

7 Early wakening

Do you wake earlier in the morning than is normal for you? How many times does this happen?

0	Absent	No early wakening.
1	Mild	Occassionally wakes (up to twice weekly) 1 h or more before normal time to wake or alarm time.
2	Moderate	Often wakes early (up to five times weekly) 1 h or more before normal time to wake or alarm.
3	Severe	Daily wakes 1 h or more before normal time.

8 Suicide

Have you felt that life wasn't worth living? Did you ever feel like ending it all? What did you think you might do? Did you actually try?

0	Absent	
1	Mild	Frequent thoughts of being better off dead, or occcasional thoughts of suicide
2	Moderate	Deliberately considered suicide with a plan, but made no attempt.
3	Severe	Suicidal attempt apparently designed to end in death (i.e., accidental discovery or inefficient means).

9 Observed depression

Based on interviewer's observations during the entire interview. The question 'Do you feel like crying?' used at appropriate points in the interview may elicit information useful to this observation

0	Absent	
1	Mild	Subject appears sad and mournful even during parts of the interview involving affectively neutral discussion
2	Moderate	Subject appears sad and mournful throughout the interview, with gloomy monotonous voice and is tearful or close to tears at times
3	Severe	Subject chokes on distressing topics, frequently sighs deeply and cries openly, or is persistently in a state of frozen misery

Participant number Date of completion

C 3. Hamilton depression rating scale

HAMILTON DEPRESSION RATING SCALE (HAM-D)

(HAM)

Participant number ..... **Date of Completion .....**

TICK APPROPRIATE BOX FOR EACH ITEM

1. Depressed mood This item covers both the verbal and the non-verbal communication of sadness, depression, despondency, helplessness and hopelessness. **WHAT HAS YOUR MOOD BEEN LIKE IN THE LAST WEEK?**	
0 - Neutral mood.	☐
1 – When it is doubtful whether the patient is more despondent or sad than usual. E.g. the patient vaguely indicates to be more depressed than usual.	☐
2 – When the patient more clearly is concerned with unpleasant experiences, although he still is without helplessness or hopelessness.	☐
3 – The patient shows clear non-verbal signs of depression and/or is at times overpowered by helplessness or hopelessness.	☐
4 – The patient's remark on despondency and helplessness or the non-verbal ones dominate the interview in which the patient cannot be distracted.	☐
2. Self-depreciation and guilt feelings This item covers the lowered self-esteem with guilt feelings. **DO YOU FEEL YOU ARE LETTING PEOPLE DOWN?**	
0 – No self-depreciation or guilt feelings.	☐
1 – Doubtful whether guilt feelings are present, because the patient is only concerned with the fact that he during the actual illness has been a burden to the family or colleagues due to reduced work capacity.	☐
2 – Self-depreciation or guilt feelings are more clearly present because the patient is concerned with incidents in the past prior to the actual episode. E.g. the patient reproaches himself small omissions or failures, not to have done his duty or to have harmed others.	☐
3 – The patient suffers from more severe guilt feelings. He may express that he feels that the actual suffering is some sort of a punishment. Score 3 as long as the patient intellectually can see that his view is unfounded.	☐
4 – The guilt feelings are firmly maintained and resist any counterargument, so that they have become paranoid ideas.	☐
3. Suicidal impulses	

DO YOU FEEL LIFE IS NOT WORTH LIVING? HAVE YOU THOUGHT ABOUT TAKING YOUR OWN LIFE?	
0 – No suicidal impulses.	☐
1 – The patient feels that life is not worthwhile, but he expresses no wish to die.	☐
2 – The patient wishes to die, but has no plans of taking his own life.	☐
3 – It is probable that the patient contemplates to commit suicide.	☐
4 – If during the days prior to the interview the patient has tried to commit suicide or if the patient in the ward is under special observation due to suicidal risk.	☐
4. Initial insomnia **HOW HAVE YOU BEEN SLEEPING IN THE LAST WEEK?**	
0 – Absent	☐
1 – When the patient 1 (-2) out of the last 3 nights has had to lie en bed for more than 30 minutes before falling asleep.	☐
2 – When the patient all 3 nights has been in bed for more than 30 minutes before falling asleep.	☐
6. Delayed insomnia = Premature awakening The patient wakes up before planned by himself or his surroundings. **DO YOU WAKE UP EARLIER THAN YOU INTEND TO?**	
0 – Absent	☐
1 – Less than 1 hour (and may fall asleep again).	☐
2 – Constantly – or more than 1 hour too early.	☐
7. Work and interests This item includes both work carried out and motivation. Note, however, that the assessment of tiredness and fatigue in their physical manifestations is included in item 13 (general somatic symptoms) and i item 23 (tiredness and pain). **A. At first rating of the patient** **ARE YOU HAVING DIFFICULTIES AT WORK? HAVE YOU BEEN PRODUCTIVE AT WORK?**	
0 – Normal work activity.	☐

1 – When the patient expresses insufficiency due to lack of motivation, and/or trouble in carrying out the usual workload, which the patient, however, manages to do without reduction.	☐
2 – More pronounced insufficiency due to lack of motivation and/or trouble in carrying out the usual work. Here the patient has reduced work capacity, cannot keep normal speed, copes with less job o in the home; the patient may stay home some days or may try to leave early.	☐
3 – When the patient has been sick-listed, or if the patient has been hospitalized (as day-activities).	☐
4 – When the patient is fully hospitalized and generally unoccupied without participation in the ward activities.	☐
B. At weekly ratings	
0 – Normal work activity. a) The patient has resumed work at his/her normal activity level. b) When the patient will have no trouble to resume normal work.	☐
1 a) The patient is working, but at a reduced activity level, either due to lack of motivation or due to difficulties in the accomplishment of his normal work. b) The patient is not working and it is still doubtfu that he can resume his normal work without difficulties.	
2 – The patient is working, but at a clearly reduced level, either due to episodes of non-attendance or due to reduced work time. The patient is still hospitalized or sick-listed, participates more than 3- hours per days in ward (or home) activities, but is only capable to resume normal work at a reduced level. If hospitalized the patient is able to change from full stay to day-patient status.	☐
3 – When the patient has been sick-listed, or if the patient has been hospitalized (as day-activities).	☐
4 – When the patient is fully hospitalized and generally unoccupied without participation in the ward activities.	☐
8. Retardation (general) **OBSERVATION**	
0 – Normal verbal activity, normal motor activity with adequate facial expression.	☐
1 – Conversational speed doubtfully or slightly reduced and facial expression doubtfully or slightly stiffened (retarded).	☐
2 – Conversational speed clearly reduced with intermissions; reduced gestures and slow pace.	☐
3 – The interview is clearly prolonged due to long latencies and brief answers; all movements were slow.	☐
4 – The interview cannot be completed, retardation approaches (and includes) stupor.	☐
9. Agitation	

OBSERVATION	
0 – Normal motor activity with adequate facial expression.	☐
1 – Doubtful or slight agitation. E.g. tendency to changing position in chair or at times scratching his head.	☐
2 – Fidgeting; wringing hands, changing position in chair again and again. Restless in ward, with some pacing.	☐
3 – Patient cannot stay in chair during interview and/or much pacing in ward.	☐
4 – Interview has to be conducted "on the run". Almost continuous pacing. Pulling off clothes, tearing his hair.	☐
10. Anxiety (psychic) This item includes tenseness, irritability, worry insecurity, fear and apprehension approaching overpowering dread. It may often be difficult to distinguish between the patient's experienc of anxiety ("psychic" or "central" anxiety phenomena) and the physiological ("peripheral") anxiety manifestations, which can be observed, e.g., hand tremor and sweating. Most important is the patient's repor on worry, insecurity, uncertainty, and experiences of dreadfulness i.e. the psychic ("central") anxiety. **ARE YOU WORRYING ABOUT THINGS MORE THAN USUAL?**	
0 – The patient is neither more nor less insecure or irritable than usual.	☐
1 – It is doubtful whether the patient is more insecure or irritable than usual.	☐
2 – The patient expresses more clearly to be in a state of anxiety, apprehension or irritability, which he may find difficult to control. It is thus without influence on the patient's daily life, because th worrying is still about minor matters.	☐
3 – The anxiety or insecurity is at times more difficult to control, because the worrying is about major injuries or harms, which might occur in the future. E.g.: the anxiety may be experienced as panic i.e. overpowering dread. Has occasionally interfered with the patient's daily life.	☐
4 – The feeling of dreadfulness is present so often that it markedly interferes with the patient's daily life.	☐
11. Anxiety (somatic) This item includes physiological concomitants of anxiety: All feeling states should be rated under item 10 and not here. **HAVE YOU GOT ANY PHYSICAL SYMPTOMS AT THE MOMENT? (If due to meds, are then symptoms not due to meds?)**	
0 – When the patient is neither more nor less prone than usual to experience somatic concomitants of anxiety feeling states.	☐
1 – When the patient occasionally experiences slight manifestations like abdominal symptoms, sweating or trembling. However, the description is vague and doubtful.	☐

2 – When the patient from time to time experiences abdominal symptoms, sweating trembling etc. Symptoms and signs are clearly described, but are not marked or incapacitating, i.e. still withou influence on the patient's daily life.	☐
3 – Physiological concomitants of anxious feeling states are marked and sometimes very worrying. Interfere occasionally with the patient's daily life.	☐
4 – The feeling of dreadfulness is present so often that it markedly interferes with the patient's daily life.	☐
12. Gastro-Intestinal Symptoms may stem from the entire gastro-intestinal tract. Dry mouth, loss of appetite, and constipation are more common than abdominal cramps and pains. Must be distinguished fron gastro-intestinal anxiety symptoms ("butterflies in the stomach") or loose bowel movements) and also from nihilistic ideas (no bowel movements for weeks or months; the intestines have withered away) whic should be rated under 15 (Hypochondriasis). **WHAT IS YOUR APPETITE LIKE?**	
0 – No gastro-intestinal complaints (or symptoms unchanged from before onset of depression).	☐
1 – Eats without encouragement by staff, and food intake is about normal, but without relish (all dishes taste alike and cigarettes are without flavour). Sometimes constipated.	☐
2 – Food intake reduced, patient has to be urged to eat. As a rule clearly constipated. Laxatives are often tried, but are of little help.	☐
13. General Somatic Central is feelings of fatigue and exhaustion, loss of energy. But also diffuse muscular achings and pains in neck, back or limbs, e.g. muscular headache. **HAVE YOU GOT ANY ACHES AND PAINS? WHAT IS YOUR ENERGY LEVEL LIKE?**	
0 – The patient is neither more nor less tired or troubled by bodily discomfort than usual.	☐
1 – Doubtful or very vague feelings of muscular fatigue or other somatic discomfort.	☐
2 – Clearly or constantly tired and exhausted, and/or troubled by bodily discomforts, e.g. muscular headache.	☐
14. Sexual Interests This subject I often difficult to approach, especially with elderly patients. In males try to ask questions concerning sexual preoccupation and drive, in females responsiveness (both t engage in sexual activity and to obtain satisfaction in intercourse). **MEN: HAVE YOU BEEN THINKING ABOUT SEX MORE THAN USUAL? HAS YOUR SEX DRIVE CHANGED (INCREASED OR DECREASED) IN THE LAST WEEK?** **WOMEN: HAS YOUR INTEREST IN SEX CHANGED IN THE LAST WEEK?**	
0 – Not unusual.	☐
1 – Doubtful or mild reduction in sexual interest and enjoyment.	☐
2 – Clear loss of sexual appetite often functional impotence in men and lack of arousal or plain disgust in women.	☐

15. Hypochondriasis Preoccupation with bodily symptoms or functions (in the absence of somatic disease). **OBSERVED**	
0 – The patient pays no more interest than usual to the slight bodily sensations of every day life.	☐
1 – Slightly or doubtfully more occupied than usual with bodily symptoms and functions.	☐
2 – Quite worried about his physical health. The patient expresses thoughts of organic disease with a tendency to "somatise" the clinical presentation.	☐
3 – The patient is convinced to suffer from a physical illness, which can explain all his symptoms (brain tumour, abdominal cancer, etc.), but the patient can for a brief while be reassured that this is no the case.	☐
4 – The preoccupation with bodily dysfunction has clearly reached paranoid dimensions. The hypochondriacal delusions often have a nihilistic quality or guilt associations: to be rotting inside; insect eating the tissues; bowels blocked and withered away, other patients are being infected by the patient's bad odour or his syphilis. Counter-argumentation is without effect.	☐
16. Loss of insight This item has, of course, only meaning if the observer is convinced that the patient at the interview still is in a depressive state. **IF DEPRESSION SUSPECTED: HAVE YOU BEEN FEELING DEPRESSED?**	
0 – The patient agrees to have depressive symptoms or a "nervous" illness.	☐
1 – The patient still agrees to being depressed, but feels this to be secondary to non-illness related conditions like malnutrition, climate, overwork.	☐
2 – Denies being ill at all. Delusional patients are by definition without insight. Enquiries should therefore be directed to the patient's attitude to his symptoms of Guilt (item 2) or Hypochondriasis (item 15), bu other delusional symptoms should also be considered.	
17. Weight loss Try to get objective information; if such is not available be conservative in estimation. **A. At first interview this item covers the whole actual period of illness** **HAS YOUR WEIGHT CHANGED NOTICEABLY IN THE LAST MONTH?**	
0 – No weight loss.	☐
1 – 1-2.5 kg weight loss.	☐
2 – Weight loss of 3 kg or more.	☐
B. At weekly interviews	
0 – No weight loss.	☐

1 – ½ kg pr week.	☐
2 – 1 kg or more per week.	☐

C 4. Young mania rating scale

Young Mania Rating Scale (YMRS)

1. Elevated Mood
0 Absent
1 Mildly or possibly increased on questioning
2 Definite subjective elevation; optimistic, self-confident; cheerful; appropriate to content
3 Elevated; inappropriate to content; humorous
4 Euphoric; inappropriate laughter; singing

2. Increased Motor Activity-Energy
0 Absent
1 Subjectively increased
2 Animated; gestures increased
3 Excessive energy; hyperactive at times; restless (can be calmed)
4 Motor excitement; continuous hyperactivity (cannot be calmed)

3. Sexual Interest
0 Normal; not increased
1 Mildly or possibly increased
2 Definite subjective increase on questioning
3 Spontaneous sexual content; elaborates on sexual matters; hypersexual by self-report
4 Overt sexual acts (toward patients, staff, or interviewer)

4. Sleep
0 Reports no decrease in sleep
1 Sleeping less than normal amount by up to one hour
2 Sleeping less than normal by more than one hour
3 Reports decreased need for sleep
4 Denies need for sleep

5. Irritability
0 Absent
2 Subjectively increased
4 Irritable at times during interview; recent episodes of anger or annoyance on ward
6 Frequently irritable during interview; short, curt throughout
8 Hostile, uncooperative; interview impossible

6. Speech (Rate and Amount)
0 No increase
2 Feels talkative
4 Increased rate or amount at times, verbose at times
6 Push; consistently increased rate and amount; difficult to interrupt
8 Pressured; uninterruptible, continuous speech

7. Language-Thought Disorder
0 Absent
1 Circumstantial; mild distractibility; quick thoughts
2 Distractible, loses goal of thought; changes topics frequently; racing thoughts
3 Flight of ideas; tangentiality; difficult to follow; rhyming, echolalia
4 Incoherent; communication impossible

8. Content
0 Normal
2 Questionable plans, new interests
4 Special project(s); hyper-religious
6 Grandiose or paranoid ideas; ideas of reference
8 Delusions; hallucinations

9. Disruptive-Aggressive Behavior
0 Absent, cooperative
2 Sarcastic; loud at times, guarded
4 Demanding; threats on ward
6 Threatens interviewer; shouting; interview difficult
8 Assaultive; destructive; interview impossible

10. Appearance
0 Appropriate dress and grooming
1 Minimally unkempt
2 Poorly groomed; moderately disheveled; overdressed
3 Disheveled; partly clothed; garish make-up
4 Completely unkempt; decorated; bizarre garb

11. Insight
0 Present; admits illness; agrees with need for treatment
1 Possibly ill
2 Admits behavior change, but denies illness
3 Admits possible change in behavior, but denies illness
4 Denies any behavior change

Participant number …….. **Date of completion ……..**

C 5. Clinical global impression severity rating scale and global assessment of functioning scale

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

Clinical global impression severity scale (CGI-S)

0	Not assessed
1	Normal, not at all ill
2	Borderline mentally ill
3	Mildly ill
4	Moderately ill
5	Markedly ill
6	Severely ill
7	Among the most extremely ill patients

Global Assessment of Functioning(GAF) scale (DSM - IV Axis V)

91 - 100	Person has no problems OR has superior functioning in several areas OR is admired and sought after by others due to positive qualities
81 - 90	Person has few or no symptoms. Good functioning in several areas. No more than "everyday" problems or concerns.
71 - 80	Person has symptoms/problems, but they are temporary, expectable reactions to stressors. There is no more than slight impairment in any area of psychological functioning.
61 - 70	Mild symptoms in one area OR difficulty in one of the following: social, occupational, or school functioning. BUT, the person is generally functioning pretty well and has some meaningful interpersonal relationships.
51 - 60	Moderate symptoms OR moderate difficulty in one of the following: social, occupational, or school functioning.
41 - 50	Serious symptoms OR serious impairment in one of the following: social, occupational, or school functioning.
31 - 40	Some impairment in reality testing OR impairment in speech and communication OR serious impairment in several of the following: occupational or school functioning, interpersonal relationships, judgment, thinking, or mood.
21 - 30	Presence of hallucinations or delusions which influence behavior OR serious impairment in ability to communicate with others OR serious impairment in judgment OR inability to function in almost all areas.
11 - 20	There is some danger of harm to self or others OR occasional failure to maintain personal hygiene OR the person is virtually unable to communicate with others due to being incoherent or mute.
0 - 10	Persistent danger of harming self or others OR persistent inability to maintain personal hygiene OR person has made a serious attempt at suicide.

C 6. Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)

ASSIST - Drug Use Frequency Questionaire

I am going to ask you some questions about your experience of using substances across your lifetime and in the past three months. These substances can be smoked, swallowed, snorted, inhaled, injected or taken in the form of pills. Some of the substances listed may be prescribed by a doctor (like amphetamines, sedatives, pain medications). For this interview, we will not record medications that are used as prescribed by your doctor. However, if you have taken such medications for reasons other than prescription, or taken them more frequently or at higher doses than prescribed, please let me know. While we are also interested in knowing about your use of various illicit drugs, please be assured that information on such use will be treated as strictly confidential

Question 1: In your life, which of the following substances have you used.

	YES	NO	
Tobacco			*Probe if all answers are negative: "Not even when you were in school?", If "No" to all items, skip substance use questionaire. If "Yes" to any of these items, ask Question 2 for each substance ever used.*
Alcoholic Beverages (beer, wine etc)			
Cannabis (dagga, marijuana)			
Cocaine (rocks, coke, crack)			
Amphetamine Type Stimulants (Tik)			
Inhalants (nitrous glue, petrol)			
Sedatives or sleeping pills (			
Hallucinogens (LSD, acid, mushrooms, PCP, special K)			
Opioids (heroin, morphine, methadone, unga)			
Other (eg Mandrax, Buttons)			

Question 2: In the past three months, how often have you used the substances you mentioned (FIRST DRUG, SECOND DRUG, ETC)

	Never	Once or Twice	Monthy	Weekly	Daily or Almost Daily
Tobacco	0	2	3	4	6
Alcoholic Beverages (beer, wine etc)	0	2	3	4	6
Cannabis (dagga, marijuana)	0	2	3	4	6
Cocaine (rocks, coke, crack)	0	2	3	4	6
Amphetamine Type Stimulants (Tik)	0	2	3	4	6
Inhalants (nitrous glue, petrol)	0	2	3	4	6
Sedatives or sleeping pills	0	2	3	4	6
Hallucinogens (LSD, acid, mushrooms, PCP, special K)	0	2	3	4	6
Opioids (heroin, morphine, methadone, unga)	0	2	3	4	6
Other (eg. Mandrax/Buttons)	0	2	3	4	6

If "Never" to all items in Question 2, skip to Question 6. If any substances in Question 2 were used in the previous three months, continue with Questions 3, 4 & 5 for <u>each substance</u> used.

Question 3: During the past three months, how often have you had a strong desire or urge to use?

	Never	Once or Twice	Monthy	Weekly	Daily or Almost Daily
Tobacco	0	3	4	5	6
Alcoholic Beverages (beer, wine etc)	0	3	4	5	6
Cannabis (dagga, marijuana)	0	3	4	5	6
Cocaine (rocks, coke, crack)	0	3	4	5	6
Amphetamine Type Stimulants (Tik)	0	3	4	5	6
Inhalants (nitrous glue, petrol)	0	3	4	5	6
Sedatives or sleeping pills	0	3	4	5	6
Hallucinogens (LSD, acid, mushrooms, PCP, special K)	0	3	4	5	6
Opioids (heroin, morphine, methadone, unga)	0	3	4	5	6
Other (eg. Mandrax/Buttons)	0	3	4	5	6

Question 4: During the <u>past three months</u>, how often has your use of substances led to health, social, legal or financial problems? (please circle)

	Never	Once or Twice	Monthy	Weekly	Daily or Almost Daily
Tobacco	0	4	5	6	7
Alcoholic Beverages (beer, wine etc)	0	4	5	6	7
Cannabis (dagga, marijuana)	0	4	5	6	7
Cocaine (rocks, coke, crack)	0	4	5	6	7
Amphetamine Type Stimulants (Tik)	0	4	5	6	7
Inhalants (nitrous glue, petrol)	0	4	5	6	7
Sedatives or sleeping pills	0	4	5	6	7
Hallucinogens (LSD, acid, mushrooms, PCP, special K)	0	4	5	6	7
Opioids (heroin, morphine, methadone, unga)	0	4	5	6	7
Other (eg. Mandrax/Buttons)	0	4	5	6	7

Question 5: During the past three months, how often have you failed to do what was normally expected of you because of your use of substance use? (please circle)

	Never	Once or Twice	Monthy	Weekly	Daily or Almost Daily
Tobacco	0	5	6	7	8
Alcoholic Beverages (beer, wine etc)	0	5	6	7	8
Cannabis (dagga, marijuana)	0	5	6	7	8
Cocaine (rocks, coke, crack)	0	5	6	7	8
Amphetamine Type Stimulants (Tik)	0	5	6	7	8
Inhalants (nitrous glue, petrol)	0	5	6	7	8
Sedatives or sleeping pills	0	5	6	7	8
Hallucinogens (LSD, acid, mushrooms, PCP, special K)	0	5	6	7	8
Opioids (heroin, morphine, methadone, unga)	0	5	6	7	8
Other (eg. Mandrax/Buttons)	0	5	6	7	8

Ask Questions 6 & 7 for all substances ever used (i.e. those endorsed in Question 1)

Question 6: Has a friend or relative or anyone else ever expressed concern about your use of specific substances?

	No, Never	Yes, in the past 3 months	Yes, but not in the past 3 months
Tobacco	0	6	3
Alcoholic Beverages (beer, wine etc)	0	6	3
Cannabis (dagga, marijuana)	0	6	3
Cocaine (rocks, coke, crack)	0	6	3
Amphetamine Type Stimulants (Tik)	0	6	3
Inhalants (nitrous glue, petrol)	0	6	3
Sedatives or sleeping pills	0	6	3
Hallucinogens (LSD, acid, mushrooms, PCP, special K)	0	6	3
Opioids (heroin, morphine, methadone, unga)	0	6	3
Other (eg. Mandrax/Buttons)	0	6	3

Question 7: Have you ever tried and failed to control, cut down or stop using specific drugs?

	No, Never	Yes, in the past 3 months	Yes, but not in the past 3 months
Tobacco	0	6	3
Alcoholic Beverages (beer, wine etc)	0	6	3
Cannabis (dagga, marijuana)	0	6	3
Cocaine (rocks, coke, crack)	0	6	3
Amphetamine Type Stimulants (Tik)	0	6	3
Inhalants (nitrous glue, petrol)	0	6	3
Sedatives or sleeping pills	0	6	3
Hallucinogens (LSD, acid, mushrooms, PCP,special K)	0	6	3
Opioids (heroin, morphine, methadone, unga)	0	6	3
Other (eg. Mandrax/Buttons)	0	6	3

Question 8: Have you ever used any drug by injection?

No, Never	Yes, in the past 3 months	Yes, but not in the past 3 months
0	2	1

Total Score Drug 1: _____ Total Score Drug 2: _____ Total Score Drug 3: _____

Total Score drug 4: _____ Total Score Drug 5: _____ Total Score Drug 6: _____

Participant Number: _____ Date of completion: _____

C 7. Simpson angus extrapyrimidal symptom scale

Simpson-Angus Rating Scale for Extrapyramidal Side Effects

Simpson GM, Angus JWS: A rating scale for extrapyramidal side effects. Acta Psychiatrica Scandinavica, 212:11-19, 1970

Instructions: The exam should be conducted in a room where the subject can wlak a sufficient distance to allow him/her to get into a natural rhythm (e.g., 15 paces). Each side of the body should be examined. If one side shows more pronounced pathology than the other, this scoure should be noted and this taken. Cogwheel rigidity may be palpated when the examination is carried out for items, 3,4, 5, and 6. It is not rated separately and is merely another way to detect rigidity. It would indicate that a minimum score of 1 would be mandatory.

1 **Gait:** The patient is examined as he walks into the examining room, his gait, the swing of this arms, his general posture, all form the basis for an overall score for this item. This is rated as follows:

0	Normal
1	Diminution in swing while the patient is walking
2	Marked diminution in swing with obvious rigidity in the arm
3	Stiff gait with arms held rigidly before the abdomen
4	Stopped shuffling gait with propulsion and retropulsion

2 **Arm Dropping:** The patient and the examiner both raise their arms to sholder height and let them fall to their sides. In a normal subject, a stout slap is hear as the arms hit the sides. In the patient with extreme Parkinson's syndrome, the arms fall very slowly:

0	Normal, free fall with loud slap and rebound
1	Fall slowed slightly with less audible contract and little rebound
2	Fall slowed, no rebound
3	Marked slowing, no slap at all
4	Arms fall as though against resistance; as though through glue

3 **Shoulder Shaking:** The subject's arms are bent at a right angle at the elbow and are taken one at a time by the examiner who grasps one hand and also clasps the other around the patient's elbow. The subject's upper arm is pushed to and fro and the humerus is externally rotated. The degree of resistance form normal to extreme rigidity is scored as follows:

0	Normal
1	Slight stiffness and resistance
2	Moderate stiffness and resistance
3	Marked rigidity with difficulty in passive movement
4	Extreme stiffness and rigidity with almost a frozen shoulder

4 **Elbow Rigidity:** The elbow joints are separately bent at right angles and passively extended and flexed, with the subject's biceps observed and simulataneously palpated, The resistance to this procedure is rated. (The presence of cogwheel rigidity is noted separately.)

0	Normal
1	Slight stiffness and resistance
2	Moderate stiffness and resistance
3	Marked rigidity with difficulty in passive movement
4	Extreme stiffness and rigidity with almost a frozen joint

5 **Wrist rigidity or Fixation of position:** The wrist is held in one hand and the fingers held by the examiner's other hand, with the wrist moved to extension, flexion and ulnar and radial deviation.

0	Normal
1	Slight stiffness and resistance
2	Moderate stiffness and resistance
3	Marked rigidity with difficulty in passive movement
4	Extreme stiffness and rigidity with almost a frozen wrist

6 **Leg Pendulousness:** The patient sits on a table with his legs hanging down and swinging free. The ankle is grasped by the examiner and raised until the knee is partially extended. It is then allowed to fall. The resistance to falling and the lack of swinging form the basis of the score on this item.

0	The legs swing freely
1	Slight diminution in the swing of the legs
2	Moderate resistance to swing
3	Marked resistance and damping of swing
4	Complete absence of swing

7 **Head Dropping:** The patient lies on a well-padded examining table and his head is raised by the examiner's hand. The hand is then withdrawn and the head allowed to drop. In the normal subject the head will fall upon the table. The movement is delayed in extrapyramidal system disorders and in extreme parkinsonism it is absent. The neck muscles are rigid and the head does not reach the examining table.

0	The head falls completely with a good thump as it hits the table
1	Slight slowing in fall, mainly noted by lack of slap as head meets the table
2	Moderate slowing in the fall quite noticeable to the eye
3	Head falls stiffly and slowly
4	Head does not reach the examining table

8 **Glabella Tap:** Subject is told to open eyes wide and not to blink. The glabella region is tapped at a steady, rapid speed. The number of times patient blinks in succession is noted

0	0-5 blinks
1	6-10 blinks
2	11-15 blinks
3	16-20 blinks
4	21 and more blinks

9 **Tremor:** Patient is observed walking into examining room and is then re-examined for this item

0	Normal
1	Mild finger tremor, obvious to sight and touch
2	Tremor of hand or arm occurring spasmodically
3	Persistent tremor of one or more limbs
4	Whole body tremor

10 **Salivation:** Patient is observed while talking and then asked to open his mouth and elevate his tongue. The following ratings are given:

0	Normal
1	Excess salivation to the extent that pooling takes place if the mouth is open and the tongue is raised.
2	When excess salivation is present and might occasionally result in difficulty in speaking
3	Speaking with difficulty because of excess salivation
4	Frank drooling

Total Score:

Participant Number: _____ Date: _____

Edinburgh Handedness Questionnaire

Oldfield,RC. (1971). The assessment and analysis of handedness: The edinburgh inventory. Neuropsychologia. 9:97-113

Which Hand?			
Right	Both	Left	Which hand do you write with?
Right	Both	Left	Which hand do you draw with?
Right	Both	Left	When throwing a ball, which hand do you use?
Right	Both	Left	When using scissors, which hand does the cutting?
Right	Both	Left	When brushing or combing your hair, which hand holds the brush/comb?
Right	Both	Left	When brushing your teeth, which hand holds the toothbrush?
Right	Both	Left	When cutting a loaf of bread, which hand holds the knife?
Right	Both	Left	When eating soup, which hand holds the spoon?
Right	Both	Left	When using a hammer, which hand hammers the nail into the wood?
Right	Both	Left	When using a screwdriver, which hand turns the screwdriver to tighten the screw?
Right	Both	Left	When playing tennis, which hand holds the racket?
Right	Both	Left	When using both a knife and a fork, which hand holds the fork?
Right	Both	Left	When hitting a ball with a cricket bat, which hand is at the top of bat?
Right	Both	Left	when hitting a golf ball with a golf stick, which hand is at the top of the club?
Right	Both	Left	When sweeping with a broom, which hand is at the top of the broom?
Right	Both	Left	When raking leaves up with a rake, which hand is at the top of the rake?
Right	Both	Left	When striking a match, which hand is holding the match?
Right	Both	Left	When opening the match box to get a match, which hand takes the match out?
Right	Both	Left	When dealing cards, which hands deals to the players?
Right	Both	Left	When threading and needle, which hand is used to put the thread through the eye of the needle?

Participant Number: Date of Completion:

Table D 1 Demographic mean and standard deviation

		Controls			Schizophrenia			Bipolar I disorder			Methamphetamine induced psychosis	
		n=27			n=27			n=28			n=21	
		Mean	***Std.Dev.***		**Mean**	***Std.Dev.***		**Mean**	***Std.Dev.***		**Mean**	***Std.Dev.***
Age on day of imaging (yrs)	*	25,74	3,75		29,67	5,43		29,64	4,91		26,05	5,47
Duration at school (yrs)		11,56	1,25		10,70	1,81		11,39	1,07	#	10,24	1,64
Tertiary education (yrs)		2,30	3,15		1,48	1,95		1,71	1,82		0,57	1,35
Total duration of education (yrs)		13,85	3,78		12,19	3,23		13,11	2,51	@	10,80	2,38
Weight (kg)	*	69,17	7,96		85,48	24,30		83,83	14,57	&	68,77	15,18
BMI	*	23,28	3,00		29,24	7,96		28,75	5,24	&	23,34	3,69
Handedness (left:right)		1:26			3:24			2:26			3:19	

** CON vs SCZ and BPD; # CON vs MPD; @ MPD vs CON and BPD & MPD vs SCZ and BPD. Non- parametric Kruskal Wallis (H- test), Significance P<0,05.*

Table D 2 Behavioural mean and standard deviation

	Controls			Schizophrenia			Bipolar I disorder			Methamphetamine induced psychosis	
	n=27			n=27			n=28			n=21	
	Mean	***Std.Dev.***		**Mean**	***Std.Dev.***		**Mean**	***Std.Dev.***		**Mean**	***Std.Dev.***
Continuous Performance Task											
Correct responses (^{X}/60)	53,59	10,71	*	44,23	13,27		51,82	10,91		46,52	14,83
Overall response time (msec)	231,56	103,55	*	459,96	233,98		315,43	141,22		330,19	142,42
Errors of commission	4,81	8,05		7,77	9,33		6,29	10,19		11,29	13,98
Errors of omission	1,59	4,84	#	8,00	11,93		1,89	4,08		2,19	3,36
Trick S responses	0,63	2,51		1,19	2,83		0,43	0,96		0,67	1,20

** CON vs SCZ # SCZ vs CON and BPD. Non- parametric Kruskal Wallis (H- test), Significance P<0,05.*

Table D 3 Clinical scales mean and standard deviation

	Psychotic groups combined n=76			Schizophrenia n=27			Bipolar I disorder n=28			Methamphetamine induced psychosis n=21	
	Mean	***Std.Dev.***		**Mean**	***Std.Dev.***		**Mean**	***Std.Dev.***		**Mean**	***Std.Dev.***
Positive & Negative Syndrome Scale											
Total score	43	30-100		48	30-100	*	35	30-73		45	30-77
Positive symptoms	8	7-25	#	12	7-24		7	7-25		7	7-19
Negative symptoms	11	7-30		13	7-30	*	9	7-20		12	7-27
General psychopathology	22	16-50	#	23	16-50		19	16-37		22	16-38
Calgary depression for schizophrenia	1	0-13		2	0-8		0	0-13		1	0-9
Hamilton depression rating scale	1	0-20		2	0-10		0	0-20		2	0-5
Young mania rating scale	2	0-16		3	0-15		1	0-16		2	0-12
Clinical global impression of illness severity	2	1-4	#	3	1-4		2	1-4		2	1-4
Global assessment of functioning scale	65	5-90	#	60	30-85		71	5-85		65	31-90
Simpson Angus scale for parkinsonism	0	0-16	#	1	0-16		0	0-1		0	0-9

* *BPD vs SCZ, and MPD ;* # *SCZ vs BPD. Non- parametric Kruskal Wallis (H- test), Significance P<0,05.*

Table D 4 ASSIST scores mean and standard deviation

		Controls		Schizophrenia		Bipolar I disorder			Methamphetamine induced psychosis	
		n=76		n=27		n=28			n=21	
		Mean	***Std.Dev.***	**Mean**	***Std.Dev.***	**Mean**	***Std.Dev.***		**Mean**	***Std.Dev.***
Total substance involvement score		17	13	27	26	27	22	*	60	25
Tobacco score		6,07	8,10	12,96	12,91	12,68	11,21	*	22,29	6,25
Alcohol score		5,81	4,95	5,93	6,24	6,96	5,36		8,48	6,40
Cannabis score		3	3	3	5	5	7	*	9	7
Cocaine score		1	1	0	0	1	1		1	2
Methamphetamine score		0	1	2	6	0	1	*	13	10
Inhalants score		0	1	1	2	0	0		0	1
Sedatives sleeping pill score		0	1	1	2	1	3		1	2
Hallucinogens score		0	1	0	1	1	2		1	1
Opioids score	%	0	1	0	1	0	1		1	1
Mandrax score		0	1	1	2	0	1	*	4	4

** MPD vs all other groups; % Denotes significant differences but not between groups. Non- parametric Kruskal Wallis (H- test), Significance P<0,05.*

Table D 5 Medication mean and standard deviation

	Psychotic groups combined n=76			Schizophrenia n=27			Bipolar I disorder n=28			Methamphetamine induced psychosis n=21	
	Mean	***Std.Dev.***		**Mean**	***Std.Dev.***		**Mean**	***Std.Dev.***		**Mean**	***Std.Dev.***
Duration of psychotic disorders (years)	6,30	5,35		7,41	*5,60*		7,59	*5,27*		3,13	*3,83*
Chlorpromazine equivalents	210,03	299,27		330,56	*438,77*		151,34	*178,79*		133,33	*108,78*
Positive & Negative Syndrome Scale											
Total score	23,03	*6,95*		52,33	*17,46*	$	39,04	*10,78*		46,62	*11,86*
Positive symptoms	45,86	*14,76*	#	12,22	*5,02*		9,07	*4,09*		8,95	*3,09*
Negative symptoms	10,16	*4,44*		14,89	*6,53*	$	9,21	*3,12*		14,43	*5,63*
General psychopathology	12,67	*5,82*	#	25,22	*8,10*		20,75	*5,76*		23,24	*6,11*
Calgary depression for schizophrenia	2,34	*2,88*		2,70	2,49		2,00	3,12		2,33	3,10
Hamilton depression rating scale	1,96	*3,42*		4,52	4,46		3,46	5,01		3,33	3,26
Young mania rating scale	3,80	*4,36*		2,22	2,69		2,04	4,86		1,52	1,50
Clinical global impression of illness severity scale	2,43	*1,04*	#	2,93	1,07		2,00	0,90		2,38	0,92
Global assessment of functioning scale	64,30	*13,51*		61,17	11,36	@	67,30	15,01		64,31	13,68
Simpson Angus scale for parkinsonism	1,17	*2,57*	#	2,15	3,46		0,07	0,26		1,38	2,46

** MPD vs SCZ, and BPD; # SCZ vs MPD ;% Denotes significant differences but not between groups; & BPD vs SCZ, and MPD ;$ BPD vs MPD. Non- parametric Kruskal Wallis (H- test), Significance P<0,05.*

Table E 1 Spearman rank order correlations for demographics

Group=Controls Spearman Rank Order Correlations (ALL groups)Marked correlations are significant at p <0,01					Group=Schizophrenia Spearman Rank Order Correlations (ALL groups)Marked correlations are significant at p <0,01				
Pair of Variables	Valid	Spearman	t(N-2)	p-value	Pair of Variables	Valid	Spearman	t(N-2)	p-value
TRICK_FP2_P300_A & yearsatschool	27	0,493	2,83681	0,008905	CUE2_FP1_P300_T & yearsatschool	27	-0,488	-2,79328	0,00986
TRICK_FP2_P300_A & totalnumberofyearseducation	27	0,524	3,07811	0,005001	STIM_P3_N200_T & yearsatschool	27	0,562	3,39402	0,00230
CUE1_C3_P300_T & weight	27	0,559	3,37479	0,002414	STIM_P3_N200_T & totalnumberofyearseducation	27	0,498	2,87303	0,00817
TRICK_F3_N200_T & BMI	27	-0,534	-3,16189	0,004079	CUE2_P3_N200_T & yearsatschool	27	0,583	3,58712	0,00142
CUE1_P3_N200_A & tertiaryeducation	27	0,536	3,17066	0,003993	CUE2_P3_N200_T & totalnumberofyearseducation	27	0,571	3,47654	0,00187
CUE1_P3_N200_A & totalnumberofyearseducation	27	0,518	3,03018	0,005615	TRICK_F4_P100_T & yearsatschool	27	-0,496	-2,85263	0,00858
TRICK_P4_P100_T & BMI	27	-0,546	-3,25562	0,003241	TRICK_F4_P100_T & totalnumberofyearseducation	27	-0,491	-2,81806	0,00931
CUE1_P3_N20-150_A & tertiaryeducation	27	0,493	2,83609	0,008920	TRICK_P3_P100_T & yearsatschool	27	-0,510	-2,96338	0,00659
CUE1_P3_N20-150_A & totalnumberofyearseducation	27	0,514	2,99277	0,006144	TRICK_P3_P100_T & totalnumberofyearseducation	27	-0,513	-2,98478	0,00626
					TRICK_P4_P100_T & yearsatschool	27	-0,508	-2,94555	0,00688
					TRICK_P4_P100_T & totalnumberofyearseducation	27	-0,510	-2,96535	0,00656

Group=Bipolar Spearman Rank Order Correlations (ALL groups)Marked correlations are significant at p <0,01					Group=MethPsychosis Spearman Rank Order Correlations (ALL groups)Marked correlations are significant at p <0,01				
Pair of Variables	Valid	Spearman	t(N-2)	p-value	Pair of Variables	Valid	Spearman	t(N-2)	p-value
TRICK_FP1_P300_A & yearsatschool	28	0,540	3,26982	0,00303	STIM_F3_P300_T & ageondayoftesting	21	0,562	2,95848	0,00807
TRICK_FP2_N200_A & ageondayoftesting	28	0,565	3,49055	0,00174	TRICK_FP1_P300_T & weight	21	-0,579	-3,09654	0,00594
CUE1_FP1_N200_T & weight	28	-0,486	-2,83420	0,00877	CUE1_P4_P300_A & ageondayoftesting	21	0,729	4,64384	0,00018
CUE1_P3_N200_T & yearsatschool	28	-0,495	-2,90858	0,00734	CUE1_P4_P300_A & tertiaryeducation	21	0,684	4,09232	0,00062
TRICK_P4_P100_T & tertiaryeducation	28	0,518	3,08607	0,00477	CUE2_C3_P300_T & yearsatschool	21	-0,553	-2,89102	0,00936
CUE1_F4_P100_T & yearsatschool	28	0,479	2,77877	0,01000	TRICK_C4_P100_T & tertiaryeducation	21	0,604	3,30477	0,00373
					CUE2_F4_P100_T & BMI	21	-0,553	-2,89329	0,00931
					CUE1_P4_N20-150_T & ageondayoftesting	21	-0,550	-2,87328	0,00973

Group=All groups Spearman Rank Order Correlations (ALL groups)Marked correlations are significant at p <0,01				
Pair of Variables	Valid	Spearman	t(N-2)	p-value
TRICK_FP2_P300_A & yearsatschool	103	0,266	2,76947	0,006682
CUE1_FP2_P300_T & yearsatschool	103	0,254	2,63670	0,009694
CUE2_C3_P300_T & yearsatschool	103	-0,305	-3,22293	0,001709
CUE1_FP1_N200_A & tertiaryeducation	103	-0,268	-2,79652	0,006185
CUE1_FP1_N200_A & totalnumberofyearseducation	103	-0,253	-2,63201	0,009820
CUE1_FP1_N200_T & yearsatschool	103	-0,259	-2,69123	0,008333
TRICK_P4_P100_T & BMI	103	-0,293	-3,08487	0,002627

Table E 2 Spearman rank order correlations for behavioural data

Pair of Variables	Group=Controls Spearman Rank Order Correlations (ALL groups)Marked correlations are significant at p <0,01 Valid	Spearman	t(N-2)	p-value
STIM_C3_N200_A & CPT1 Total number of impulsive responses	27	-0,502	-2,90261	0,007620
STIM_P3_N200_A & CPT1 Total number of omissions	27	-0,520	-3,04713	0,005390
CUE1_C3_N200_A & CPT1 Total number of correct responses	27	0,510	2,96605	0,006550
CUE1_C3_N200_A & CPT1 Total number of impulsive responses	27	-0,531	-3,13104	0,004398
CUE1_P3_N200_A & CPT1 Total number of correct responses	27	0,678	4,60770	0,000103
CUE1_P3_N200_A & CPT1 Total number of impulsive responses	27	-0,709	-5,02796	0,000035
CUE2_C3_N200_A & CPT1 Total number of impulsive responses	27	-0,522	-3,06397	0,005175
CUE1_P3_P100_A & CPT1 Total number of correct responses	27	0,565	3,42045	0,002154
CUE1_P3_P100_A & CPT1 Total number of impulsive responses	27	-0,567	-3,43874	0,002058
TRICK_P3_P70-200_T & CPT1 Total number of correct responses	27	0,498	2,87468	0,008142
TRICK_P3_P70-200_T & CPT1 Total number of impulsive responses	27	-0,488	-2,79451	0,009836
CUE1_P3_P70-200_A & CPT1 Total number of correct responses	27	0,613	3,87487	0,000683
CUE1_P3_P70-200_A & CPT1 Total number of impulsive responses	27	-0,617	-3,92458	0,000601
CUE1_P3_N20-150_A & CPT1 Total number of correct responses	27	0,651	4,29303	0,000233
CUE1_P3_N20-150_A & CPT1 Total number of impulsive responses	27	-0,653	-4,31145	0,000222
CUE1_P3_N20-150_A & CPT1 Total number of omissions	27	-0,534	-3,15505	0,004148

Pair of Variables	Group=Schizophrenia Spearman Rank Order Correlations (ALL groups)Marked correlations are significant at p <0,01 Valid	Spearman	t(N-2)	p-value
STIM_C3_P300_T & CPT1 OVERALL RESPONSE TIME	26	-0,571626	-3,41296	0,002284
STIM_C4_P300_T & CPT1 OVERALL RESPONSE TIME	26	-0,540541	-3,14756	0,004359
STIM_P4_P300_T & CPT1 OVERALL RESPONSE TIME	26	-0,516522	-2,95516	0,006902
CUE2_C4_P300_T & CPT1 OVERALL RESPONSE TIME	26	-0,531143	-3,07107	0,005238
CUE2_P4_P300_T & CPT1 OVERALL RESPONSE TIME	26	-0,521650	-2,99540	0,006274
STIM_F3_P100_T & CPT 1Total number of trick S responses	26	0,530346	3,06465	0,005319
CUE2_F4_P100_A & CPT1 Total number of omissions	26	-0,579778	-3,48602	0,001907
CUE1_P3_P70-200_T & CPT1 Total number of correct responses	26	0,504832	2,86505	0,008532
STIM_P3_N20-150_T & CPT1 Total number of impulsive responses	26	0,600286	3,67697	0,001187
CUE2_P3_N20-150_T & CPT1 Total number of impulsive responses	26	0,608707	3,75859	0,000967

Pair of Variables	Group=Bipolar Spearman Rank Order Correlations (ALL groups)Marked correlations are significant Valid	Spearman	t(N-2)	p-value
TRICK_F4_N200_A & CPT1 Total number of omissions	28	-0,492573	-2,88604	0,007747
CUE1_P4_N200_T & CPT1 Total number of omissions	28	-0,485079	-2,82849	0,008888
CUE1_P4_P100_T & CPT 1Total number of trick S responses	28	-0,593760	-3,76266	0,000866

Pair of Variables	Group=MethPsychosis Spearman Rank Order Correlations (ALL groups)Marked correlations are significant at p <0,01 Valid	Spearman	t(N-2)	p-value
CUE1_F3_P100_A & CPT1 Total number of omissions	21	0,669745	3,93131	0,000896
CUE1_C3_P100_A & CPT1 Total number of omissions	21	0,620499	3,44895	0,002689
CUE1_P3_P100_A & CPT1 Total number of omissions	21	0,617685	3,42363	0,002848
CUE2_P4_P100_A & CPT1 Total number of omissions	21	0,558590	2,93551	0,008489
CUE2_P4_P70-200_A & CPT1 Total number of omissions	21	0,579696	3,10104	0,005881
TRICK_P3_N20-150_T & CPT1Total number of correct responses	21	0,707290	4,36116	0,000336
TRICK_P3_N20-150_T & CPT1Total number of impulsive responses	21	-0,675192	-3,98987	0,000784

Pair of Variables	Group=All groups Spearman Rank Order Correlations (ALL groups)Marked correlations are significant at p <0,01 Valid	Spearman	t(N-2)	p-value
STIM_FP1_P300_T & CPT1 Total number of correct responses	102	-0,342790	-3,64898	0,000421
STIM_FP1_P300_T & CPT1 Total number of omissions	102	0,276956	2,88231	0,004832
TRICK_F4_P300_A & CPT1 Total number of omissions	102	-0,256366	-2,65230	0,009299
TRICK_C4_P300_A & CPT1 Total number of omissions	102	-0,255771	-2,64571	0,009469
CUE2_FP1_P300_T & CPT1 Total number of correct responses	102	-0,284376	-2,96623	0,003771
STIM_F4_N200_A & CPT1 OVERALL RESPONSE TIME	102	0,268737	2,79001	0,006312
TRICK_F3_N200_A & CPT1 OVERALL RESPONSE TIME	102	-0,269778	-2,80166	0,006105
TRICK_F3_N200_A & CPT1 Total number of omissions	102	-0,293126	-3,06594	0,002791
TRICK_F4_N200_A & CPT1 Total number of omissions	102	-0,275595	-2,86698	0,005054
TRICK_C3_N200_A & CPT1 Total number of omissions	102	-0,269793	-2,80182	0,006102
TRICK_C4_N200_A & CPT1 Total number of omissions	102	-0,330733	-3,50455	0,000686

Table E 3 Spearman rank order correlations for the ASSIST scores

	Group=Controls Spearman Rank Order Correlations (ALL groups)Marked correlations are significant at p <0,01					Group=Schizophrenia Spearman Rank Order Correlations (ALL groups)Marked correlations are significant at p <0,01			
Pair of Variables	Valid	Spearman	t(N-2)	p-value	Pair of Variables	Valid	Spearman	t(N-2)	p-value
STIM_FP2_P300_A & assistalcoholscore	27	-0,510991	-2,97231	0,006453	STIM_C3_P300_T & assisttabaccoscore	27	0,617233	3,92252	0,000604
STIM_F4_P300_A & assistcannabisscore	27	-0,505158	-2,92667	0,007196	STIM_C3_P300_T & tsiscore	27	0,496389	2,85905	0,008449
STIM_P3_P300_A & assisttabaccoscore	27	-0,586950	-3,62483	0,001289	STIM_P3_P300_T & assisttabaccoscore	27	0,609785	3,84690	0,000733
STIM_P3_P300_A & tsiscore	27	-0,542063	-3,22527	0,003493	STIM_P3_P300_T & tsiscore	27	0,553495	3,32289	0,002745
TRICK_C3_P300_A & assisttabaccoscore	27	-0,540199	-3,20960	0,003630	STIM_P4_P300_T & assisttabaccoscore	27	0,588085	3,63554	0,001255
TRICK_P3_P300_A & assisttabaccoscore	27	-0,577664	-3,53842	0,001603	STIM_P4_P300_T & tsiscore	27	0,563640	3,41178	0,002201
TRICK_P3_P300_A & tsiscore	27	-0,538392	-3,19447	0,003767	CUE1_C3_P300_A & assistmandraxscore	27	0,530579	3,12976	0,004412
TRICK_C3_N200_A & assisttabaccoscore	27	-0,526110	-3,09325	0,004821	CUE2_P3_P300_T & tsiscore	27	0,535194	3,16784	0,004020
CUE1_FP1_N200_T & assisttabaccoscore	27	-0,500763	-2,89263	0,007803	CUE2_P4_P300_T & assisttabaccoscore	27	0,543897	3,24075	0,003362
CUE1_FP2_N200_A & assistcocainescore	27	0,501486	2,89821	0,007701	CUE2_P4_P300_T & tsiscore	27	0,504308	2,92006	0,007311
CUE1_C3_N200_T & assistcannabisscore	27	-0,524601	-3,08100	0,004966	STIM_P3_N200_A & tsiscore	27	-0,562183	-3,39888	0,002273
CUE1_C4_N200_T & tsiscore	27	-0,490509	-2,81437	0,009388	STIM_P4_N200_A & tsiscore	27	-0,550516	-3,29720	0,002925
CUE1_P3_N200_T & assistcannabisscore	27	-0,498424	-2,87464	0,008143	CUE1_F3_N200_T & assisttabaccoscore	27	0,547594	3,27217	0,003112
CUE1_P3_N200_T & tsiscore	27	-0,502986	-2,90981	0,007491	STIM_P4_P100_A & assisttabaccoscore	27	-0,571265	-3,48008	0,001856
CUE2_F3_N200_A & assistalcoholscore	27	0,559672	3,37675	0,002402	STIM_P4_P100_A & tsiscore	27	-0,578456	-3,54571	0,001574
CUE2_C3_N200_A & assistmethamphetaminescore	27	0,529574	3,12152	0,004501	CUE1_F3_P100_A & assisttabaccoscore	27	0,503457	2,91345	0,007426
CUE2_C4_N200_A & assistmethamphetaminescore	27	0,499313	2,88146	0,008013	CUE1_F4_P100_A & assisttabaccoscore	27	0,611517	3,86434	0,000701
CUE2_P4_N200_A & assistcannabisscore	27	0,536812	3,18129	0,003890	CUE1_P3_P100_T & assisttabaccoscore	27	-0,511918	-2,97961	0,006341
STIM_F4_P100_T & assistcannabisscore	27	-0,550875	-3,30028	0,002903	CUE1_P3_P100_T & tsiscore	27	-0,502544	-2,90639	0,007552
TRICK_C4_P100_T & assisttabaccoscore	27	-0,526512	-3,09651	0,004783	CUE2_P4_P100_A & assistcannabisscore	27	-0,505669	-2,93064	0,007129
TRICK_P3_P100_T & assistcocainescore	27	0,532305	3,14395	0,004262	STIM_P3_N20-150_A & assisttabaccoscore	27	-0,561667	-3,39432	0,002299
CUE2_F4_P100_T & assistcannabisscore	27	-0,547643	-3,27259	0,003109	STIM_P3_N20-150_A & assistmandraxscore	27	-0,575286	-3,51662	0,001693
CUE2_C4_P100_T & assisthallucinogensscore	27	0,490432	2,81379	0,009400	STIM_P3_N20-150_A & tsiscore	27	-0,614072	-3,89023	0,000656
CUE2_P3_P100_A & assisthallucinogensscore	27	0,529318	3,11942	0,004524	STIM_P4_N20-150_A & assisttabaccoscore	27	-0,517080	-3,02055	0,005747
CUE2_P4_P100_A & assisthallucinogensscore	27	0,496865	2,86270	0,008377	STIM_P4_N20-150_A & tsiscore	27	-0,553279	-3,32102	0,002758
CUE2_P3_P70-200_A & assisthallucinogensscore	27	0,529318	3,11942	0,004524					
CUE2_P4_P70-200_A & assisthallucinogensscore	27	0,496865	2,86270	0,008377					
CUE2_P3_N20-150_A & assisthallucinogensscore	27	0,500223	2,88846	0,007881					
CUE2_P4_N20-150_A & assistcannabisscore	27	0,502575	2,90662	0,007548					

Group=Bipolar
Spearman Rank Order Correlations (ALL groups)Marked correlations are significant at p <0,01

Pair of Variables	Valid	Spearman	t(N-2)	p-value
CUE1_C4_N200_A & assisttabaccoscore	28	0,507432	3,00270	0,005847
CUE1_C4_N200_A & tsiscore	28	0,494860	2,90378	0,007424
CUE2_F3_N200_A & assisthallucinogensscore	28	0,482943	2,81223	0,009237
CUE2_F3_N200_A & tsiscore	28	0,525292	3,14773	0,004100
CUE1_C4_P100_A & assisttabaccoscore	28	0,490380	2,86911	0,008067
CUE1_C4_P100_A & tsiscore	28	0,480056	2,79036	0,009728
STIM_P3_N20-150_A & assistmethamphetaminescore	28	0,478877	2,78147	0,009935
STIM_P3_N20-150_A & assistmandraxscore	28	0,478877	2,78147	0,009935

Group=MethPsychosis
Spearman Rank Order Correlations (ALL groups)Marked correlations are significant at p <0,01

Pair of Variables	Valid	Spearman	t(N-2)	p-value
CUE1_C4_P300_T & assisttabaccoscore	21	0,620446	3,44847	0,002692
CUE2_FP1_P300_A & assistalcoholscore	21	-0,728674	-4,63776	0,000179
CUE2_FP1_P300_T & tsiscore	21	0,558595	2,93554	0,008488
CUE2_FP2_P300_A & assistalcoholscore	21	-0,661823	-3,84817	0,001084
STIM_P3_N200_A & assistmethamphetaminescore	21	-0,569198	-3,01761	0,007080
CUE1_F4_N200_A & assistalcoholscore	21	0,588956	3,17658	0,004968
CUE2_FP1_N200_A & assistalcoholscore	21	-0,763437	-5,15224	0,000057
CUE2_FP2_N200_A & assistalcoholscore	21	-0,631740	-3,55233	0,002127
TRICK_P3_N20-150_T & assistcannabisscore	21	-0,771556	-5,28660	0,000042

Group=All groups
Spearman Rank Order Correlations (ALL groups)Marked correlations are significant at p <0,01

Pair of Variables	Valid	Spearman	t(N-2)	p-value
STIM_P3_P300_A & assistcocainescore	103	-0,274803	-2,87231	0,004966
STIM_P3_P300_T & assistcannabisscore	103	0,271919	2,83975	0,005460
CUE2_P3_P300_T & assistcannabisscore	103	0,307084	3,24285	0,001604
STIM_P4_N200_T & assistalcoholscore	103	0,280785	2,94013	0,004067
CUE1_F3_N200_A & assisttabaccoscore	103	0,299324	3,15272	0,002130
CUE1_F4_N200_A & assisttabaccoscore	103	0,257004	2,67263	0,008776
CUE1_F4_N200_A & assistcannabisscore	103	0,268055	2,79625	0,006190
CUE2_C4_N200_T & assisthallucinogensscore	103	0,260684	2,71367	0,007825
TRICK_P3_P100_A & assisthallucinogensscore	103	0,266959	2,78394	0,006412
TRICK_P3_P100_T & assistopiodssocre	103	0,276562	2,89222	0,004685
TRICK_P4_P100_A & assisthallucinogensscore	103	0,304283	3,21023	0,001779
CUE1_F3_P100_A & assisttabaccoscore	103	0,292639	3,07563	0,002703
CUE1_F3_P100_A & tsiscore	103	0,253948	2,63865	0,009642
CUE1_F4_P100_A & assisttabaccoscore	103	0,342591	3,66477	0,000397
CUE1_F4_P100_A & assistcannabisscore	103	0,331951	3,53661	0,000614
CUE1_F4_P100_A & tsiscore	103	0,331884	3,53580	0,000615
CUE1_C4_P100_A & tsiscore	103	0,275507	2,88028	0,004852
CUE1_P4_P100_A & tsiscore	103	0,279251	2,92271	0,004283
TRICK_P4_P70-200_A & assisthallucinogensscore	103	0,270414	2,82279	0,005735
CUE1_P4_P70-200_A & tsiscore	103	0,255493	2,65582	0,009195
CUE2_P4_N20-150_T & assistcannabisscore	103	-0,255838	-2,65965	0,009098
CUE2_P4_N20-150_T & assistmethamphetaminescore	103	-0,264900	-2,76084	0,006849

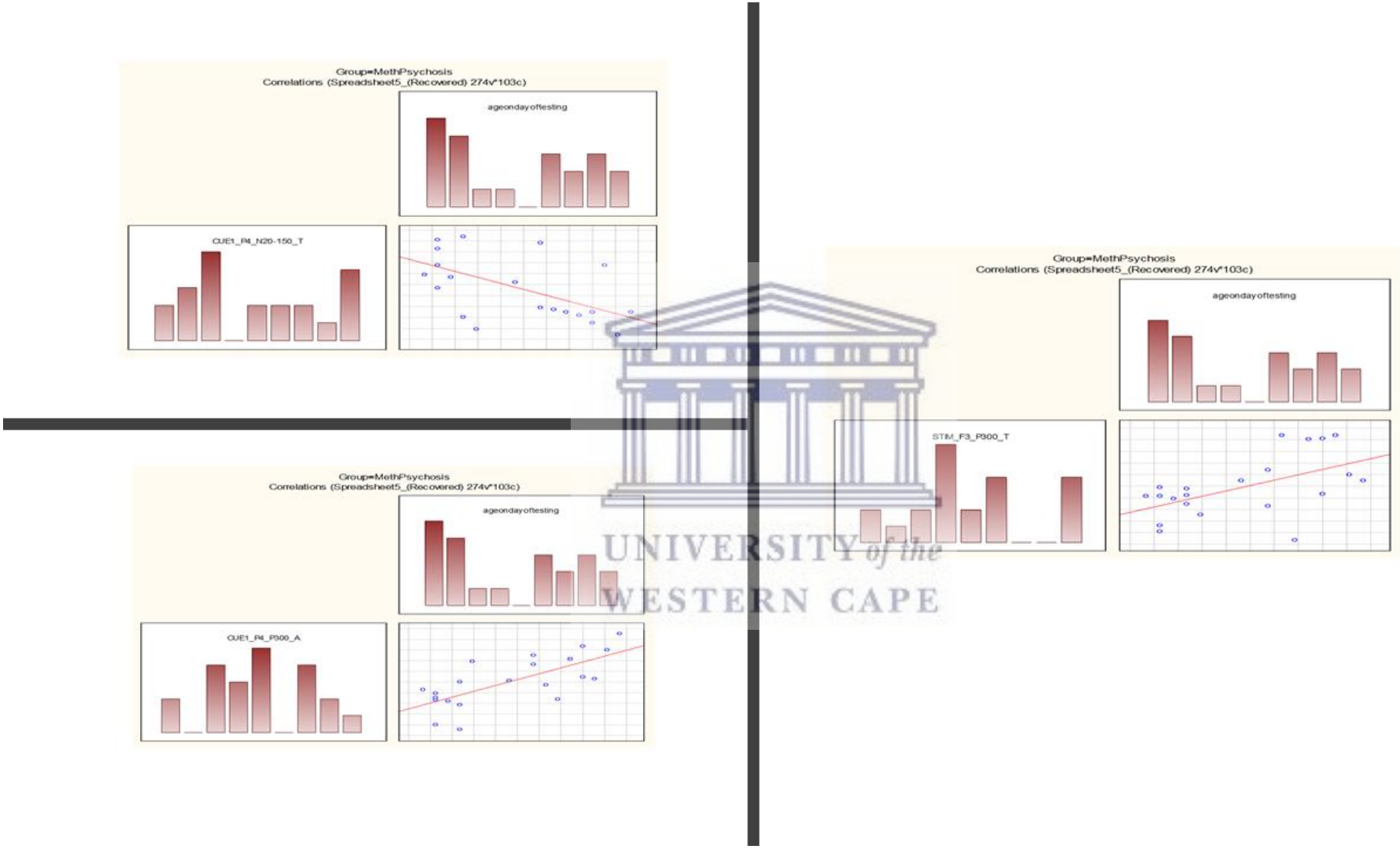
Table E 4 Spearman rank order correlations for the clinical scales

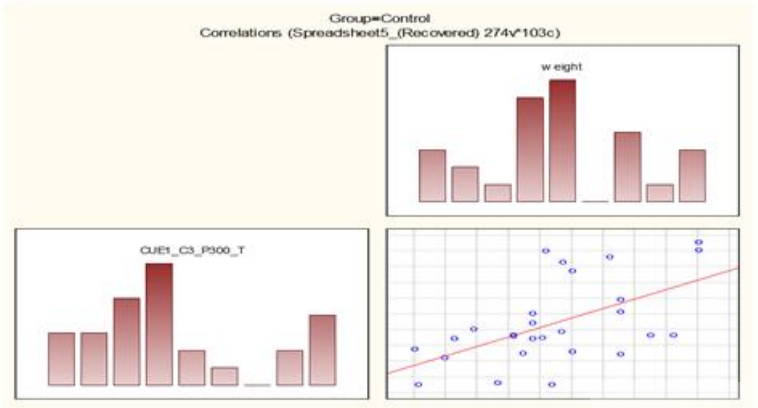
	Group=All Psychotic groups Spearman Rank Order Correlations (ALL groups)Marked correlations are significant at p <0,01					Group=Schizophrenia Spearman Rank Order Correlations (ALL groups)Marked correlations are significant at p <0,01			
Pair of Variables	Valid	Spearman	t(N-2)	p-value	Pair of Variables	Valid	Spearman	t(N-2)	p-value
STIM_FP1_P300_T & hamdtotalscore	76	0,313413	2,83913	0,005837	STIM_P4_P300_A & hamdtotalscore	27	-0,526071	-3,09293	0,004825
TRICK_FP1_P300_T & cdsstotal	76	0,294333	2,64930	0,009856	CUE1_C3_P300_A & pansstot	27	0,521540	3,05628	0,005272
CUE1_C4_P300_T & cdsstotal	76	-0,303271	-2,73778	0,007743	CUE1_C4_P300_A & pansstot	27	0,537122	3,18387	0,003866
CUE1_C4_P300_T & hamdtotalscore	76	-0,330359	-3,01091	0,003562	CUE1_C4_P300_A & panssgen	27	0,552512	3,31439	0,002804
CUE2_FP1_P300_T & hamdtotalscore	76	0,311860	2,82354	0,006099	CUE1_P3_P300_A & pansstot	27	0,625726	4,01084	0,000482
TRICK_P4_N200_T & appendixb6gaf	76	-0,308586	-2,79075	0,006685	CUE1_P3_P300_A & panssneg	27	0,582762	3,58560	0,001424
CUE2_C4_N200_T & totalscoreyoungmaniaratingscaley	76	-0,347913	-3,19229	0,002073	CUE1_P3_P300_A & panssgen	27	0,565390	3,42733	0,002117
CUE1_C4_P100_T & totalscoreyoungmaniaratingscaley	76	-0,297518	-2,68074	0,009051	CUE1_P4_P300_T & hamdtotalscore	27	-0,525543	-3,08864	0,004875
CUE1_P3_P70-200_T & hamdtotalscore	76	0,313968	2,84470	0,005746	CUE1_F4_N200_T & hamdtotalscore	27	-0,512441	-2,98374	0,006278
STIM_P4_N20-150_T & pansstot	76	-0,350532	-3,21968	0,001907	CUE1_P3_N200_A & hamdtotalscore	27	0,601092	3,76068	0,000914
STIM_P4_N20-150_T & panssneg	76	-0,363088	-3,35217	0,001266	CUE1_P3_N200_T & appendixb5cgis	27	-0,508085	-2,94950	0,006815
STIM_P4_N20-150_T & panssgen	76	-0,296035	-2,66609	0,009418	CUE1_P4_N200_A & hamdtotalscore	27	0,551898	3,30909	0,002841
STIM_P4_N20-150_T & appendixb5cgis	76	-0,351613	-3,23100	0,001842	CUE1_C4_P100_T & totalscoreyoungmaniaratingscaley	27	-0,615178	-3,90149	0,000638
CUE2_P3_N20-150_T & appendixb5cgis	76	-0,300064	-2,70594	0,008450	STIM_P4_P70-200_T & panssgen	27	-0,538012	-3,19129	0,003796
CUE2_P4_N20-150_T & pansstot	76	-0,338067	-3,09010	0,002819	CUE2_P4_P70-200_T & panssgen	27	-0,525708	-3,08998	0,004859
CUE2_P4_N20-150_T & panssneg	76	-0,351789	-3,23285	0,001832	TRICK_P3_N20-150_T & appendixb6gaf	27	0,563099	3,40698	0,002228
CUE2_P4_N20-150_T & appendixb5cgis	76	-0,344410	-3,15580	0,002315	CUE1_P4_N20-150_T & ChlorpromazineEquivalentDose	27	0,614827	3,89791	0,000644

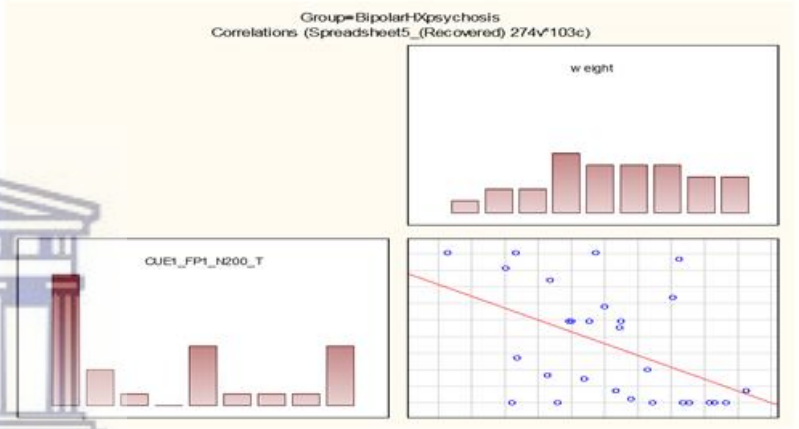
Group=Bipolar Spearman Rank Order Correlations (ALL groups)Marked correlations are significant at p <0,01				
Pair of Variables	Valid	Spearman	t(N-2)	p-value
TRICK_FP2_P300_A & hamdtotalscore	28	0,535454	3,23278	0,003321
CUE1_P4_P300_A & panssneg	28	0,505531	2,98758	0,006065
CUE1_P4_P300_A & totalscoreyoungmaniaratingscaley	28	0,494740	2,90284	0,007441
STIM_FP1_N200_A & appendixb6gaf	28	0,509582	3,01988	0,005608
STIM_FP2_N200_A & ChlorpromazineEquivalentDose	28	-0,520542	-3,10862	0,004514
STIM_FP2_N200_A & appendixb6gaf	28	0,555307	3,40472	0,002159
STIM_C4_N200_A & cdsstotal	28	0,508020	3,00739	0,005781
TRICK_FP2_N200_A & yearswithdiagnosis	28	0,482222	2,80676	0,009358
TRICK_FP2_N200_A & timesincediagmonths	28	0,482222	2,80676	0,009358
TRICK_F4_N200_A & yearswithdiagnosis	28	0,531927	3,20304	0,003576
TRICK_F4_N200_A & timesincediagmonths	28	0,531927	3,20304	0,003576
CUE2_FP1_N200_A & appendixb6gaf	28	0,502696	2,96514	0,006404
CUE2_FP2_N200_A & appendixb6gaf	28	0,512888	3,04643	0,005257
CUE2_P4_N200_A & pansspos	28	-0,506664	-2,99659	0,005934
CUE1_C3_P100_A & pansstot	28	0,542189	3,29022	0,002878
CUE1_C4_P100_A & pansstot	28	0,504872	2,98236	0,006143
CUE1_P3_P100_A & panssgen	28	0,517763	3,08593	0,004773
CUE1_P3_P70-200_T & panssgen	28	0,487027	2,84337	0,008578
STIM_P3_N20-150_T & cdsstotal	28	-0,499873	-2,94292	0,006757
TRICK_P3_N20-150_T & pansspos	28	0,561862	3,46330	0,001862
CUE2_P3_N20-150_T & cdsstotal	28	-0,491190	-2,87536	0,007948
CUE2_P4_N20-150_T & appendixb5cgis	28	-0,485695	-2,83319	0,008789

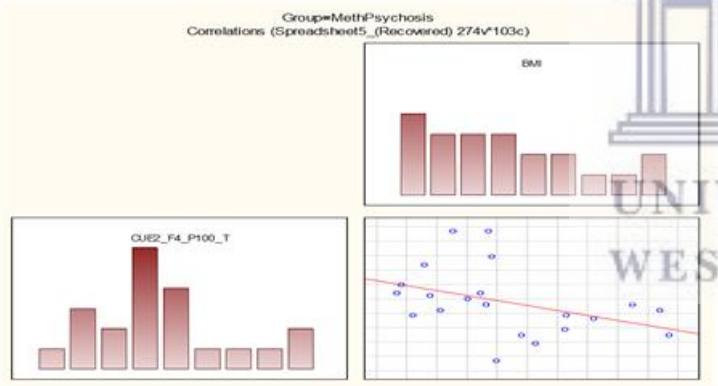
Group=MethPsychosis Spearman Rank Order Correlations (ALL groups)Marked correlations are significant at p <0,01				
Pair of Variables	Valid	Spearman	t(N-2)	p-value
STIM_F3_P300_T & cdsstotal	21	0,566905	2,99968	0,007367
STIM_F3_P300_T & hamdtotalscore	21	0,559697	2,94398	0,008332
STIM_F4_P300_T & hamdtotalscore	21	0,582966	3,12751	0,005544
STIM_P4_P300_A & panssneg	21	0,614037	3,39111	0,003066
TRICK_F4_P300_A & panssgen	21	-0,587817	-3,16719	0,005074
TRICK_P4_P300_T & panssneg	21	0,618354	3,42962	0,002810
CUE1_F3_P300_A & cdsstotal	21	-0,658360	-3,81255	0,001176
CUE1_F4_P300_A & cdsstotal	21	-0,621557	-3,45853	0,002632
CUE2_C3_P300_A & panssneg	21	0,569012	3,01614	0,007103
CUE2_P4_P300_A & panssneg	21	0,569012	3,01614	0,007103
TRICK_FP2_N200_T & appendixb6gaf	21	-0,744270	-4,85747	0,000109
TRICK_C3_N200_T & pansstot	21	0,692909	4,18892	0,000498
TRICK_C3_N200_T & panssneg	21	0,607193	3,33104	0,003511
TRICK_C3_N200_T & panssgen	21	0,605093	3,31284	0,003658
TRICK_P3_N200_T & pansstot	21	0,606913	3,32861	0,003530
TRICK_P3_N200_T & appendixb6gaf	21	-0,630321	-3,53908	0,002192
TRICK_P4_N200_T & appendixb6gaf	21	-0,685951	-4,10912	0,000597
CUE1_F3_N200_A & cdsstotal	21	-0,560901	-2,95321	0,008164
CUE2_P3_N200_A & panssneg	21	0,571622	3,03667	0,006787
STIM_F3_P100_T & yearswithdiagnosis	21	-0,561456	-2,95748	0,008087
STIM_F3_P100_T & timesincediagmonths	21	-0,561456	-2,95748	0,008087
STIM_C3_P100_T & cdsstotal	21	-0,563336	-2,97197	0,007833
TRICK_F4_P100_T & hamdtotalscore	21	-0,579379	-3,09850	0,005915
CUE1_P3_P100_T & yearswithdiagnosis	21	0,564741	2,98285	0,007646
CUE1_P3_P100_T & timesincediagmonths	21	0,564741	2,98285	0,007646
CUE2_F3_P100_T & yearswithdiagnosis	21	-0,572955	-3,04721	0,006630
CUE2_F3_P100_T & timesincediagmonths	21	-0,572955	-3,04721	0,006630
CUE2_F4_P100_T & appendixb5cgis	21	-0,564537	-2,98126	0,007673
CUE2_P3_P100_A & panssneg	21	0,550741	2,87611	0,009673
CUE1_P3_P70-200_T & yearswithdiagnosis	21	0,706633	4,35307	0,000342
CUE1_P3_P70-200_T & timesincediagmonths	21	0,706633	4,35307	0,000342
CUE2_P3_P70-200_A & panssneg	21	0,613384	3,38533	0,003106
CUE2_P4_P70-200_A & panssneg	21	0,575537	3,06772	0,006334

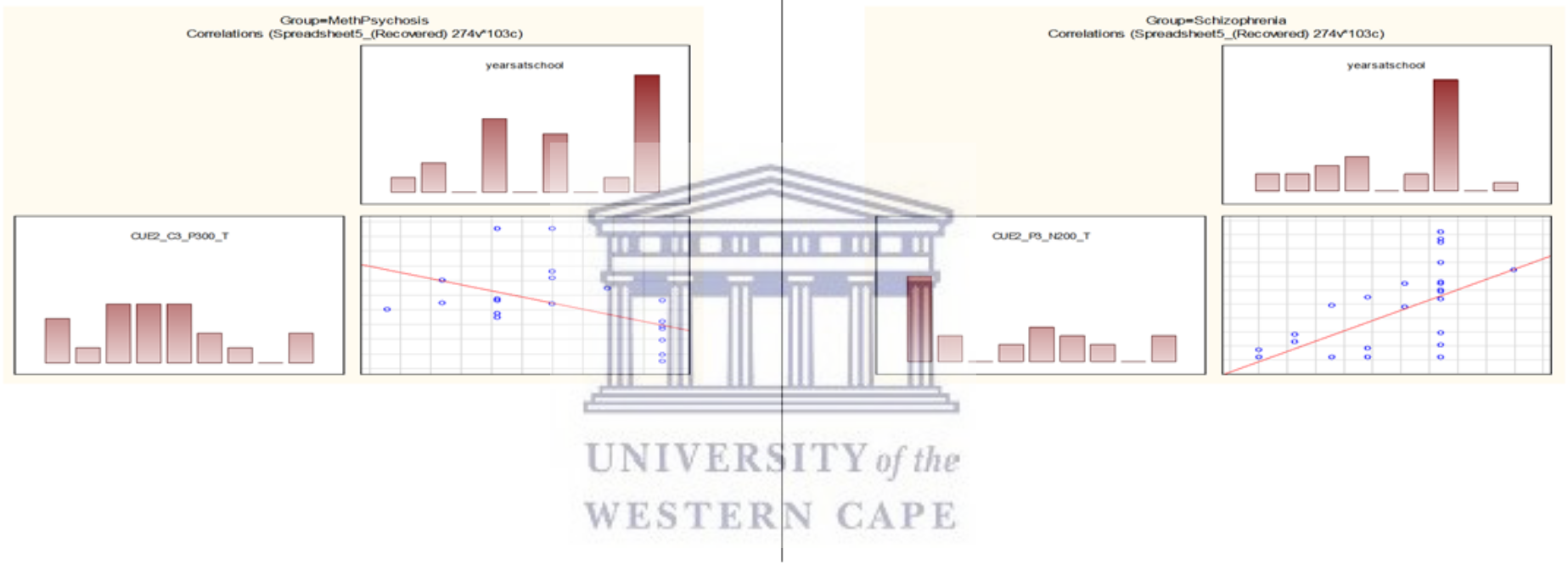
Appendix F Spearman rank order correlation graphical representation

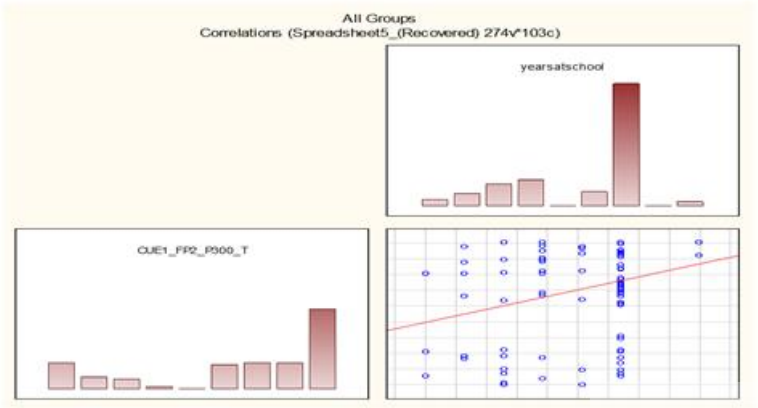


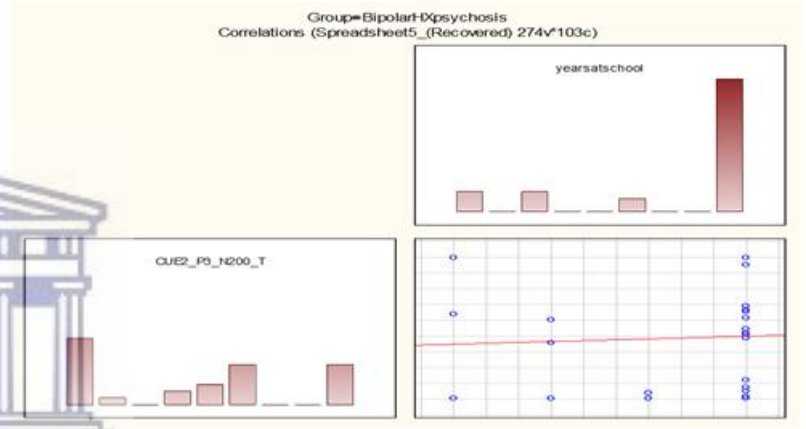


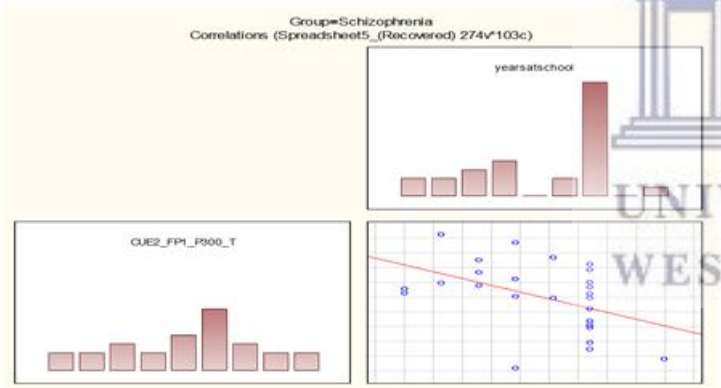


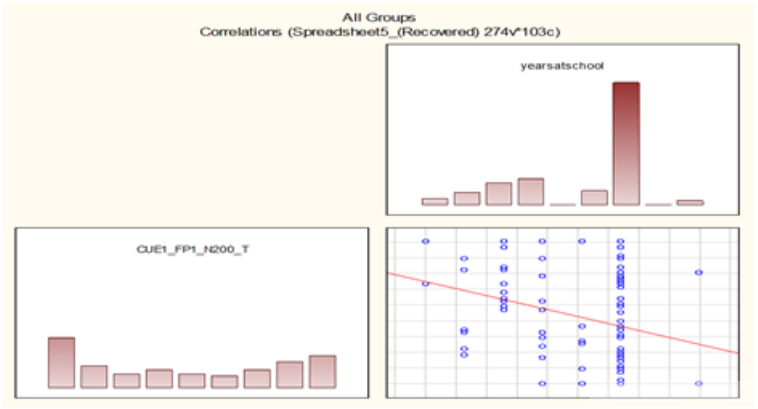


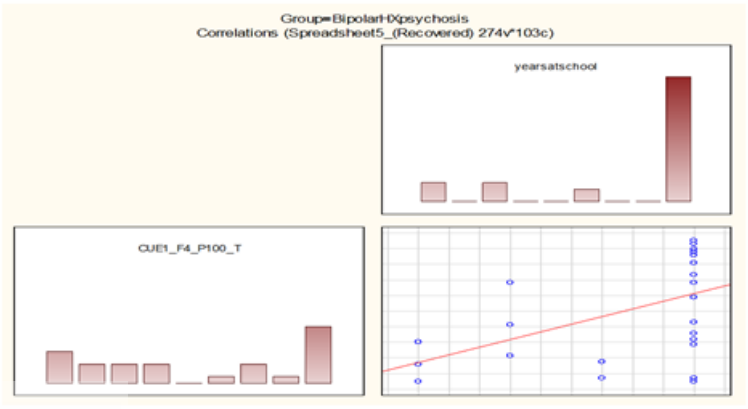


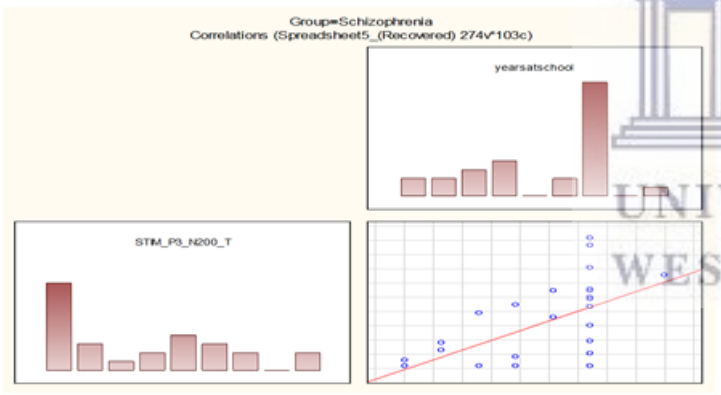


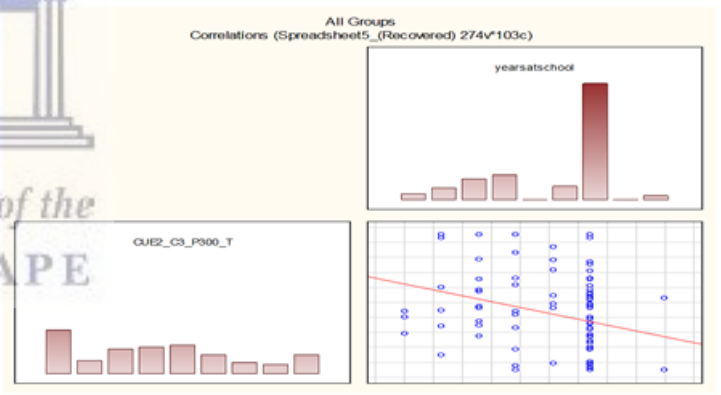


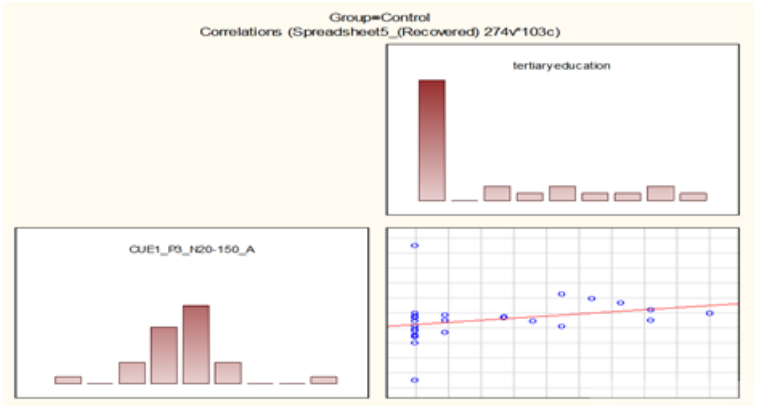


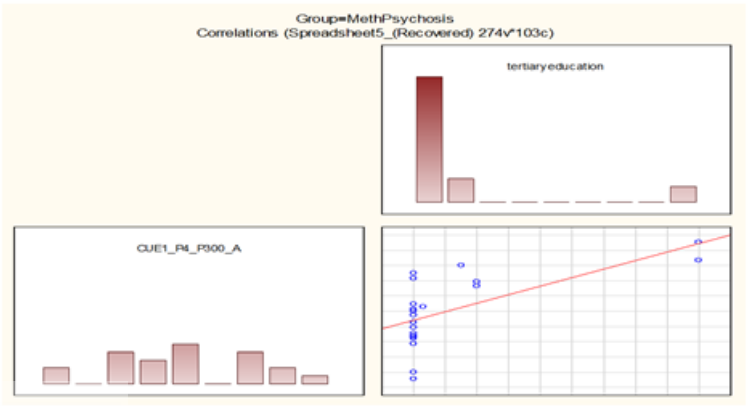


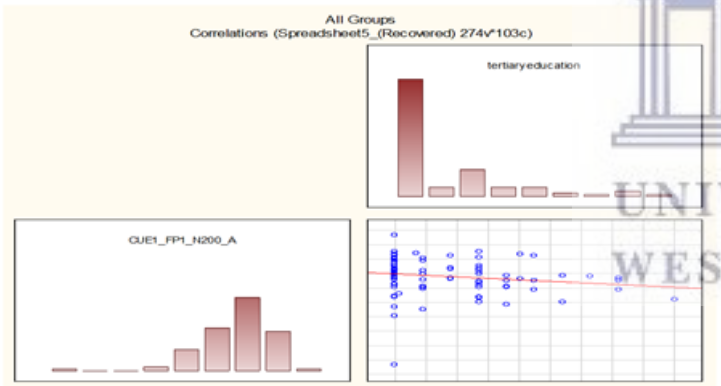


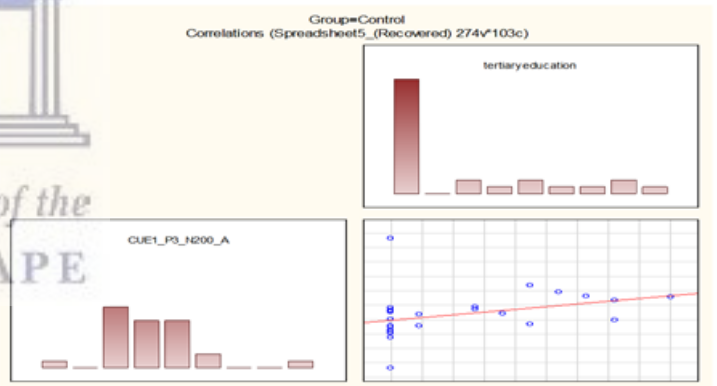


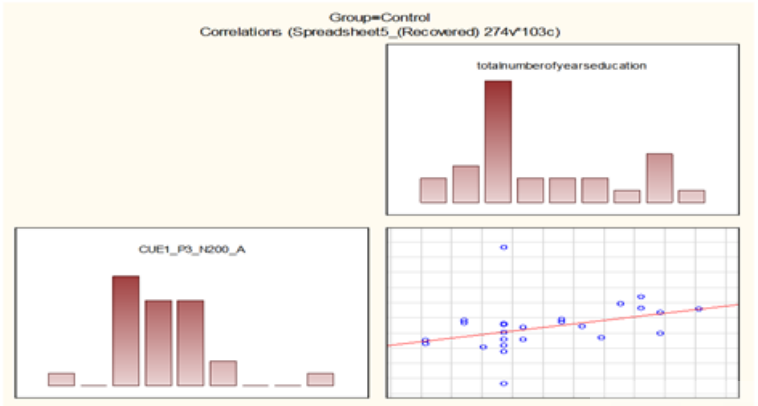


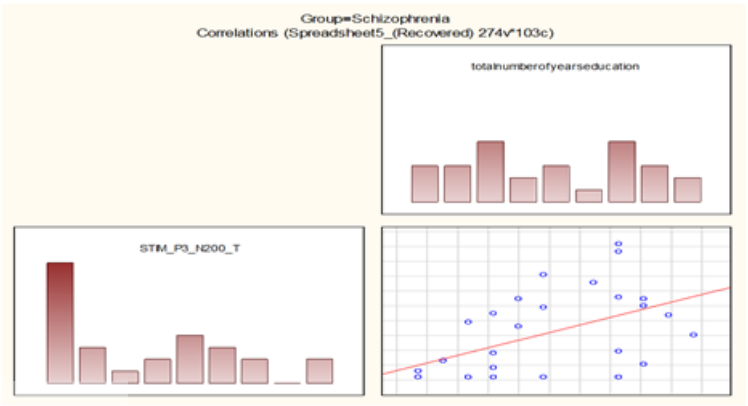


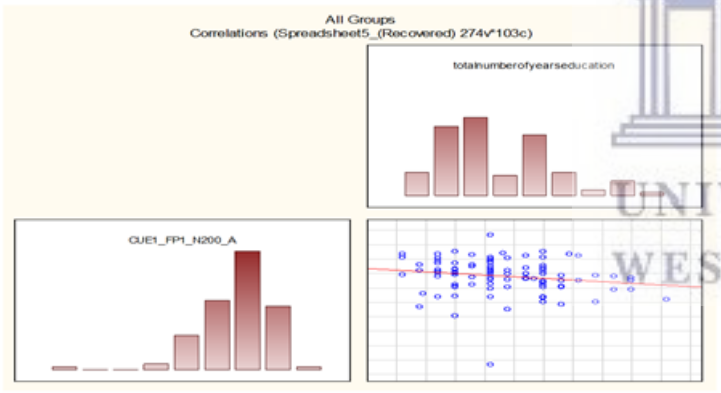


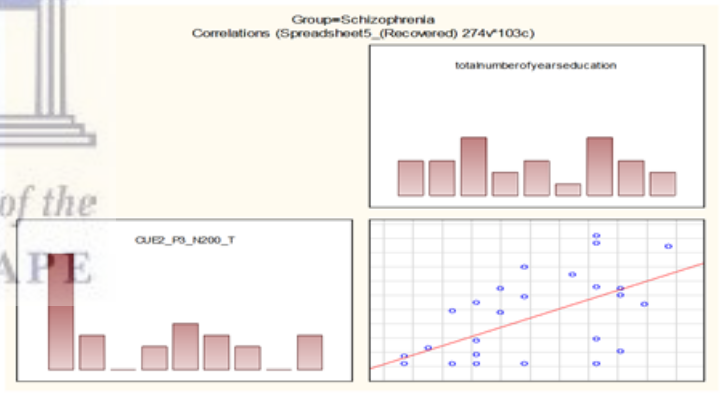


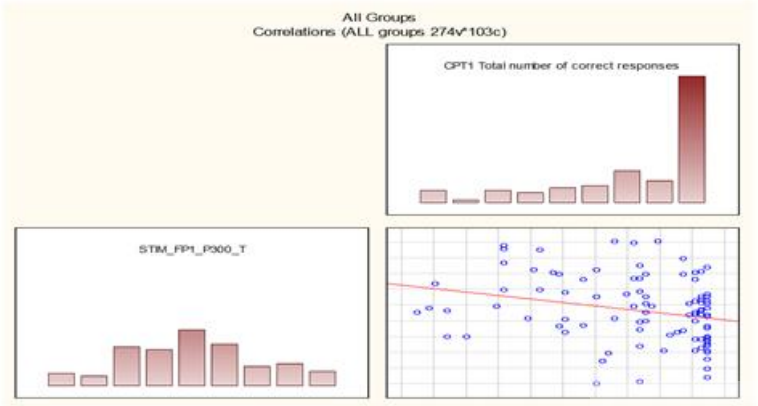


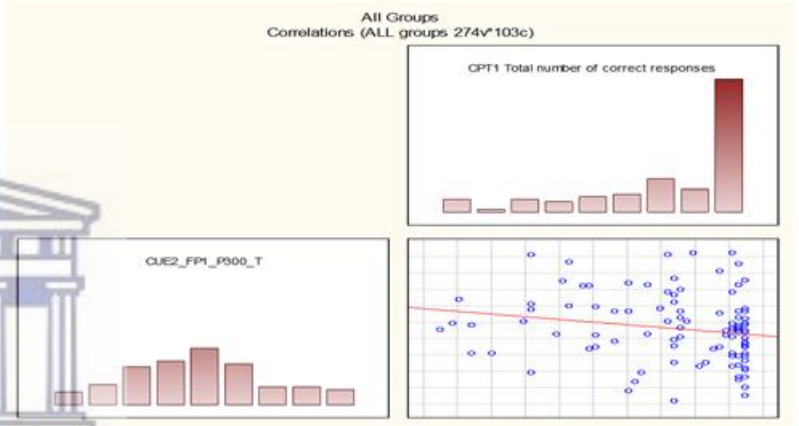


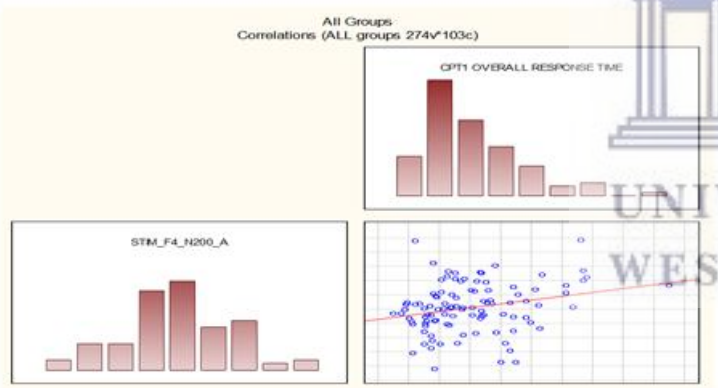


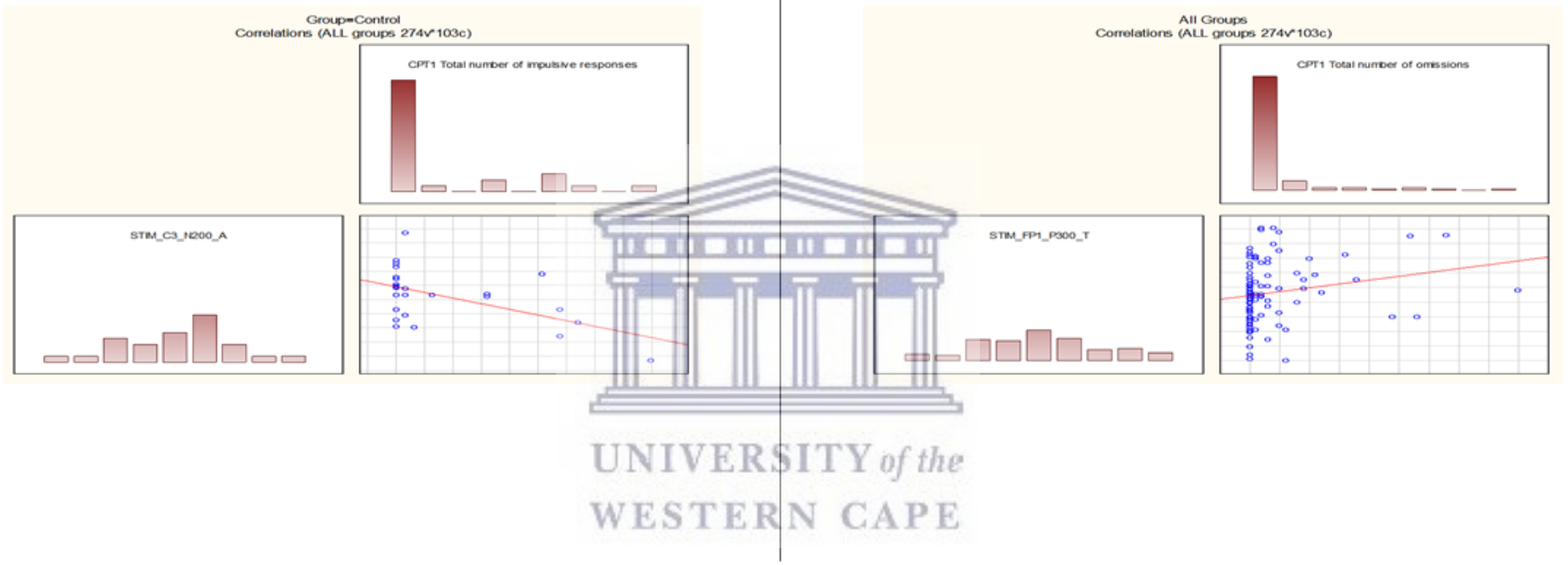


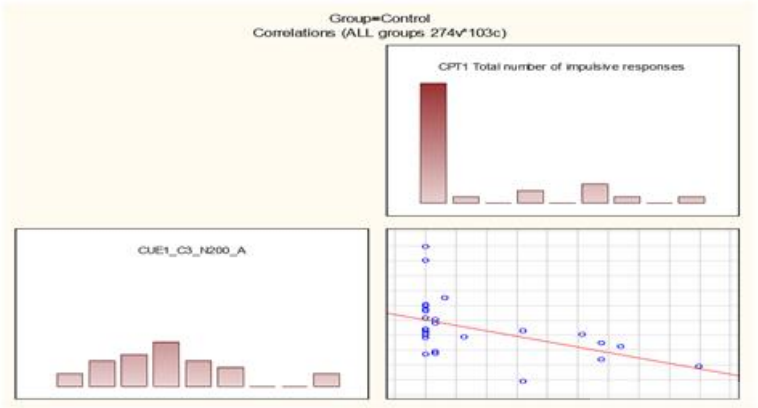


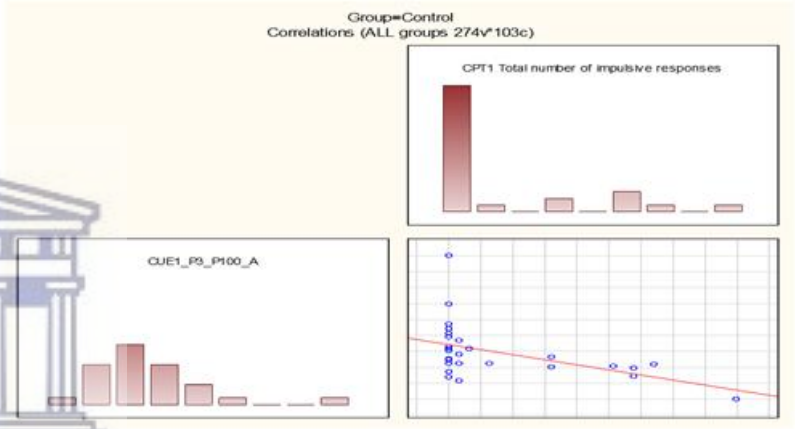


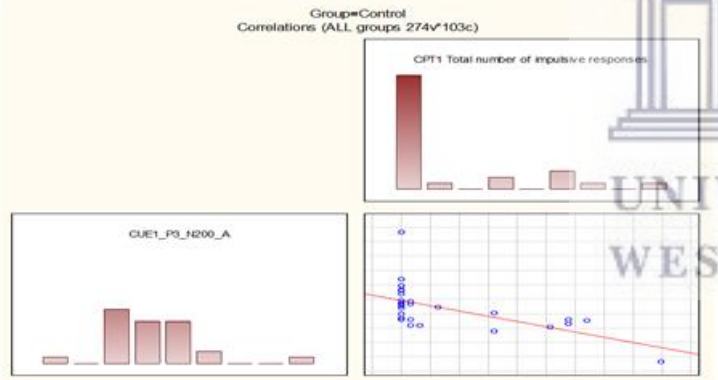


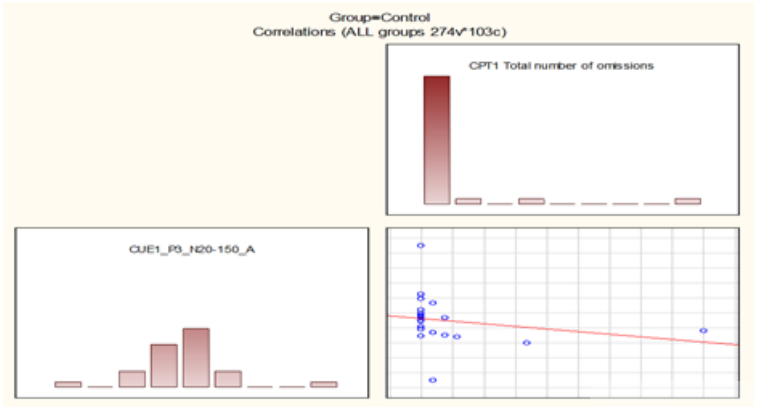


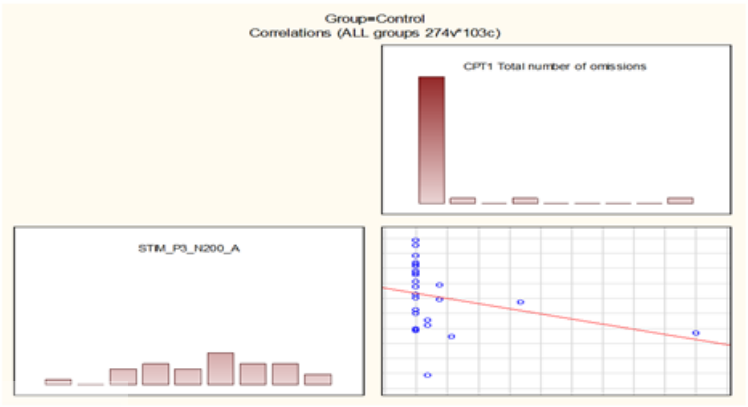


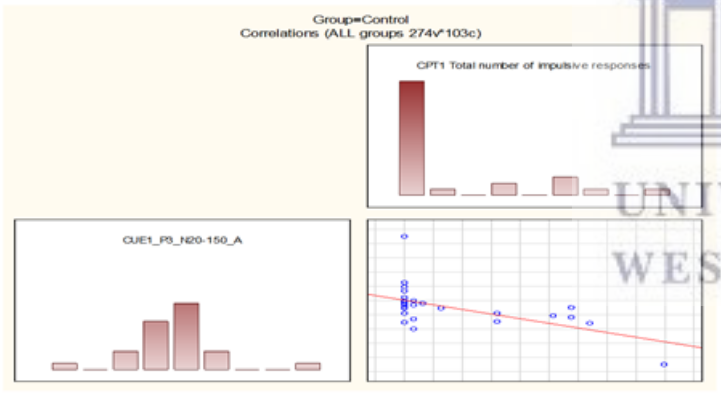


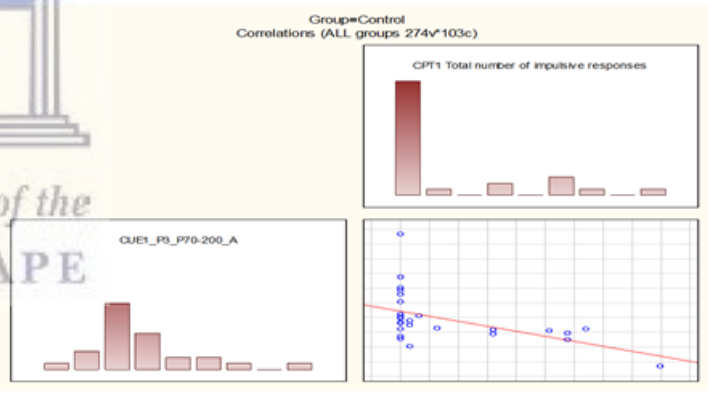


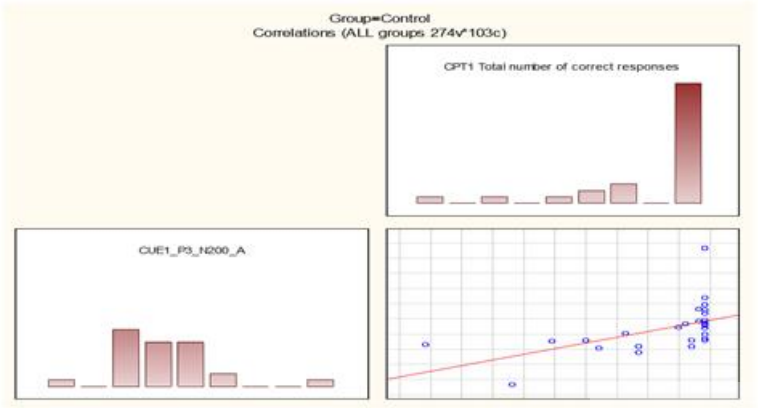


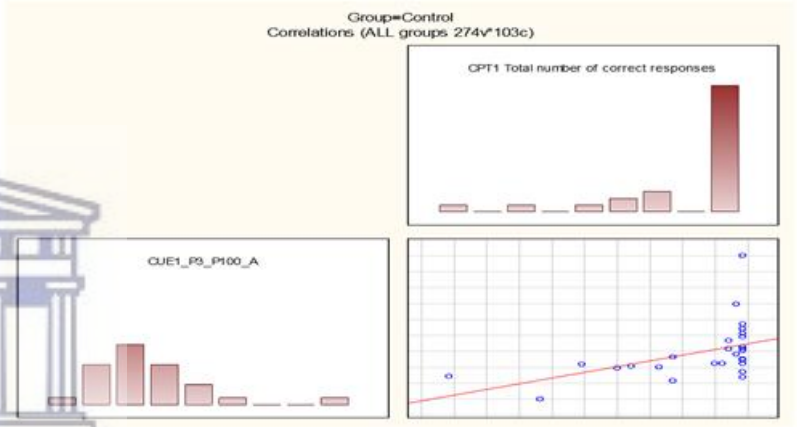


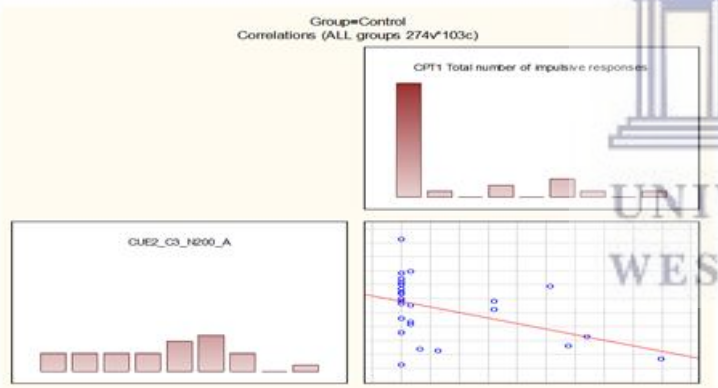


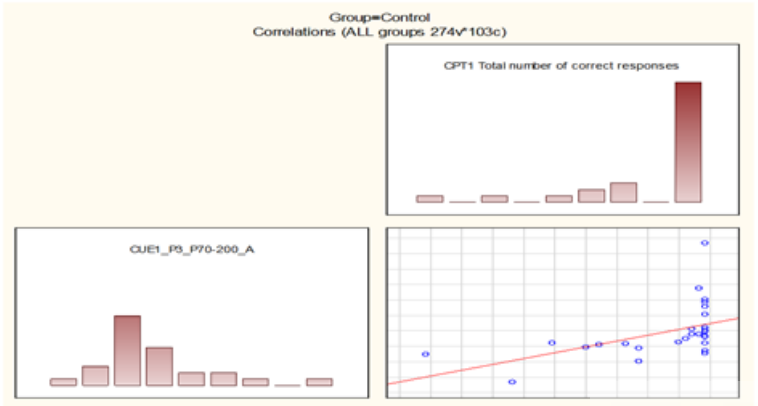


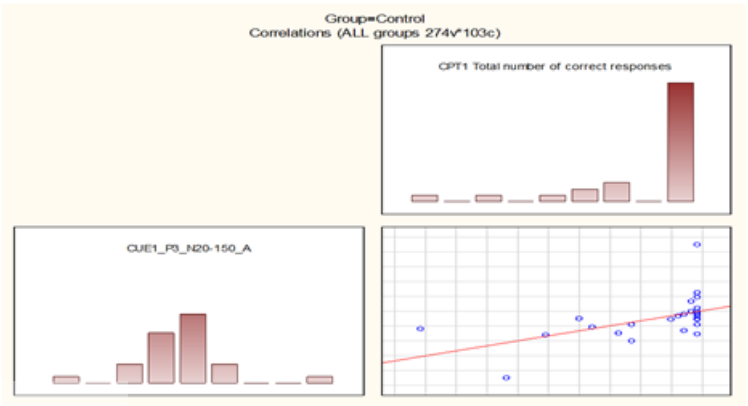


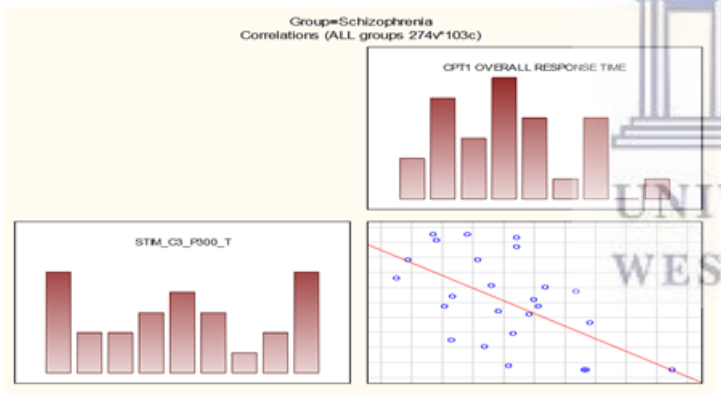


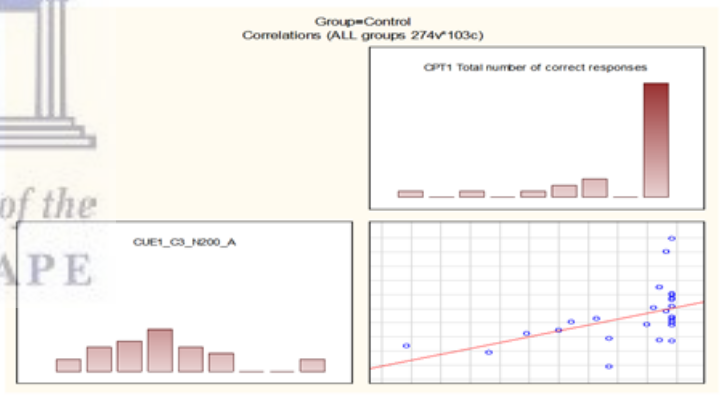


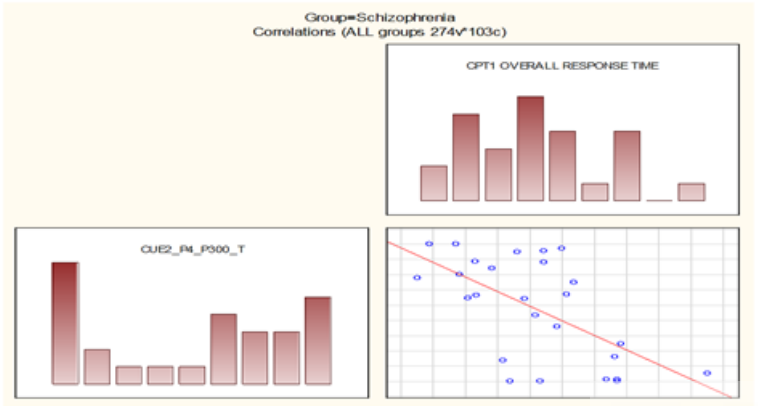


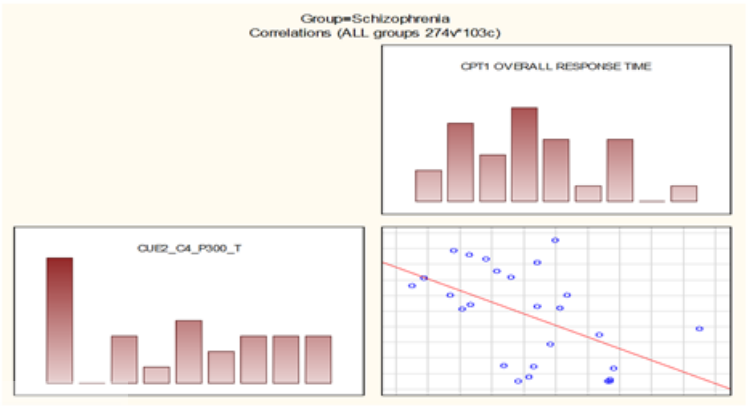


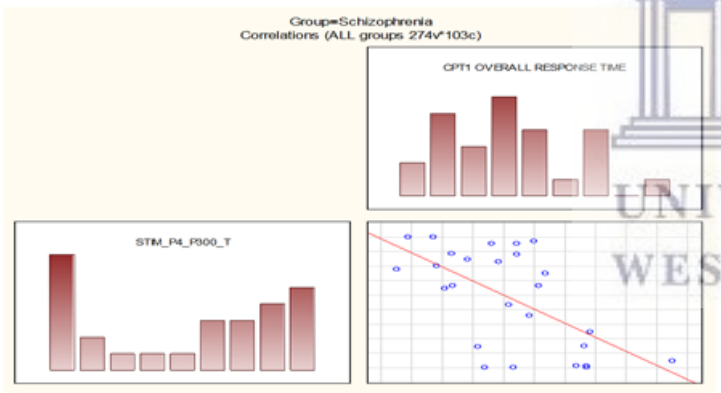


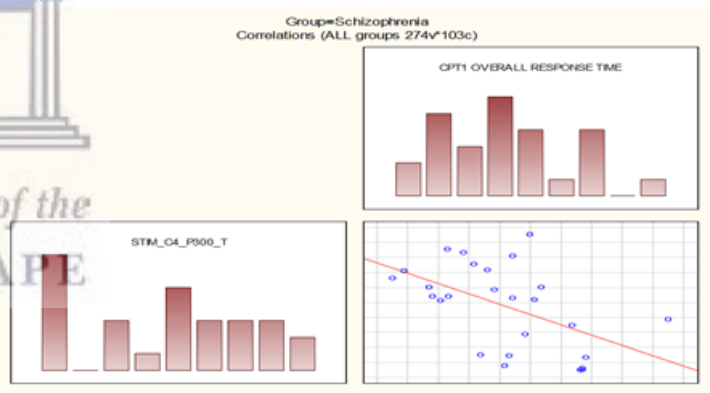


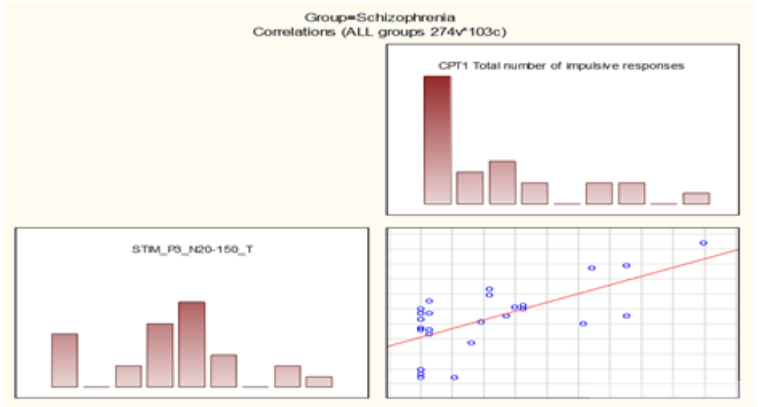


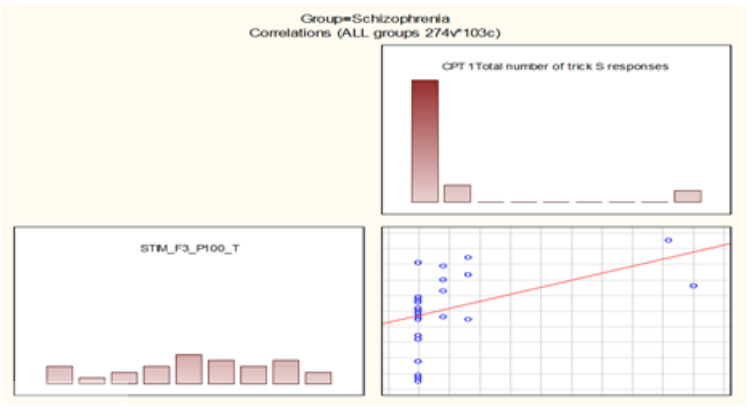


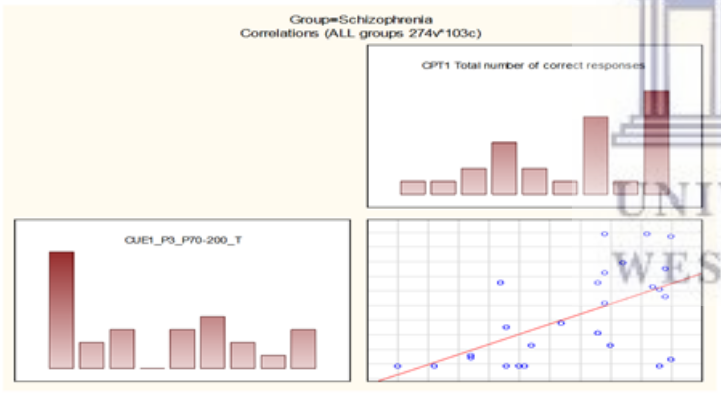


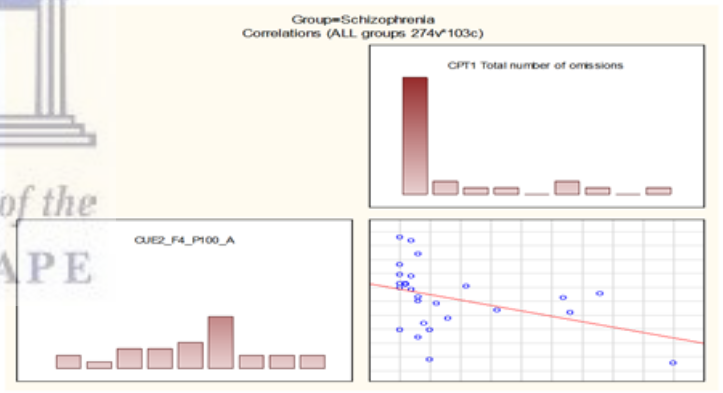


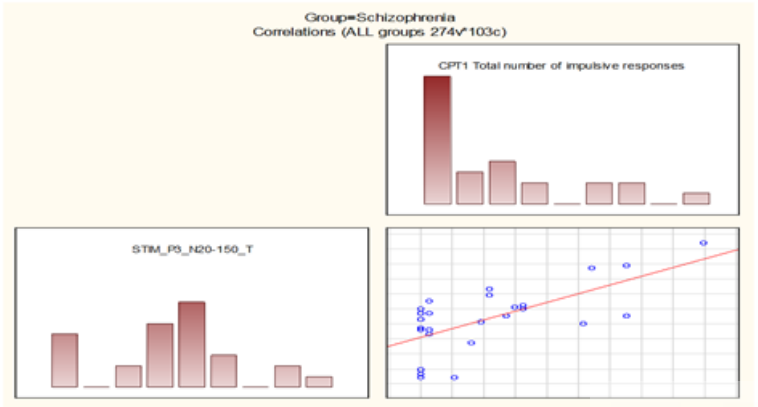


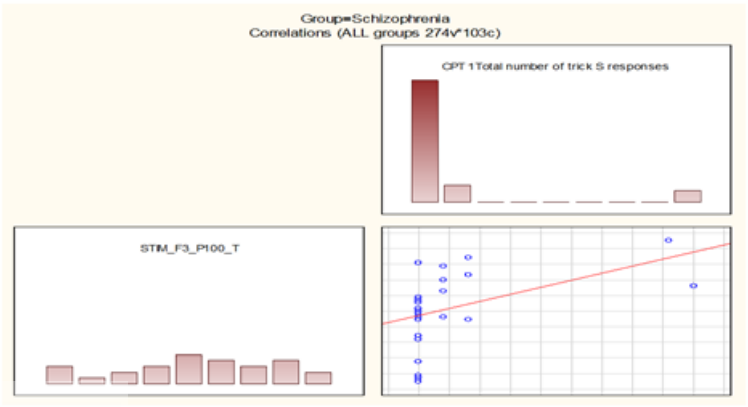


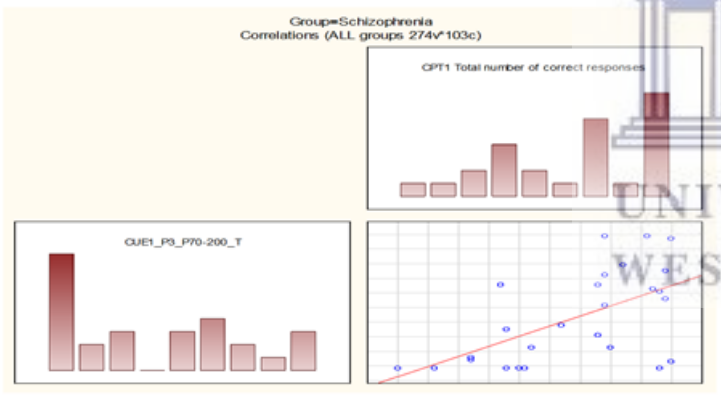


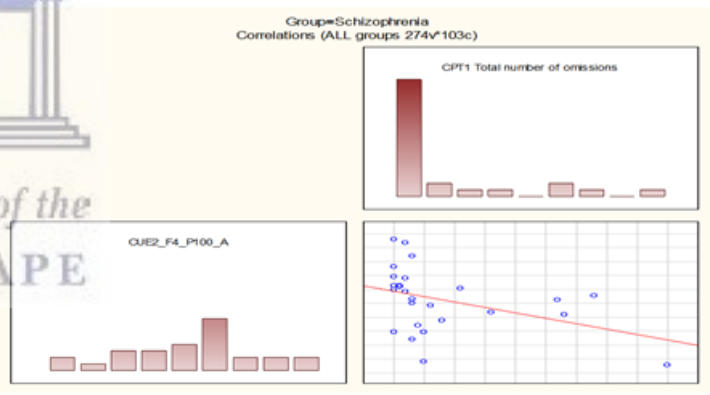


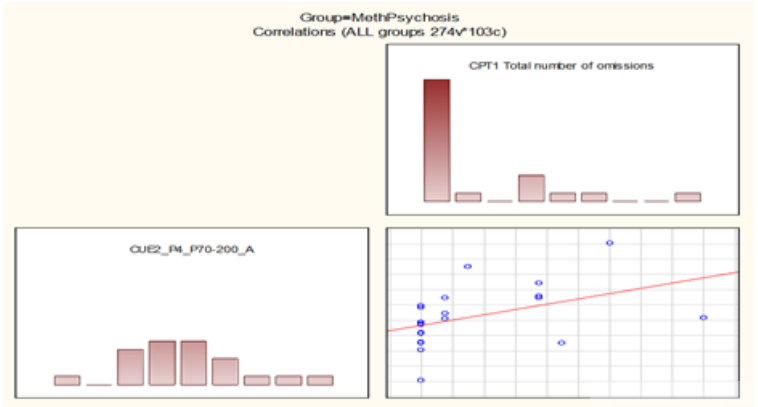


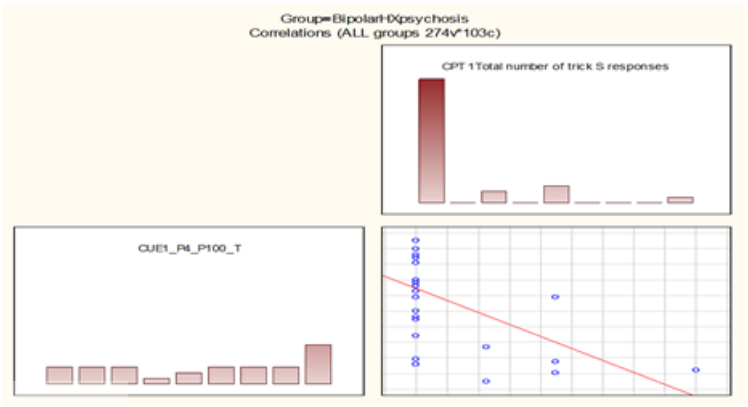


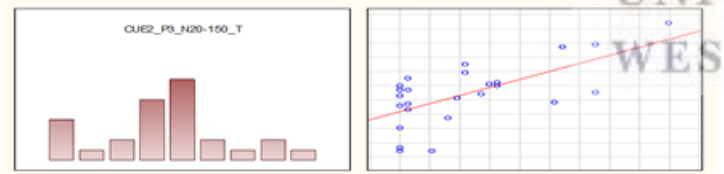


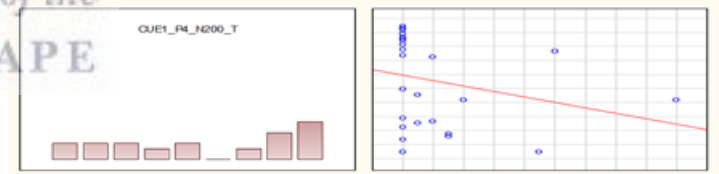


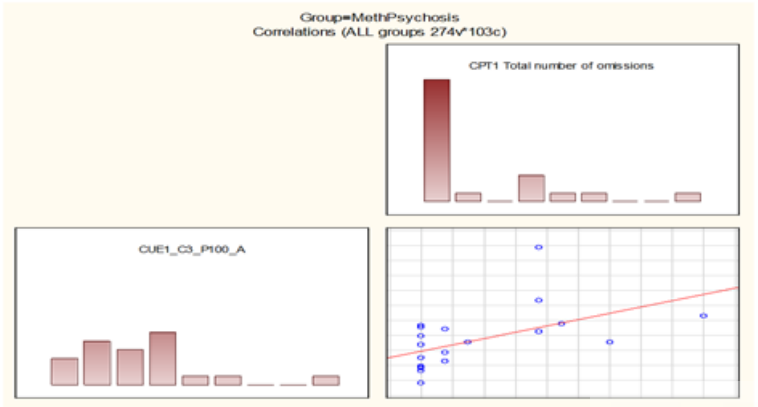


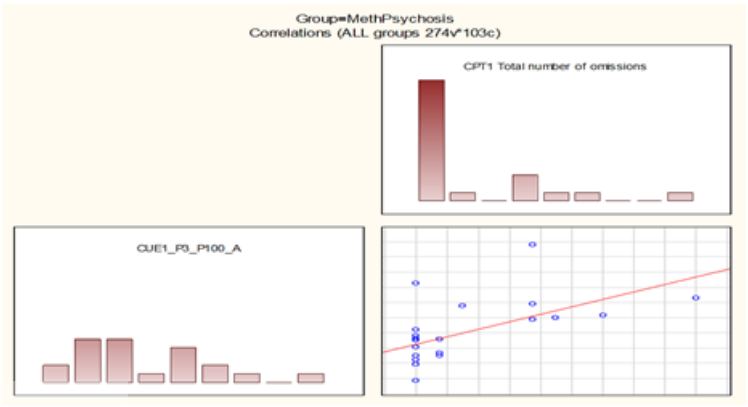


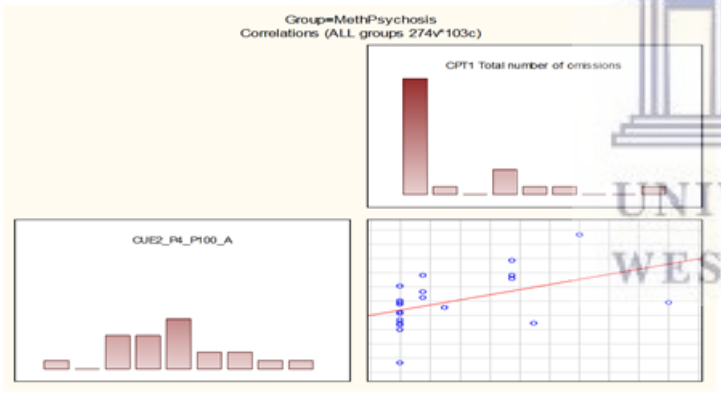


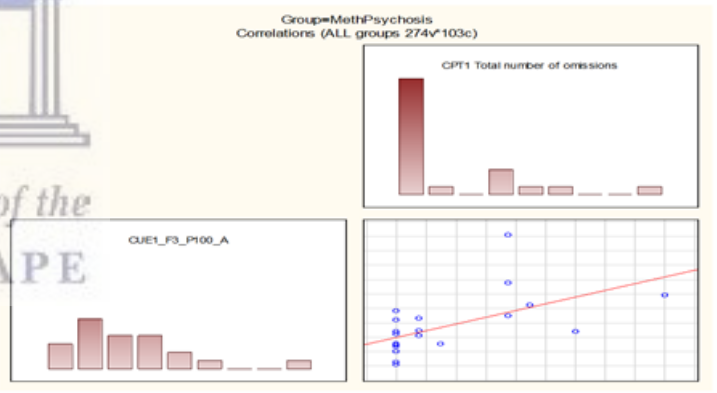


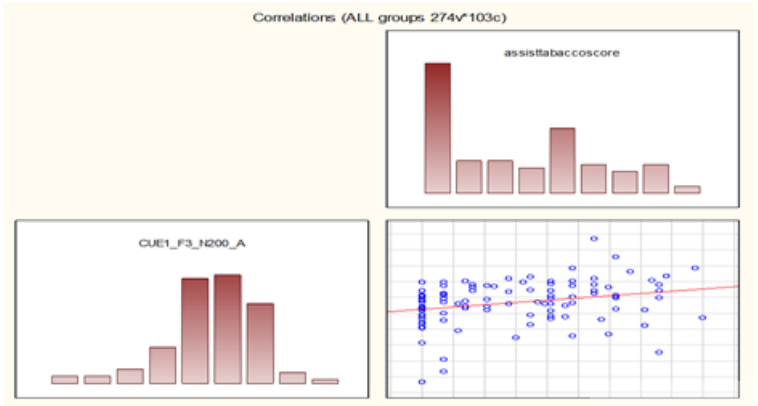


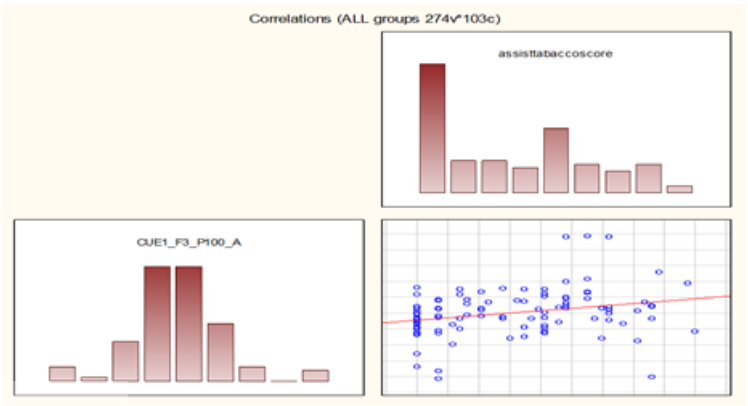


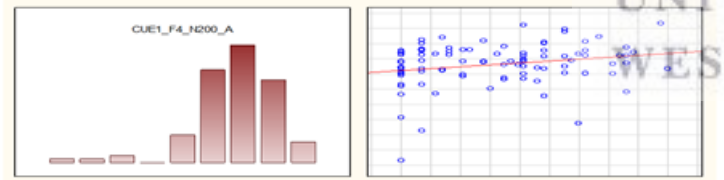


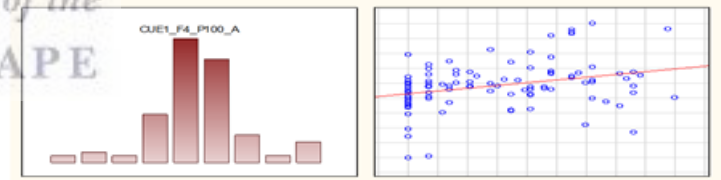


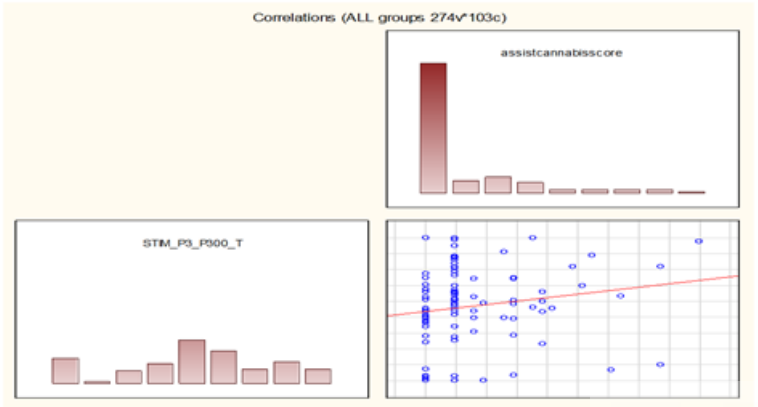


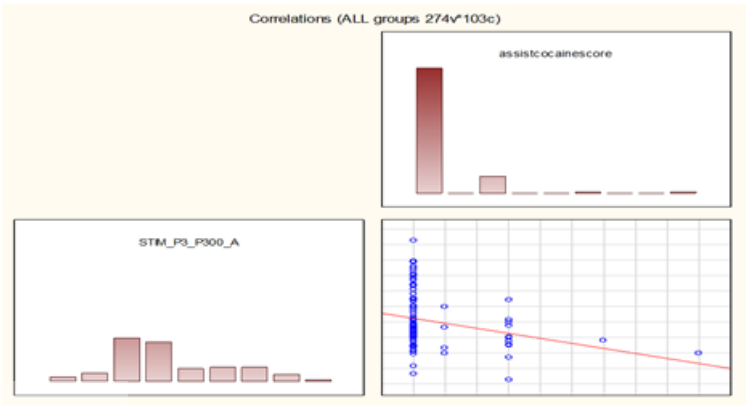


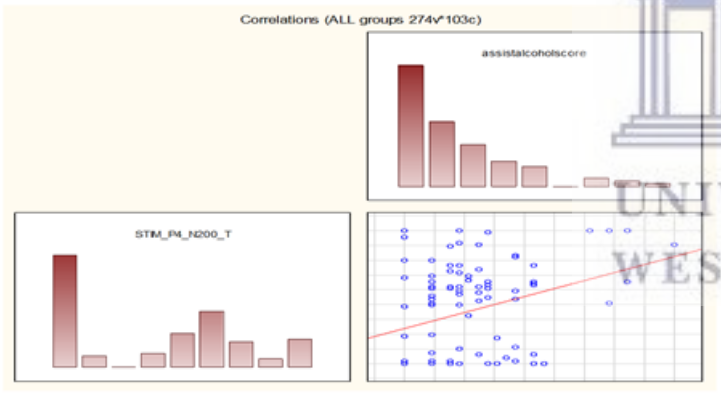


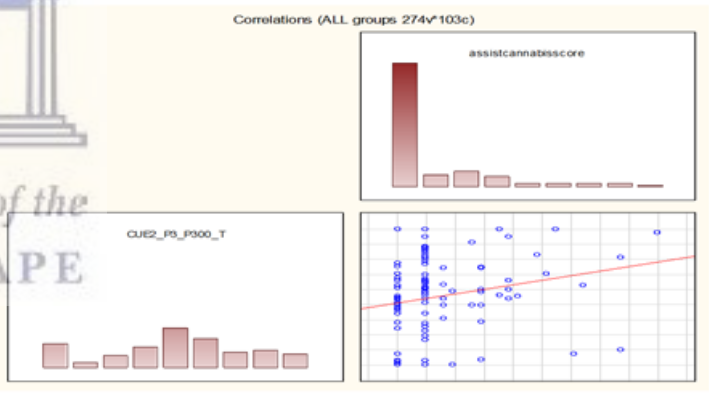


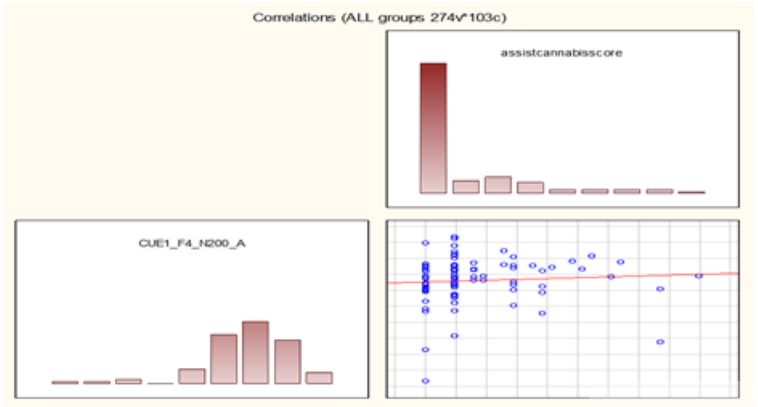


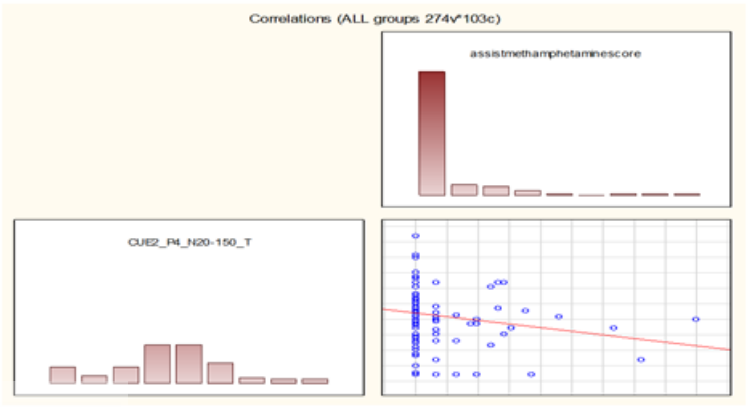


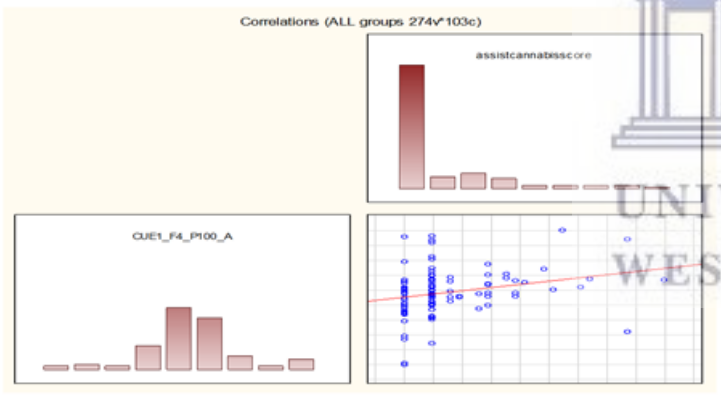


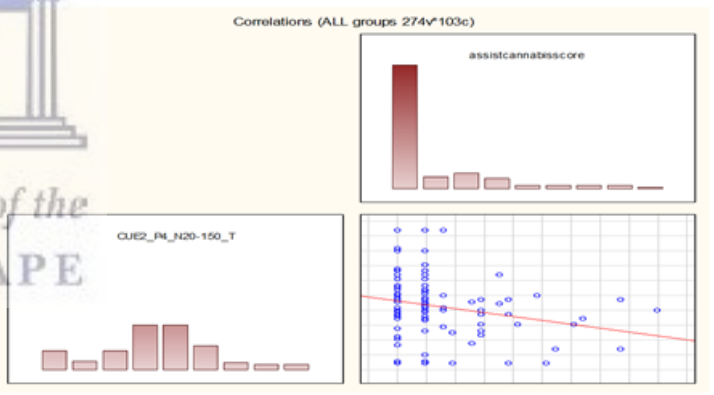


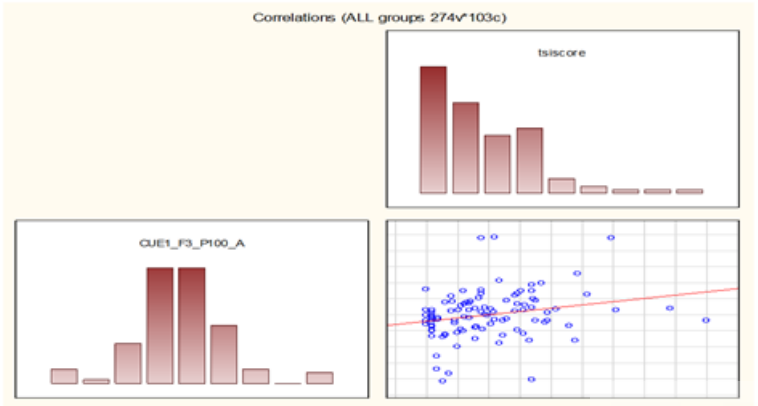


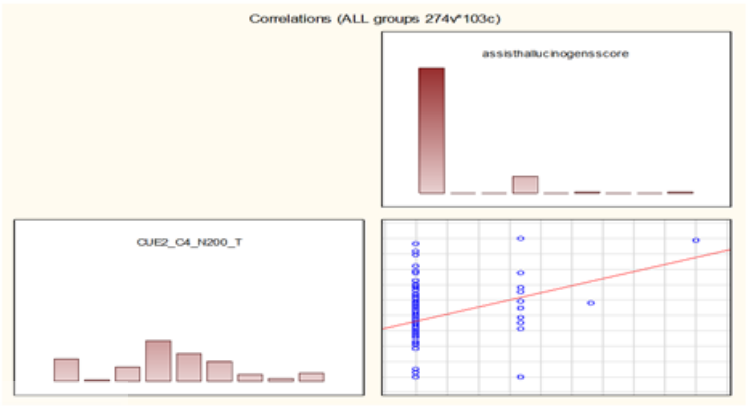


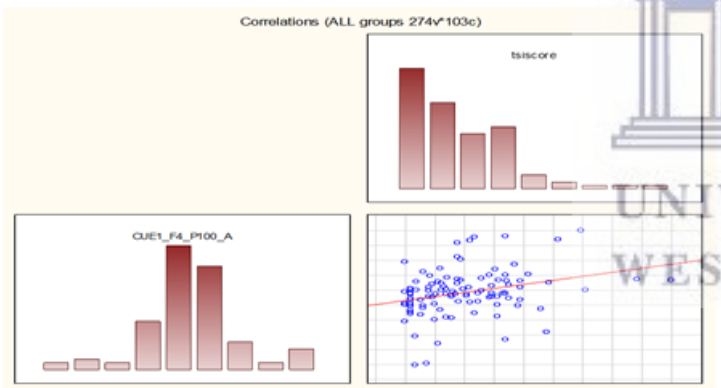


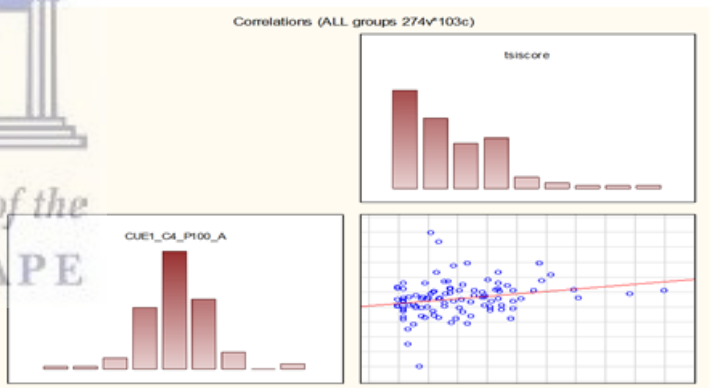


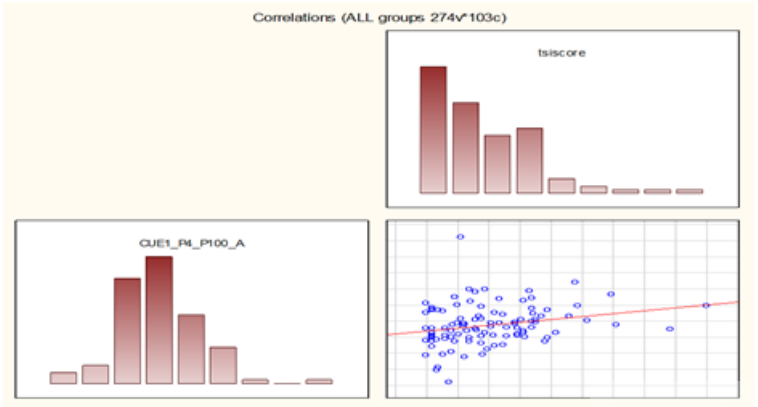


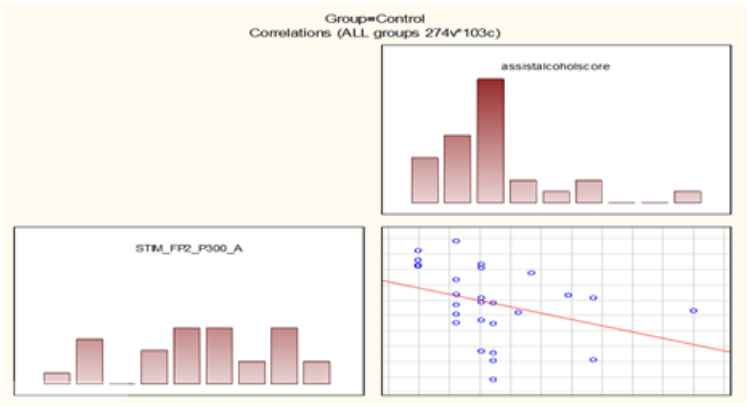


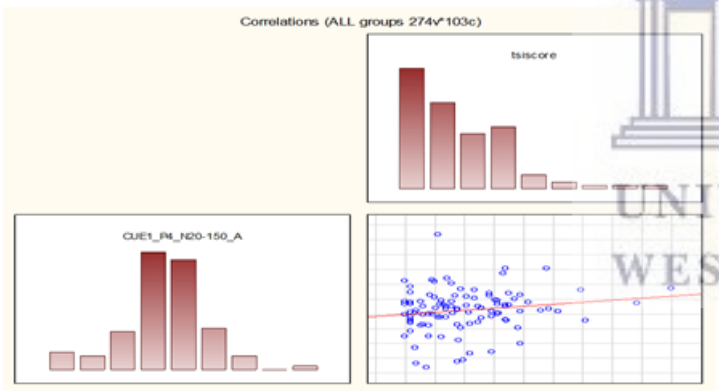


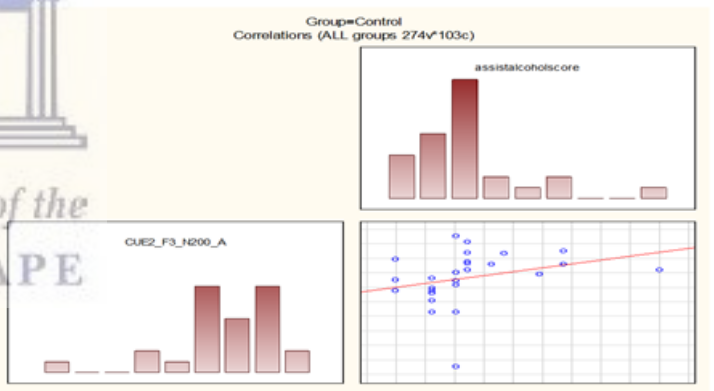


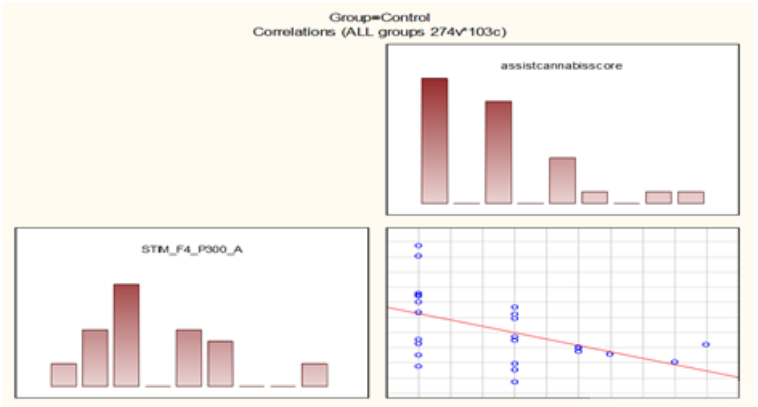


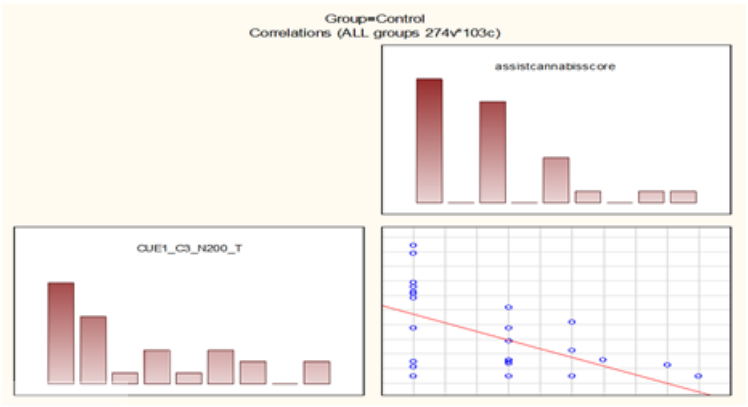


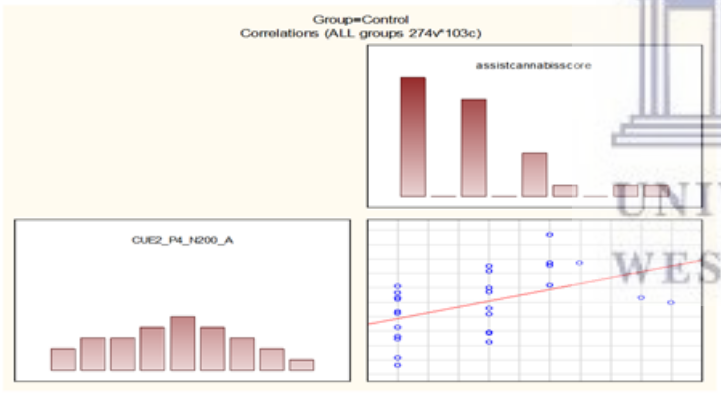


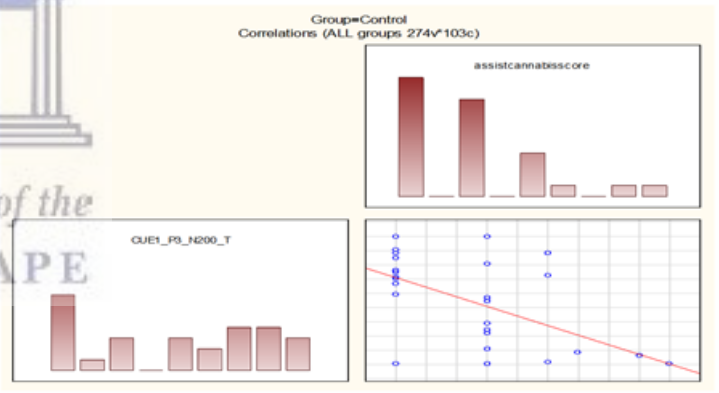


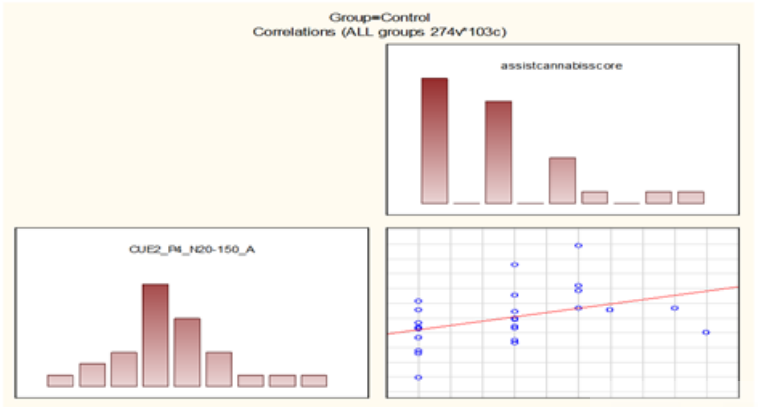


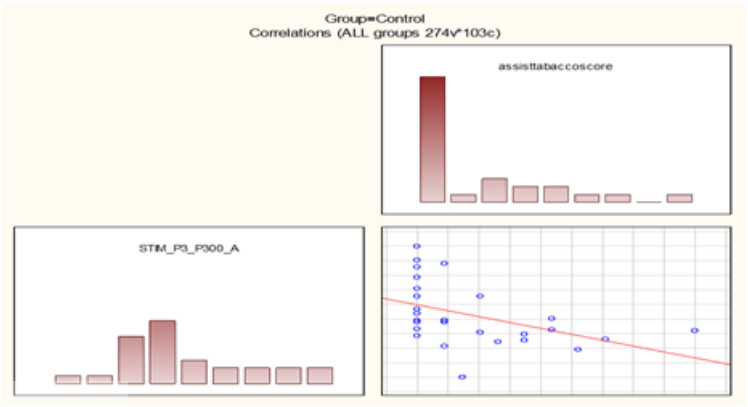


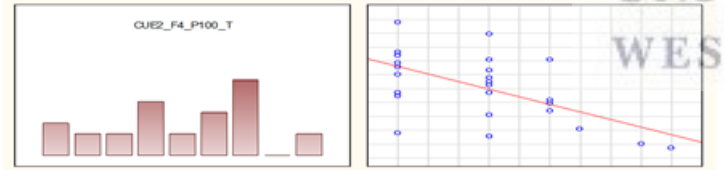


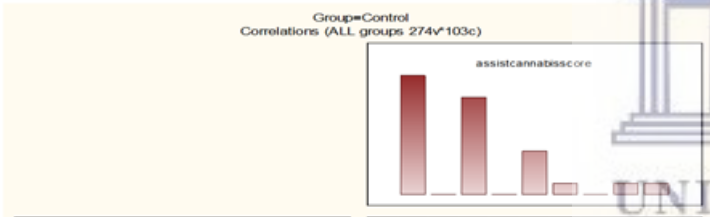


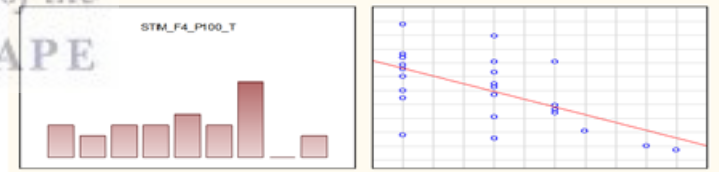


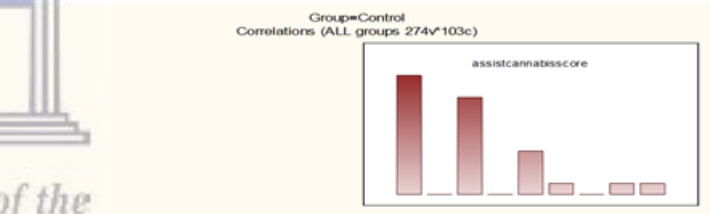


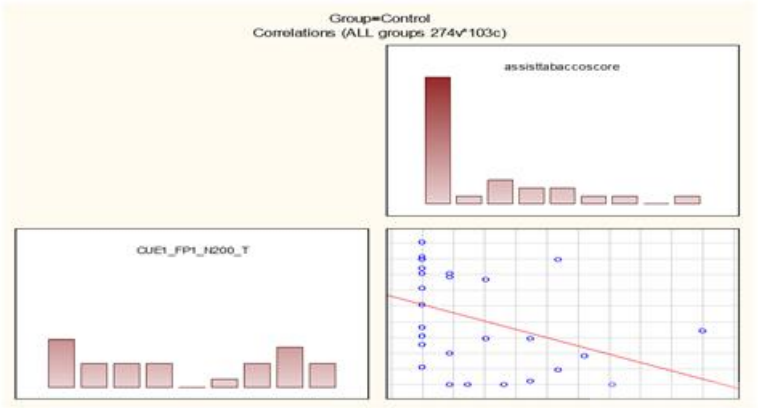


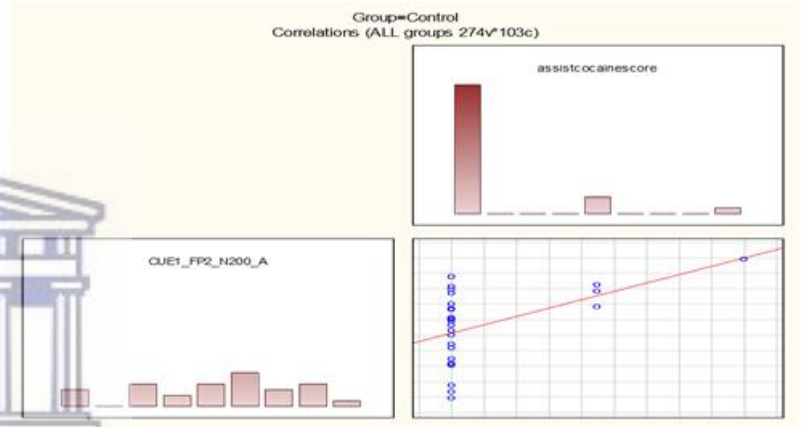


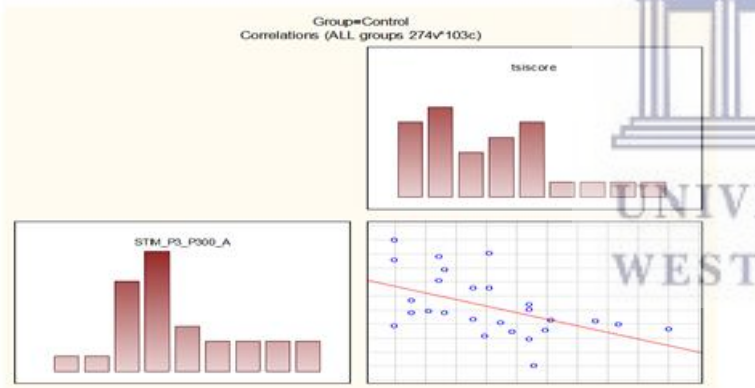


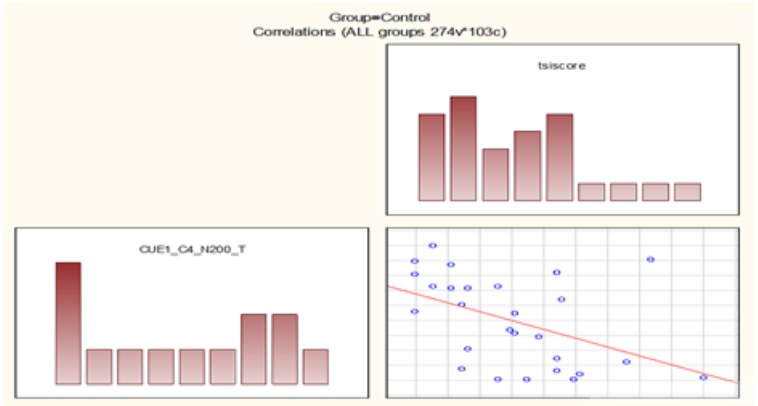


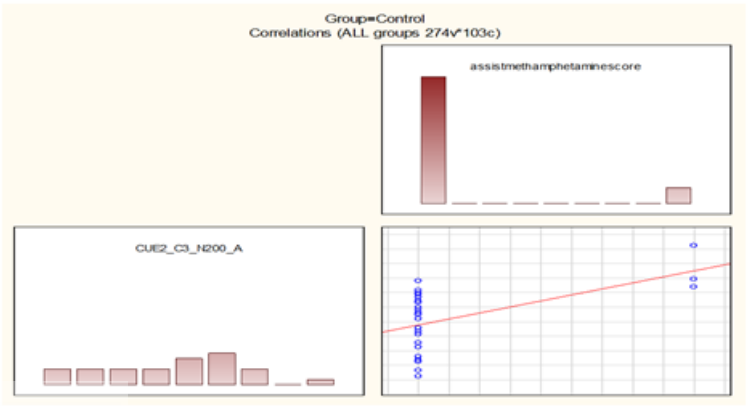


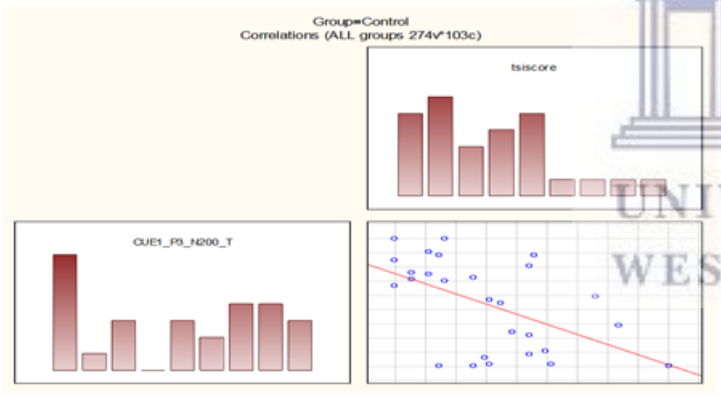


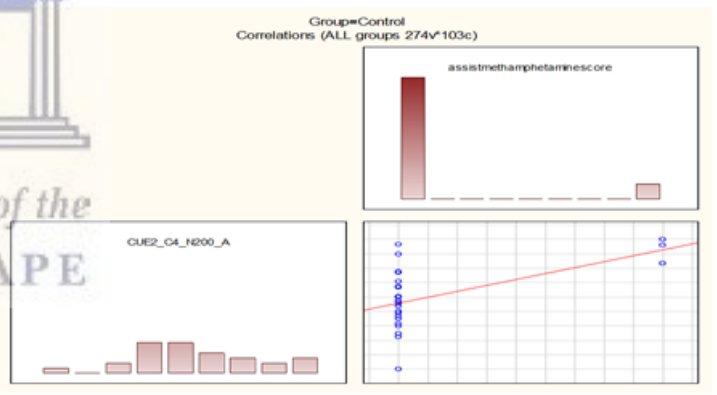


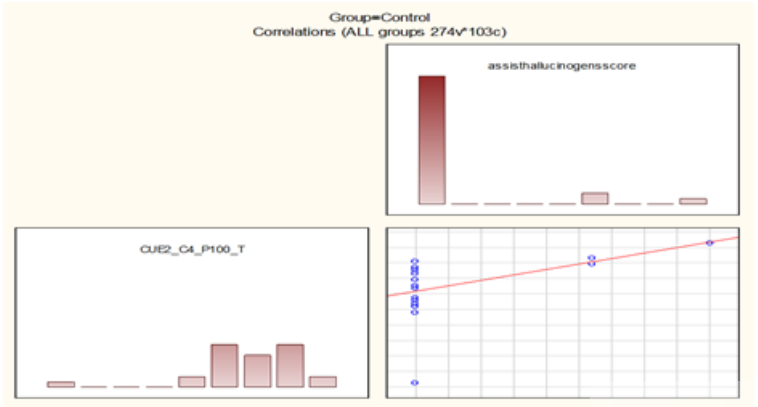


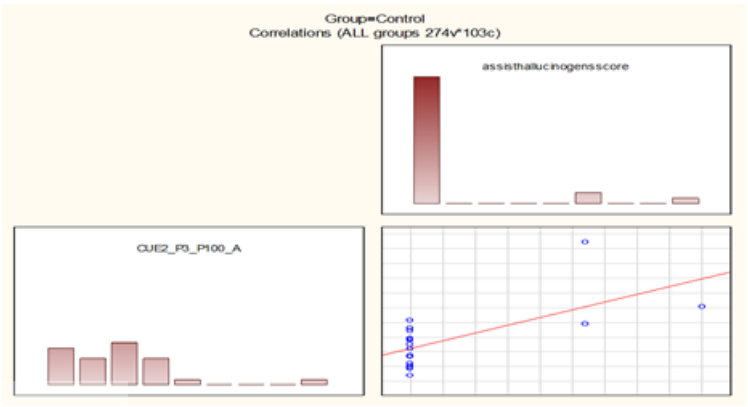


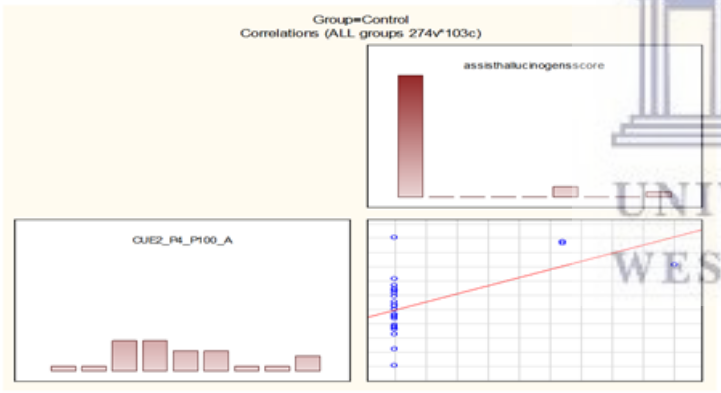


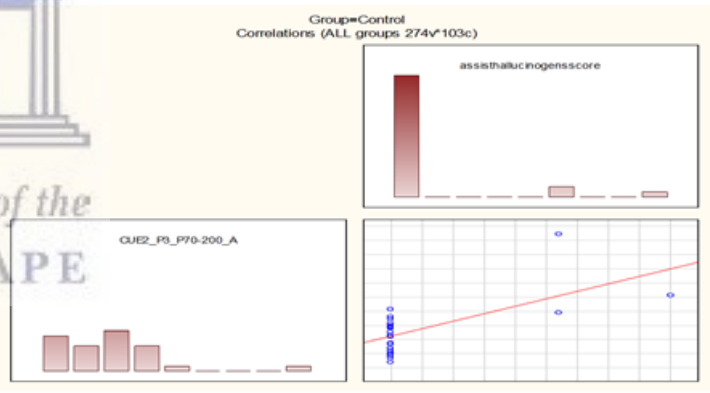


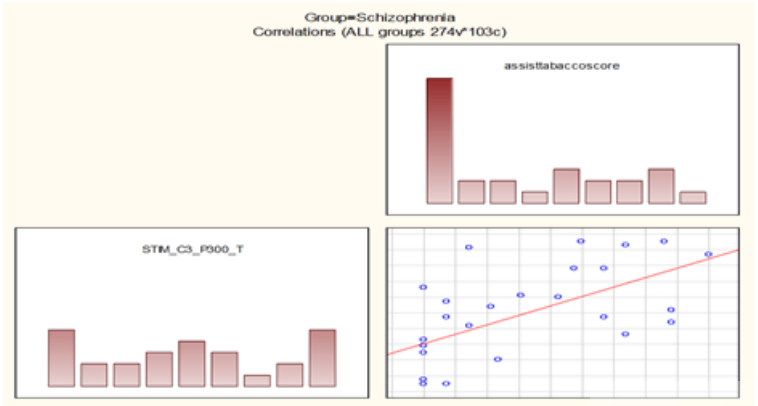


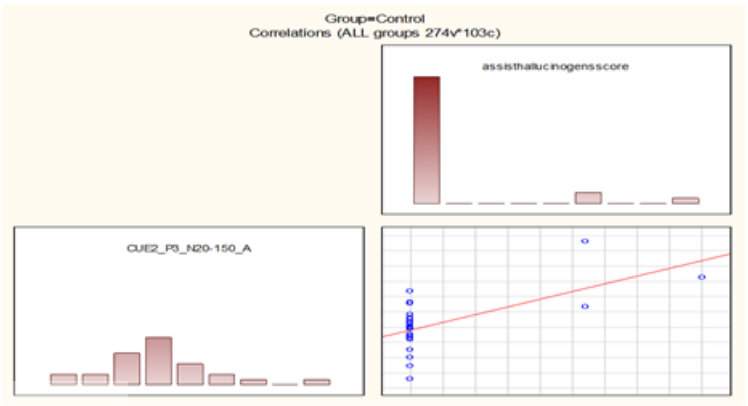


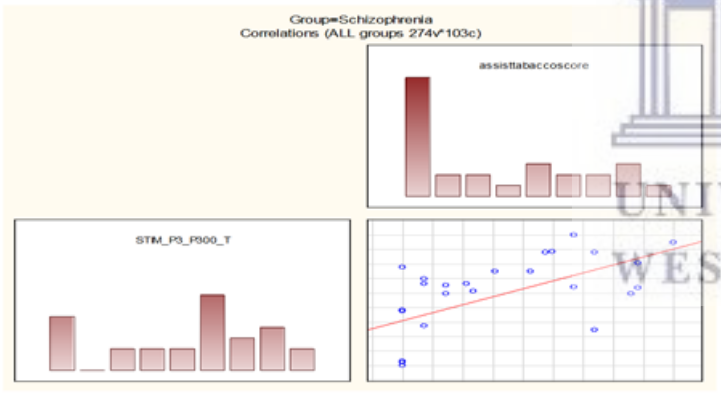


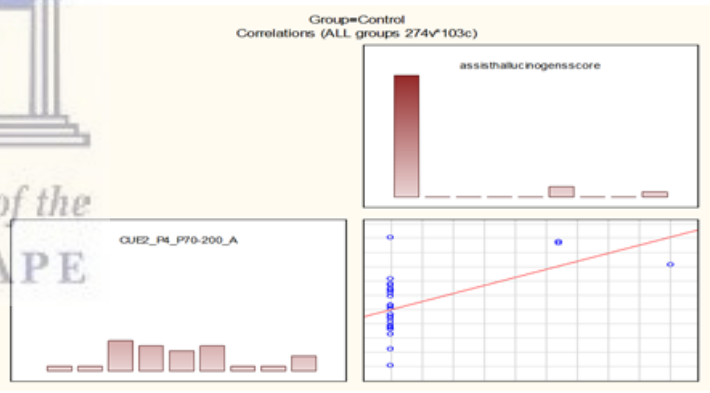


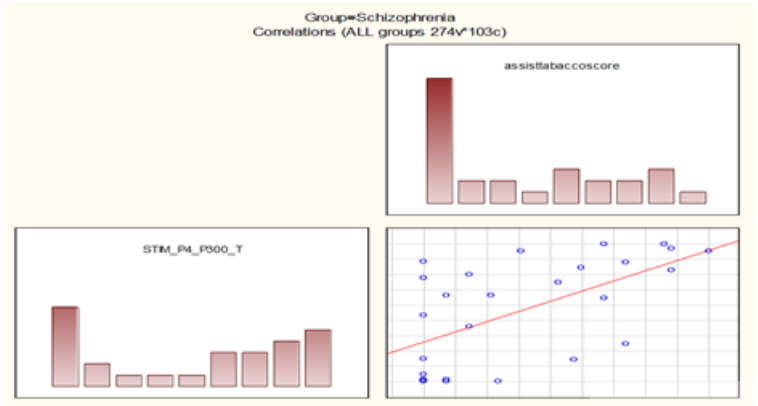


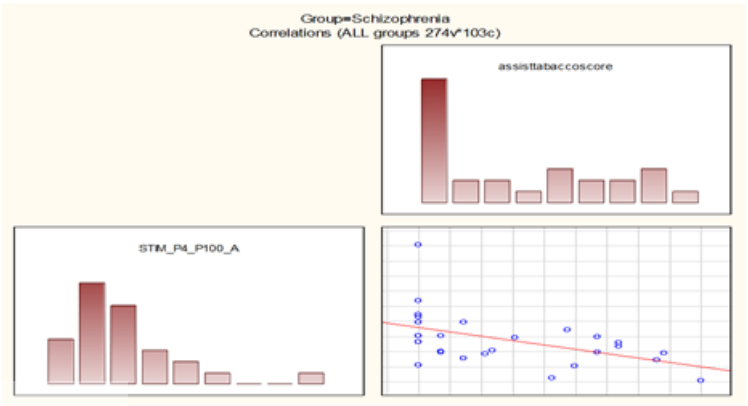


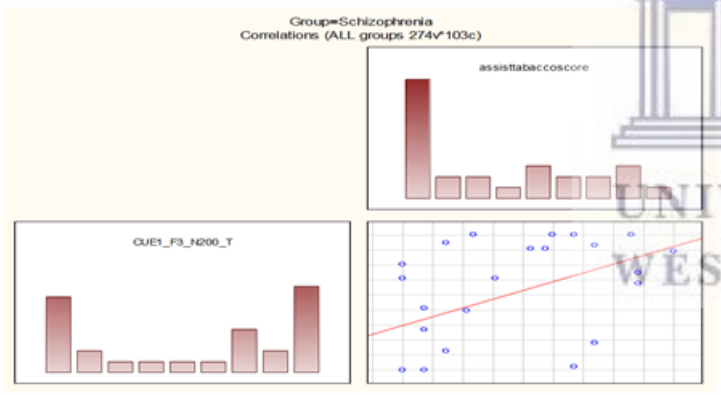


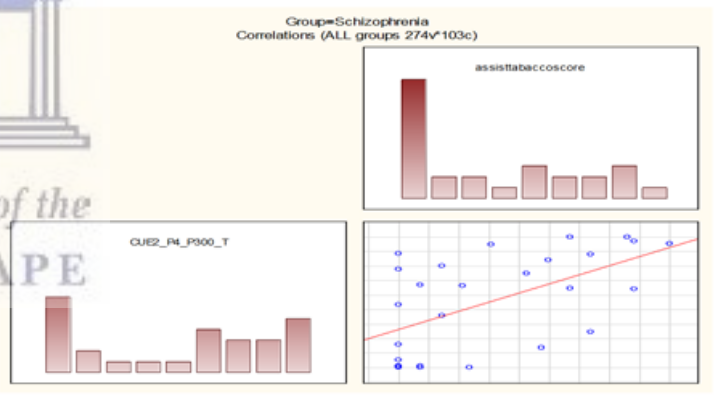


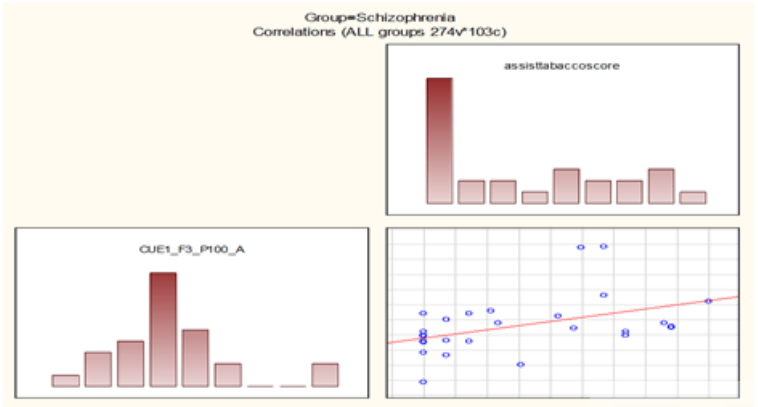


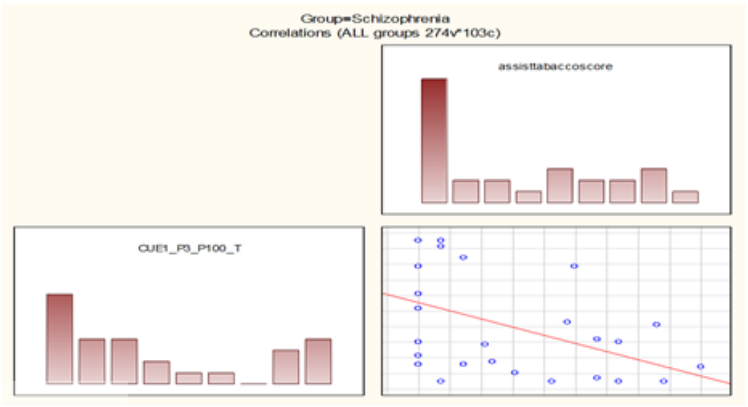


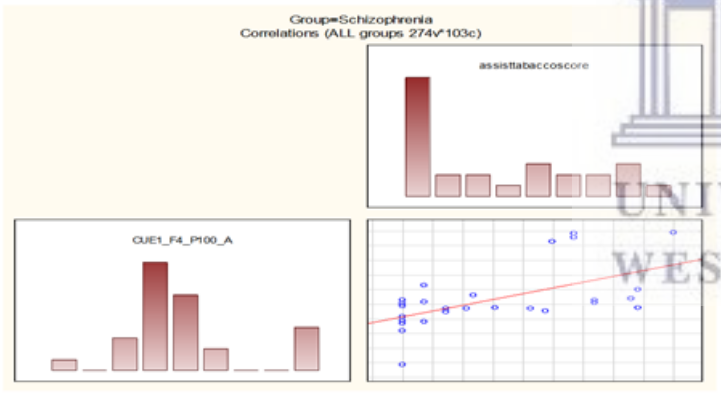


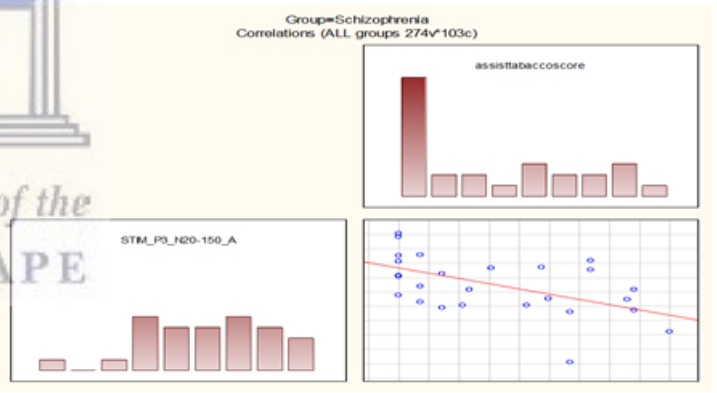


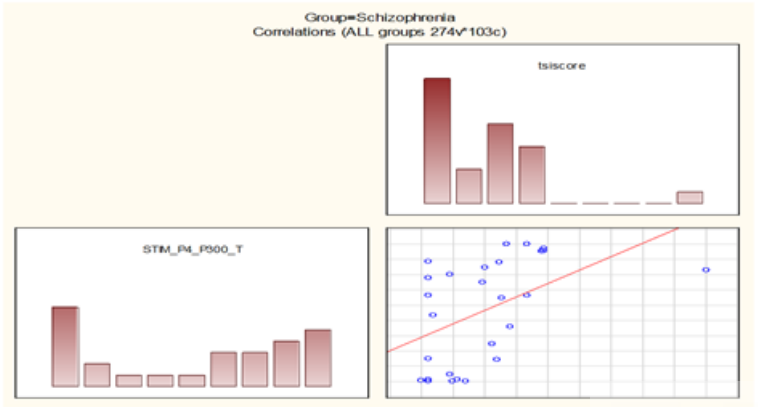


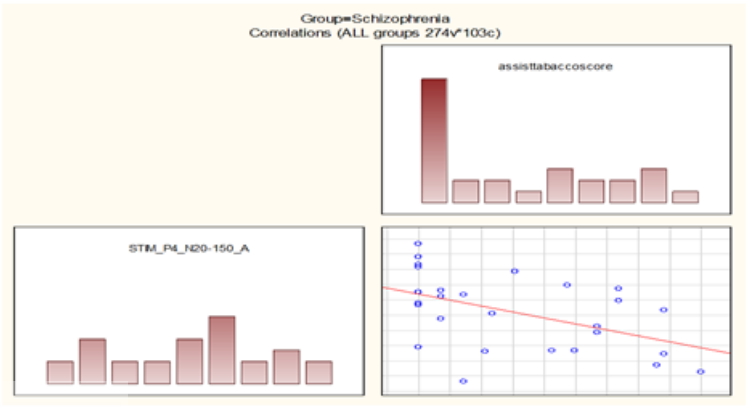


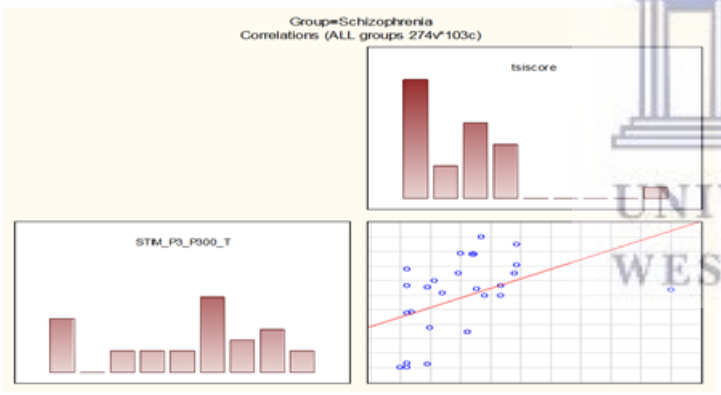


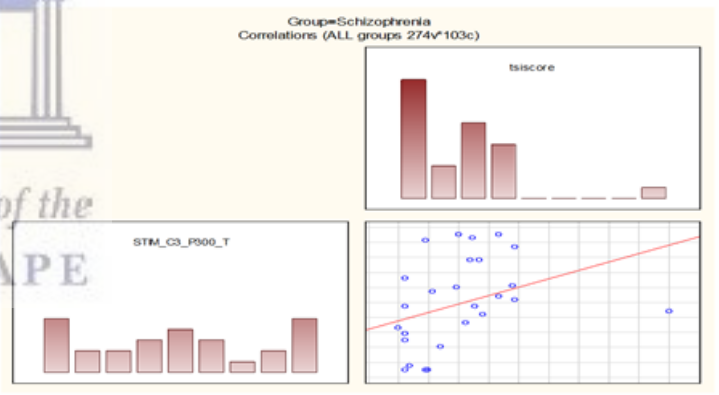


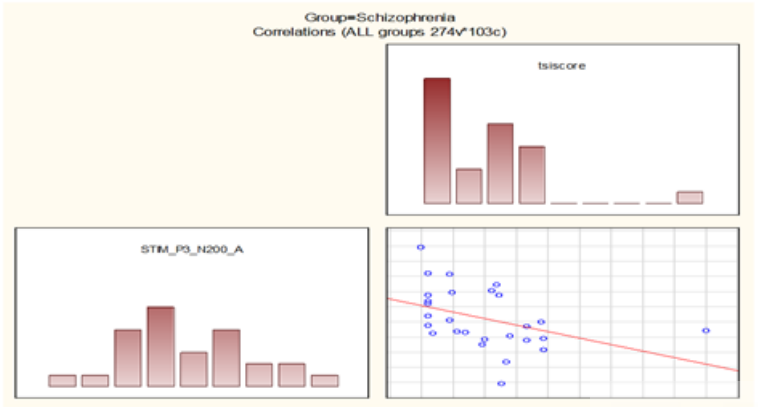


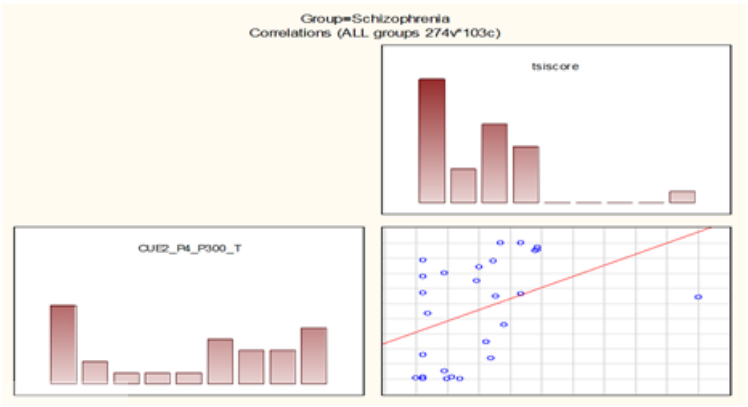


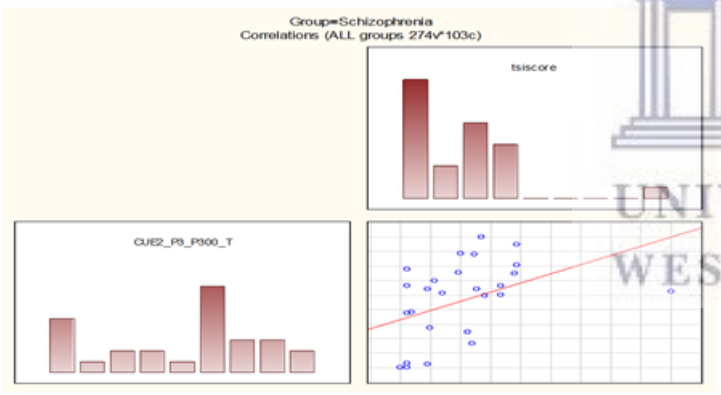


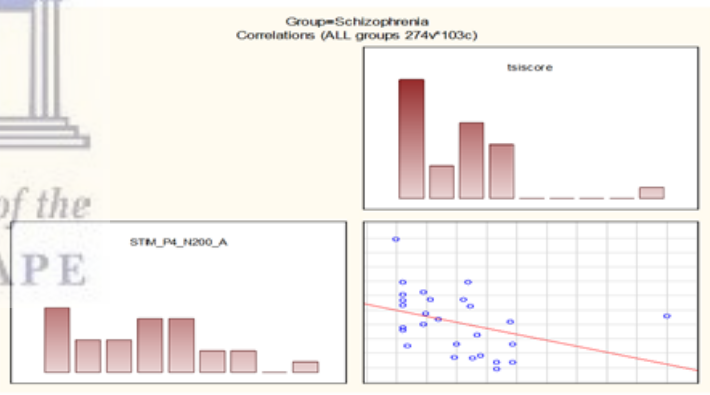


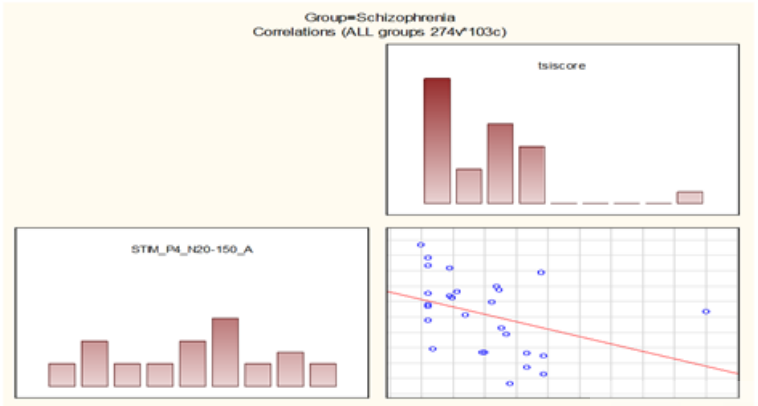


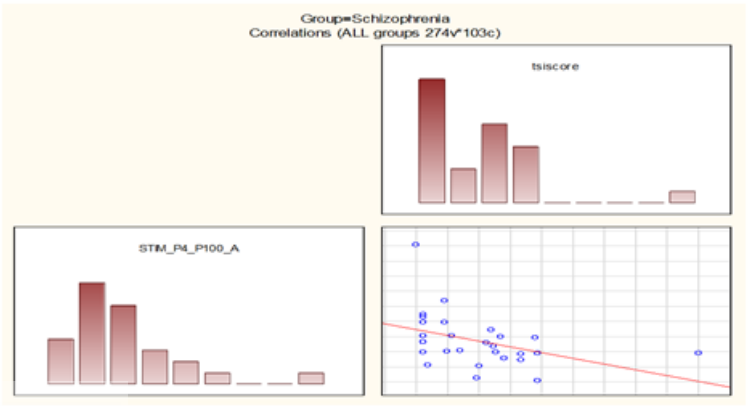


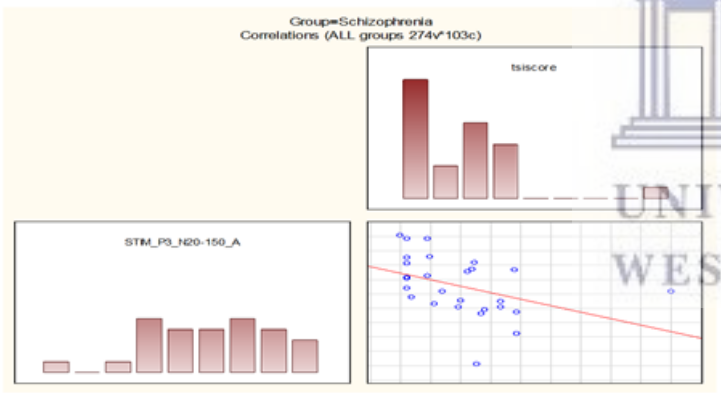


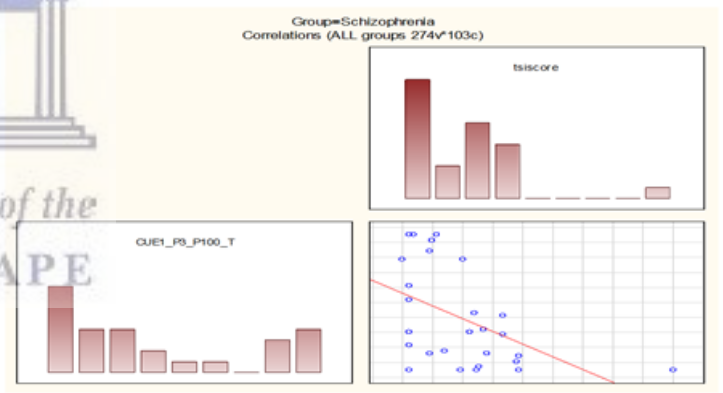


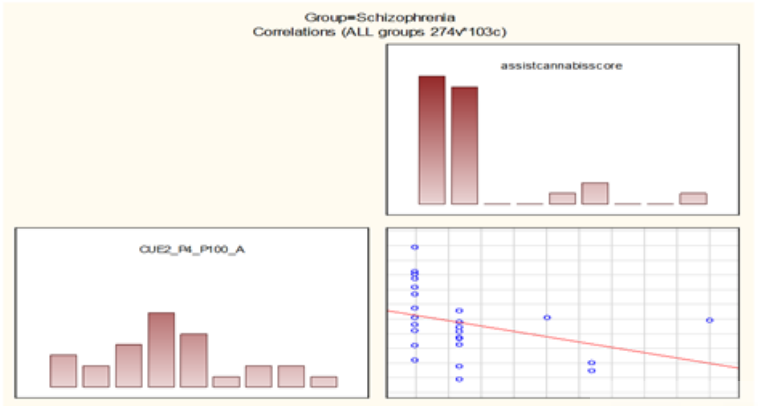


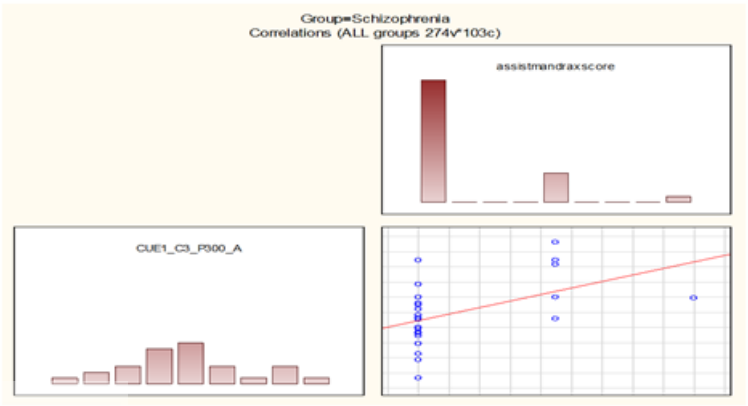


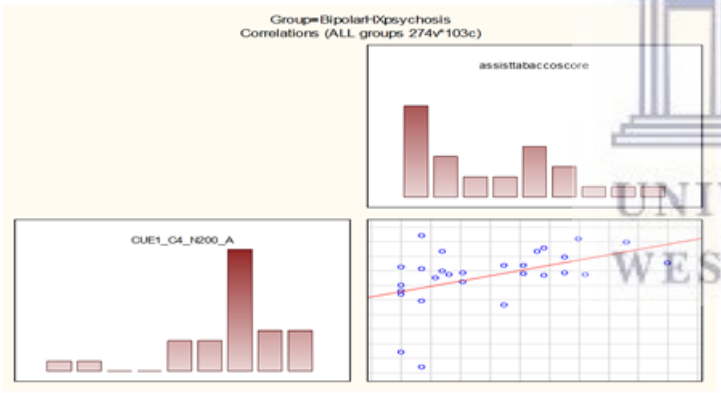


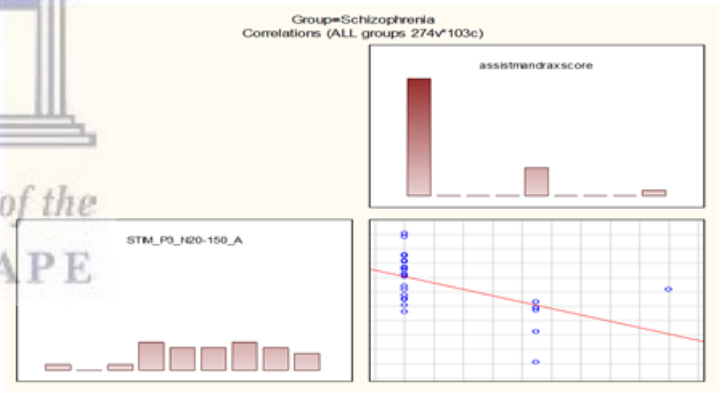


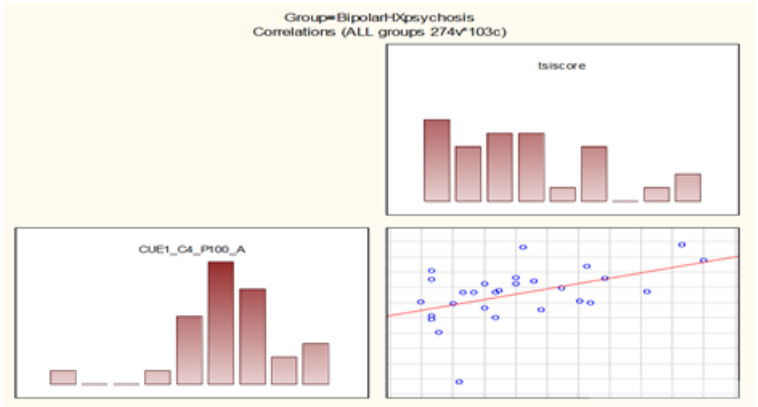


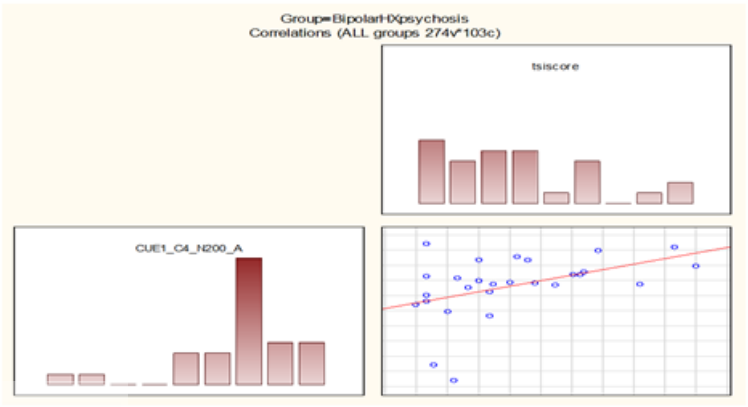


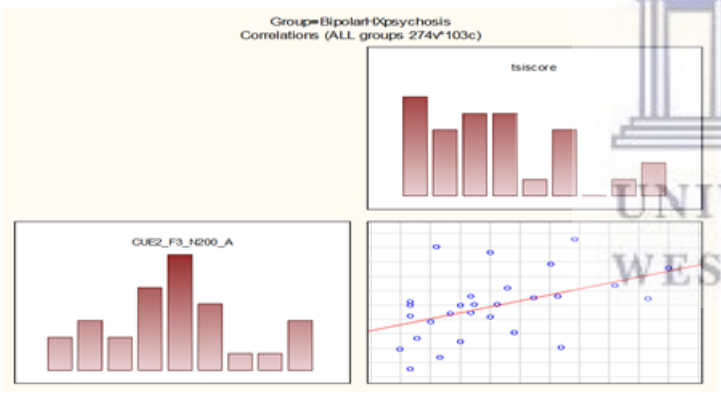


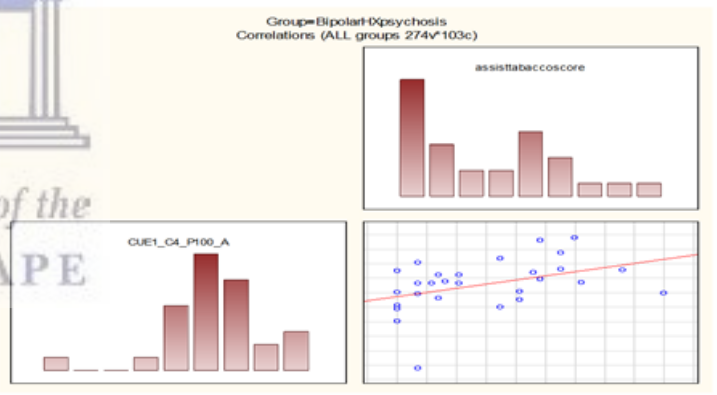


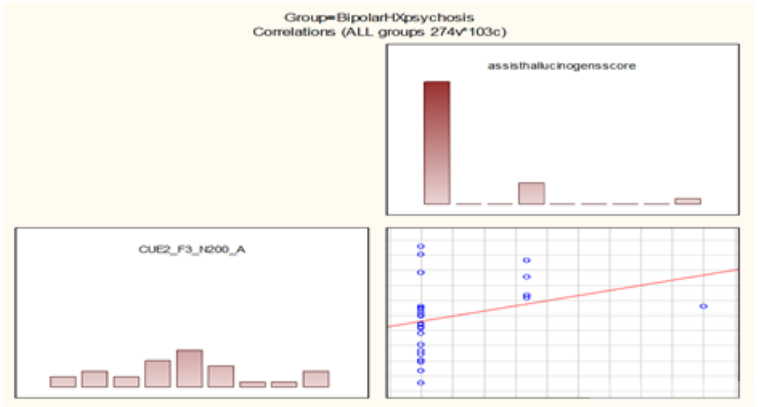


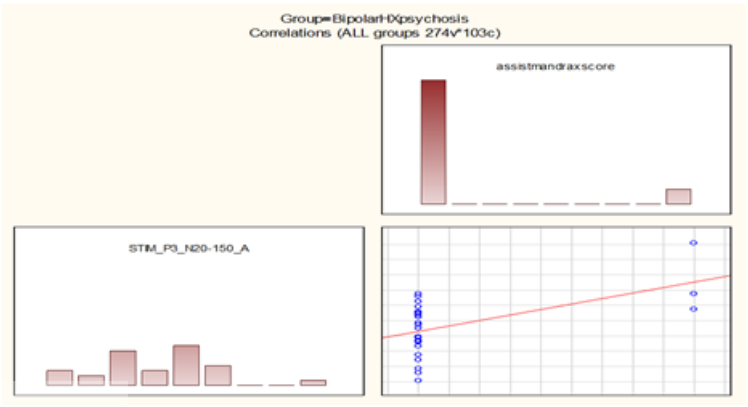


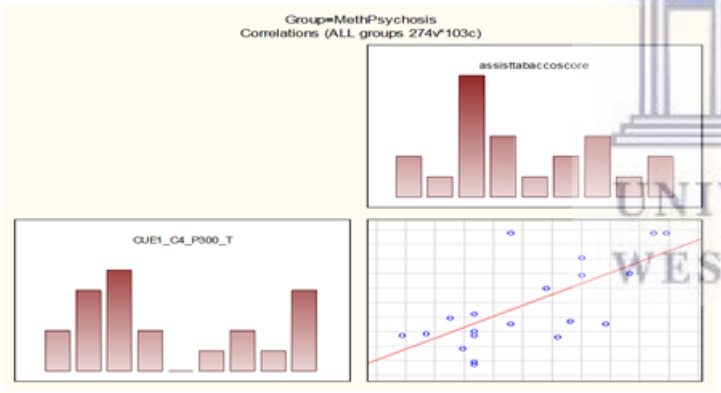


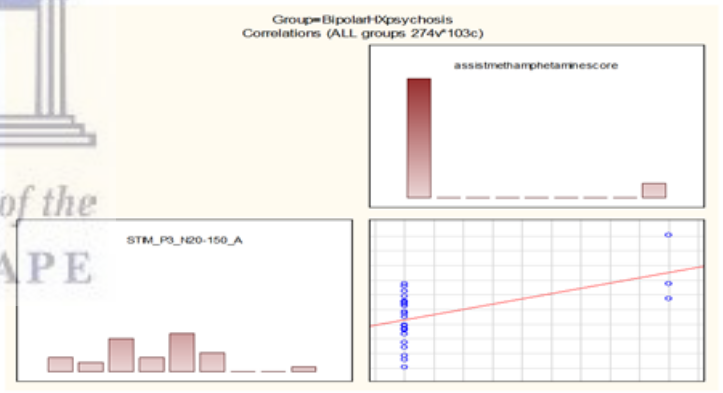


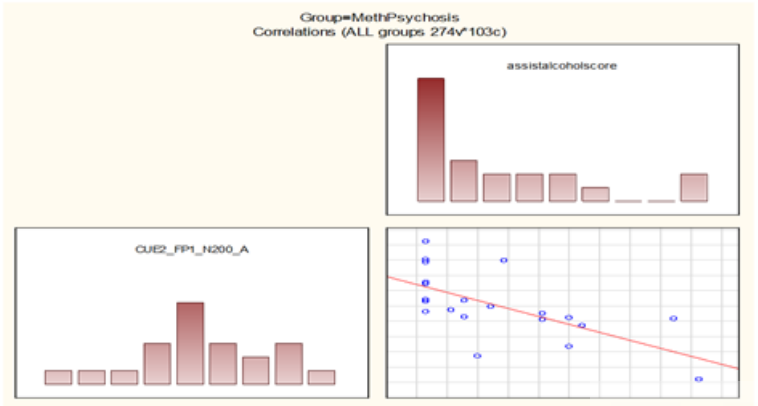


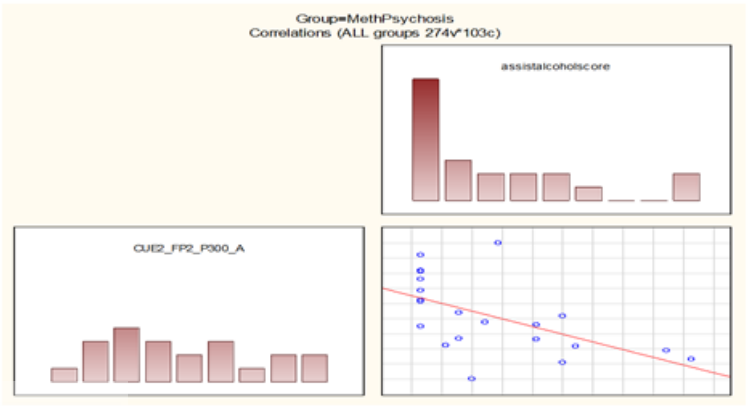


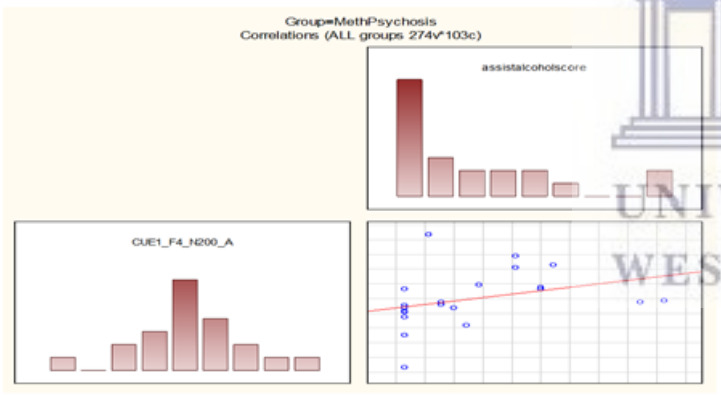


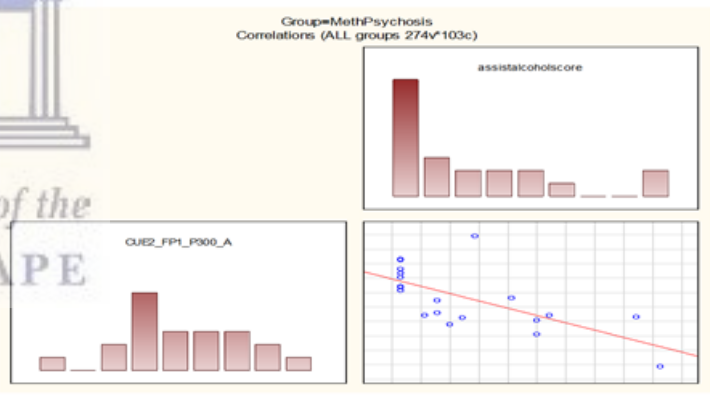


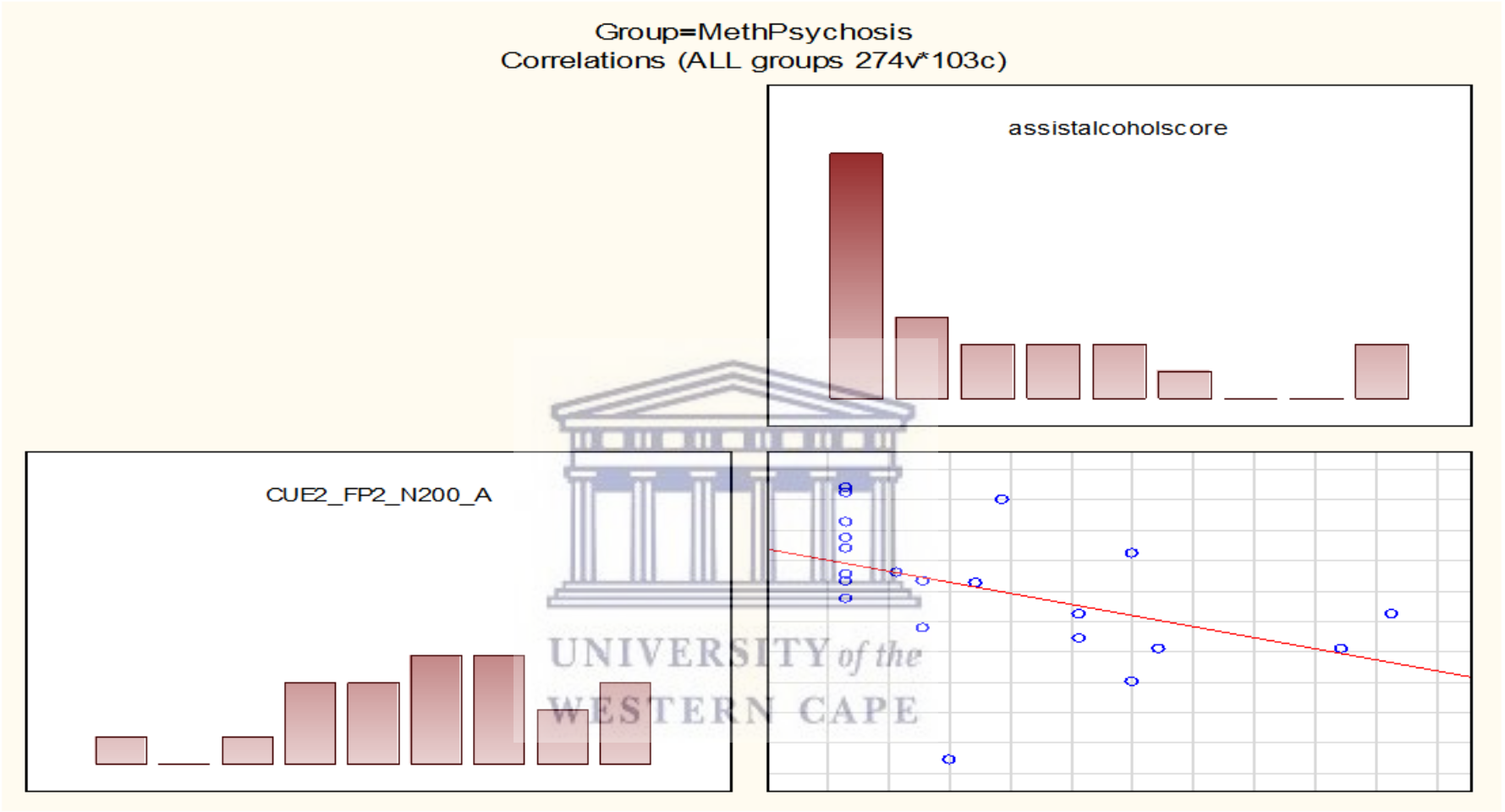


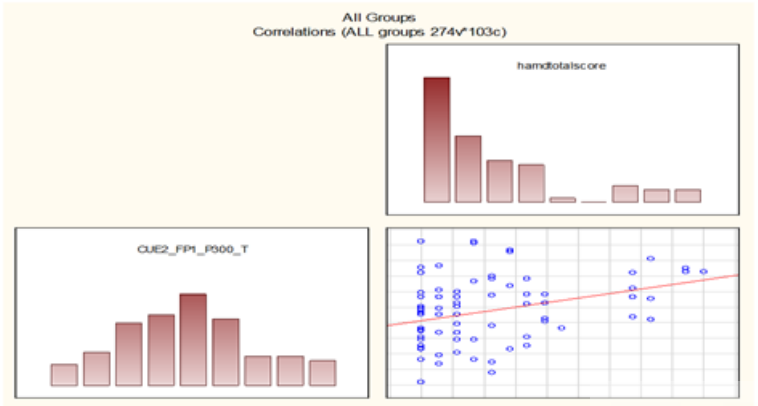


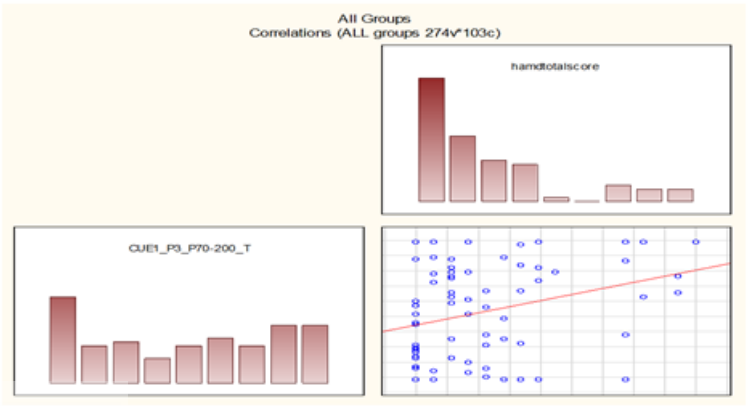


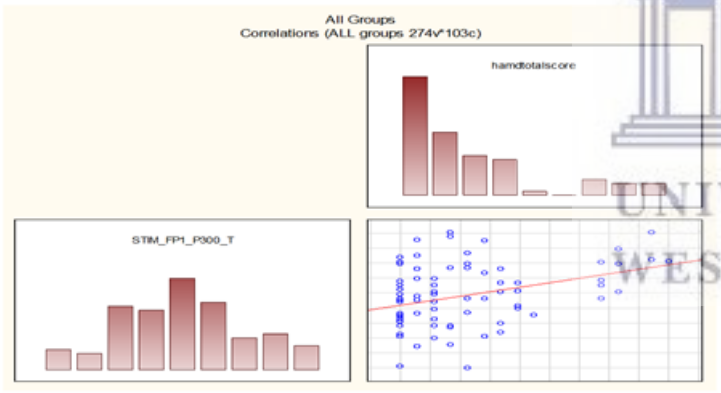


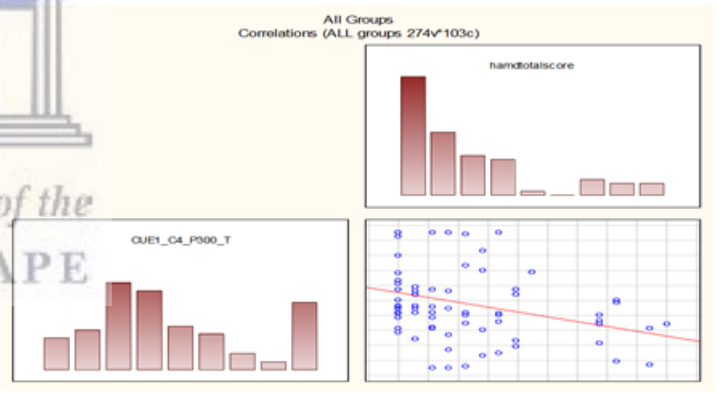


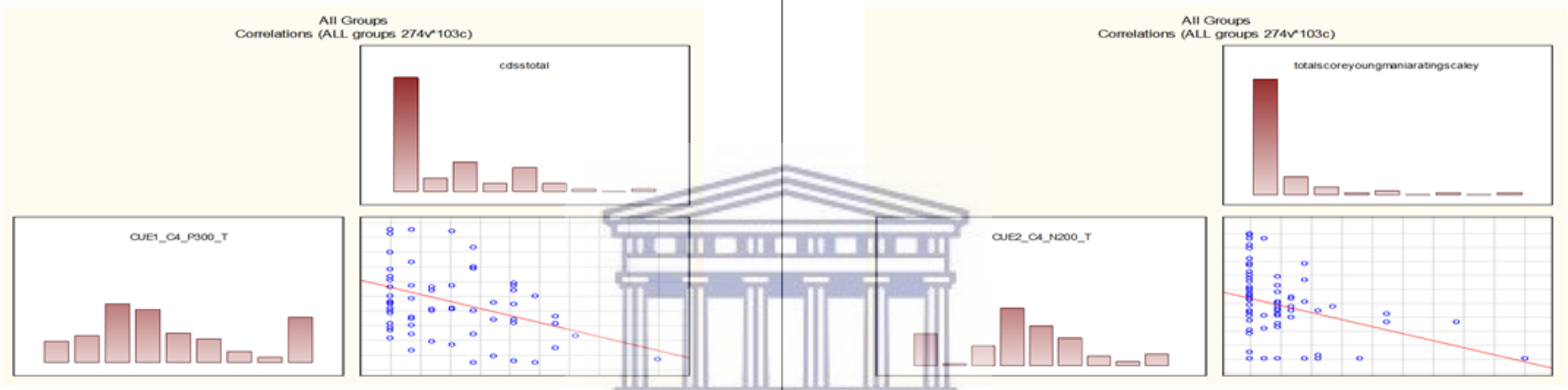


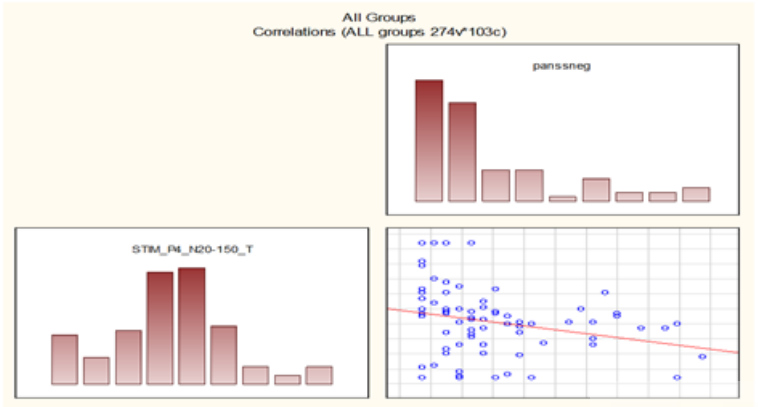


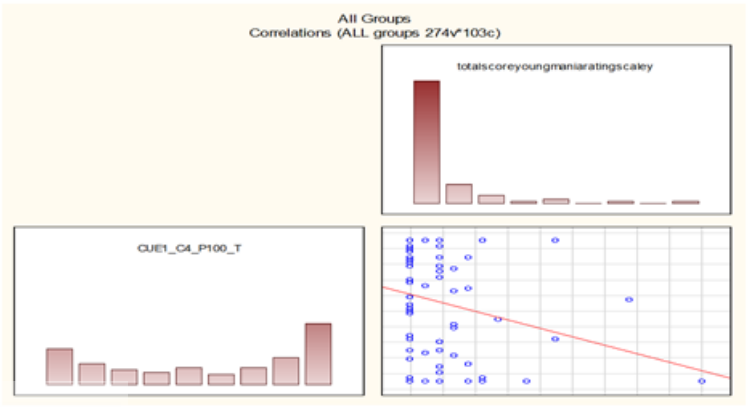


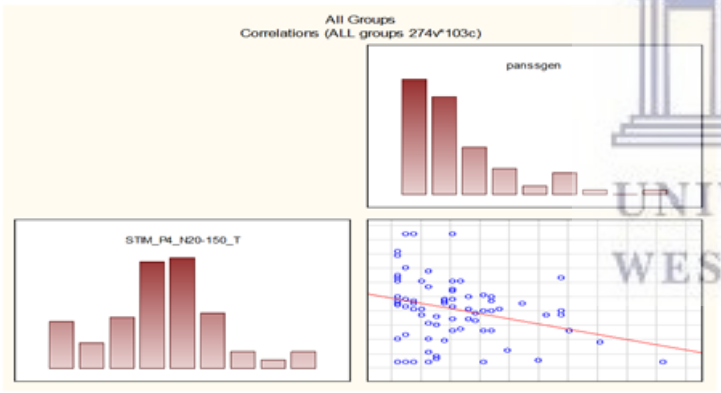


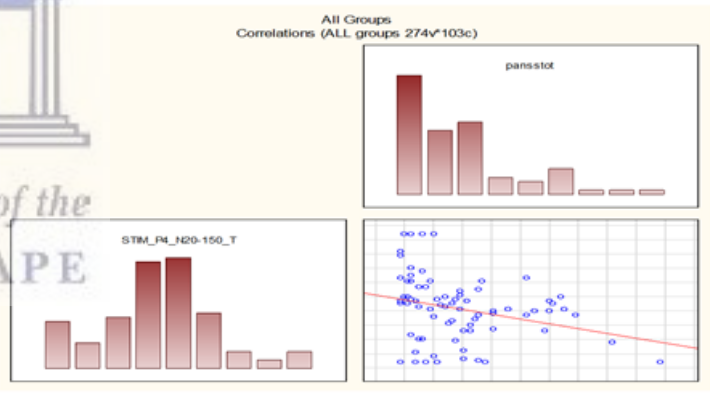


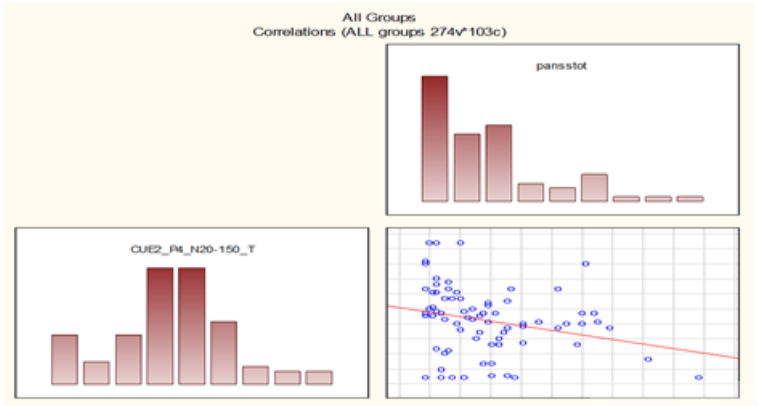


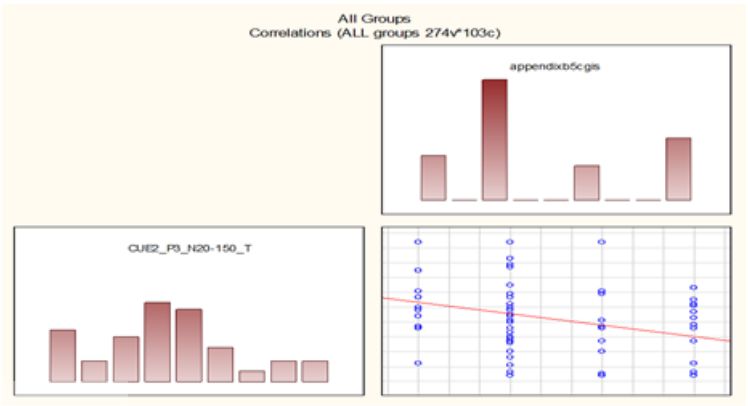


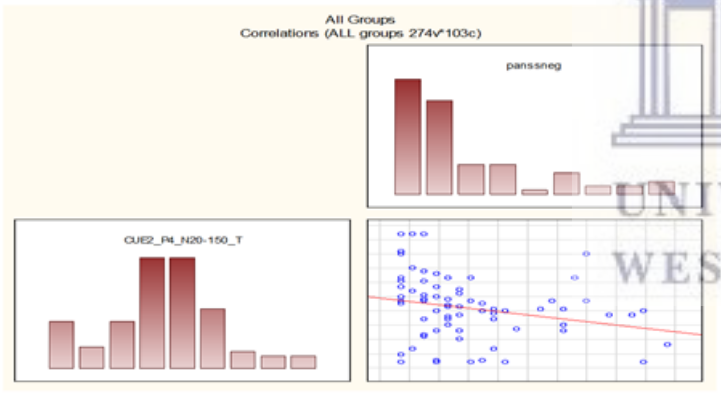


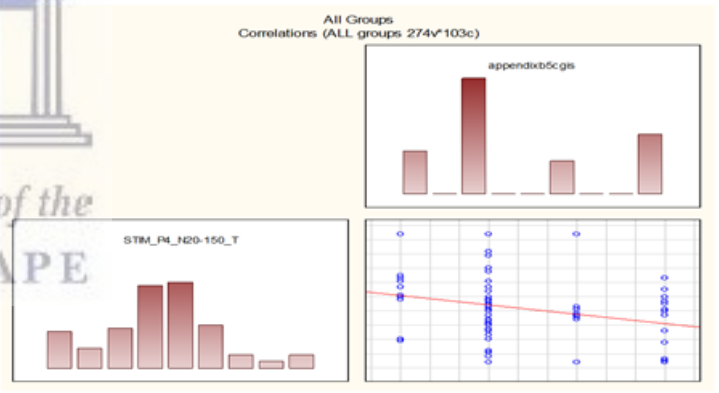


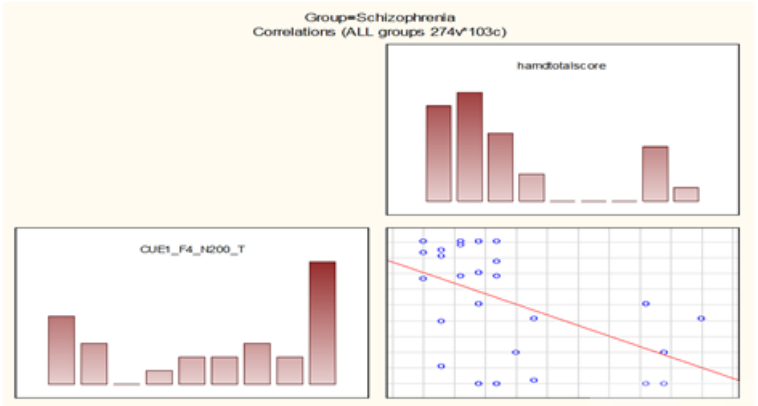


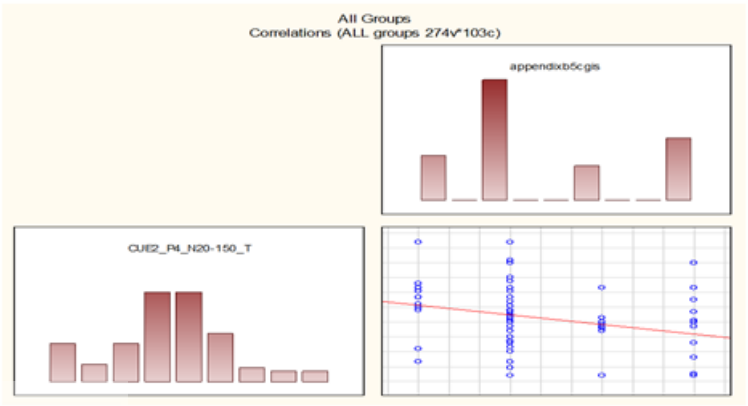


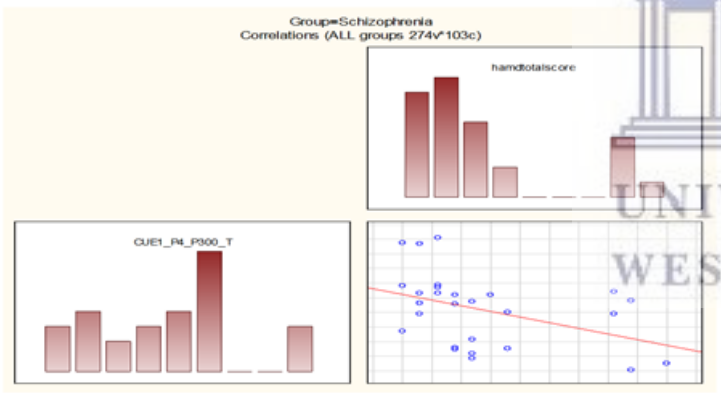


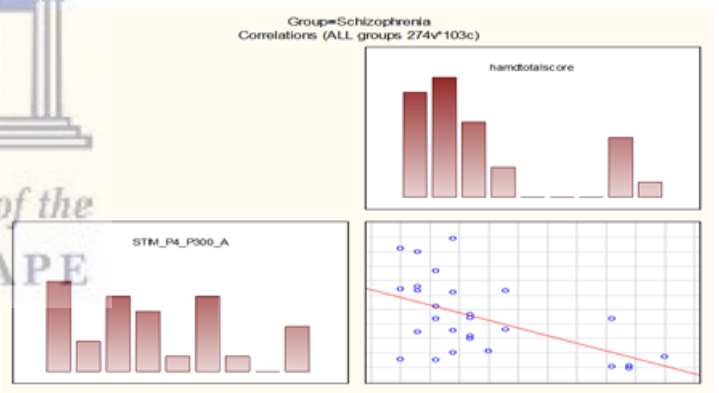


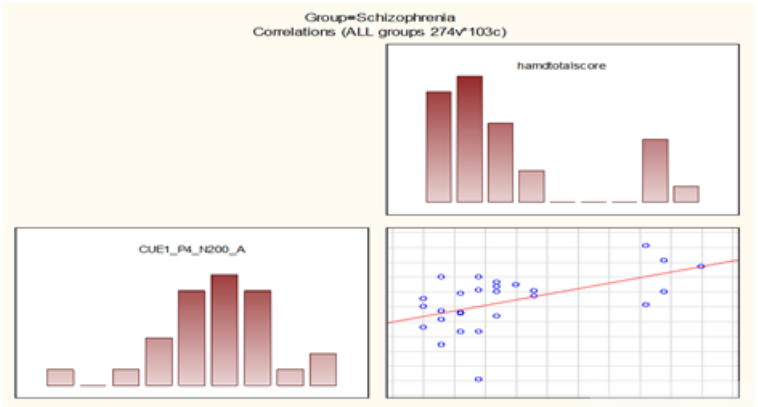


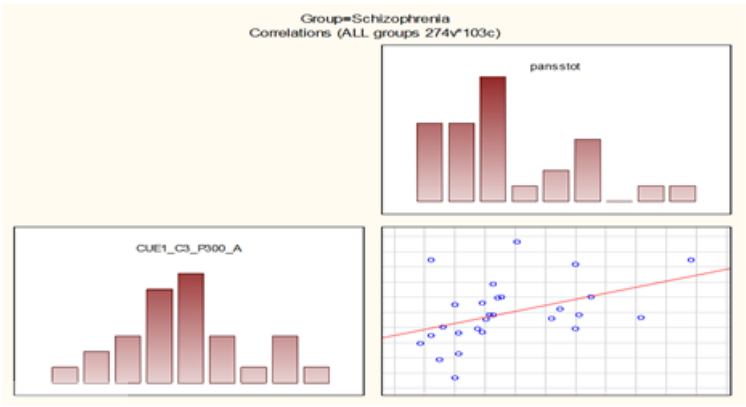


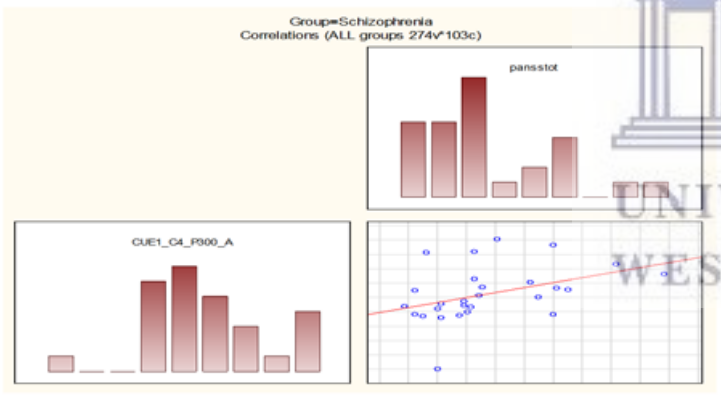


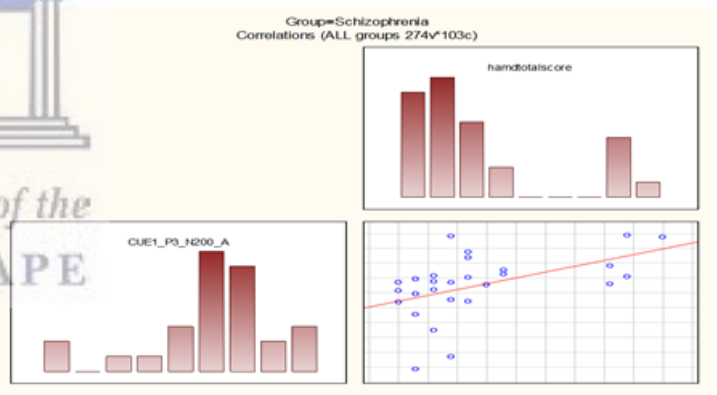


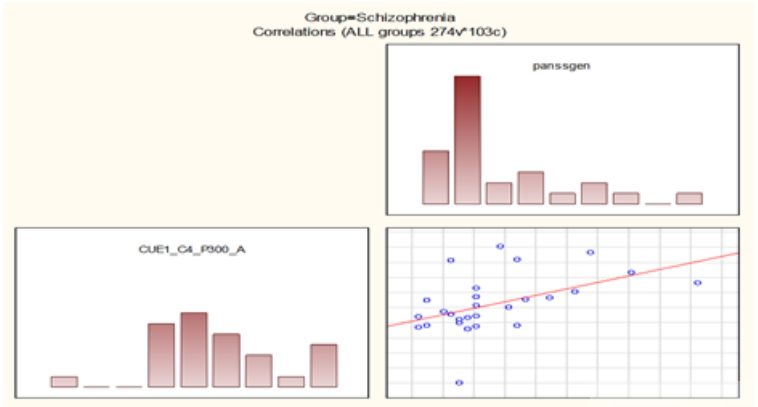


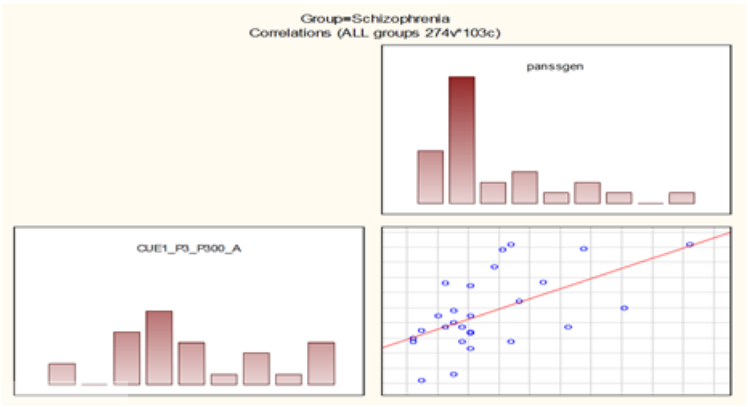


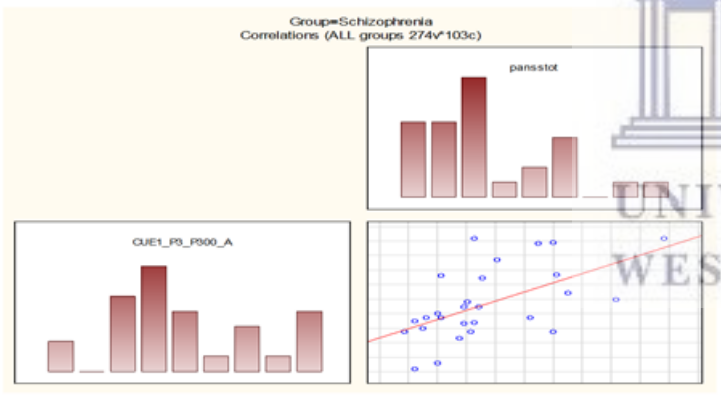


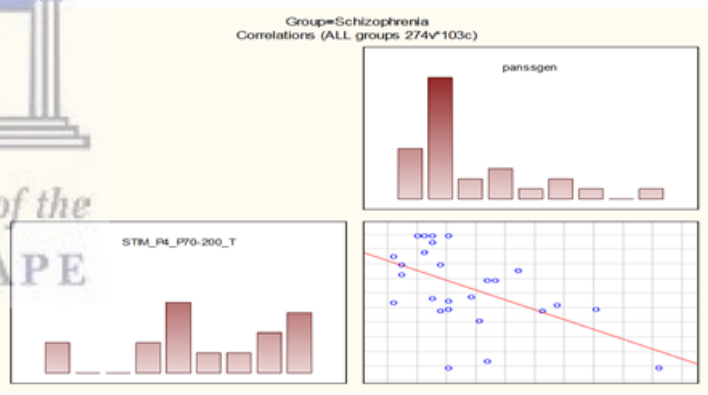


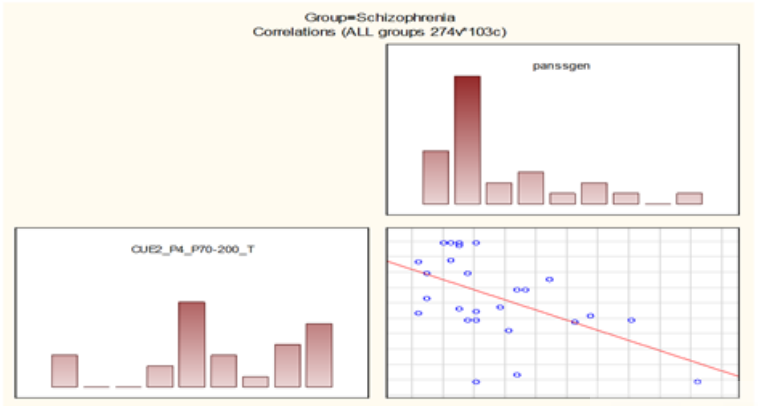


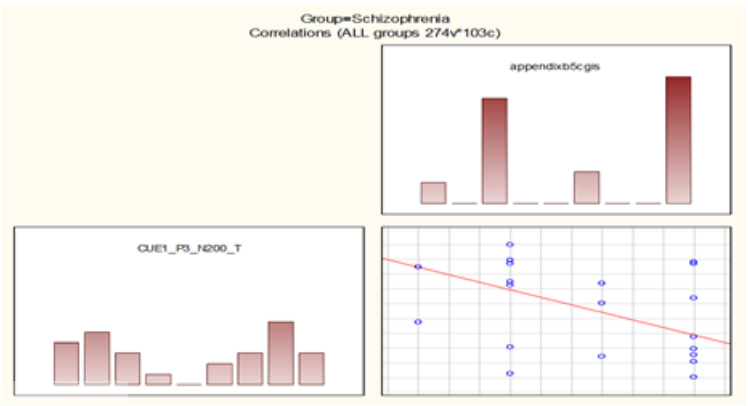


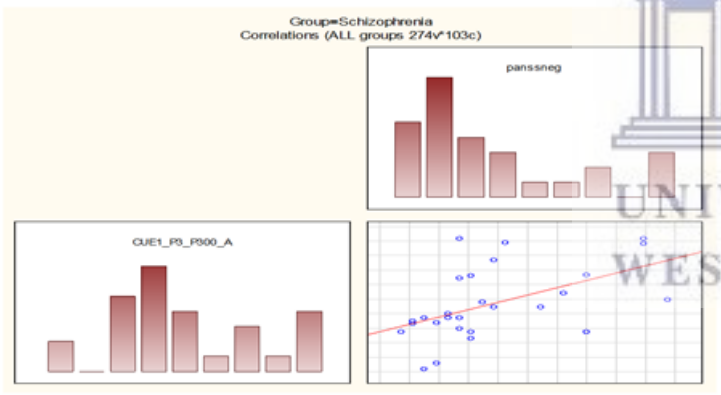


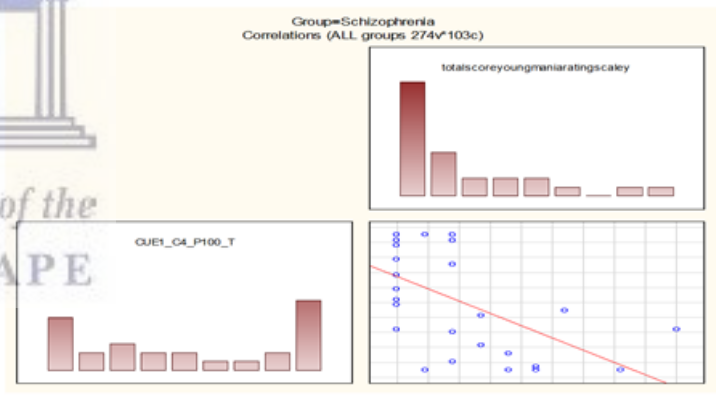


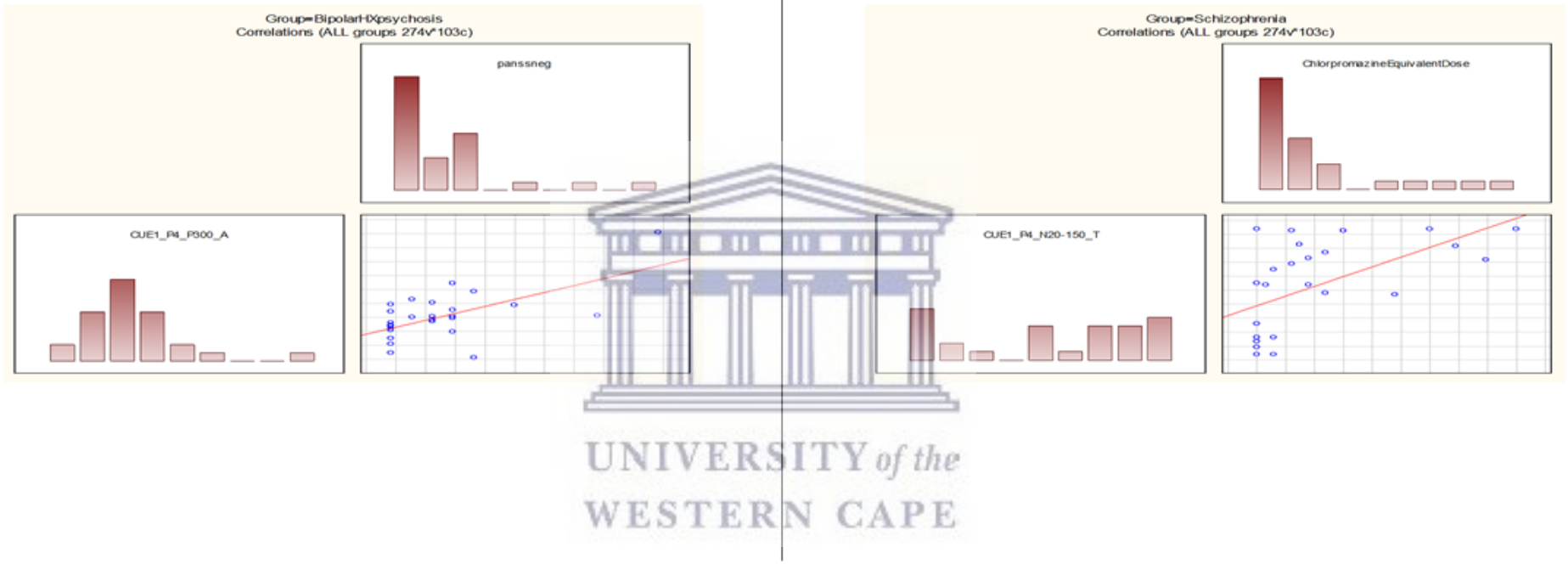


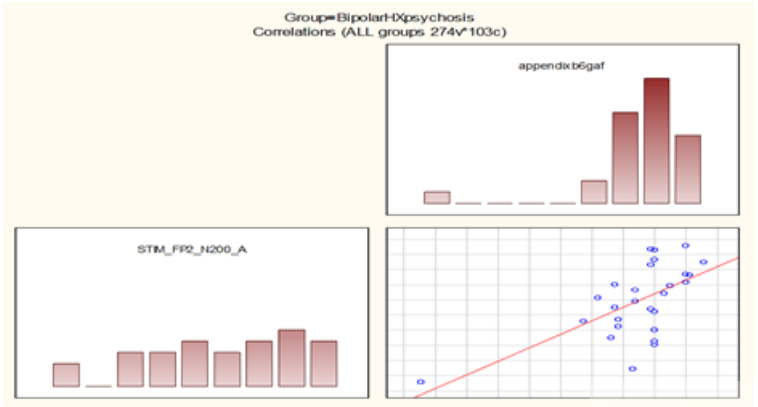


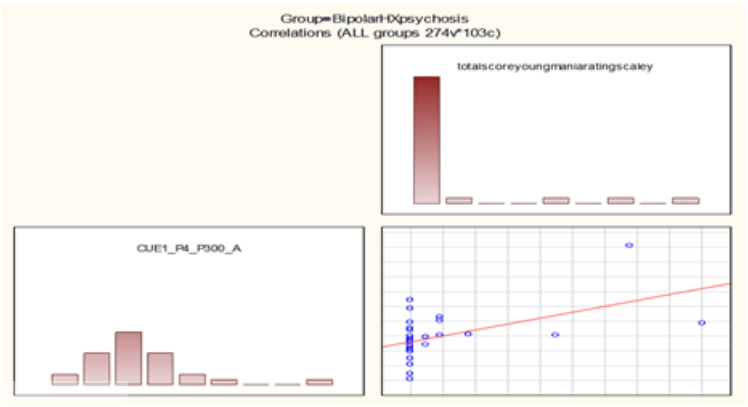


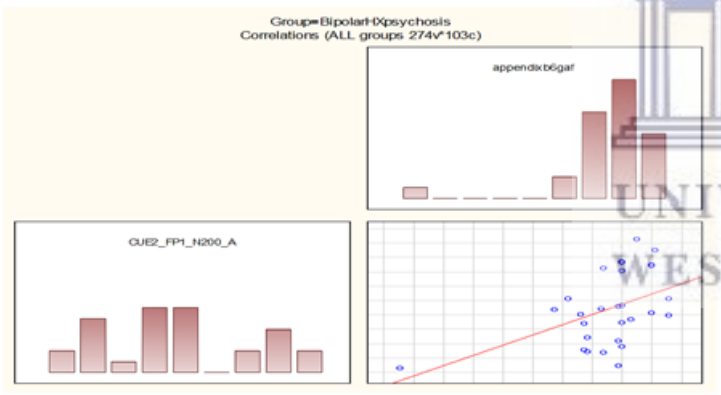


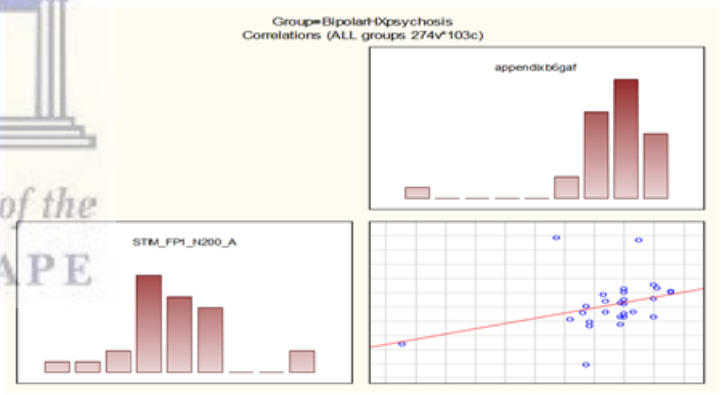


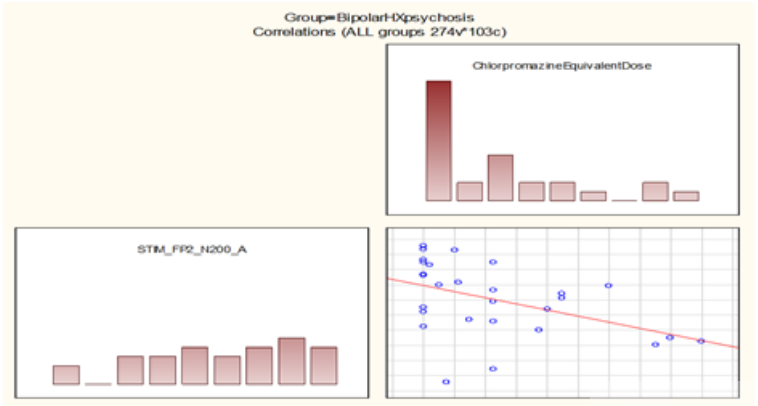


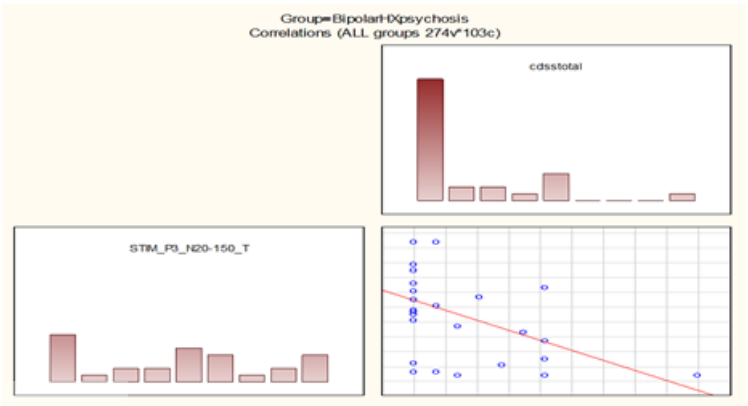


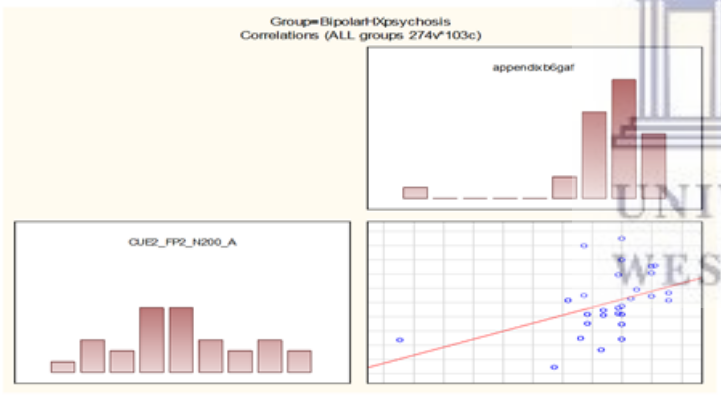


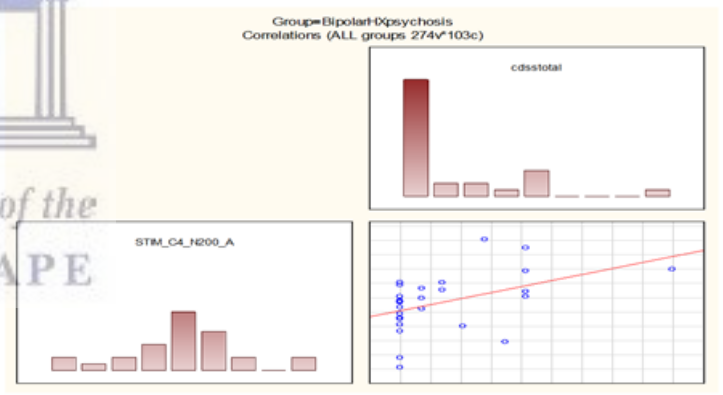


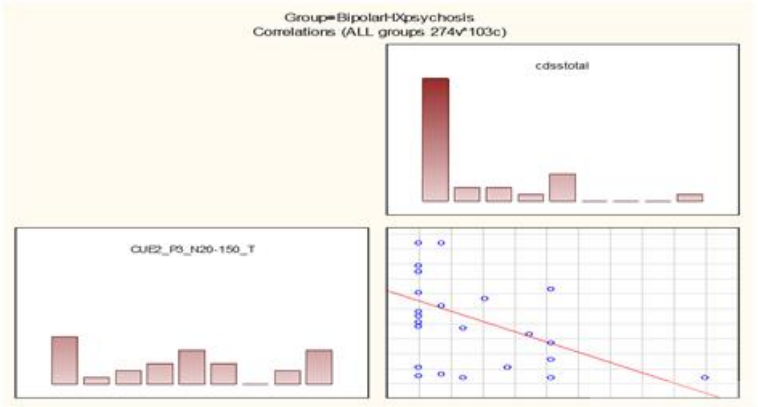


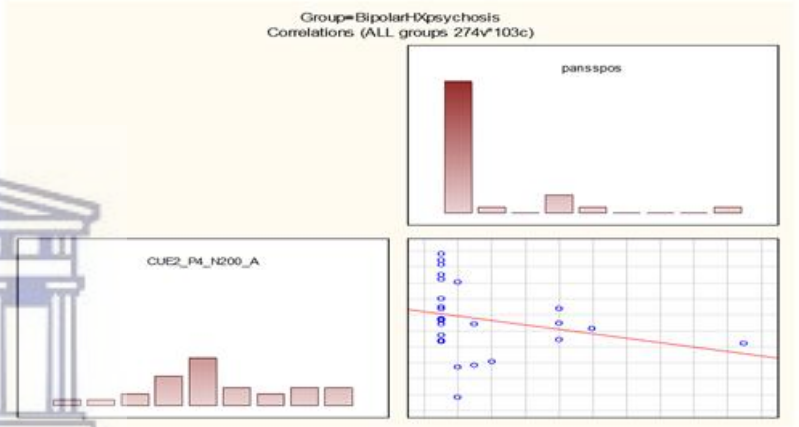


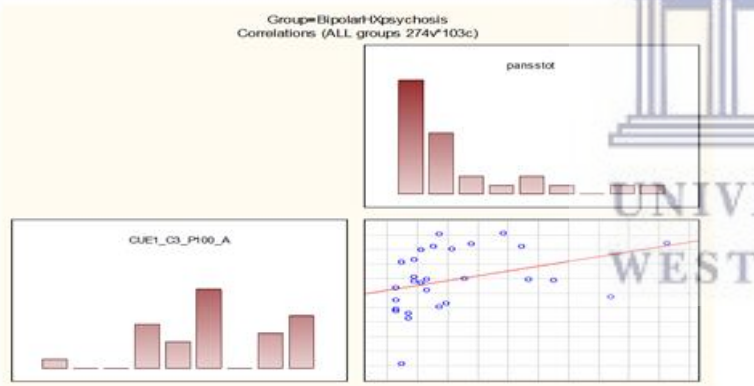


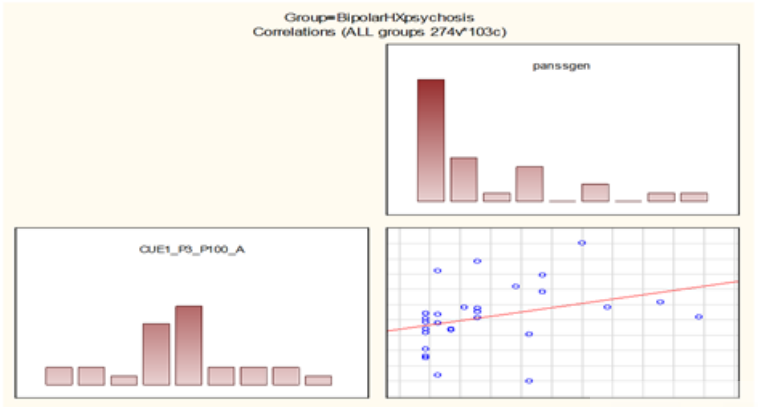


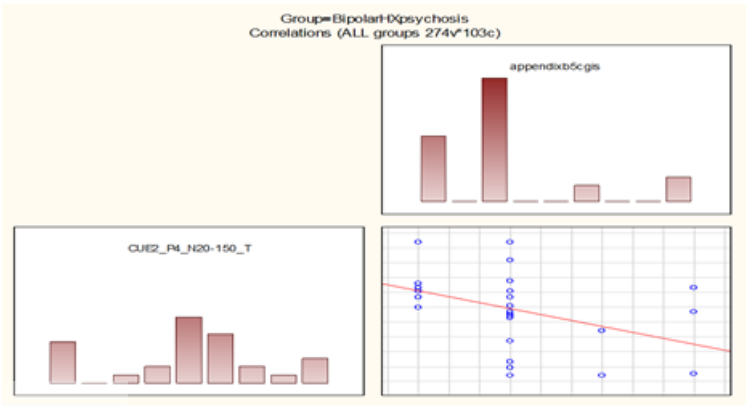


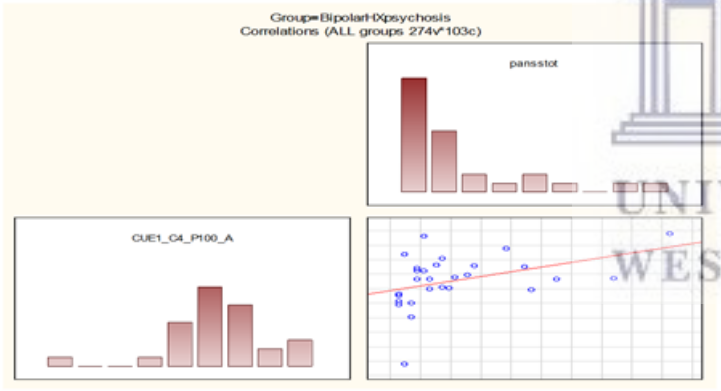


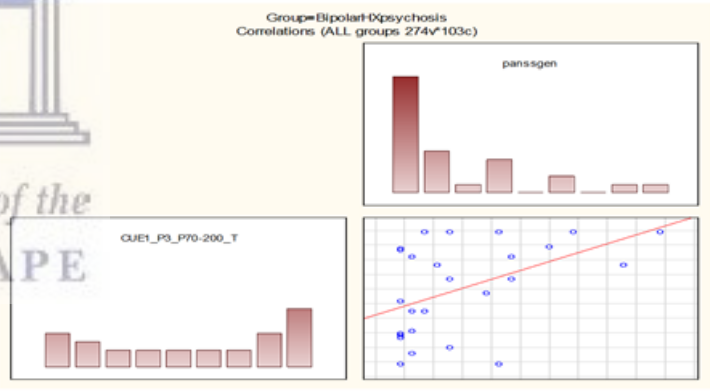


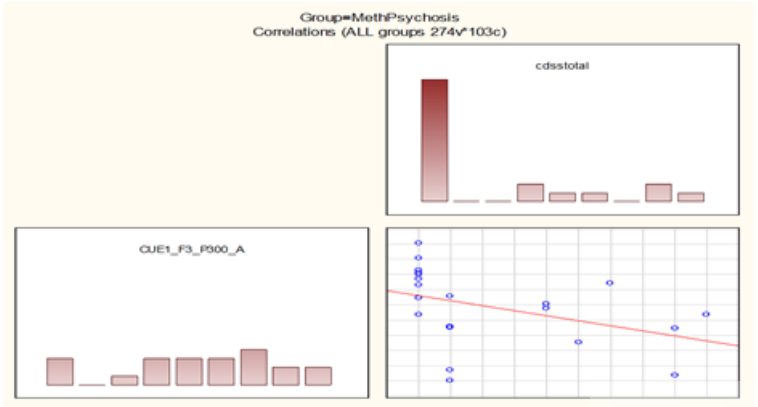


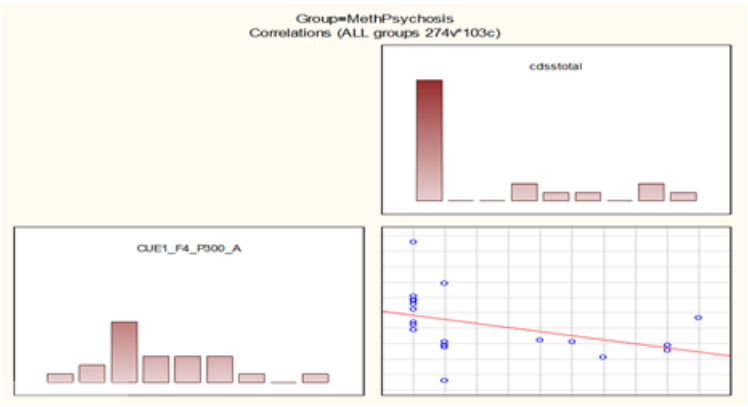


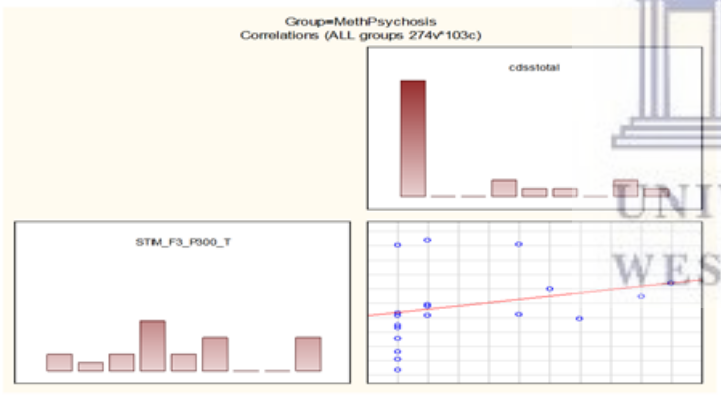


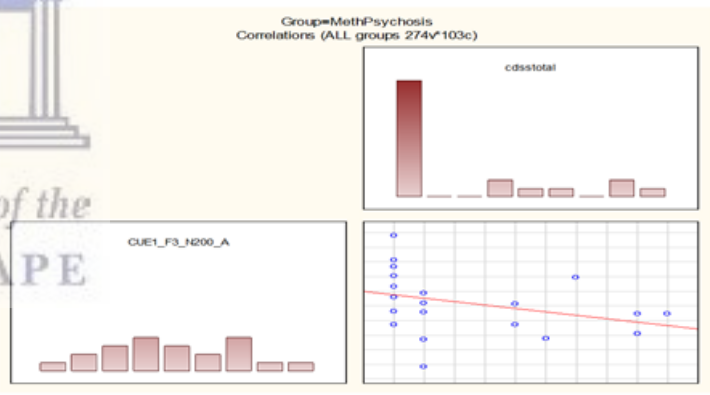


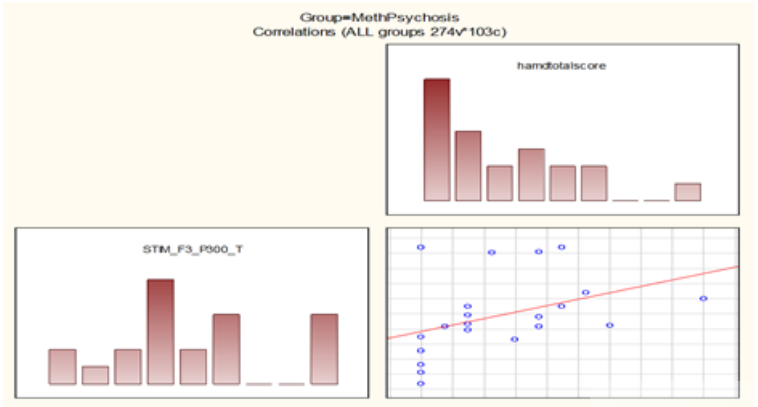


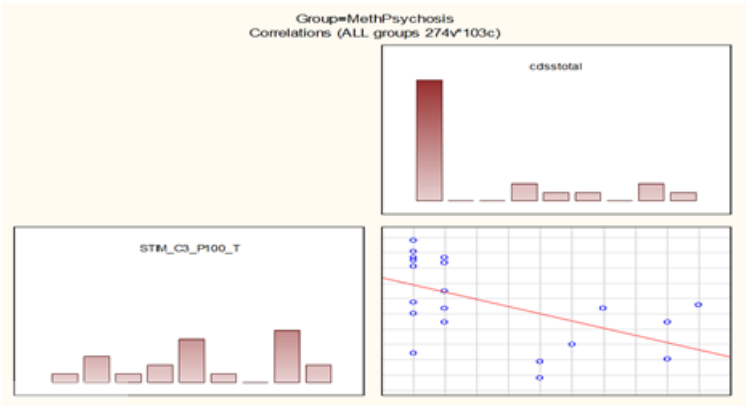


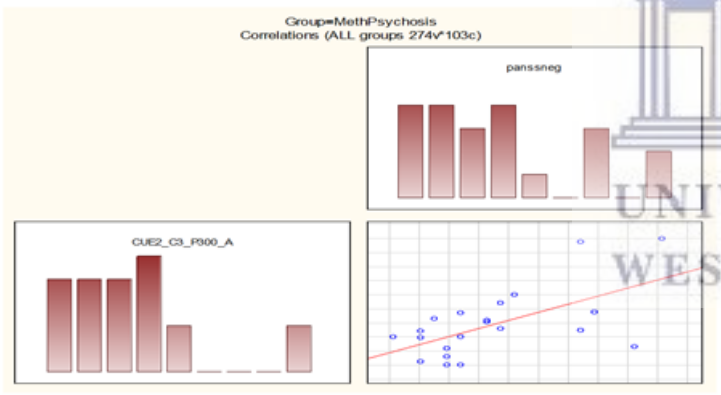


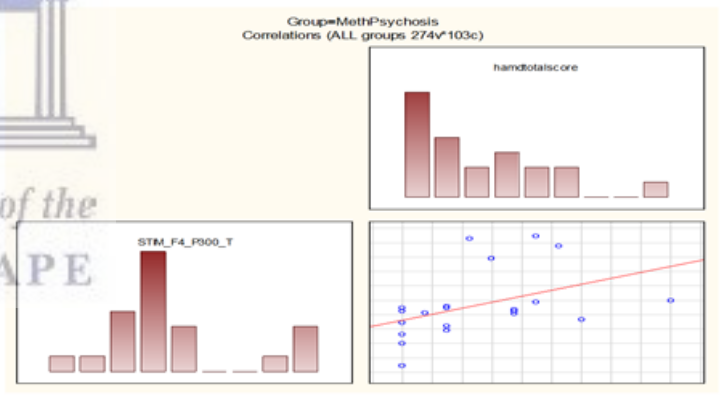


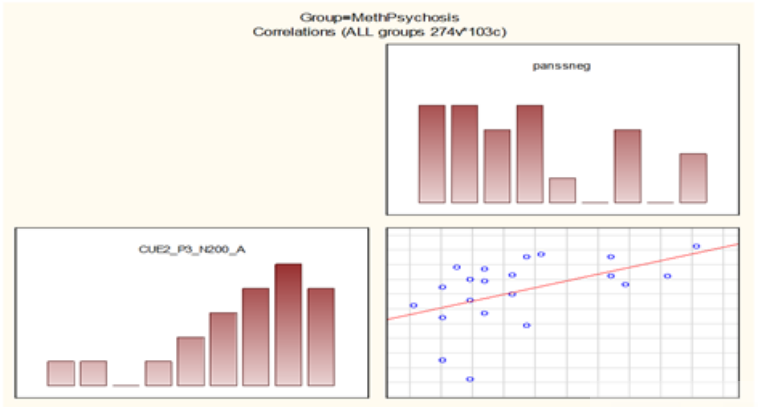


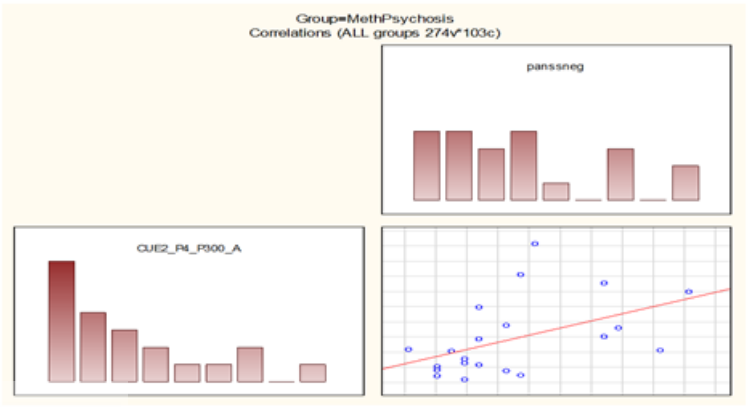


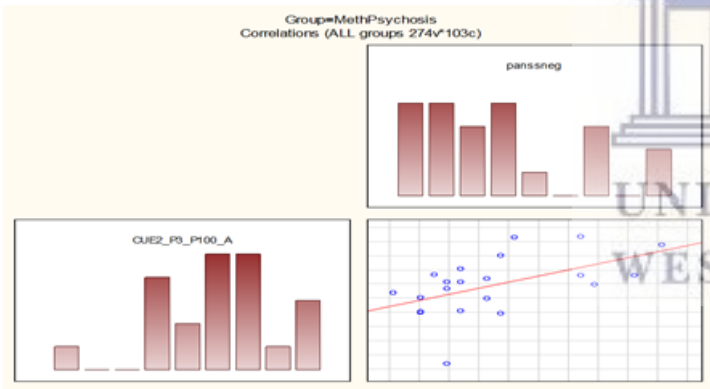


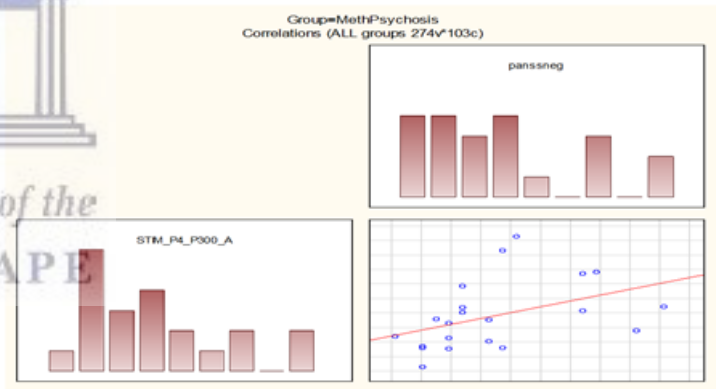


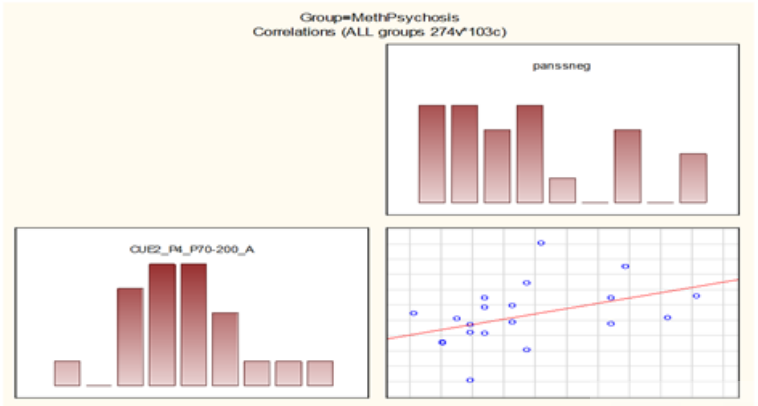


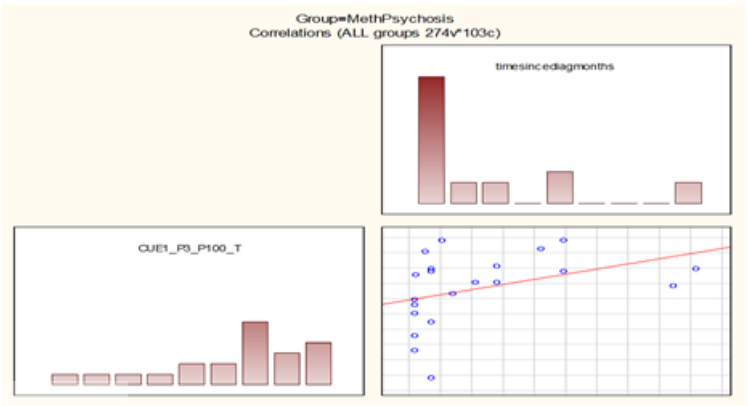


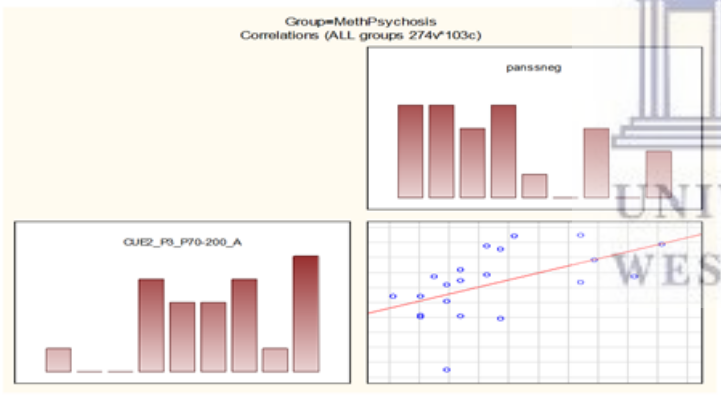


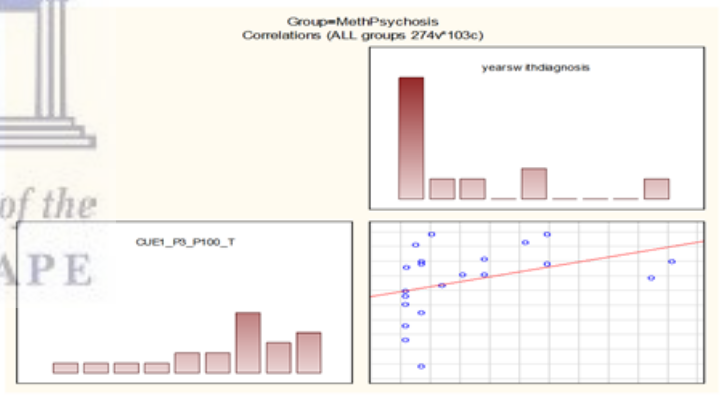


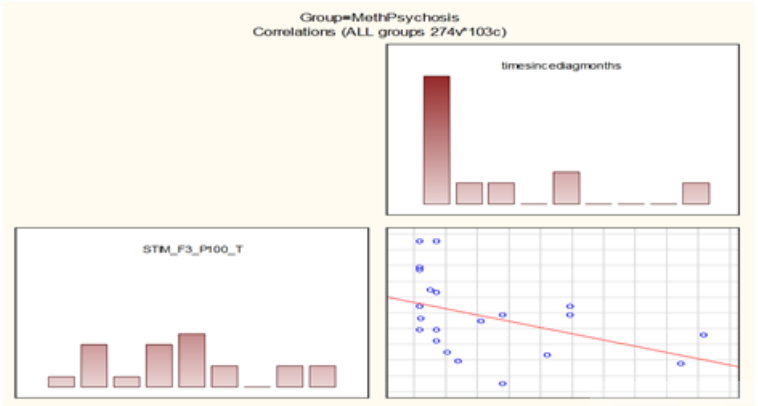


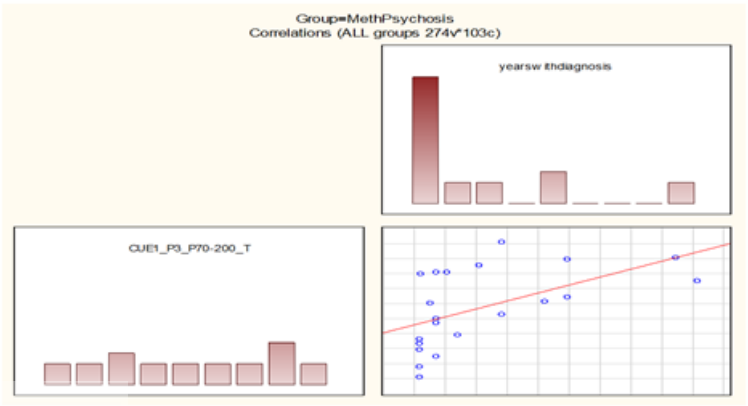


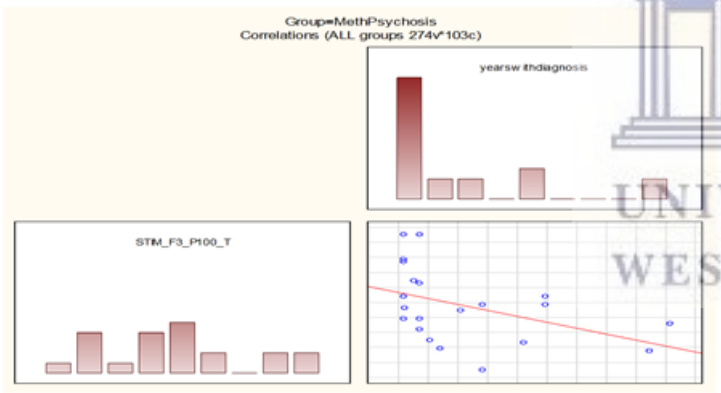


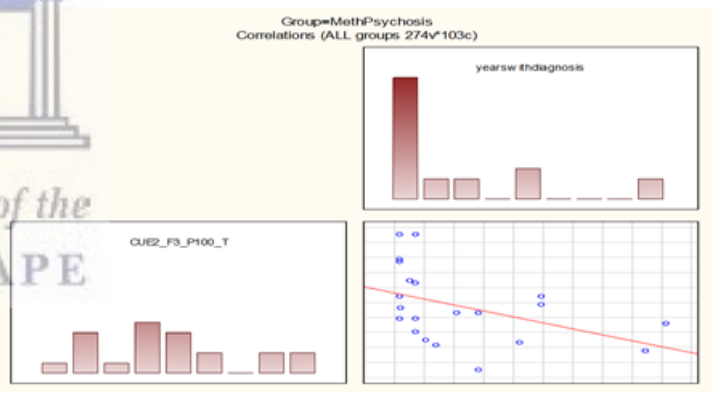


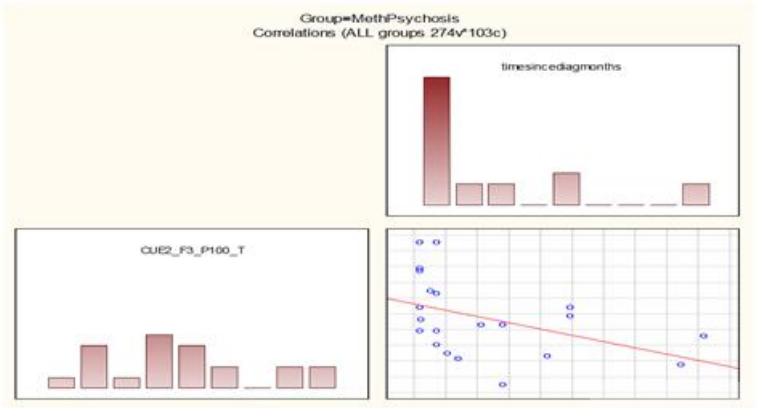


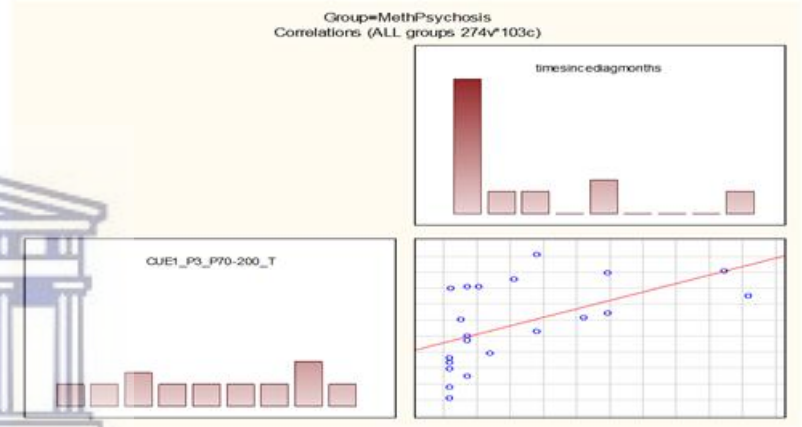


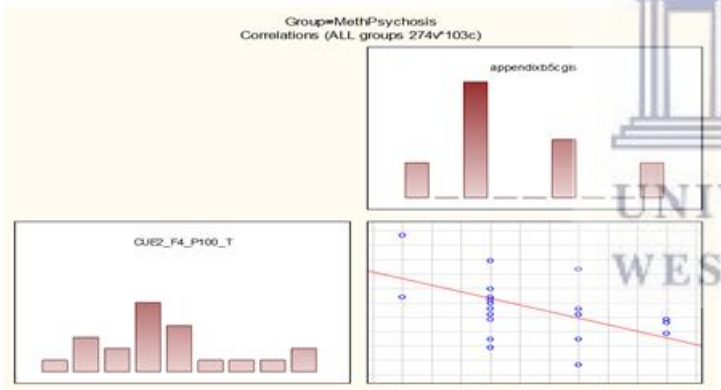












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