Investigating cortical arousal and cognition in schizophrenia and methamphetamine-induced psychotic disorder: an electroencephalography and cytokine study

By

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Acknowledgements

The journey of education is not an easy one as everyone knows. And completing a PhD is truly an emotional journey. There is quote which I came across when writing up my MSc thesis which resonates with me.

"*There is no sudden leap into the stratosphere… there is only advancing step by step, slowly and tortuously, up the pyramid towards your goals*".

- Ben Stein

Throughout our schooling we are asked what we would like to be when we "grow up". I have always known that I wanted to be a doctor. After many years of studying, and slowly working my way up that ladder, I can officially say that I have accomplished my goal.

With completing any goal, there are always steps which need to be taken. Some of those steps will be more difficult to climb but knowing that you have supportive friends, family, and mentors to get you through it gives you that motivation to continue going.

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Declaration

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I _____ hereby:

a) Declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree at this or any other university

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Abstract

Introduction: Schizophrenia (SCZ) and methamphetamine-induced psychotic disorder (MPD), are psychotic disorders characterized by positive symptoms (e.g., hallucinations and delusions), negative symptoms (e.g., social withdrawal, apathy), and impaired cognitive function. Despite the overlap in the clinical presentation of SCZ and MPD, no studies have compared electroencephalography (EEG) and inflammation across these two conditions. This study aimed to investigate key differences in brain electrical activity on EEG between SCZ and MPD by investigating; (1) relative frequency (alpha, theta, beta and delta) at rest; (2) cognitive performance and relative frequency activity during the continuous performance task (CPT) and cued target detection task (CTD); (3) differences in the P300 event-related potential waveform (ERP), a measure of attention, during the CPT and CTD; (4) cognitive performance and relative frequency and ERP (N170, P300) during the STROOP task, a measure of working memory and executive function; (5) the associations of (neuro) inflammatory markers with relative frequency and the P300 ERP waveform.

Methods: 104 South African individuals, between the ages of 20 and 45 years, participated in this study: 69 outpatients (38 with SCZ (8 females/30 males), 31 with MPD (7 females/24 males)), and 35 healthy controls (CON: 15 females/20 males). All participants underwent a Structured Clinical Interview for Diagnostic Systematic Manual-IV (SCID-DSM-IV), with modifications to include changes made in DSM-5. EEG band frequency oscillations were recorded during baseline conditions: resting eyes open and resting eyes closed, and cognitive tasks (CPT, CTD and the Stroop task). Blood was drawn via venepuncture and serum was used for the analysis of cytokines (interleukin (IL) -1β IL-8, IL-10, IL-12p70, tumour necrosis factor-alpha and interferon-gamma (IFN-γ)) concentrations. Statistical analysis included assessment of normality using the Shapiro- Wilk test, with univariate one-way analysis of variance (ANOVA) of parametric data, and multiple independent Kruskal-Wallis ANOVA for non-parametric data ($p<0.05$). Correlations were conducted with Pearson's or Spearman's tests as appropriate ($p<0.01$).

Results: (1) Compared to CON, at rest with eyes closed, decreased relative alpha, and increased relative theta and beta frequencies were found in SCZ, while reduced relative delta activity was found in MPD. (2) During the CPT, cognitive performance was poorer in SCZ and MPD compared to CON, with increased left central and parietal theta activity in MPD. (3) Compared to CON, P300 amplitude was attenuated in frontal-parietal regions in SCZ and in frontal

regions in MPD. (4) During the STROOP task, compared to CON there were increased errors of commission and reduced working memory, as well as decreased theta activity in frontal through to parietal regions in SCZ, while compared to MPD and CON there were delayed N170 and P300 ERP waveform latencies. (5) IFN-γ correlated negatively with CTD no cue P300 latency in SCZ but correlated positively with this measure in MPD. IL-12p70 correlated positively with CTD incongruent P300 amplitude in the right occipital cortex in MPD.

Conclusion: Impairments in cognitive function, including reduced attention and cognitive control in both SCZ and MPD are consistent with prior work, although this is one of the first studies to have directly compared the two disorders. Different resting state functional networks are altered in SCZ and MPD, suggesting that they are underpinned by different neurobiological mechanisms. The delayed N170 and P300 ERP waveform found in SCZ compared to MPD and CON indicates particularly impaired cognitive processing in this condition. There was preliminary evidence of an association between alterations in the P300 ERP waveform and some cytokines, but with different findings in SCZ and MPD, suggestive of differences in underlying (neuro) immune mechanisms. Taken together, these findings point to both overlap in and differences between SCZ and MPD, a conclusion consistent with other work. The results of this study show potential clinical applications to improve the diagnosis and treatment of individuals with SCZ or MPD that should be verified by further research.

Abbreviations

µl	Microliters
µV	Microvolts
5-HT	Serotonin
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxasolpropionic acid
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BMI	Body mass index
C3	Left central
C4	Right central
CDS	Calgary depression rating scale
cm	centimetres
CON	Healthy controls
CPT	Continuous performance task
CTD	Cued target detection task
DSM-5	The Diagnostic and Statistical Manual of Mental disorders 4th edition
DSM-IV	The Diagnostic and Statistical Manual of Mental disorders 5th edition
EDTA	Ethylenediaminetetraacetic acid
EEG	Electroencephalography
EOG	Electrooculography
ERP	Event-related potential
F3	Left frontal
F4	Right frontal
1st	First generation antipsychotic
Fp1	left prefrontal
Fp2	right prefrontal
GABA	Gamma-aminobutyric acid
GUI	Graphical user interface
HAMD	Hamilton depression rating scale
HREC	Human resource ethics committee
Hz	Hertz
ICA	Independent component analysis
IFN-y	Interferon-gamma

IL-10	Interleukin 10
IL-12p70	Interleukin 12
IL-1b	Interleukin 1 beta
IL-2	Interleukin 2
IL-3	Interleukin 3
IL-4	Interleukin 4
IL-5	Interleukin 5
IL-6	Interleukin 6
IL-8	Interleukin 8
KMSK	Kreek- McHugh- Schluger- Kellogg
mg	milligrams
MPD	Methamphetamine- induced psychotic disorder
msec	milliseconds
nm	nanometres
NMDA	N-methyl- D-aspartate
NONE	Patients not taking antipsychotics
O1	Left occipital
O2	Right occipital
P	Positive
P3	Left parietal
P4	Right parietal
PANSS	Positive and negative symptom scale
N	Negative
pg/ml	Picograms per millilitre
REC	Resting eyes closed
REO	Resting eyes open
RT	Room temperature
SCID-DSM-V	Structural clinical interview for diagnostic and statistical manual of mental disorders
SCZ	Schizophrenia
2nd	Second generation antipsychotics
TNF-a	Tumour necrosis factor-alpha
TNF-b	Tumour necrosis factor beta
VIGALL	Vigilance algorithm Leipzig

1 Neurophysiology of psychotic disorders: Review of the literature

1.1 Background to psychotic disorders

Schizophrenia and other psychotic disorders affect 1% of the world's population (Mandelli, Toscano, Porcelli, Fabbri, & Serretti, 2014; Rudolph et al., 2015). According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) classification of psychotic disorders, the psychotic disorder spectra comprises of several different disorders which is either inherited genetically or is triggered through environmental causes such as prior physical and/or mental trauma, genetic heritability and substance use or abuse (Mandelli et al., 2014; Quach, Lerch, Honnorat, Khanna, & Duchemin, 2016). Psychotic disorders often present with psychosis, a severe mental disorder defined as a functionally disruptive symptom of psychiatric, neurodevelopmental, and mental condition which affects the person's ability to make good judgements, alters the ability to think clearly, behave appropriately and understand reality (Serper & Berenbaum, 2008). Psychosis is comprised of positive symptoms, negative symptoms and general psychopathology (Pridmore, 2016; Serper & Berenbaum, 2008; Tandon et al., 2013). Positive symptoms include hallucinations, delusions, and formal thought disorder; negative symptoms include affect impairment, diminished emotional impairment, reduced facial emotion, reduced speech and movement, anhedonia, avolition and alogia; and impaired attention and cognitive dysfunction.

Methamphetamine-induced psychotic disorder (MPD) is a substance-induced psychotic disorder, which occurs in as many as 40% of methamphetamine-dependent users (Farrell, Marsden, Ali, & Ling, 2002; Mahoney, Kalechstein, De La Garza, & Newton, 2008; McKetin, McLaren, Lubman, & Hides, 2006), and further accounts for approximately 1 in 4 individuals diagnosed with schizophrenia (SCZ) (Murrie, Lappin, Large, & Sara, 2020). According to the DSM-5, MPD is derived from long-term use, intoxication or withdrawal of the drug methamphetamine (American Psychiatric Association, 2013). The clinical features of methamphetamine and other amphetamine drugs include persecutory delusions, facial blindness, body image distortion and tweaking. Methamphetamine users are typically between the ages of 15 and 30 years of age when the onset of psychosis occurs (Hermens, Lubman, Ward, Naismith, & Hickie, 2009). The use of methamphetamine is at record highs in Africa, the United States of America and Europe with up to 16 million people using methamphetamine (Breen et al., 2016). The high incidence of methamphetamine use is due to recreational use or individuals testing the product and ultimately enjoying the high and eventually becoming

addicted. However, the risk of psychosis through the use of recreational drugs is more pronounced after using methamphetamine (McKetin, Hickey, Devlin, & Lawrence, 2010; Pikalov et al., 2014).

1.2 Differences in schizophrenia and methamphetamine-induced psychotic disorder

As early as 1958, similarities between MPD and SCZ have been reported (Wearne & Cornish, 2018b). SCZ is characterized as a mental disorder with cognitive abnormalities including impairment of executive function (planning, problem-solving, and other higher-level thought processing), attention, working memory, episodic memory, language, perception, and motor processes (Weickert & Goldberg, 2005). It is difficult to differentiate between the presentation of MPD and SCZ (Srisurapanont et al., 2011), and this is particularly the case for the presentation of positive symptoms (Bramness et al., 2012; Medhus et al., 2015) and cognitive dysfunction (Jacobs, Fujii, Schiffman, & Bello, 2008; Scott et al., 2007).

Similarly to SCZ, methamphetamine users can also have the occurrence of psychotic episodes or periods of psychosis. After an initial diagnosis of MPD, if there is a second psychotic episode in the absence of methamphetamine, the individual's diagnosis is changed to SCZ, as per the DSM-5 diagnostic criteria (American Psychiatric Association, 2013). The diagnosis of MPD remains if episodes of psychosis coincide with methamphetamine use. Methamphetamine causes the user to have a sense of euphoria as well as hours of stimulation, excitation, alertness and feeling powerful due to the release of dopamine, norepinephrine, and epinephrine (Buxton & Dove, 2008). Dopamine is a neurotransmitter that is released by the central nervous system which is involved in the control of locomotion, cognition, and neuroendocrine secretion (Jaber, Robinson, Missale, & Caron, 1996). Users of methamphetamine also describe feeling increased libido, endless energy, and increased productivity. However, the effects of methamphetamine do not last and can contribute to feelings of anxiety and depression (Buxton & Dove, 2008). Tachyphylaxis occurs after long-term methamphetamine use, however, symptoms of psychosis have been noted in these long-term high-dosage users (Petit, Karila, & Chalmin, 2012). Long-term users tend to increase their does of methamphetamine. Increased doses of methamphetamine can cause damage to dopamine neurons however, it has been speculated that even clinically low doses may lead to atrophy in certain regions of the brain (Yu, Zhu, Shen, Bai, & Di, 2015).

1.3 Pathophysiology of schizophrenia and methamphetamine-induced psychotic disorder

Brain imaging research in recent years has focused on understanding the mechanisms which can help identify and diagnose psychotic disorders through structural and functional studies. These studies include brain imaging techniques relating to magnetic resonance imaging, functional magnetic resonance imaging, magnetic resonance spectroscopy, positron emission tomography, and single-photon emission computed tomography (Wiedemann, 2011). Results obtained from brain imaging studies have shown structural abnormalities in SCZ which can be linked to cognitive deficits, altered processing speed and executive functioning, and other schizophrenia-related symptoms (Karlsgodt, Sun, & Cannon, 2010). MRI has allowed detailed structural information of the brain to be seen, from neuronal cell bodies or grey matter to myelinated tracts or white matter (Bunge & Kahn, 2010). Structural brain abnormalities frequently found in SCZ have been related to reductions in brain matter volume. Reduced grey matter volume was found across the cortex, however, the most significant reductions were found across the frontal and temporal lobes (Hazlett et al., 2008). Distinct connectivity abnormalities were found through grey matter volume reductions in the middle frontal gyrus and medial frontal cortex (Jiang et al., 2019). Furthermore, reductions in grey matter volume, increased ventricle volume and altered white matter tracts were also found in SCZ (Vita, Peri, Silenzi, & Dieci, 2006). These studies indicate that structural abnormalities could contribute to the symptomology of SCZ (Karlsgodt et al., 2010).

The risk of psychosis in SCZ is often increased in individuals where symptoms are left untreated. Environmental and genetic risks are known influences for the development of a psychiatric illness. Studies conducted on patients who are clinically high risk for developing psychosis, were found to have reduced grey matter volume in the left post-central gyrus, bilateral para hippocampal gyri and left anterior cingulate cortex. This decrease in grey matter across the post-central gyrus and anterior cingulate cortex correlated with self-reported social impairment across the group (Lincoln & Hooker, 2014). Magnetic resonance imaging studies conducted on SCZ showed reductions in grey matter volume density and cortical surface area in patients with SCZ compared to genetically high- risk patients and controls (Xiaobo Li et al., 2012). Cortical thickness reduction in SCZ cross the frontal, temporal, and superior parietal lobe and several other limbic areas was found to be associated with psychotic symptoms (Oertel-Knöchel et al., 2013). Further, smaller volumes of the mediodorsal and pulvinar were found in SCZ compared to controls (Kemether et al., 2003). Among SCZ patients, decreased

activation within the thalamus, anterior nuclei and medial dorsal nucleus was observed (Andrews, Wang, Csernansky, Gado, & Barch, 2006).

Other symptoms of SCZ, such as cognitive impairments were found to be associated with structural brain abnormalities. Structural and abnormal cerebellar functional connectivity were found in brain regions associated with the dorsal attention network, default mode network and ventral attention network in SCZ compared to controls (Guo et al., 2018). Functional studies have seen correlates to the central and frontal cortex areas in SCZ. Strong correlations between insight and the frontal and central cortex were found to match the distribution of cortical volume in SCZ patients (Raij, Riekki, & Hari, 2012). Prefrontal cortex dysfunction in SCZ is well known. However, in the current literature on working memory response, the activation of the right dorsolateral prefrontal cortex in response to working memory has still not been seen in SCZ (Barch, Sheline, Csernansky, & Snyder, 2003). In other studies, the activation of the anterior cingulate cortex was found during a response to conflict. The anterior cingulate cortex is in the frontal and central cortex and is involved in the activation of working memory. A study involving a conflict based global and local task, resulted in the observation of anterior cingulate cortex activation in response to conflict. The anterior cingulate cortex was however also found to be activated through perceptual and semantic conflict processing which arose through global distractors presented in the local task (Weissman, Giesbrecht, Song, Mangun, & Woldorff, 2003).

Mounting literature on how methamphetamine interacts with the structure and chemistry of the human brain has emerged over recent years. Brain structural abnormalities were investigated in human subjects using methamphetamine. Studies using structural magnetic resonance imaging (Chang, Alicata, Ernst, & Volkow, 2007a; Heidari, Mahmoudzadeh-Sagheb, Shakiba, & Charkhat Gorgich, 2017), single photon emission computed tomography (Laruelle et al., 1996), and proton magnetic resonance spectroscopy (Ernst, Chang, Yee, & Speck, 2000) have suggested that methamphetamine produces detrimental effects. The selective damage which methamphetamine causes can result in atrophy to the medial temporal lobe and white matter due to altered modulation of myelination and changes to glial cells (Thompson et al., 2004). Methamphetamine-related neurocognitive impairment was found to be caused by frontostriatal and limbic abnormalities (Grant et al., 2012; Petit et al., 2012). A study conducted by Warton et al (2018), aimed to identify volumetric changes to the subcortical areas in the brains of new-borns who were exposed to methamphetamine prenatally (Warton et al., 2017). As hypothesized, they observed reduced volumes of the left and right caudate nuclei in individuals

exposed to methamphetamine in utero (Warton et al., 2017). Studies of white and grey matter volume in individuals using methamphetamine observed reduced hippocampal grey matter, reduced critical grey matter and increased white matter in the temporal and occipital regions (Thompson et al., 2004). Further differences were noted in the cingulate gyrus, subgenual cortex and paralimbic belts grey matter in methamphetamine abusers. However, more research needs to be conducted to completely distinguish these two disorders.

The present literature has presented many theories regarding the underlying cause of SCZ and other psychotic disorders. A 2010 study analysed SCZ to determine whether it is a neurodevelopmental or neurodegenerative disorder, or a complex combination of both (Gupta & Kulhara, 2010). Gupta and Kulhara (2010) discussed two different models that various studies were proposing. One model of SCZ is a neurodevelopmental disorder, where evidence was grouped as obstetric complications, genes, clinical signs of aberrant neurodevelopment and neuroimaging of first episode psychosis and childhood-onset schizophrenia, post-mortem neuropathological studies, and developmental proteins. This model was based on a proposed hypothesis of SCZ being a result of defective neural connectivity and altered biochemical functioning during embryonal and foetal development. The second model of SCZ is a neurodegenerative disorder, where evidence was grouped as total neuronal volume, neuronal structure, neurotrophins, second messenger system, metabolic changes, vascular changes, and neurotransmitter receptors. Despite presenting these theories, studies investigating the underlying mechanisms of schizophrenia are still lacking.

1.4 Neural networks involved in cognitive functioning

Neurotransmitters are involved in many processes of early human development. Neurotransmitters are known for their synaptic communication between neurons however, recent findings have shown neurotransmitters play a role in targeting neuron migration, and axon growth during neuron circuitry formation (Südhof, 2017). A neural circuit is formed when a population of neurons connect through synapses to conduct a specific function. The function and behaviour of these neurons are based on their specific connections formed with other neurons (Richter & Gjorgjieva, 2017). These neural circuits are formed by a highly motile structure at the tip of an extending axon or dendrite called a growth cone which directs the axon or dendrite. Growth cones react with signalling molecules and receptors which results in the complex and well-defined peripheral and central axonal pathways with the detailed synaptic circuitry we know today (Henley & Poo, 2011; Weiner, Jontes, & Burgess, 2013). The

activation of neurons occurs through neuronal connections which cause it to function globally and locally as a fine network which is associated with complex human perception, action and cognition (Kida, Tanaka, & Kakigi, 2016). Due to the nature of the current study, three main neural networks will be discussed. These neural networks include the default mode network, salience network and central executive network.

The default mode network is mainly active when an individual is in a wakeful state, such as when daydreaming or mind-wandering. The default mode network is also involved in emotion perception, the theory of the mind and morality (W. Li, Mai, & Liu, 2014). The default mode network comprises of the medial prefrontal cortex, posterior cingulate cortex, precuneus and the angular gyrus. The posterior cingulate cortex is a combination of attention with the information received from memory and perception. The precuneus is involved in attentional, visual, and sensorimotor information. The medial prefrontal cortex controls decision- making and the angular gyrus is involved in the connection between attention, perception, and memory recall. The default mode network is further divided into subsections including the dorsal medial subsection which is associated with social-related thoughts and the medial temporal subsection is associated with memory and somatosensory information. Studies on the default mode network revealed an increase in activity during self-reflection-based tasks with eyes closed were noted compared to attention-based tasks (Raichle, 2015).

The salience network is involved in the switching between the default mode network and the central executive network. The salience network is composed of the anterior insula and dorsal anterior cingulate cortex, as well as the substantia nigra, ventral tegmental area, hypothalamus, amygdala, dorsomedial thalamus, and ventral striatum. The salience network functions to detect and filter incoming salient information and further recruit the relevant functional networks required. The salience network is associated with contributing to communication, social behaviour, and sensory, emotional, and cognitive information. Research revealed that the interactions between salience networks and nodes of multiple demands suggested salient information detection in the anterior insula is in a proportional manner to cognitive demand and individual capacity (McTeague et al., 2017). The insula plays an essential role in attention and working memory. Both the insula and anterior cingulate cortex share an important role in emotion regulation, autonomic regulation, and recognition of sensory input stimuli (Song et al., 2017). The salience network and central executive network are known to be dysfunctional in SCZ. Furthermore, it is known that in SCZ the interaction between the default mode network

and the central executive network has abnormal regulation during the completion of cognitively demanding tasks (Q. Chen et al., 2016).

The central executive network is also known as the frontoparietal network due to it being composed of the dorsolateral prefrontal cortex and posterior parietal cortex. The central executive network functions in sustained attention, problem-solving, working memory, goal-oriented tasks and executive function (Dai, Zhou, Xu, & Zuo, 2019). General task processing was found to be supported by the activation of the default mode network and central executive network (Oldehinkel et al., 2016). A study which investigated the effects of stress on the salience network and central executive network in SCZ siblings found decreased upregulation of the functional connectivity needed to cope with a stressor (van Leeuwen et al., 2020). This result could be due to other processes occurring during stress response or some resilience built towards it. Furthermore, studies relating to the neural networks within MPD are lacking (Lai et al., 2021) and from the few studies available, the focal groups are methamphetamine administration in mice (Hudson et al., 2022; Ni et al., 2022).

1.5 The role of neurotransmitters and the effects of medication in schizophrenia and methamphetamine-induced psychotic disorder

Over the past few years, more research into neurotransmission has been conducted on psychotic disorders and substance use/ abuse to understand the mechanisms underlying psychosis and modes of treatment (Kerner, 2009). Dopamine, serotonin, and glutamatergic neurotransmitters have all been linked to the pathophysiology of SCZ, and amphetamines (i.e. methamphetamine) were found to dysregulate multiple neural systems such as dopamine and serotonin release and reuptake (Halpin, Collins, & Yamamoto, 2014).

1.5.1 Dopamine

Dopamine is a neurotransmitter produced and released by the dopaminergic pathway via projection neurons in the brain. Executive functioning (Guzman & Farinde, 2016), reward system (Brisch, 2014; Guzman & Farinde, 2016), control of muscle movement (Jibson, 2017), and neuroendocrine control (e.g. immune regulation) (Hodo, de Aquino, Shimamoto, & Shanker, 2020) are all functions of the dopaminergic pathway (Gurevicha, Gainetdinov, & Gurevich, 2016). Over the years, research on the dopaminergic system has led to many theories regarding the association between the dopamine pathway and the structure and functioning of brain. One dopamine hypothesis suggests psychosis arises from imbalances in the dopaminergic neuronal pathways or mesolimbic pathway which connects to the ventral

tegmental area and prefrontal cortex (Kerner, 2009). Another theory suggested that SCZ is a result of excess dopamine particularly in the mesolimbic and striatal brain regions, resulting in positive symptoms and decreased dopamine in the prefrontal cortical regions resulting in negative symptoms (Lang, Puls, Müller, Strutz-Seebohm, & Gallinat, 2007). Other theories regarding the dopaminergic system in SCZ are based on the release of dopamine in response to rewards resulting in emotional salience (van Os & Kapur, 2009). However, more research is needed on the involvement of dopamine in cognitive dysfunction.

Studies have shown that cognitive impairment is associated with increased binding of dopamine at dopamine 1 receptors in the prefrontal cortex in SCZ (Brisch, 2014; Li, L. Snyder, & E. Vanover, 2016). The increased concentration of dopamine results in the activation of the brain's consciousness to focus and attend to stimuli (Yanofski, 2010). An increase in dopamine synthesis, dopamine release and resting-state dopamine concentrations were found in acute SCZ (van Os & Kapur, 2009). Furthermore, a diagnosis of SCZ was associated with structural brain alterations and changes in dopamine neurotransmission (Lang et al., 2007). Symptoms of psychosis in SCZ were also seen in methamphetamine users, where psychosis was found to be associated with methamphetamine use (Kerner, 2009). This was based on research showing that amphetamines reverse dopamine transport and block dopamine transporters leading to psychotic symptoms.

The dopaminergic system is one of the primary systems affected by methamphetamine (Hsieh, Stein, & Howells, 2014). Methamphetamine functions by displacing dopamine at dopamine receptors as it has a higher affinity (Jaber et al., 1996; M. Paulus, 2017). Methamphetamine forms a stronger bond at the dopamine receptors site causing excessive dopamine levels. Overactivation of the dopamine system has detrimental effects as it can lead to increased glutamate release which can then induce an excitotoxic state via excessive N-methyl-D-aspartate receptor activation. This further leads to damage to dopaminergic neurons and their receptors and in the long term reduces the efficacy of dopamine neurotransmission, however, the exact mode of action is unclear (Hedges et al., 2018).

1.5.2 Serotonin

Serotonin or hydroxytryptamine (5-HT) has been linked to the modulation of sleep, mood, and wakefulness (D. L. Murphy et al., 1998). 5-HT is produced by the 5-HT pathway which starts from the pons and the midbrain, and projects to the cortex and limbic area of the brain. The dorsal raphe nuclei and median raphe nuclei form part of the serotonin pathway, where

serotonergic neurons are most abundant (Fischer & Ullsperger, 2017). The dorsal raphe nucleicontrol functions such as learning, memory and affect, whereas the median raphe nuclei modulate long-term memory and emotional processing (W. Huang, Ikemoto, & Wang, 2022). Although serotonergic neurons are abundant in the dorsal raphe nuclei, the remaining neurons form part of the gamma-aminobutyric (GABA)-ergic pathway and glutamatergic pathway. The 5-HT released in the raphe nuclei of the brain stem prompts the dopamine neurons in the midbrain (Di Giovanni, Esposito, & Di Matteo, 2010). However, 5-HT released in the midbrain has an inhibitory effect on dopamine in the mesolimbic area of the brain. Furthermore, 5-HT modulates the dopaminergic system by altering the GABAergic and glutamatergic systems to the ventral tegmental area and substantia nigra pars compacta. Dysfunction of the 5-HT pathway and dopamine transmission was found to be linked to the pathophysiology of psychiatric disorders including those involved in drug abuse, depression, and SCZ (Di Giovanni et al., 2010).

The 5-HT hypothesis for SCZ states that the disease is a result of excessive 5-HT levels, caused by chronic stress, in the anterior cingulate cortex and dorsolateral frontal lobe (Eggers, 2013). This hypothesis along with many others, has led to questions regarding the mechanisms at a cellular level. Furthermore, by introducing substances such as Lysergic acid diethylamide which binds to serotonin receptors or antipsychotic medication, altered 5-HT serotonin can occur and can have acute effects on an individual. However, researchers have debated whether hallucinogenic substances are the best way to study psychosis present in SCZ (Quednow & Geyer, 2009).

5-HT dysfunction in SCZ has been widely studied across blood platelet research, cerebrospinal fluid, and post-mortem research (Abi-Dargham, Laruelle, Aghajanian, Charney, & Krystal, 1997). 5-HT concentrations varied from increases in 5-HT concentration to decreased levels of 5-HT, to no significant changes in 5-HT concentration in SCZ compared to healthy controls (CON) (Mohammadi, Rashidi, & Amooeian, 2018). An increase in 5-HT in the brain can result in a decrease in arousal and decreased 5-HT levels have been associated with depression and hallucinations. The decreased 5-HT levels can result from fast reuptake of serotonin or an increase in monoamine oxidase B which functions to metabolize serotonin into melatonin, which is responsible for sleep cycles (Palego, Betti, Rossi, & Giannaccini, 2016). It was also shown that abnormalities in the function of 5-HT receptors are present in SCZ. These abnormalities present in SCZ are a reduction in receptor function in the prefrontal cortex when compared to CON (Geyer & Vollenweider, 2008). The literature presents that altered serotonin

levels in SCZ can affect sleep cycles and arousal levels, however, the effects of methamphetamine on the 5-HT pathway have mostly been studied in mice.

The effects of amphetamines including methamphetamine on 5-HT is often studied using 5-HT_{1A} receptor knockout mice (Jaehne, Ameti, Paiva, & van den Buuse, 2017). A study in 5-HT_{1A} knockout mice showed that psychosis-associated behaviour was not caused by chronic methamphetamine use (Mohammadi et al., 2018). Further, it was found that methamphetamine use causes a reduction in the level of serotonin transporters and can result in an increase in memory deficits (Tellez, Rocha, Castillo, & Meneses, 2010).

Dysfunction of the serotonin pathway can have vast effects on the modulation of other neurotransmitter systems. Serotonin modulates glutamate and GABA at a presynaptic level, and the modulation of glutamate occurs through the activation of the 5-HT1A, 5-HT1B and 5-HT6 receptors. This activation of the 5-HT3 receptors promotes synaptic GABA release (Ciranna, 2006). However, further investigation is needed to identify the mechanisms involved in the modulation of serotonin in human subjects.

1.5.3 Glutamate and Gamma-aminobutyric acid

Glutamate is a non-essential amino acid neurotransmitter which is the most abundant excitatory neurotransmitter in the central nervous system (Takahashi, Foster, & Lin, 2015). Glutamate plays a role in synaptic plasticity, learning and memory. Glutamate also modulates synaptogenesis during foetal development and the formation of growth cones. Due to the importance of glutamate transmission in the central nervous system, the modulation of its' release, uptake, metabolism and signalling is tightly regulated (Miladinovic, Nashed, & Singh, 2015). Glutamate transmission requires the involvement of various receptors and transporters. These receptors include the α-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid (AMPA) receptor, N-methyl-D-aspartate (NMDA) receptor and metabotropic glutamate receptors (Simeone, Sanchez, & Rho, 2004). NMDA receptors are ionic receptors which are activated when glycine and glutamate attach to them (Kerner, 2009). AMPA receptors are ionotropic receptors which aid in the fast synaptic transmission of glutamate into the central nervous system. Metabotropic glutamate receptors are G-protein receptors which inhibit glutamatergic transmission (Crupi, Impellizzeri, & Cuzzocrea, 2019). The glutamatergic receptors can be found throughout the brain and spinal cord. The glutamatergic pathway connects the ventral tegmental area and nucleus accumbens to the prefrontal cortex (Kerner, 2009).

Glutamatergic transmission and dopaminergic transmission in SCZ are widely studied (Rubio, Drummond, & Meador-Woodruff, 2012). Studies have shown increased levels of glutamate in the basal ganglia, hippocampal and prefrontal cortex (Miladinovic et al., 2015). The glutamatergic hypothesis for SCZ suggests that SCZ is the result of the hypofunction of glutamate in the cortico-striatal projections opening the thalamocortical loop and resulting in an increase in sensory flooding. This results in psychotic symptoms and changes in dopamine concentration (Lang et al., 2007). These changes to the glutamatergic pathway may also be found in methamphetamine users. It was found that methamphetamine toxicity increases glutamate concentration, which can cause apoptosis and neuronal cell death and can result in intellectual disability and memory-related illnesses such as Alzheimer's disease (Kerdsan, Thanoi, & Nudmamud-Thanoi, 2009). A decrease in glutamate concentration can result in the failure of glutamate receptor activation and ultimately glutamate receptor expression, ultimately causing an individual to feel mentally exhausted, and have issues with concentrating (Kerdsan et al., 2009). Interactions of dopamine and glutamate in the nucleus accumbens are suggested to play a role in drug dependence, sensitization, and psychosis (Miyazaki et al., 2013). Research on the effects of methamphetamine on the glutamatergic pathway revealed increases in extracellular glutamate concentration (Stephans & Yamamoto, 1994).

Glutamate is a known precursor for the neurotransmitter GABA. GABA is an inhibitory neurotransmitter which functions to reduce neuronal activity and plays a role in motor control, vision, and other cortical functions (Wearne & Cornish, 2018b). The GABAergic pathway was found to regulate neuronal excitability in the prefrontal cortex. The regulation of GABA is controlled through GABA synthesis, release, reuptake, and metabolism. GABA synthesis occurs through the decarboxylation of glutamate. Two types of GABA receptors are known to be involved in GABA neurotransmission: $GABA_A$ receptors and $GABA_B$ receptors. $GABA_A$ receptors are ionotropic receptors which function to inhibit GABA neurotransmission (Bak, Schousboe, & Waagepetersen, 2006). $GABA_B$ receptors are metabotropic receptors which function to slow synaptic transmission through inhibiting postsynaptic pathways (Wearne & Cornish, 2018b).

The GABAergic hypothesis for SCZ suggests that a neurotransmitter imbalance (i.e. reduced GABA and increased glutamate) disrupts the modulation between the inhibitory GABAergic neurons and the excitatory glutamatergic neurons (Lang et al., 2007). It was proposed that GABAergic neurons control the neural circuits involved in behavioural response and that GABA transmission dysfunction results in the symptoms seen in SCZ (Blatt, 2005). Studies

have shown increases in GABA binding to GABA receptors and decrease in GABA synthesis in SCZ (D. Stan & A. Lewis, 2012). It was also revealed that there is a disruption of GABA neurotransmission in the dorsolateral prefrontal cortex in SCZ. The dorsolateral prefrontal cortex is known to be involved in working memory, which is often dysfunctional in SCZ patients (Bolkan et al., 2017). Further research into understanding the effects of methamphetamine on neurotransmitter systems has revealed a reduction in GABA levels in the prefrontal cortex. These reduced GABA levels in the prefrontal cortex are said to be caused by increased GABA metabolism (Wearne & Cornish, 2018b). It is important to note that experiments with GABA receptor antagonists have been conducted in order to help improve cognition deficits in SCZ (Munoz et al., 2016). However, past research on GABA receptor antagonists resulted in motor relaxation and heavy sedation (Enna, 1997; Lewis, Volk, & Hashimoto, 2004).

1.5.4 Acetylcholine

Acetylcholine is the primary neurotransmitter in the parasympathetic nervous system. It functions as both a neurotransmitter and a neuromodulator. Acetylcholine plays a role in arousal, attention, memory, and motivation. Acetylcholine is an excitatory neurotransmitter which is present in the striatum (Vetrivelan, Qiu, Chang, & Lu, 2010). Both dopamine and GABA interact with acetylcholine in the striatum. GABA inhibits the excitatory effects of acetylcholine in cholinergic interneurons whereas dopamine levels are increased as acetylcholine is released (Brisch, 2014). In the central nervous system, the cholinergic system projects from the basal ganglia to the cerebral cortex and hippocampus to control the cognitive functions within those areas. In the parasympathetic nervous system, the cholinergic system plays a role in controlling muscle activation and is a signal transducer for the autonomic nervous system.

Acetylcholine binds to two different receptors in the central nervous system and parasympathetic nervous system to control different mechanisms. These receptors are ionotropic nicotinic receptors, and metabotropic muscarinic receptors (Dean, 2002). It is often noted in studies that a large percentage of SCZ patients are heavy smokers. Nicotine plays a role in regulating a dysfunctional mesolimbic dopamine system by increasing dopamine concentration. The increased dopamine helps to reduce the positive and negative symptoms found in SCZ (Jiloha, 2008). The acetylcholine system plays a role in the dopaminergic reward system (Jiloha, 2008) and aids in reorienting visual spatial attention (Thiele & Bellgrove, 2018). Post-mortem studies have revealed decreased nicotinic receptors in the hippocampus,

cortex and caudate in SCZ. However, in the case of SCZ patients who smoke, decreased levels of nicotinic receptors were found compared to increased levels of nicotinic receptors found in controls who smoked cigarettes (Dean, 2002). In another study, similar results of decreased nicotinic receptors were found in the hippocampus and thalamic nuclei in SCZ (Perkovic et al., 2017). Furthermore, muscarinic receptors were found to be downregulated in SCZ.

Studies on the cholinergic system in the basal ganglia revealed the interaction of orexin, a neuropeptide regulating arousal and attention, and acetylcholine may affect the arousal and attention deficits found in drug addiction and age-related cognitive decline (Fadel & Burk, 2010). In another study, orexin was found to increase the production of acetylcholine in the cerebral cortex, thus promoting attention (Villano et al., 2017). However, too high a level of acetylcholine at neuromuscular synapses can result in nicotinic and muscarinic toxicity (Adeyinka, Kondamudi, Brooklyn, & Brooklyn, 2009). These cognitive deficits including motor control could potentially be managed with the use of antipsychotic medication administration (Weickert & Goldberg, 2005).

1.5.5 Medication effects

Currently, the treatment available to both SCZ and MPD patients is to manage symptoms by manipulating neurotransmitter function. The most studied pharmacological treatment of SCZ was based on the functioning of the dopaminergic system. These dopamine treatments were focused on whether the dopamine levels were too high or too low in the brain (Yanofski, 2010). Dopamine 2 receptor dysfunction was shown to increase dopamine concentration in psychiatric disorders such as SCZ and depression (Schwalbe, Kaindl, Hübner, & Gmeiner, 2017). This was supported by the remission of psychotic symptoms with the administration of typical antipsychotics and atypical antipsychotics which selectively block the dopamine 2 postsynaptic receptors in the brain (Sampaio et al., 2017). Most typical antipsychotic prescriptions function by blocking dopamine 2 receptors to effectively target positive symptoms of SCZ. However blocking dopamine 2 receptors can result in low dopamine levels in the brain thus resulting in negative symptoms of SCZ (P. Li et al., 2016). The treatments which cause negative effects in SCZ may be useful in the treatment of the symptoms produced by methamphetamine use. Dopamine uptake blockers and dopamine receptor antagonists aid in protecting a user of methamphetamine from methamphetamine-induced neurotoxicity (Stephans & Yamamoto, 1994).

Medication was found to have negative effects on cognition when comparing SCZ patients using medication to those who were medication-naïve or were not using any forms of pharmacological support (Rehse et al., 2016). Further, in SCZ, worsening cognitive function was found after the administration of 15mg of haloperidol (Babin et al., 2011). One form of treatment was looking at GABA-based therapy to help with cognitive impairments in SCZ (D. Stan & A. Lewis, 2012). In another study, serotonin antagonists improved cognitive function in SCZ (Quednow & Geyer, 2009). EEG activity, specifically alpha activity, was shown to be altered by antipsychotic medication (Blume, 2006). Widespread increases in theta activity in psychotic patients prescribed antipsychotic medication (Knott, Labelle, Jones, & Mahoney, 2001). Some studies have found medication to have negative effects on cognition in SCZ patients using medication and those who were not using medication (Rehse et al., 2016). Unfortunately, we do not fully understand the exact mechanisms which underlie cognitive symptoms found in psychosis, and further studies are needed to investigate these treatment effects. However, the research conducted to understand the underlying mechanisms of cognitive dysfunction is still ongoing, in both clinical research and through animal models (Emilien, Maloteaux, Geurts, Hoogenberg, & Cragg, 1999; Harvey, 2011; Weiss, Bilder, & Fleischhacker, 2002).

1.6 Cognitive function in schizophrenia and methamphetamine-induced psychotic disorder

Cognitive impairment in SCZ has been widely studied and is seen as a primary limitation for individuals to integrate into society (Hill, Bishop, Palumbo, & Sweeney, 2010; Trivedi, 2006). Impaired cognitive performance was labelled as a marker for distinguishing individuals who are at risk for developing SCZ (Lesh, Niendam, Minzenberg, & Carter, 2011). The cognitive deficits seen in SCZ include delayed memory recall, reduced processing speed, poor attention and concentration and impaired executive functioning (Harvey, 2011). These cognitive deficits were found to be associated with the negative symptoms of SCZ (Nielsen et al., 2015), and have also been linked to various regions of the brain. One of these brain regions is the prefrontal cortex, where dysfunction of the prefrontal cortex is often observed in SCZ with a variety of cognitive impairments including working memory deficits (Bolkan et al., 2017).

Brain areas that are often associated with cognitive deficits are the frontal and parietal areas. The frontal lobe, including areas such as the dorsolateral prefrontal cortex, lateral orbitofrontal cortex and the anterior cingulate and medial orbitofrontal cortices are involved in planning, working memory, attention and emotion regulation (Bonelli & Cummings, 2007). The frontal

lobe is also associated with executive functioning, reasoning, and problem-solving (Dias, Butler, Hoptman, & Javitt, 2011). Patients with frontal lobe impairment often have difficulty completing goal-directed tasks (E. K. Miller & Cohen, 2001). The parietal area is associated with perception of stimuli, word recognition and association, and orientation. Research has revealed that deficits residing from the parietal lobe has led to failure in recognizing salient information.

Research into the mechanisms involved in SCZ showed decreased activation of the bilateral dorsolateral prefrontal cortex, anterior cingulate cortex and mediodorsal thalamus for executive functioning (Lesh et al., 2011). Executive function is associated with cognitive regulatory systems or executive control systems which are spread across the frontoparietal network, including the dorsolateral and dorsomedial prefrontal cortex and posterior parietal cortex (Jaworska et al., 2018). Executive functions can be divided into three sections which have varying functions: inhibitory control, working memory and cognitive flexibility (Etkin, Gyurak, & O'Hara, 2013).

In SCZ, a decrease in connectivity between the prefrontal cortex and working memory was found to be related to deficits in the central executive component of working memory (H.-L. S. Wang, Rau, Li, Chen, & Yu, 2015). Working memory is involved in the temporary storage and manipulation of limited amounts of information (Featherstone, Kapur, & Fletcher, 2007), and is important for executive functioning (Andre, Picchioni, Zhang, & Toulopoulou, 2015). Working memory tasks such as the Stroop task have been used to assess impairments within SCZ. Delays in response times and more errors being made have been noted in SCZ as opposed to healthy controls (Sidse Marie Arnfred, Hemmingsen, & Parnas, 2006). However, despite working memory deficits resulting in poor cognitive performance in SCZ, there are more underlying factors which contribute to the deficits seen.

Changes in dopamine transmission in the thalamus and striatum are involved in the decline of cognitive performance, specifically in working memory and visual attention (Koob & Volkow, 2010). In SCZ, executive function deficits are said to result from a failure of dopamine release signals (Weinstein et al., 2017), where reduced dopamine activity in the prefrontal cortex was shown to be associated with impaired working memory and negative symptoms in SCZ (Gibert-Rahola & Villena-Rodriguez, 2014). Proper working memory function is dependent on dopamine modulation in the prefrontal cortex (Featherstone et al., 2007). It was found that dopaminergic and serotonergic neurotransmitter systems are linked to impulsive behaviour

(Atmaca, 2014; Blum et al., 2008), and it was suggested that antipsychotic medication influenced impulsive behaviour in SCZ (Hoptman, 2015). Altering neurotransmitter modulation can influence neurotransmitter levels. It was found that decreased serotonin levels can increase risky decision-making (Cools, Nakamura, & Daw, 2011).

Noting the importance of dopamine transmission modulation in the prefrontal cortex, amphetamines were shown to disrupt dopamine modulation resulting in working memory dysfunction (Featherstone et al., 2007). Similar research has been conducted on the effects of methamphetamine on cognitive functioning however, more information is needed to understand the mechanisms involved as research has revealed contradictory results (Hart, Marvin, Silver, & Smith, 2012; M. Paulus, 2017; Scott et al., 2007). Methamphetamine is associated with deficits in impulse control, working memory, decision-making, attention and motor coordination (Halpin et al., 2014). A study with methamphetamine-dependent users, who completed a decision-making task, showed that these users had increased blood flow to the orbitofrontal cortex, dorsolateral prefrontal cortex, anterior cingulate cortex and parietal cortex compared to controls (M. P. Paulus, Hozack, Frank, Brown, & Schuckit, 2003). Methamphetamine has been shown to cause atrophy of the anterior cingulate cortex and orbitofrontal cortex which can have adverse effects on the ability to make advantageous decisions (Chapman, Hanson, Kesner, & Keefe, 2001; Ruan et al., 2018).

The anterior cingulate cortex, which is located within the frontal lobe, was previously found to be involved in decision-making, attention, error detection and modulation of emotional responses (Bush, Luu, & Posner, 2000; Pardo, Pardo, Janer, & Raichle, 1990; Weissman, Gopalakrishnan, Hazlett, & Woldorff, 2005). Decision-making is a cognitive process which involves the selection of options given. According to the National Institute of Mental Health, decision-making is part of the positive valence system which is responsible for reward-seeking behaviour and reward or habit learning (Schlochtermeier et al., 2013; The National Institute of Mental Health, 2015). Multiple brain regions are involved in decision-making, these are the anterior cingulate cortex, orbitofrontal cortex, and ventromedial prefrontal cortex (Medford & Critchley, 2010). The activity of the anterior cingulate cortex was found to increase with task difficulty in SCZ (O'Connell et al., 2007).

Studies which recruited CON, SCZ and MPD observed frontal lobe dysfunction in both SCZ and MPD (Ezzatpanah, Shariat, & Tehrani-Doost, 2014; Shin et al., 2017; Thompson et al., 2004). SCZ had a subtle variation in the parietal cortex in SCZ as opposed to MPD (Ezzatpanah

et al., 2014). In another study, no difference was found for SCZ and MPD in tasks relating to verbal memory, working memory, motor speed, verbal fluency, attention, information processing speed, executive functioning, and total cognitive ability (Wearne & Cornish, 2018b). Further, studies relating to event-related potentials found enhanced error-related amplitudes have been linked to increased working memory span scores, indicating that increased working memory may increase total capacity for conflicting response options (Larson, Clayson, & Clawson, 2014). These event-related potentials also allow for studying attention while assessing working memory.

1.6.1 Attention

Attention and working memory were found to be essential in cognitive control and goal-directed behaviour (Slotboom et al., 2017). Attention is described as an operational series arranged from central control of goals and tasks in the prefrontal cortex to the mid-level translation of goals in the dorsal brain and then to peripheral representations in the posterior cortex (Tamber-Rosenau & Marois, 2016). Attention is suggested to be a selective process where stimulus representations are transferred between sensory memory and working memory to further contribute to the processing of information once the information is in the working memory (Sciarini, Grubb, & Fatolitis, 2014). Attentional control is modulated through the basal ganglia which includes the globus pallidus, putamen, and caudate nucleus (Ikuta et al., 2014).

The frontoparietal network is activated during object orienting, working memory and attention. It was hypothesized that the frontal-parietal network is a multiple-demand system which is supported by the orientation network (Roiser et al., 2013). The ability to recognize and decide what information in the environment can be ignored or what needs tending to be called attentional control. SCZ generally have deficits in attentional control (Ikuta et al., 2014). Further literature revealed methamphetamine use and abuse had reduced the ability to maintain attentional control and impaired decision-making (Mizoguchi & Yamada, 2019).

Attention is modulated through top-down or stimulus-driven attention, and bottom-up or goal-directed attention (Pinto, Leij, Sligte, Lamme, & Scholte, 2013). Normal attentional control is the ability to maintain top-down processing which is under the individuals' control (Ikuta et al., 2014). Two cases of attention exist; normal where attention helps filter out irrelevant information and abnormal where too much information is brought in causing stimulus competition or distractions resulting in a loss of information (Sciarini et al., 2014). Arousal changes are recorded through EEG which behavioural data can be extracted to measure

attention (Villano et al., 2017). With attention being a behavioural and cognitive process in attending to specific information, there are several neural networks which can be accessed via different tasks. These neural networks are models of attention and consist of three subsystems. The vigilance subsystem consists of the prefrontal and frontal cortex, thalamus and basal ganglia which controls sustained attention and arousal. The anterior attention system which consists of the anterior cingulate, basal ganglia and dorsolateral prefrontal cortex controls executive control, target detection and selective attention. Lastly, the posterior attention subsystem which consists of the parietal cortex, superior colliculus and pulvinar controls spatial attention (Villano et al., 2017). These subsystems are important in understanding cognitive functioning in SCZ and MPD.

1.6.1.1 Sustained attention

Sustained attention is a type of attention which can be described as the ability to maintain focus on a specific stimulus within a task (Featherstone et al., 2007). Sustained attention is labelled as top-down attention (Pinto et al., 2013), and is controlled by elaborated processing (Shipp, 2004). Sustained attention is suggested to be based on the mindfulness theory which states that any errors created within sustained attentional tasks are a result of an internal shifting of focus to thoughts (Helton, Kern, & Walker, 2009). Sustained attention is tested through tasks which have stimuli presented infrequently between non-stimuli (Dillard et al., 2014). The issue with sustained attention is the increase in mental fatigue resulting in decreased attention over time (Reteig, van den Brink, Prinssen, Cohen, & Slagter, 2019).

Two different attentional processes aid in detecting the target stimuli in an attention-based task, dorsal (sustained) and ventral (salience) attentional networks. The dorsal network includes the inferior frontal junction, medial intraparietal sulcus, superior parietal lobule and middle temporal area. The ventral attentional network includes the temporal parietal junction, anterior insula, anterior middle frontal gyrus, bilateral anterior cingulate cortex, and supplementary motor area (Jonathan K. Wynn et al., 2015). The basal ganglia were found to be involved in reaction time, cognition, emotion regulation and voluntary movement (Gruendler, Ullsperger, & Huster, 2011). The basal ganglia consist of a mesolimbic pathway which interacts with the prefrontal cortex to control attentional processing and is involved in reward processing (Van Schouwenburg, Den Ouden, & Cools, 2015). Reward processing is supported by the default mode network, frontal-parietal, lateral visual and salient networks (Oldehinkel et al., 2016). In a study which addressed the basal ganglia's role and sustained attention in first-episode psychosis, hyperactivation of the globus pallidus during attention-based tasks was found before

the initial psychotic episode (Ikuta et al., 2014). SCZ and at-risk individuals were shown to exhibit a decline in sustained attention (Liu, Chen, Chang, & Lin, 2000). This decline could be a result of dysconnectivity in the frontoparietal network in SCZ (Roiser et al., 2013). A study conducted by Ezzatpanah and colleagues found that both MPD and SCZ had deficits in selective and sustained attention, as well as deficits in executive functioning and impaired memory (Ezzatpanah et al., 2014). However, the impairments were found to be worse in SCZ.

1.6.1.2 Selective attention

Selective attention is a type of attention which refers to peripheral attentional mechanisms, including associations with working memory representations of sensory information (Tamber-Rosenau & Marois, 2016). Selective attention has different mechanisms which aid in prioritizing the processing of objects, events and locations which are indicated by two forms of attention: passive attention and active attention. Active attention reflects the intended effort needed to search for a target stimulus, whereas passive attention reflects the effort needed to capture the novelty and speed of a target stimulus (Schupp, Flaisch, Stockburger, & Junghöfer, 2006).

An electroencephalography study comparing SCZ to healthy controls showed controls had an increase in task-related theta than SCZ across the prefrontal, parietal, and occipital brain regions. The difference in task-related theta was due to patients who could process, and patients who could not process the unexpected event. SCZ also showed an increase in theta band activity during a resting-eyes open task compared to controls. There was no difference between groups in theta power values during the selective attention task (Hanslmayr et al., 2013). A study reporting age of onset of methamphetamine use contributed to increased attentional and motor impulsivity (Cservenka & Ray, 2017). However, research has shown education can have an impact on attentional control development, more specifically selective attention (Hampton Wray et al., 2017).

1.6.1.3 Spatial attention

Spatial attention is a type of attention controlled through a top-down and bottom-up mechanism (Shipp, 2004). Top-down is controlled by the frontoparietal cortex which sends information to the occipital-infero-temporal cortex. It is proposed that the subcortical circuit for the mediation of attention is influenced by the superior colliculus (mid-brain) and the pulvinar nucleus of the thalamus (Shipp, 2004). Spatial attention can be divided into two different areas: overt and covert orienting of attention. Overt orienting of attention is selectively attending to an object,

whereas covert orienting of attention is fixating the eyes on a central object while mentally shifting or attending to a different point or stimuli (Carrasco, 2018; Vossel, Geng, & Fink, 2014). Visual attention involves a process where relevant information is selected, while the irrelevant information is filtered out. The response to a cued stimulus in the visual cortex can occur between 80msec and 130msec after stimulus onset for cues which occur in either the left or right visual field. Methods to record an individual's response to a stimulus is through a technique called electroencephalography, where brain frequency activity and event-related potentials can be extracted.

1.7 Electroencephalography abnormalities in schizophrenia and methamphetamine-induced psychotic disorder

Electroencephalography (EEG) is a non-invasive functional imaging technique which allows for the measurement of the electrical activity of the brain (Kida et al., 2016). The electrical activity is caused by the energy emitted by the neurons firing in the brain (neuronal activity) (Bunge & Kahn, 2010). The first EEG on humans was conducted in 1924 by Dr. Hans Berger (Berger, 1929), and since then EEG has become one of the best methods to study neural circuits due to the ability to record and observe neural oscillations at multiple spatiotemporal scales (Cohen, 2017).

When an EEG is performed, the data is captured in real-time (Bunge & Kahn, 2010). The EEG trace is composed of mixed frequency bands of activity, which can be decomposed to provide discrete frequency bands of activity (i.e., alpha (α), beta (β), theta (θ), delta (δ) and gamma (γ)), this is also a representation of cortical arousal. Cortical arousal refers to the activation of the reticular formation of the brain which results in increased wakefulness, respiratory, heart rate and muscle tone. Cortical activity is increased the higher the electrical activity, from delta to gamma. Each frequency is labelled according to the number of waves found per second (Hz). Each frequency can be linked to a specific function. Delta frequency (0-4Hz) is detected during periods of wakefulness and sleep, such as through meditation, internal focus, prayer, and spiritual awareness. Theta frequency (4-8Hz) is detected during a test of visual imagery, hypnotic or hypoapoptic imagery and light sleep. Alpha frequency (8-13Hz) is a sign of the current physiological state of being awake, relaxed, drowsy or non-vigilant and non-focused (Busch, Dubois, & VanRullen, 2009). Beta frequency (13-30Hz) is detected when a person is awake, alert, and focused, during problem-solving and during rapid eye movement sleep. Gamma frequency is detected at 30Hz and above and is often seen during meditation,

neurostimulation, working memory, and attention, however, a notch filter will need to be used to block out any static, **Table 1.1**.

Table 1.1 Frequency and activity

Frequency	Activity	Wave
Delta (0-4Hz)	During periods of wakefulness and sleep, such as through meditation, internal focus, prayer, and spiritual awareness	
Theta (4–7Hz)	During a test of visual imagery, hypnotic or hypoapoptic imagery and light sleep	
Alpha (7–13Hz)	Current physiological state of being awake, relaxed, drowsy, or non-vigilant and non-focused	
Beta (13–30Hz)	Awake, alert, and focused, during problem-solving and during rapid eye movement sleep	
Gamma (30–80Hz)	During working memory, and attention	

EEG can reveal multiple neuronal activity patterns for certain regions of the scalp (Bunge & Kahn, 2010; Kida et al., 2016). Although this technique does not allow us to record directly from a brain area, it can however aid in distinguishing varying stages and states of arousal (Fleur M. Howells, Stein, & Russell, 2010). The stages and states of arousal refer to the brain's period of wakefulness. Wakefulness stages and states are based on the Vigilance Algorithm Leipzig (VIGALL) stages created to classify states in EEG recordings and corresponding behaviour (J. Huang et al., 2017). According to VIGALL, the behavioural states are divided into four different states; cognitively active wakefulness (i.e. VIGALL stage 0-desynchronized non-alpha EEG with no horizontal slow eye movements or active state; A1-dominant alpha activity in the occipital area), relaxed wakefulness (i.e. VIGALL stage A2-alpha shifts to frontal and central areas; A3-localization of alpha to the frontal area), drowsiness (i.e. VIGALL stage B1-decreased amplitude with desynchronized EEG with horizontal slow eye movements); B2 and B3-delta and theta are dominant), and lastly sleep onset (i.e. VIGALL stage C-K complex which is the presence of sharp negative peaks immediately followed by a strong positive peak). Wakefulness is a state-regulated by neurotransmitter systems, these are dopamine, serotonin, acetylcholine, norepinephrine, and histamine. When neurotransmitter systems are stimulated, cortical activity and alertness are produced resulting in the modulation of attention, consciousness, and information processing. Therefore, EEG can help guide us to

a better understanding of which neural circuits are active during behaviour (Bunge & Kahn, 2010).

Variations in electroencephalography (EEG) frequency activity are known in SCZ (Bunge & Kahn, 2010; Kida et al., 2016). However, variations in EEG frequency activity in MPD are lacking due to limited research (Fleur M. Howells et al., 2018), **Table 1.2**. Frequency (alpha, beta, theta, delta, and gamma) activity was compared in SCZ, during resting state tasks. The resting state tasks, resting eyes open (REO) and resting eyes closed (REC), revealed altered frequency activity in SCZ. Throughout the literature, increases in alpha, beta, theta, and delta were observed in SCZ (Ranlund et al., 2014). However, some studies obtained conflicting results showing decreased frequency activity for alpha in SCZ (Hirano & Uhlhaas, 2021). Delta and theta frequency activity were identified during REO (Soh et al., 2015), whereas contradicting results were found showing frequencies of 16 Hz or more were dominant during REO (Jaworska et al., 2018). Studies which had only focused on REO in SCZ found increased beta (Venables, Bernat, & Sponheim, 2009), increased theta (Hanslmayr et al., 2013), and increased delta (Ranlund et al., 2014). Further studies including SCZ, and MPD found increased delta and alpha activity in REO when compared to CON (Fleur M. Howells et al., 2018). Conflicting results were found for alpha frequency in SCZ compared to CON during REC where alpha was increased (Fleur M. Howells et al., 2018). Howells and colleagues also found increased REC alpha and delta in SCZ compared to MPD (Fleur M. Howells et al., 2018). In REC, SCZ had increased beta, theta, and gamma frequency (Andreou et al., 2015) and decreased alpha frequency (Goldstein, Peterson, Sanguinetti, Tononi, & Ferrarelli, 2015; J. W. Kim et al., 2015). The literature presents data showing altered frequency during resting states in SCZ and MPD, however further research shows that there are associations between altered frequency activity and cognitive functioning.

Table 1.2 Electroencephalography studies of resting state tasks

			Frequency bands				
		Participants	**Delta**	**Theta**	**Alpha**	**Beta**	**Symptom correlates**
Resting eyes open condition							
Hanslmayr et al., 2013		26 SCZ 26 CON	SCZ > CON	-	-	-	
Howells et al., 2018	*	28 SCZ 29CON	SCZ > CON	-	SCZ < CON	-	
Omori et al., 1995		20 SCZ 20 CON	-	SCZ > CON	SCZ > CON	-	
Venables et al., 2009		48 SCZ 61 SCZr 79 CON	SCZ > CON SCZ > SCZr	SCZ > CON SCZ > SCZr	SCZr < CON SCZ > SCZr	SCZr < CON	
Resting eyes closed condition							
Andreou et al, 2015		19 SCZ 23 CON	-	SCZ > CON	-	-	
Begić et al., 2011		30 SCZ 30 CON	SCZ > CON	SCZ > CON	SCZ < CON	SCZ > CON	
Begić et al., 2000		25 SCZp 22 SCZn 50 CON	SCZp < CON SCZn > CON	SCZn > CON	SCZp < CON SCZn < CON	SCZp > CON SCZn > CON	
Garakh et al. 2015		32 SCZ 40 CON	-	SCZ > CON	SCZ < CON	-	
Goldstein et al., 2015		13 SCZ, 13 CON	SCZ < CON	SCZ < CON	-	-	
Howells et al., 2018	*	28 SCZ 29CON	SCZ > CON	-	SCZ < CON	-	
Itoh et al., 2011		17 neuroleptic naive SCZ 17 CON	SCZ > CON	-	-	-	
John et al., 2009		28 neuroleptic naive SCZ 25 CON	SCZ > CON	SCZ > CON	SCZ > CON		PANSS showed characteristic spectral power profiles in the alpha, delta, and theta bands
Kam et al., 2013		132 SCZ 136 CON	SCZ > CON	-	SCZ > CON	SCZ > CON	
Kim et al, 2015		90 SCZ 90 CON	SCZ > CON	SCZ > CON	SCZ < CON	-	
Knyazeva et al, 2008		14 SCZ 14 CON	SCZ < CON	SCZ < CON	SCZ < CON	-	Negative correlation between PANSS and alpha in SCZ
Narayanan et al., 2014		225 SCZ 200 CON	SCZ > CON	SCZ > CON	SCZ > CON	-	Negative correlation between PANSS and alpha in SCZ

Omori et al., 1995	20 SCZ 20 CON	-	SCZ > CON	SCZ > CON	-
Razavi et al, 2013	11 SCZ 11 CON	SCZ > CON	SCZ > CON	SCZ < CON	SCZ > CON
Shreekantiah-Umesh et al, 2016	20 SCZ 20 CON	-	SCZ > CON	-	-
Veiga et al., 2003	25 SCZ 40 CON	SCZ > CON	SCZ > CON	-	-
Venables et al., 2009	48 SCZ 61 SCZr 79 CON	SCZ > CON SCZ > SCZr	SCZ > CON SCZ > SCZr	-	-

**Delta alpha ratio*

Abbreviations: Healthy controls (CON), Schizophrenia (SCZ), Schizophrenia presenting with positive symptoms only (SCZp), Schizophrenia presenting with negative symptoms only (SCZn), first relatives of schizophrenia patients (SCZr), Positive and negative symptom scale of schizophrenia (PANSS)

Further literature revealed associations between frequency abnormalities and brain region or structure. In SCZ, increased beta activity across the frontal-central region was found (Balaji Narayanan et al., 2014), and increased delta and theta frequency activity was found over the frontal regions (Begić, Hotujac, & Jokić-Begić, 2000). A study conducted on the resting state frequencies in SCZ observed significant differences compared to healthy controls. Another study showed increased delta and alpha frequency activity in SCZ compared to healthy controls, where SCZ presented increased synchronization across and within hemispheres (Kam, Bolbecker, O'Donnell, Hetrick, & Brenner, 2013). Further studies compared frequency activity in SCZ and schizoaffective individuals to CON. One such study found SCZ and schizoaffective individuals had increased midline theta, off-midline anterior beta and decreased central posterior alpha frequency power (Garakh et al., 2015). Another study revealed the SCZ spectra had altered frequency band oscillations (Boutros et al., 2008). Increased delta activity during REC was found in SCZ compared to CON (Goldstein et al., 2015). These alterations in delta and theta frequency band activity were found to correlate with genetic coding for brain development, neurogenesis, and synaptogenesis (Balaji Narayanan et al., 2016). Furthermore, a review conducted on delta frequency activity presented associations between delta frequency and, salience detection and attention (Knyazev, 2012). The results indicate that increased delta activity is associated with dysfunction in attention and within the brain reward system (i.e., the nucleus accumbens, medial prefrontal cortex and the nucleus reticularis thalami and ventral tegmental area).

Literature indicates strong correlations between increased alpha frequency across frontal regions and cognitive dysfunction in SCZ (Knyazeva et al., 2008). Negative symptoms in SCZ were found to correlate negatively with delta frequency activity in the left inferior temporal gyrus, right middle frontal gyrus, right superior frontal gyrus, right inferior frontal gyrus, and right parahippocampal gyrus (Itoh, Sumiyoshi, Higuchi, Suzuki, & Kawasaki, 2011). In a study comparing CON and SCZ, elevated levels of absolute power and positive correlations with the severity of psychopathology in the frontal-central and posterior regions were observed (Baradits et al., 2019). Results from a review assessing creativity and insight showed a lack of significance regarding beta frequency (Dietrich & Kanso, 2010). Decreases in alpha frequency activity found across regions may indicate alterations in cortical arousal and impaired attentional processing. Further, abnormal theta oscillations could indicate impaired working memory as a result of theta gamma coupling (Mitra, Nizamie, Goyal, & Tikka, 2017). The increased frequency of activity during resting states in SCZ has been suggested to relate to

dysfunction of the prefrontal cortex, which is a result of neural abnormalities (Venables et al., 2009). Thus, the altered frequency could indicate a possible phenotype for schizophrenia, however, the incorporation of event-related potentials can strengthen the results found when investigating cognitive functioning.

1.8 Event-related potential

Event-related potentials (ERPs) have been used for years to study the brain's direct response to specific stimuli. ERPs are defined by their positive (P) and negative peaks (N), and average record of time-locked stimuli during the completion of cognitive tasks (Hume et al., 2015; Ranlund et al., 2014; Tong, Lin, Xiao, & Ding, 2016). These peaks are a result of the excitatory and inhibitory postsynaptic potential caused by the release of neurotransmitters at the synapses of neurons (Hegerl, Gallinat, & Juckel, 2001). The goal of recording EEG and extracting ERPs is to collect information about the neural processes involved in the higher-order, complex cognitive operations, including attention (Gu, Ali, L ', Lacas, & Debruille, 2014).

ERP waveform components have been classified into two different types which represent sensory and cortical updating. Sensory ERP waveforms are seen after the brain processes a simple stimulus, such as during an auditory task. It is proposed that sensory ERP waveforms capture decision-making as it occurs, 0-100msec post-stimulus (Davies, Chang, & Gavin, 2010), and cognitive ERP waveform components occur after 100msec and have been associated with attentional processing and memory recognition (Sur & Sinha, 2009). Several different visual ERP components have been noted in the literature. The first visual ERP component, C1, occurs post-stimulus between 40 to 60msec and peaks at 80 to 100msec (S. A. Hillyard, 2002). The polarity of the C1 can either be a positive or negative waveform which can be seen in the primary visual cortex. The C1 is extremely sensitive to the contrast and frequency set for the stimuli.

The next visual ERP is the P100 ERP waveform component peaks between 70-130msec post-stimulus and is the largest peak in the lateral occipital area (S. A. Hillyard, 2002). Determining the onset of the P100 can be difficult, as there is a significant overlap between the C1 ERP waveform component. The P100 ERP waveform component is sensitive to the direction of spatial attention and state of arousal (S. a Hillyard & Anllo-Vento, 1998; Steven J. Luck, Woodman, & Vogel, 2000). The P100 and N100 were linked to activation in the dorsal (sustained) network, with no group differences in the level of activation (Jonathan K. Wynn et al., 2015). The N100 ERP waveform component follows after the P100 waveform component

and peaks between 150msec and 190msec (S. A. Hillyard, 2002). An increased amplitude of the P100 and N100 post-stimulus suggests spatial attention is exerted for a stimulus which is attended in the visual-cortical pathways (S. A. Hillyard, 2002). The P200 ERP waveform component peaks around anterior and central sites during tasks containing target stimuli.

The N170 ERP waveform component is a negative deflection which occurs approximately 170 msec after stimulus presentation (Feuerriegel, Churches, Hofmann, & Keage, 2015). The range in which the N170 ERP waveform component typically occurs is between 150msec to 200msec. The N170 was found to be right-lateralized (Hileman, Henderson, Mundy, Newell, & Jaime, 2011), however, there are instances where the N170 amplitude was found bilaterally in relation to expert or executive functioning.

The most widely studied ERP waveform component is the P300. The P300 waveform is a positive wave component which occurs approximately 300msecs after the presentation of a stimulus. The P300 ERP waveform component was found to represent updating of the working memory system. The P300 ERP waveform component is divided into two sections: P3a and P3b. The P3a is elicited for unexpected stimuli and represents the orienting response to a stimulus which is often reduced in patients with prefrontal injuries. The P3b is elicited by infrequent stimuli. The P300 waveform component was found to be associated with the activation of the salience network, including the anterior cingulate, anterior insula, and temporal parietal junction, where SCZ showed lower activation (Jonathan K. Wynn et al., 2015).

Many studies have investigated the ERPs present in audio and visual-related cognitive tasks, **Table 1.3**. These studies have observed wave components which include: P100, P150, N170 and P300.

Table 1.3 Event-related potential literature on schizophrenia and methamphetamine-induced psychotic disorder

			Event-related potential waveform				
	Participants	**Task**	**P100**	**N170**	**P200**	**P300**	**Symptom correlates**
Bates et al, 2002	21 SCZ 21 CON	Go/no-go	-	SCZ < CON	-	-	
Campanella et al, 2006	14 SCZ 7 CON	Visual face-detection task	SCZ < CON	SCZ < CON	-	-	Reduced N170 was positively correlated to positive symptoms
Lee et al, 2010	38 SCZ 38 CON	Facial affect processing	-	A SCZ < CON T SCZ > CON	T SCZ > CON	-	
Kirino, 2004	25 SCZ 25 CON	Continuous Performance Task	-	-	A SCZ < CON	-	
Roth et al, 2007	16 SCZ 16 CON	Auditory Go/Nogo task	-	-	-	A SCZ > CON T SCZ > CON	
Souza et al 1995	29 SCZ 27 CON	Auditory-National adult reading test (NART) Wechsler Adult Intelligence State (WAIS)				A SCZ < CON T SCZ > CON	
Wynn et al, 2015	21 SCZ 22 CON	Visual oddball task				A SCZ < CON	
Wynn et al, 2013	30 SCZ 30 CON	Facial Affect Processing		A SCZ < CON T SCZ > CON			
Yang et al, 2017	30 SCZ 30 CON	Facial emotion recognition task	A SCZ > CON				

Abbreviations: Healthy controls (CON), Schizophrenia (SCZ), Amplitude (A), Latency (T)

In reviewing the literature, differences in ERP waveforms are reported for SCZ during tasks assessing attentional processing. However, certain traits are often seen for SCZ such as delayed P300 latencies and attenuated amplitudes (Kuperberg, 2004). For the N170 and P300 ERP waveforms, associations were found between cognitive processes of perception and selective attention (Patel & Azzam, 2005).

The engagement of attention when updating working memory is shown by an increase in P300 amplitude with an increase in demand (Saliasi, Geerligs, Lorist, & Maurits, 2013). The P300 ERP waveform was suggested to be linked to salience network activation. When comparing SCZ to controls, SCZ had reduced activation of the salience network. It was also noted that the P100 and N100 ERP waveforms were associated with the activation of the sustained attentional network (Jonathan K. Wynn et al., 2015). Concluded remarks from a visual spatial attention study stated that N100 and P100 ERP waveforms could represent orienting attention and the facilitation of early processing (S.J. Luck, Heinze, Mangun, & Hillyard, 1990). Decreased N170 amplitudes were associated with a global deficit in visual processing in SCZ. The decreased amplitude for P100, N160 and P200 was seen as cortical gating (Sidse M. Arnfred, 2005). Studies unveiling knowledge of attentional cues have shown alterations in the ERP waveform which could potentially indicate dysregulation of systems such as the central noradrenergic system (Iwanami, Shinba, Sumi, Ozawa, & Yamamoto, 1995).

ERP waveform components show insight into attentional and emotional processing which occurs during the completion of specific tasks. ERP tasks are either auditory or visual-based tasks. Visual-based tasks have been widely used to assess emotional processing (Lee, Kim, Kim, & Bae, 2010; Minami, Nakajima, Changvisommid, & Nakauchi, 2015; J. K. Wynn, Jahshan, Altshuler, Glahn, & Green, 2013; Yang et al., 2017). Processing of facial cues depends on configural processing as opposed to facial feature processing. Processing of facial features has three different stages: first-order processing (i.e. processing the nose and eyes), holistic processing (i.e. seeing the face as a whole) and lastly second-order processing (i.e. seeing the characteristics of an individual's face) (Tsantani, Gray, & Cook, 2020). During visual face detection tasks, SCZ showed reduced P300 amplitudes and increased P300 latencies as a result of early visual processing involvement (Campanella, Montedoro, Streel, Verbanck, & Rosier, 2006). The N170 ERP waveform component was larger for blue-coloured faces compared to

neutral-coloured faces. Further, the N170 was larger for inverted natural-coloured faces compared to upright faces. Therefore, it was said that facial inversion is the hallmark of studying facial configuration as opposed to local featural processing (Minami et al., 2015; Nakajima, Minami, & Nakauchi, 2012). For SCZ the N170 amplitude was decreased during a facial affect task compared to controls. Facial affect processing was shown to be delayed in SCZ compared to controls, as seen by longer latencies for the N170 and P300 ERP waveform components (Lee et al., 2010). Decreased N170 and P300 amplitudes were associated with cortical gating and a global deficit in visual processing in SCZ (Sidse M. Arnfred, 2005). These cognitive impairments found within SCZ and MPD can further be investigated by assessing cognitive performance.

Markers reported for poor cognitive performance, including the P100, P200, N170 and P300 are being labelled as attention selection indicators and the P300 is an interpretation of the target stimuli (Sokhadze et al., 2017). Poor cognitive performance during the continuous performance task is a trait of SCZ (Stöber et al., 2009). Delayed reaction times in responding to target stimuli are often seen during attention-based tasks for SCZ (Larrison-Faucher, Briand, & Sereno, 2002). Despite the lack of information on MPD, it is evident that ERPs help understand cognition in SCZ and MPD. However, studies lack the effect medication and other influences such as inflammation have on cognitive performance within SCZ and MPD.

1.9 Neuroinflammation in schizophrenia and methamphetamine

Neuroinflammatory and immunological abnormalities have been a prime topic in understanding the biological mechanisms that are involved in psychiatric diseases (Najjar, Pearlman, Alper, Najjar, & Devinsky, 2013). Cytokines are small signalling proteins which aid in modulating immune responses and regulating the growth, maturation, and function of immune cells. Cytokines are produced by macrophages, B and T lymphocytes, mast cells, endothelial cells, fibroblasts, and stromal cells. Cytokines can be classified into interleukins (IL-), chemokines, interferons (IFN), lymphokines and tumour necrosis factors (TNF).

Several studies have investigated blood cytokine concentrations in SCZ (Momtazmanesh, Zare-Shahabadi, & Rezaei, 2019). Altered levels of peripheral cytokines IL-1β, IL-6, IL12-p70, soluble IL-2 receptor, TNF-α, and IFN-γ were found in patients diagnosed with SCZ (Radtke, Chapman, Hall, & Syed, 2017). Increased levels of proinflammatory cytokines IL-1β

and IL-6 have been found in SCZ (Reale, Costantini, & Greig, 2021). In another study, elevated levels of peripheral cytokines IL-1β, IL-6 and TNF-β were found in SCZ (Lesh et al., 2018). Further research identified that IL-1β, IL-6, and TNF-β are state markers in SCZ and IL-12, IFN-γ, and TNF-α are possible trait markers for SCZ (B. J. Miller, Buckley, Seabolt, Mellor, & Kirkpatrick, 2011). Trait markers refer to the behavioural properties and biological processes that play an important role in the predisposition of SCZ whereas state markers refer to the status of clinical manifestations in the patient. In a study conducted on amphetamine-dependent individuals presenting with psychosis, a similar increase in serum IL-5, IL-10, and TNF-α was found compared to controls. But when comparing amphetamine-dependent individuals presenting with psychosis with amphetamine-dependent individuals presenting without psychosis, decreased levels of IL-1β, IL-6, IL-8, and IFN-γ were found (Chang Kuo et al., 2018). However, the study by Chang and colleagues (2018) was conducted on women only, and they further concluded that future studies should be conducted to extend the study. These results show that there are cytokines specific to processes involved in SCZ, however, more information is needed to identify cytokines specific to the mechanisms underlying MPD.

More research has been conducted investigating the underlying mechanisms of cognitive impairments and their association with proinflammatory cytokines in SCZ and MPD. Current literature has found cognitive impairments were associated with (neuro) inflammation in SCZ, however, little information is known about MPD. In a study conducted by Maes and colleagues, cognitive functioning and the overall severity of SCZ were found to be mediated by TNF-α mediated immune-neurotoxicity (Maes et al., 2020). Another study by Dahan and colleagues (2018) found an increase in serum levels of IL-6, IL-2R and IL-8 in SCZ compared to controls. Furthermore, a positive association was found between the PANSS scale, measuring symptom severity, and the IL-6 in SCZ compared to controls (Dahan et al., 2018). The literature suggests that cognitive impairment is mediated by (neuro) inflammation in SCZ, however, in MPD further investigations are needed to understand if cognitive impairment is the result of (neuro) inflammation or a deeper underlying cause of the disorder itself.

In literature, methamphetamine use and abuse were found to cause severe changes in the regulation of cytokine expression. However, the exact mechanisms which underlie (neuro) inflammation in methamphetamine-induced psychosis are related to an interaction between

glial cells and methamphetamine-induced inflammation (Shi, Chen, & Zhao, 2022). Methamphetamine alters cytokine levels by causing an increase in TNF-α and a reduction in glial cells, ultimately affecting the immune system (Papageorgiou, Raza, Fraser, Nurgali, & Apostolopoulos, 2019). IL-1β concentrations in methamphetamine users were also found to be increased (Numachi et al., 2007). Furthermore, increased levels of IL-1β, IL-2, IL-6 and IL-8 were found after methamphetamine use (Papageorgiou et al., 2019).

Most research on neuroinflammation in SCZ needs to account for medication, as the medication prescribed to SCZ may contain anti-inflammatory properties, such as non-steroidal anti-inflammatory drugs (Pasternak, Kubicki, & Shenton, 2016; Radtke et al., 2017). The effects of antipsychotic medication on inflammation are dependent on whether the antipsychotic is atypical or typical. Typical antipsychotics decrease the levels of IL-1β, IL-6 and TNF-α in SCZ, whereas atypical antipsychotics increase inflammatory responses (Na, Jung, & Kim, 2014). In a meta-analysis conducted on drug-naïve first-episode psychosis, acute relapse of psychosis, and SCZ with treatment-resistant psychosis, increased levels of IL-1β, IL-6, TNF-α, IFN-γ, and IL-12 were found in patients diagnosed with first-episode psychosis and those with acute relapse of psychosis. Further, a decrease in IL-6, IL-1β, and IFN-γ and a rise in IL-12 concentration levels were found in patients under antipsychotic treatment (B. J. Miller et al., 2011). These results indicate that antipsychotic medication prescribed to SCZ patients significantly decreased levels of IL-1β, IL-6, TNF-α, and IFN-γ which is generally found to be increased. This suggested that by prescribing antipsychotics, (neuro) inflammation can be reduced and further lessen the effects of a psychotic episode.

Associations between immune function, EEG frequency band oscillations and ERP waveform components in SCZ have been explored (Balaji Narayanan et al., 2014, 2016). In a study by Miller and Goldsmith, the effects of (neuro) inflammation on attention specifically alerting, orienting and executive control was assessed. They found that in alerting attention inflammation produced an increase in cue-induced suppression of the alpha power (B. J. Miller & Goldsmith, 2017). It was also noted that inflammation did not affect the orienting or executive control attentional process (Balter et al., 2019). These studies suggest that (neuro) inflammation has adverse effects on the outcome of frequency activity for cued tasks. Brain imaging studies revealed inverse correlations between whole brain grey matter and IL-12 in

SCZ (Lesh et al., 2018). Lesh and colleagues (2018) suggested that the association between decreased brain grey matter and the increase in IL-1β, IL-6 and TNF-β could be involved in the aetiology of SCZ.

These results indicate the presence of cytokines abnormalities in SCZ disease. And further provide strong evidence of an association between inflammatory activity in SCZ and illness course (Rodrigues-Amorim et al., 2018).

1.10 Conclusion

Literature indicates that the underlying neurophysiological mechanisms involved in SCZ, and more so in MPD are still misunderstood. Several gaps have been noted, the first is that SCZ is known to have variations in EEG frequency activity. However, these variations in EEG frequency activity in MPD are lacking due to limited research. Second, although cognitive dysfunction, including executive function, attention and working memory in SCZ, is well known, literature on cognitive functioning in MPD is lacking. There are few studies which have presented both focal and peripheral attention in SCZ, and there is only limited research on sustained attention ERP waveforms in MPD. Third, decreased executive functioning due to frontal lobe dysfunction is a common problem in SCZ. Knowledge of working memory, executive functioning and conflict resolution is lacking in MPD, however, it can be assessed using the Stroop task. The Stroop task (Stroop, 1935), designed to identify executive functioning in frontal lobe dysfunction, will be used in this study. The Stroop task assesses selective attention, cognitive flexibility, processing speed and executive functioning directed to frontal lobe dysfunction. The Stroop task also measures the ability to suppress irrelevant information, which is one of the most used tests of inhibitory control in neuropsychiatric patients. It was found that chronic meth use is associated with poorer performance in the Stroop task in adolescents (A. A. Guerin et al., 2019). Lastly, the link between (neuro) inflammation and frequency/ ERPs are not yet known. It is important to understand the role inflammation plays in causing the cognitive decline in SCZ and MPD due to the impact it has on an individual's recovery before, during and after a psychotic episode. Current research on cytokine expression in SCZ has supported a new line of research to improve our neurobiological understanding of psychotic disorders. This research has not yet been translated into the serious epidemic of MPD. Further, the relationship between cytokine profiles and EEG,

frequency band activity and event-related potential activity, is largely absent in SCZ and completely absent in MPD. This thesis will address these gaps mentioned and will aid in understanding the neurophysiological mechanisms within SCZ and MPD.

1.11 Aims and objectives

The purpose of this thesis is to investigate the neurophysiological properties between SCZ and MPD to understand the overlapping and distinct mechanisms involved between these two psychotic disorders. It is important to understand the electrophysiological and associated immune mechanisms underlying psychosis, and cognitive impairments within SCZ and MPD. This distinction may serve to improve our neurobiological understanding in the presentation of psychotic disorders, to aid diagnosis and support treatment strategies. To conduct this investigation five aims will be addressed;

(1) Investigate differences in relative frequency activity at rest between SCZ, MPD and healthy controls by extracting relative frequency (alpha, theta, beta, and delta) from resting states.

(2) Investigate differences in relative frequency activity and cognitive performance during the continuous performance task and cued target detection task between SCZ, MPD and healthy controls.

(3) Investigate differences in attention between SCZ, MPD and healthy controls, by extracting the P300 event-related potential waveform from the continuous performance task and cued target detection task.

(4) Investigate working memory and executive functioning between SCZ, MPD and healthy controls, by extracting relative frequency and N170 and P300 event-related potentials from the STROOP task.

(5) As an exploratory measure we investigated the associations of (neuro) inflammatory markers with relative frequency and the P300 ERP waveform to potentially explain underlying biological mechanisms that are involved in SCZ, MPD and healthy controls.

In the next chapter, the methodology will be explained in full, where clinical scales, neuroimmune markers, and electroencephalography setup, hardware and analysis are explained. Further, the above aims will be discussed in the chapters following; chapter 3 will

address Aim 1, chapter 4 will address Aim 2, chapter 5 will address Aim 3, chapter 6 will address Aim 4 and Chapter 7 will address Aim 5. Lastly, the results of all the aims will be summarized and concluded in Chapter 8.

2 Research methods

2.1 Research participants

A total of one hundred and four South African individuals, between the ages of 20 and 45 years, were recruited for this study: thirty-one participants with a diagnosis of a methamphetamine-induced psychotic disorder (MPD, n=31; 7 females/24 males), thirty-eight participants with a diagnosis of schizophrenia (SCZ, n=38; 8 females/30 males) as per DSM-IV structured clinical interview (SCID) (American Psychiatric Association, 1994), as well as thirty-five socio-demographically matched control participants (CON, n=35; 15 females/20 males). Patients were required to be older than 20 and younger than 45 to ensure that cognitive impairment was not a result of age and rather that of either MPD or SCZ (Trammell, MacRae, Davis, Bergstedt, & Anderson, 2017). The experimental groups were recruited via Valkenberg Hospital and the Groote Schuur Hospital catchment areas in Cape Town. The two hospitals were included as they were in the catchment areas in Cape Town, and participants were in part recruited via clinician referral. All participants underwent a Structured Clinical Interview for Diagnostic Systematic Manual-IV (SCID-DSM-IV) (American Psychiatric Association, 1994), with consideration to the diagnostic changes made to the DSM-5.

All participants were screened to ensure that all inclusion and exclusion criteria were met; initial screening was completed by the researchers who contacted the potential participants. Only participants who were able to provide written informed consent were included. Participants from Valkenberg Hospital and the Groote Schuur Hospital catchment areas in Cape Town were required to be stable outpatients by the clinical research personnel who performed the diagnostic interview. Any participants who were found to be too ill at the time of the SCID or unable to provide written informed consent were referred to relevant clinical facilities for treatment. A few of these individuals were contacted at a later date if deemed appropriate by both the research personnel and the participant.

Participants that were recruited for the SCZ group had a clear diagnosis of schizophrenia. Other diagnoses from the schizophrenia spectrum were excluded, e.g. schizophreniform and schizoaffective disorder (American Psychiatric Association, 1994). Further, individuals were excluded if they presented with psychosis due to a general medical condition, or if preceding a psychotic episode, substance use may have played a causative role. Participants that were

recruited for the MPD group were excluded if the cause for psychosis was not a result of methamphetamine use (American Psychiatric Association, 2013), and if it was unclear as to which drug resulted or led to the presentation of their psychosis, i.e. it should be clear that methamphetamine was likely the cause which led to the presentation of all psychotic episodes experienced. Participants that were recruited for the CON group were included when there was no personal or family history of psychotic symptoms, psychosis or a psychotic disorder (DSM Axis I disorders) (American Psychiatric Association, 1994).

Additional exclusion criteria were as follows: a reported 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 human immunodeficiency virus-positive status; females that were pregnant or breastfeeding; and any individual who after interview presented incapable to undergo the intensive brain imaging day.

This study was a component of a larger study that included a magnetic resonance imaging scan, which lead to the addition of the following exclusion criterion: any physiological device implants (e.g. pacemaker, cochlear implant, aneurism clip); extensive tattoos on the 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, and claustrophobia.

2.2 Ethical considerations

Patients that were recruited for this study were psychiatric patients that were previously admitted to either Groote Schuur Hospital or Valkenberg Hospital. Ethics approval was obtained from the Western Cape Provincial Government and respective hospitals, and the University of Cape Town under the umbrella project (HREC Ref No: 413/2016), where a priori power analysis was conducted. A priori power analysis, to determine the minimum required sample size (n) required (Cohen, 2004), was conducted with G*Power 3 (Faul et al., 2007) as a function of the required power level ($1 - \beta$ error probability = 0.8), the pre-specified significance level ($\alpha = 0.05$), and the population effect size ($d = 0.5$) with an allocation ratio of

N2/N1 = 1. The a priori power analysis yielded a required total sample size of n = 102, with a statistical power of 0.81.

Furthermore, ethical clearance for this research study was obtained from the University of Cape Town's Health Sciences Research Ethics Committee (HREC Ref No: 479/2019) and was conducted in accordance with the Declaration of Helsinki (World Medical Association, 2001). The protocol was renewed annually as needed and once all data have been collected the protocol will be closed with the Health Sciences Faculty HREC as required.

Participants were required to sign an informed consent prior to participating in the study (Appendix A). The informed consent took place on the first day of participation. A research study staff member took the participant through the information sheet which explained all procedures in simple language and the consent form prior to obtaining signatures and the participant entering the study. Where the participant was unsure and unable to explain what was required of them, the participant was not included. For the individuals who were not able to participate in the study, a voucher was provided to thank the individual for coming to meet with us and a lift via Uber was arranged to take the participant home. Participants were able to leave the study at any time as their participation was voluntary. All necessary regulations were followed, including adherence to human research guidelines as stipulated in the Declaration of Helsinki (World Medical Association, 2013).

2.3 Study design

Each participant was required to attend two research days. The first day included the attainment of informed consent, demographic information; gender, date of birth, body mass index (BMI), education, and handedness. Further, peripheral blood draw, SCID, and completion of several clinical scales to assess symptom severity. Then for participants with a psychotic disorder the age of first hospitalization for a psychotic episode, duration of illness and current medication regime were collected.

The brain imaging day (day 2) included the EEG record, saliva sample collection, and the completion of subjective questionnaires. The participants were required to be present at 08h00. All the recordings were collected between 09h00-11h00 during a working weekday. The

subjective questionnaires included; the Kreek-McHugh-Schluger-Kellogg scale (KMSK scale), Edinburgh's handedness questionnaire, and the Mental effort scale.

2.4 Assessing participants using clinical measures

The inclusion of clinical scales and questionnaires was to assess whether an individual had any underlying anxiety and depression and to assess symptoms of psychosis and daily function. The clinical scales that were used are; the Positive and negative syndrome scale (PANSS), the Calgary depression scale, and the Hamilton depression rating scale.

2.4.1 Positive and negative syndrome scale

An operationalised and drug-sensitive instrument, the positive and negative syndrome scale (PANSS), was used to assess the positive and negative psychotic symptoms of schizophrenia and provide and comparison between symptoms and general psychopathology (Stanley R Kay, Fiszbein, & Opler, 1982). The PANSS contains three subscales; the positive symptom subscale addresses 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 utilizes a 1 to 7 score system to rate an individual for each subscale. 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, the score of the ratings across items is between 7-49 for the positive and negative subscales and 16-112 for the general psychopathology scale.

The PANSS scale has been tested in an international multi-centre study with 25 countries, including South Africa showed that the PANSS can be used on a global level to record symptomology (Fountoulakis et al., 2019). A 2017 study revealed correlations between the

PANSS positive scores and the P100, N170 and N250 event-related potentials (ERP) in SCZ (D.-W. W. Kim, Kim, Lee, & Im, 2013). Further correlates between the PANSS negative scores and the P100 and N250 ERP were also found (D.-W. W. Kim et al., 2013). Significant positive correlations for the PANSS general psychopathology scale and frontal EEG complexity (i.e. the more severe the symptoms of psychopathology) were reported (Cerquera, Gjini, Bowyer, & Boutros, 2017). Furthermore, their data suggested a relationship between the degree of emotion and EEG signal complexity.

2.4.2 Calgary depression rating scale

Then two mood-related clinical scales were included to assess mood polarity; two depression rating scales the Calgary depression rating scale (CDS) which is a scale used to measure the level of depression in schizophrenia (J. Addington, Shah, Liu, & Addington, 2014), and the Hamilton depression rating scale (HAM-D) a clinical scale used to assess symptoms of depression (Hamilton, 1960a). The CDS scale was included along with the HAM-D as it was found to be more specific to depression in SCZ compared to the HAM-D scale. Studies have shown that the CDS scale helps distinguish depression from negative symptoms of SCZ (Grover, Sahoo, Dua, Chakrabarti, & Avasthi, 2017). Furthermore, studies have shown correlations between the CDS and EEG and ERP data. There are a few studies which contradict the current knowledge of the CDS. Thoma et al (2005) found no significant correlations between the CDS and ERP data, specifically sensory gating (Thoma et al., 2005). 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. By including the CDS scale we will be able to add to current research.

2.4.3 Hamilton depression rating scale

The HAM-D clinical scale was designed to assess depression severity (Hamilton, 1960a). The HAM-D scale consists of 21 questions of which only the first 17 items are calculated. Each item is rated on either a 5-point scale (0−4) or a 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).

2.4.4 Kreek-McHugh-Schluger-Kellogg scale (KMSK scale)

Substance use was measured using the Kreek-McHugh-Schluger-Kellogg (KMSK) scale which reported lifetime use of a substance. The participant was asked if they had used any of the following substances: alcohol, tobacco, cocaine, heroin, opiates, cannabis and methamphetamine or Amphetamines. For each substance used, the question of how much was used, when it was used, how long it was used for and if the substance is the participants' drug of choice. A scoring system of 0-5 points was used. Substance use and abuse were previously found to correlate with EEG and ERP data (Ceballos, Bauer, & Houston, 2009). The use of substances has also been found to alter brain structure and function (L. M. Squeglia, Jacobus, & Tapert, 2009; Lindsay M. Squeglia, Jacobus, & Tapert, 2014). The systems substance use is known to alter is the dopamine and serotonin systems within an individual. These alterations to neurotransmitter systems can have adverse changes to the firing of neurons causing dysfunction of attentional networks.

2.4.5 Edinburgh's handedness questionnaire

To further characterise each participant, Edinburgh's handedness questionnaire was included as a quantitative scale to assess an individual's handedness (R. C. C. Oldfield, 1971). The scale contains 20 items pertaining to actions of an individual carries out with either their "left" or "right" or "both" hands. The scores are calculated for each individual by subtracting the total score on the left from the total score on the right. The final answer is then multiplied by 100. A positive score indicates right-handedness and negative scores indicate left-handedness.

2.4.6 Colour blindness

The Ishihara test for colour blindness was used to test each participant for colour blindness prior to EEG testing. This quick assessment was conducted to distinguish whether an individual had any visual colour impairment which could influence the results obtained for the ERPs extracted from the Stroop task. There are four different designs within the Ishihara test for colour blindness; the vanishing design can only be seen by individuals with good colour vision, and colour-blind individuals cannot see the sign. The transformation design will be seen differently with individuals who are colour-blind and those who have good vision. The hidden digit design can only be seen by individuals who are colour-blind. Lastly, the classification

design is where individuals are tested to differentiate between red and green-colour blind persons.

2.5 Medication analysis

The analysis was performed by grouping all medications according to the category each antipsychotic medication falls under. The following groups of antipsychotic medications were investigated: No antipsychotic prescribed (NONE); 1st generation antipsychotics (1^{st}); 2nd generation antipsychotics (2^{nd}).

This permitted us to determine the differences between SCZ and MPD. Statistical analysis was applied to the parametric data by one-way analysis of variance (ANOVA), and non-parametric data by Kruskal Wallis testing was applied.

2.6 Peripheral immune function preparation and analysis

To determine the cytokine concentration of an array of cytokines, which have previously been implicated in SCZ and MPD, were analysed in serum from blood.

All analyses were conducted in a blinded manner with coded samples. Blood tubes were clearly labelled, and blood samples were collected by sufficiently trained personnel. Personal protective equipment was worn while blood is collected. Good clinical practice and quality control protocols were adhered to closely. Provision for repeats and control protocols were made for quality control purposes.

2.7 Sample collection, extraction, and storage

In total, 48 ml of blood was obtained through peripheral venepuncture on the first research day with a clinician. For plasma, a total of 27ml blood was collected in three Ethylenediaminetetraacetic acid (EDTA) vacutainer tubes (purple top, 9ml each). For serum, a total of 21ml of blood were collected in two serum silicone-coated vacutainer tubes (red top, 9ml each). EDTA tubes were kept on ice and serum tubes were stored at room temperature for approximately 30min to allow clotting. The handling and storage of samples were executed according to a protocol for long-term storage (at least 6 years) for the measurement of inflammatory markers (Elliott & Peakman, 2008). Serum of plasma extracted and stored at Red Cross War Memorial Children's Hospital.

2.7.1 Participant arrival

Blood collection was explained during the completion of the consent form. The clinician and researcher wore gloves during the drawing of blood. The clinician proceeded to clean the potential site of venepuncture with an alcohol swab(s). A 23G needle packet was opened and a needle and tube holder were attached. The needle was carefully inserted into the site of venepuncture and the first EDTA tube (purple top) was inserted into the needle tube holder and filled. If no blood filled the tube, the venepuncture site was checked for a possible collapsed vein or incorrect placements. Further, if no blood filled the tube, a new tube was used in case the tube vacuum was lost. Once the first tube was filled, the tube was removed and replaced with the first serum tube (red top) continue replacing the tubes with a new labelled tube until all 5 tubes are filled. Each EDTA tube was inverted eight times once filled and placed into the cooler box for transport. After each serum tube was filled, the tubes were inverted eight times and then left standing upright in a tube rack at room temperature for 30 minutes (to allow the clot to form) before transportation.

2.8 Serum Separation Procedure from whole blood

The serum and EDTA tubes were centrifuged in a horizontal rotor (swing out head) for 20 minutes at 1800 x g at room temperature. After centrifuging serum and plasma were aliquoted into labelled 2ml cryovials. A maximum aliquot volume of 1.5ml was recommended, however, if a sample contained serum in surplus, the tubes were filled to 2ml. This process was completed within an hour of centrifugation. Prior to storing the aliquots, all caps were tightly secured, and the tubes were checked for accurate labelling and placement in an 81-place cryo box map for -80°C storage. For data collection purposes, the following were noted; the date and time of blood collection, the number and volume of each aliquot prepared, the date and time into -80°C, any freeze and thaw, any variations or deviations from the Standard Operating Procedure, problems, or issues and whether the serum haemolysed.

2.8.1 Luminex assay principle

The serum samples were prepared at Red Cross War Memorial Children's Hospital and transported to the Institute for Diseases and Molecular Sciences for analysis using the Merck multiplex assay and read on a Luminex system (Bio-Plex 200 System; Bio-Rad). The Merck multiplex assay, based on the Luminex multi-analyte profiling (xMap) technology, comprised

of magnetic beads with a unique blend of red ultraviolet dye able to detect and quantify secreted proteins (i.e., cytokines, chemokines, growth factors, etc.). This unique blend of dye gives each bead a signature which can be identified by the Luminex LX200 when the bead was excited by the laser.

The Luminex assay principle consisted of adding a sample of interest to a mix of analyte-specific beads containing antibodies. The analytes within the sample bind to the antibodies on the beads. Specific detection antibodies are added to the sample-bead mixture to form an antibody-antigen sandwich. The UV-sensitive Phycoerythrin-conjugated Streptavidin was added and allowed to bind to the detection antibodies. The beads were read on a dual laser flow-based instrument (i.e., Luminex 200). A 633nm laser first classified the bead and determined which analyte was being read. A second laser (532nm) determined the magnitude of the Phycoerythrin signal, **Figure 2.1**.

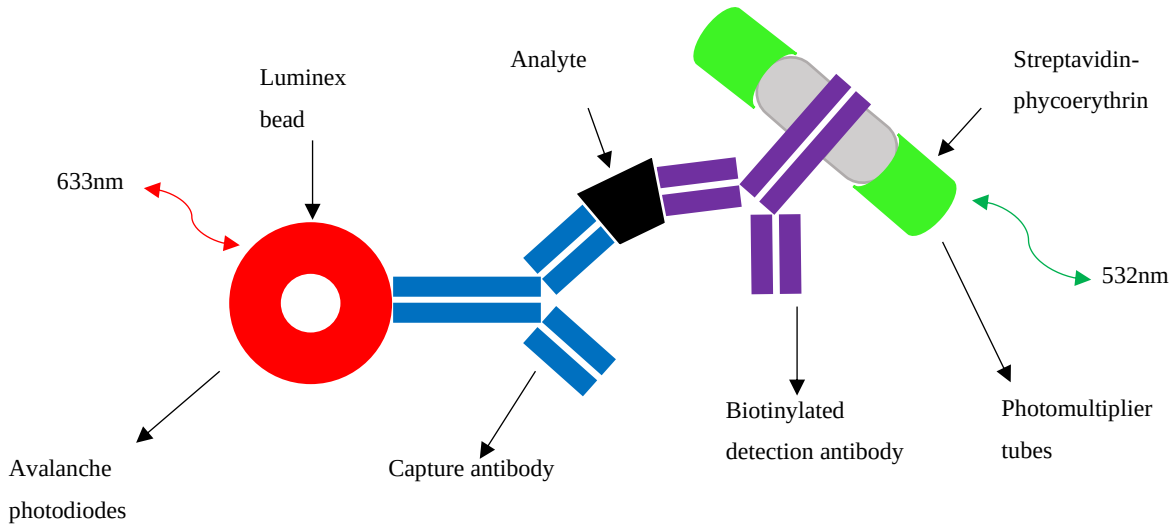


Figure 2.1 Luminex assay principle. This method consisted of adding a sample of interest to a mix of analyte-specific beads containing antibodies. The analytes within the sample bind to the antibodies on the beads. Specific detection antibodies are added to the sample-bead mixture to form an antibody-antigen sandwich. The UV-sensitive Phycoerythrin conjugated Streptavidin was added and allowed to bind to the detection antibodies. The beads were read on a dual laser flow-based instrument (i.e., Luminex 200). A 633nm laser first classified the bead and determined which analyte was being read. A second laser (532nm) determined the magnitude of the Phycoerythrin signal.

2.8.2 Preparation of samples for multiplex:

Prior to preparing the samples, all Eppendorf tubes were labelled, and the fume hood area was wiped down with 70% ethanol. The samples were prepared in a fume hood containing a

Styrofoam container filled with ice, to ensure samples were kept in a sterile and cold environment. Only 10 samples were worked with at a time. The serum cryovial was fully thawed on ice. Once thawed, 500µl of serum was extracted and pipetted into a clean labelled tube. The samples were centrifuged for 10 minutes at 2000rpm. While the samples were being centrifuged, the next ten samples were removed from the -80°C freezer to be thawed on ice and the first few thawed samples were stored at -80°C. From the 500µl centrifuged aliquot, 100µl of supernatant was transferred to a clean tube and the rest was discarded. The process was repeated for all samples. The melted ice was replaced with fresh ice to keep the samples cold. Gloves were always worn during the handling of specimens. This included during removal of the rubber stopper from the blood tubes, centrifugation, pipetting, disposal of contaminated tubes, and clean-up of any spills. The tubes, needles, and pipet tips were properly disposed of in biohazard containers, in accordance with institutional requirements. All equipment (storage, shipping, and centrifuge) was labelled as a biohazard. It was important to take steps to prevent haemolysis in these samples. A vacutainer was recommended, and a 21-gauge needle was recommended.

2.8.3 Sample analysis: Merck Luminex cytokine assay kit

The following cytokine concentrations were determined with Merck multiplex assays: IL-1β, IL-8, IL-12p70, IFN-γ, IL-10 and TNF-α. Milliplex® MAP high sensitivity multiplex assay (HSTCMAG28SK07; Merck) was used for the analysis of cytokine samples. This set of inflammatory proteins was selected due to their potential involvement in the pathophysiology of schizophrenia, as they have been shown to strongly associate with clinical symptoms of schizophrenia (Tomasik et al. 2014, Noto et al. 2015, Lepeta and Kaczmarek 2015, Audet et al. 2014, Eisenberger et al. 2010, Fillman et al. 2013).

2.8.3.1 Instrumentation / Materials

According to Milliplex® MAP high sensitivity multiplex assay (HSTCMAG28SK07; Merck), the following items were needed before starting cytokine extraction and analysis.

- Luminex® Sheath Fluid (EMD Millipore Catalog # SHEATHFLUID) or Luminex® Drive Fluid (EMD Millipore Catalog # MPXDF-4PK)
- Adjustable Pipettes with Tips capable of delivering 25µl to 1000µl.

- Multichannel Pipettes capable of delivering 5µl to 50µl or 25µl to 200µl.
- Reagent Reservoirs
- Polypropylene Microfuge Tubes
- Aluminium Foil
- Absorbent Pads
- Laboratory Vortex Mixer
- Sonicator (Branson Ultrasonic Cleaner Model # B200 or equivalent)
- Titre Plate Shaker (VWR® Microplate Shaker Cat # 12620-926 or equivalent)
- Luminex® 200™, HTS, FLEXMAP 3D®, or MAGPIX® with xPONENT® software by Luminex® Corporation
- Luminex system (Bio-Plex 200 System; Bio-Rad).
- Automatic Plate Washer for magnetic beads (BioTek® 405 LS and 405 TS, EMD Millipore Catalog # 40-094, # 40-095, # 40-096, # 40-097 or equivalent) or Handheld Magnetic Separation Block (EMD Millipore Catalog # 40-285 or equivalent).

2.8.4 Preparation of reagents for immunoassay

2.8.4.1 Preparation of Antibody-Immobilized Beads

The kit ordered for this study contained individual vials of antibody beads. Each vial of antibody beads was sonicated for 30 seconds and vortexed for 1 minute. Open the mixing bottle given with the kit and add 60µl from each antibody-bead vial. Bring the final volume of the antibody-bead mixture to 3ml with bead diluent and vortex the mixed beads well.

2.8.4.2 Preparation of Quality Controls

The vials marked Quality Control 1 and Quality Control 2 were reconstituted the vials with 250µl deionized water. The vial was inverted several times and vortexed. The vial was left to sit for 5-10 minutes and then the controls were transferred to appropriately labelled polypropylene microfuge tubes.

2.8.4.3 Preparation of Wash Buffer

The 10X Wash Buffer was allowed to warm to room temperature and mixed to bring all salts into the solution. To create the 1X wash buffer solution, 60ml of 10X Wash Buffer was diluted with 540ml deionized water.

2.8.4.4 Preparation of Serum Matrix

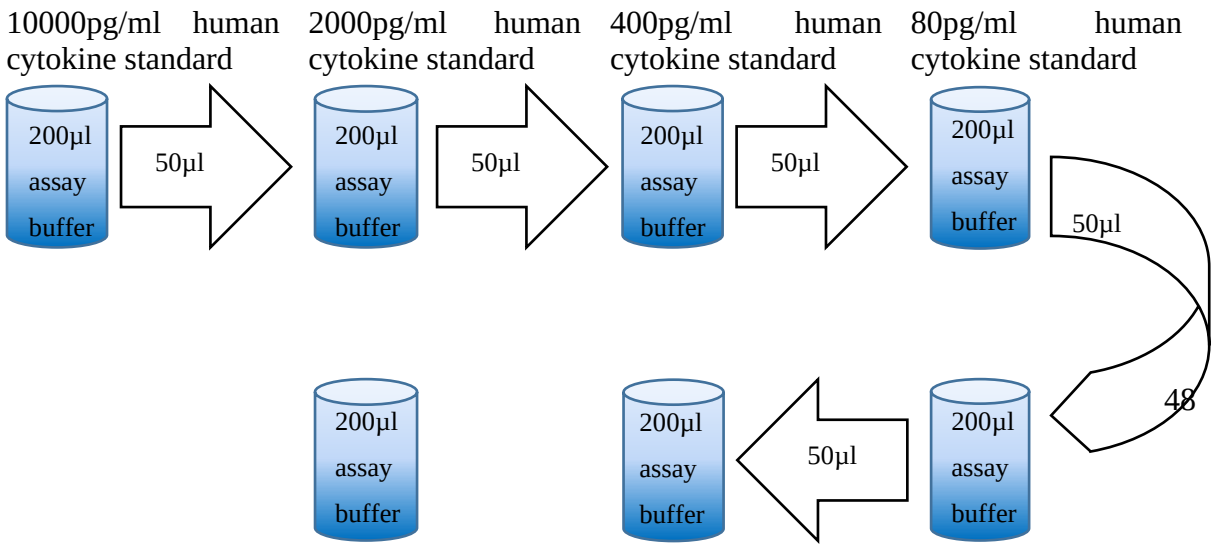
The serum matrix was prepared by adding 1.0ml deionized water to the bottle containing lyophilized Serum Matrix. The solution was mixed well and allowed for at least 10 minutes for complete reconstitution.

2.8.4.5 Preparation of Human Cytokine Standard

The Human Cytokine Standard was reconstituted with 250µl deionized water to give a 10,000pg/ml concentration of standard for all analytes. The vial was inverted several times and vortexed for 10 seconds. The vial was allowed to sit for 5-10 minutes and then the standard was transferred to an appropriately labelled polypropylene microfuge tube. This was used as the 10,000pg/ml standard.

2.8.4.6 Preparation of Working Standards

To create the working standards, five polypropylene microfuge tubes were labelled 2,000, 400, 80, 16, and 3.2pg/ml. The tubes were filled with 200µl of Assay Buffer. Serial dilutions were prepared by adding 50µl of the 10,000pg/ml reconstituted standard to the 2,000pg/ml tube, mixed well and then 50µl of the 2,000pg/ml standard was transferred to the 400pg/ml tube, mixed well and then 50µl of the 400pg/ml standard was transferred to the 80pg/ml tube, mixed well and 50µl of the 80pg/ml standard was transferred to 16pg/ml tube, mixed well and 50µl of the 16pg/ml standard was transferred to the 3.2pg/ml tube and mixed well. The 0pg/ml standard (Background) will be Assay Buffer, **Figure 2.2**.



0pg/ml human cytokine standard

3.2pg/ml human cytokine standard

16pg/ml human cytokine standard

Figure 2.2 Human cytokine working standards for the Luminex protocol. The serial dilution was completed by adding 200µl of assay buffer into six labelled tubes. The first standard was created by removing 50µl of 10000pg/ml human standard and pipetting it into the tube labelled 2000pg/ml human cytokine standard. The second standard was created by removing 50µl of 2000pg/ml human standard and pipetting it into the tube labelled 400pg/ml human cytokine standard. The third standard was created by removing 50µl of 400pg/ml human standard and pipetting it into the tube labelled 80pg/ml human cytokine standard. The fourth standard was created by removing 50µl of 80pg/ml human standard and pipetting it into the tube labelled 16pg/ml human cytokine standard. The fifth standard was created by removing 50µl of 16pg/ml human standard and pipetting it into the tube labelled 3.2pg/ml human cytokine standard. The 0pg/ml standard consisted only of assay buffer.

2.8.5 Immunoassay procedure

Prior to starting the assay, the kit protocol was read thoroughly, and all technical guidelines were understood. All the reagents were warmed to room temperature (20-25°C) before use. All remaining solutions should be returned to a -20°C freezer to be stored for a maximum of 30 days. All samples were run in duplicate, and simultaneously on the same day, according to the kit 96-well Map worksheet. To wash the 96-well plate, 200µl of Wash Buffer was added to each well. Seal and mix on a plate shaker at 800rpm for 10 minutes at room temperature (20-25°C). Decant the Wash Buffer and remove the residual amount from all wells by inverting the plate and tapping it lightly onto an absorbent towel several times. Add 25µl of each Standard or Control into the appropriate wells. Assay Buffer should be used for 0pg/mL standard (Background). Add 25µl of Assay Buffer to the sample wells. Add 25µl of serum matrix solution to the background, standards, and control wells. Add 25µl of serum sample into the appropriate wells. Vortex the Mixing Bottle and add 25µl of the Mixed or Premixed Beads to each well. During the addition of Beads, shake the bead bottle intermittently to avoid settling. Seal the plate with a plate sealer and wrap the plate with foil and incubate with agitation on a plate shaker overnight at 4°C for (16-18hr), this may improve assay sensitivity for some analytes.

After overnight incubation, gently wash the plate two times using the Magnetic plate washer (EMD Millipore Catalog #40-094, #40-095, #40-096 and #40-097)**.** Allow the Detection

Antibodies to warm to room temperature prior to addition. Add 25µl of Detection Antibodies into each well. Seal and cover the plate with foil then incubate with agitation on a plate shaker for 1 hour at room temperature (20-25°C). The 96-well plate was not aspirated after incubation**.** Add 25µl Streptavidin-Phycoerythrin to each well containing the 25µl of Detection Antibodies. Seal and cover the plate with foil then incubate with agitation on a plate shaker for 30 minutes at room temperature (20-25°C). Gently remove the well contents and wash the plate two times using the Magnetic plate washer (EMD Millipore Catalog #40-094, #40-095, #40-096 and #40-097)**.** Add 150µl of Sheath Fluid to all wells. Resuspend the beads on a plate shaker for 5 minutes. Run the plate on Luminex® 200™with xPONENT® software (LuminexCorp., Austin, TX). Save and analyze the Median Fluorescent Intensity data using a 5-parameter logistic or spline curve-fitting method for calculating cytokine/chemokines concentrations in samples. (Note: For diluted samples, multiply the calculated concentration by the dilution factor.) The R^2 values for the standard curves ranged between 0.996–1. As per the manufacturer, the values obtained for the controls were within the range and the intra-assay coefficients of variation for the markers were <14%.

2.8.5.1 Equipment settings

These specifications are for the Luminex® 200™, with xPONENT® software. For magnetic bead assays, the Luminex® 200™ and HTS instruments must be calibrated with the xPONENT® 3.1 compatible Calibration Kit (EMD Millipore Catalog # 40-275) and performance verified with the Performance Verification Kit (EMD Millipore Catalog # 40-276).

2.9 Electroencephalography (EEG)

Electrical brain signals measured in microvolts (µV) are collected via the EEG electrodes of the EEG cap and amplified using the Biopac MP150 data acquisition system with ten 100C amplifiers attached (Biopac Systems Incorporated, 2012).

2.9.1 Electroencephalography hardware

The 100C amplifiers are biopotential transducers able to amplify voltages smaller than 10 microvolts. The ten 100C biopotential amplifiers attached to the Biopac MP150 system included the prefrontal (Fp1 = channel A1, Fp2 = channel A2), frontal (F3 = channel A3, F4 = channel A4), central (C3 = channel A5, C4 = channel A6), parietal (P3 = channel A7 and P4 =

channel A8) and occipital (O1 = channel A9, O2 = channel A10). EEG100C amplifiers were set on normal mode, with the low pass filter on 100Hz and the high pass filter on 0.1Hz, with a gain of 1000 times. The sampling frequency of the software was set at 500Hz.

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. Each of the 10 amplifiers was connected via a ribbon cable (1m long), that fans into the international 10/20 montage EEG electrode cap (CAP100C).

The EEG lycra cap used to collect the EEG recordings had a standard 10/20 system containing recessed pure tin (Sn) electrodes attached to the fabric (Electro-cap International inc, n.d.). Channels of the 10/20 montage that were recorded included the left pre-frontal (Fp1), right pre-frontal (Fp2), left frontal (F3), right frontal (F4), left central (C3), right central (C4), left parietal (P3), right parietal (P4), left occipital (O1), and right occipital (O2) respectively. Electrooculography (EOG 100C-500 gain, 0.05Hz), taken below and to the right of the right eye, will be recorded and used to remove artefacts from the EEG traces.

2.9.2 Electroencephalography software

The MP150 system data were collected and visualized using the Biopac software Acqknowledge 4.1 data acquisition and analysis software. Acqknowledge 4.1 allows for real-time viewing, measure, replay and transforming and analysis of the EEG data recorded (Biopac Systems Incorporated, 2012).

2.9.3 Behavioural data software

Behavioural data were recorded during the collection of EEG data. E-prime 2.0, a software tool, was used to design behavioural tasks and collect and analyse behavioural data. 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 (Biopac Systems Incorporated, 2012).

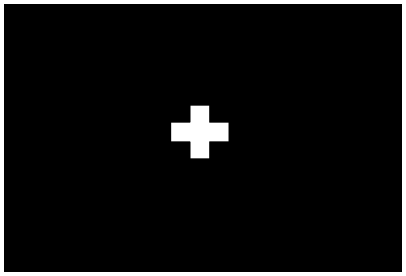
2.10 Electroencephalography task design

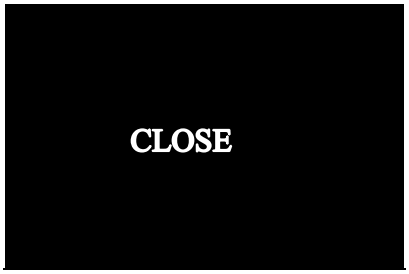
Participants were required to complete an EEG record sequence starting with resting eyes open (3:00min) and resting eyes closed (3:00min) tasks, to record resting state data. Participants will

then complete the cognitive tasks; continuous performance task (5:00min), cued target detection task (6:20min) and Stroop task (5min). The EEG testing took place at the Cape Universities Body Imaging Centre (CUBIC), at Groote Schuur Hospital in a partially dark room.

2.10.1 Resting-state tasks

Resting-state conditions were incorporated into the study to collect data for when the participant was at rest. These tasks consisted of a resting eyes open (REO) condition and resting eyes closed (REC) condition, **Figure 2.3**. The REO instructed the participant to look at a black screen consisting of a single off-white cross placed centrally on the screen. The participant was asked to remain as still as possible and to not talk. Once the condition was complete, the participant was asked to relax. The mental effort scale was handed to the participant for them to mark how much effort was applied to conduct the condition. The REC consisted of a screen showing the words "CLOSE EYES" which instructed the participant to keep their eyes closed. Once the condition was complete, the participant was asked to open their eyes and relax. The mental effort scale was handed to the participant for them to mark how much effort was applied to conduct the condition. Both the REO and REC ran for 3 minutes each.


(a)



(b)

Figure 2.3 Resting eyes open (REO) and resting eyes closed (REC) baseline task: (a) The REO condition was conducted in 3 minutes by asking the participant to look at a white cross situated on a white screen. (b) During the REC condition, the participant is asked to keep their eyes closed to breathe as normal. For both tasks, the participant is asked to remain as still as possible.

2.10.2 Continuous performance task

The continuous performance task (CPT) involves the presentation of three consecutive S's within a series of randomized letters of the alphabet (Williams, 2019). 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 are presented with 60 trials with three consecutive S's, the presentation of the third S requires a behavioural response.

In addition, 40 single S's or trick S's are embedded in the task with 300 inter-stimuli letters. The trick stimulus was presented to distract the participant from the presentation of the three consecutive S's**, Figure 2.4**. The task contains 20 letters of the alphabet and excluded the vowels, A, E, I, O, and U as well as the letter X. Each letter was presented for 500msec with a 100 msec inter-stimulus interval before the next stimulus. However, the participant can shorten the presentation of the third S if a response is given before the 500msec time limit. Once the task was complete, the participant was asked to relax. The mental effort scale was handed to the participant for them to mark how much effort was applied to conduct the task. The behavioural data collected were extracted using E-prime and were cross-checked with the digital inputs to an EEG data file, **Figure 2.5** Acknowledge 4.1 (Biopac Systems, Inc.). The behavioural data extracted included the number of correct responses, response time duration, errors of omission and commission.

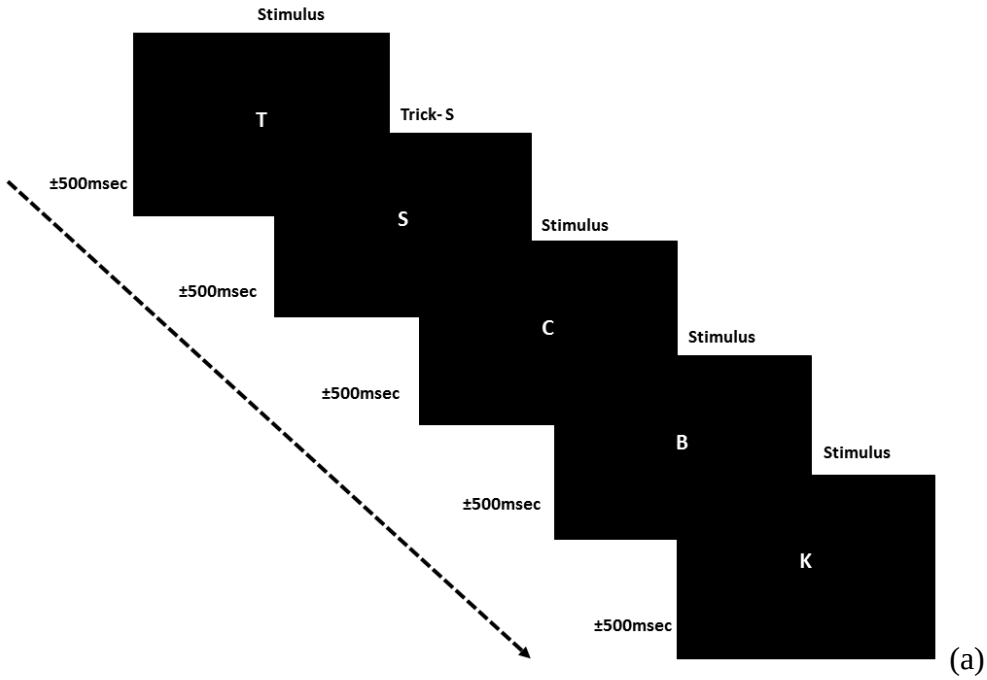


Figure 2.4 Representation of the visual Continuous Performance task. The continuous performance task was designed as a time-locked response task, where the letters appeared in a randomized order. Each letter was presented individually, appearing for 500 msec and disappearing for 100 msec before the next 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.

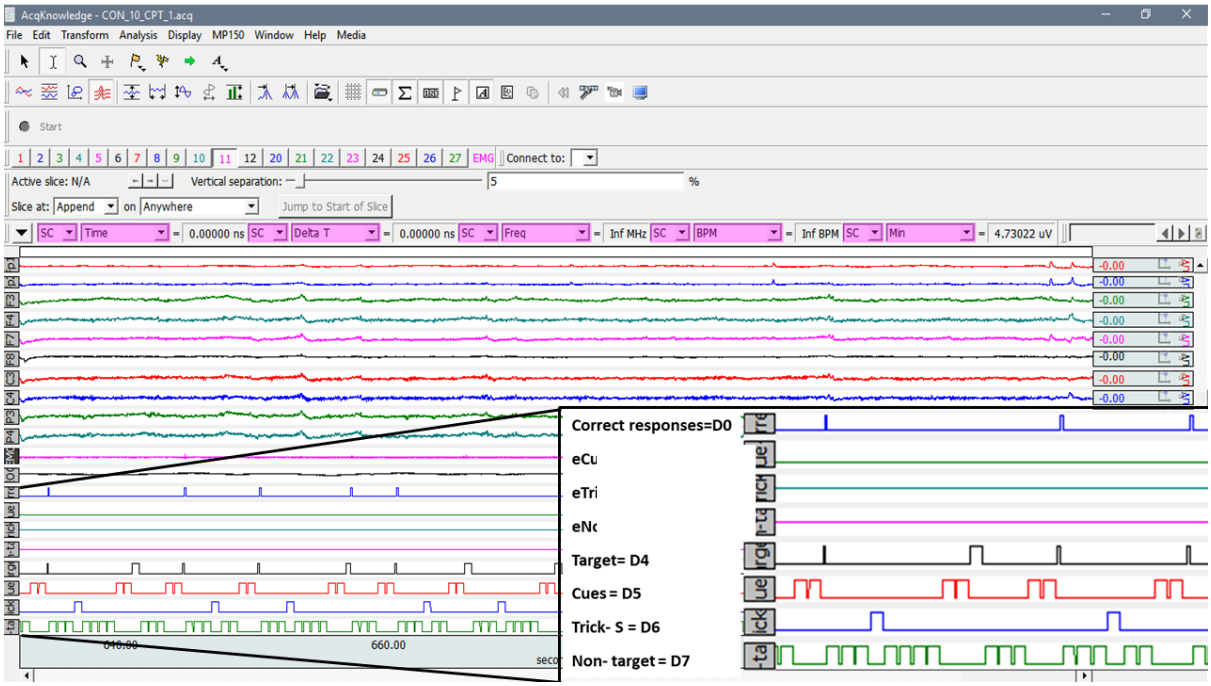


Figure 2.5 Representation of the cues in the Continuous Performance task. The digital channels for trigger collection included eight different channels: participant responses (digital channel D0), target S (digital channel D4), cueing S's (digital channel D5), trick-S (digital channel D6) and non-target (digital channel D7). All channels were collected at 500Hz. Behavioural data were collected through recorded through E-prime.

2.10.3 Cued target detection task

The cued target detection (CTD) task used in the present study is a derivative of Posner's exogenous covert orienting task (Hayward & Ristic, 2013). The task was designed to measure the covert reflexive attentional ability while looking at a fixed central solid circle. The cued target detection task (CTD) focuses on assessing attention, more specifically divergent attention. The CTD requires participants to focus on a solid grey circle in the centre of the computer screen. An outline of a grey rectangle was positioned on either side of the central cue, which remained throughout the cognitive task. The participant was required to respond to the presentation of a square within either of the rectangles. For this task, there were four conditions: (1) congruent cue and stimulus presented by a solid central fixation point with two peripheral greyed rectangles. Followed by the brightening of either rectangle then the presentation of a solid white square in the centre of the rectangle indicated a congruent trial, **Figure 2.6**; (2) incongruent cue and stimulus presented a solid central fixation point with two peripheral greyed rectangles. Followed by the brightening of either rectangle then the presentation of a solid white square in the centre of the opposing rectangle indicated an incongruent trial, **Figure 2.7**; (3) double cue and stimulus presented a solid central fixation

point with two peripheral greyed rectangles. Followed by the brightening of both peripheral rectangles then the presentation of a solid white square in the centre of either rectangle indicated a double cue trial, **Figure 2.8**; and (4) no cue and stimulus presented a solid central fixation point with two peripheral greyed rectangles. Followed by no brightening of either rectangle then the presentation of a solid white square in the centre of the opposing rectangle indicated a no-cue trial, **Figure 2.9**. The cues were presented for 500 msec and the stimulus was presented for 500 msec. The inter-stimulus interval was variable throughout the task, with durations of 500, 1000, or 1500 msec. The CTD had 64 congruent stimuli; 16 incongruent stimuli; 16 double-cueing stimuli; and 16 no-cue stimuli. Once the task was complete, the participant was asked to relax. The mental effort scale was handed to the participant for them to mark how much effort was applied to conduct the task. The behavioural data collected were extracted using E-prime and were cross-checked with the digital inputs to an EEG data file, **Figure 2.10** Acknowledge 4.1 (Biopac Systems Incorporated, 2012). The Behavioural data extracted included the number of correct responses, response time duration, errors of omission and commission.

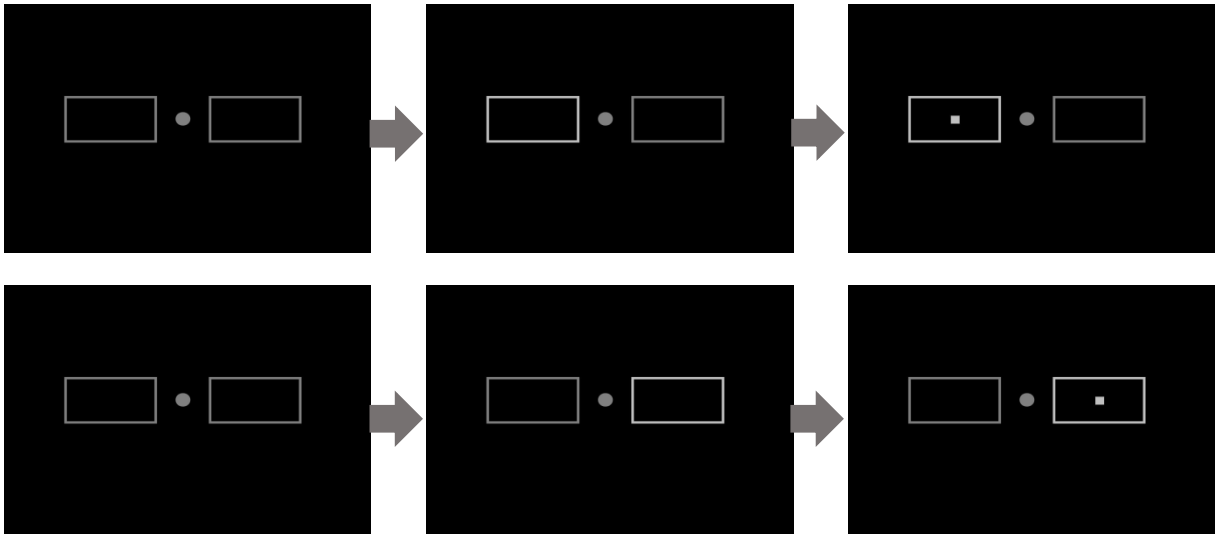


Figure 2.6 Congruent Cued target detection task trials. Showing a solid central fixation point with two peripheral greyed rectangles. Showing the brightening of either rectangle followed by the presentation of a solid white square in the centre of the rectangle indicated a congruent trial.

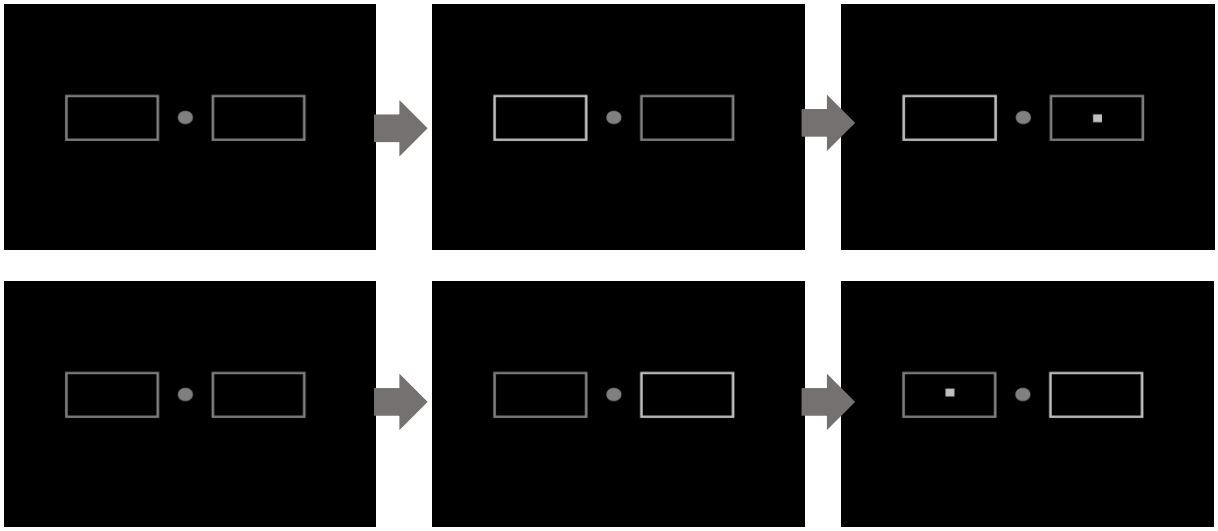


Figure 2.7 Incongruent Cued target detection task trials. showing a solid central fixation point with two peripheral greyed rectangles. The brightening of either rectangle followed by the presentation of a solid white square in the centre of the opposing rectangle indicated an incongruent trial.

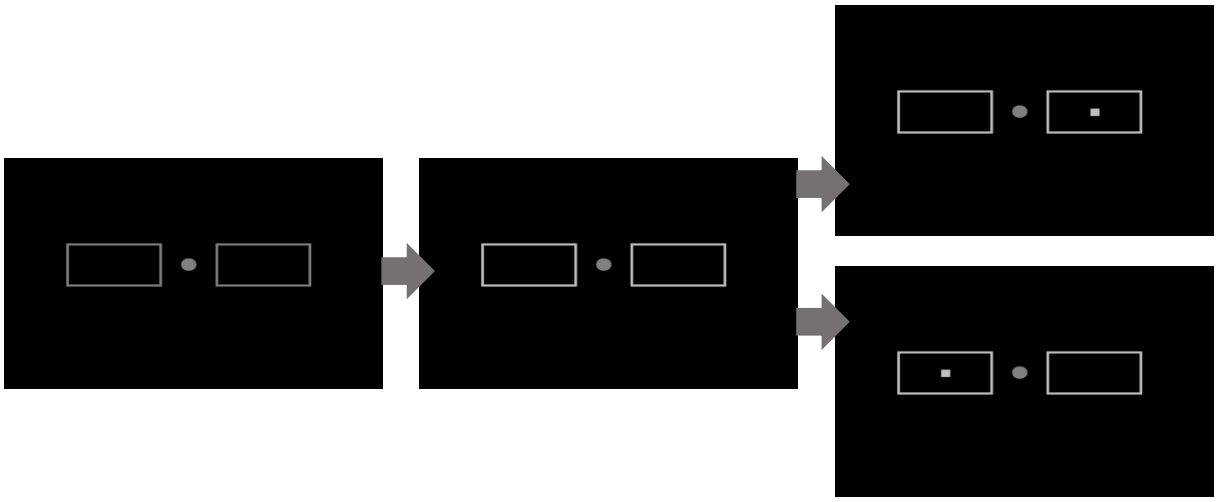


Figure 2.8 Double cue cued target detection task trials. showing a solid central fixation point with two peripheral greyed rectangles. The brightening of both peripheral rectangles followed by the presentation of a solid white square in the centre of either rectangle indicated a double cue trial.

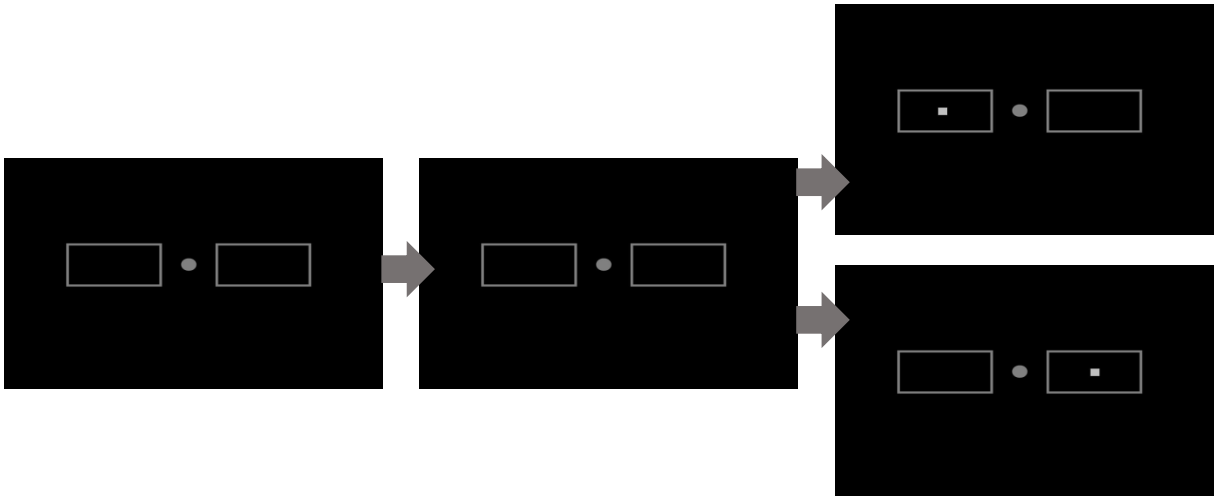


Figure 2.9 No-cue cued target detection task trails. Showing a solid central fixation point with two peripheral greyed rectangles. No brightening of either rectangle followed by the presentation of a solid white square in the centre of the opposing rectangle indicated a no-cue trial.

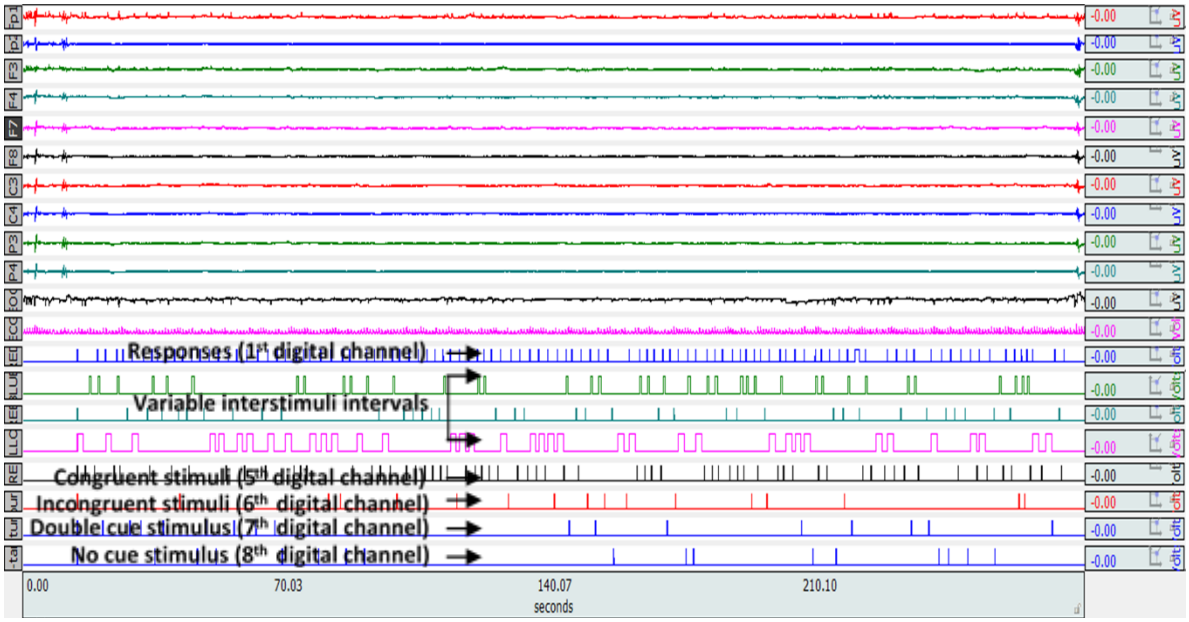


Figure 2.10 Cued target detection task full data set obtained from the Acqknowledge 4.1 software, indicating the duration of the CTD task and the recording of eight digital channels used for this task. The participants' responses were recorded on digital channel 1, variable inter-stimuli intervals were recorded on digital channels 2, 3 and 4, digital channel 5 represented the target for congruent trials, channel 6 represents the target for incongruent trials, channel 7 represents the target for double cue trails, and channel 8 represents the target for no cue trials. All channels were collected at 500Hz. Behavioural data were collected through recorded through E-prime.

2.10.4 Stroop colour word conflict task

Electroencephalography (EEG) is recorded while the participant completes the Stroop task. The Stroop task is approximately 5 minutes long containing a total of 95 cues; of colour words in each of the 4 colours red, blue, green, and yellow (60 incongruent words in total) and 15 grey words (red, blue, green, yellow written in grey ink) and are 2cm in height, in the centre of a black background on a computer monitor and 20 white squares inserted randomly throughout the task. Each cue is displayed every 3 seconds for 400ms in either coloured (incongruent cues) or grey ink (neutral cues) but never in the same colour as the written word (i.e., the word "red" displayed in red font). The cues were then followed by a response period displayed for 2600ms, **Figure 2.11**.

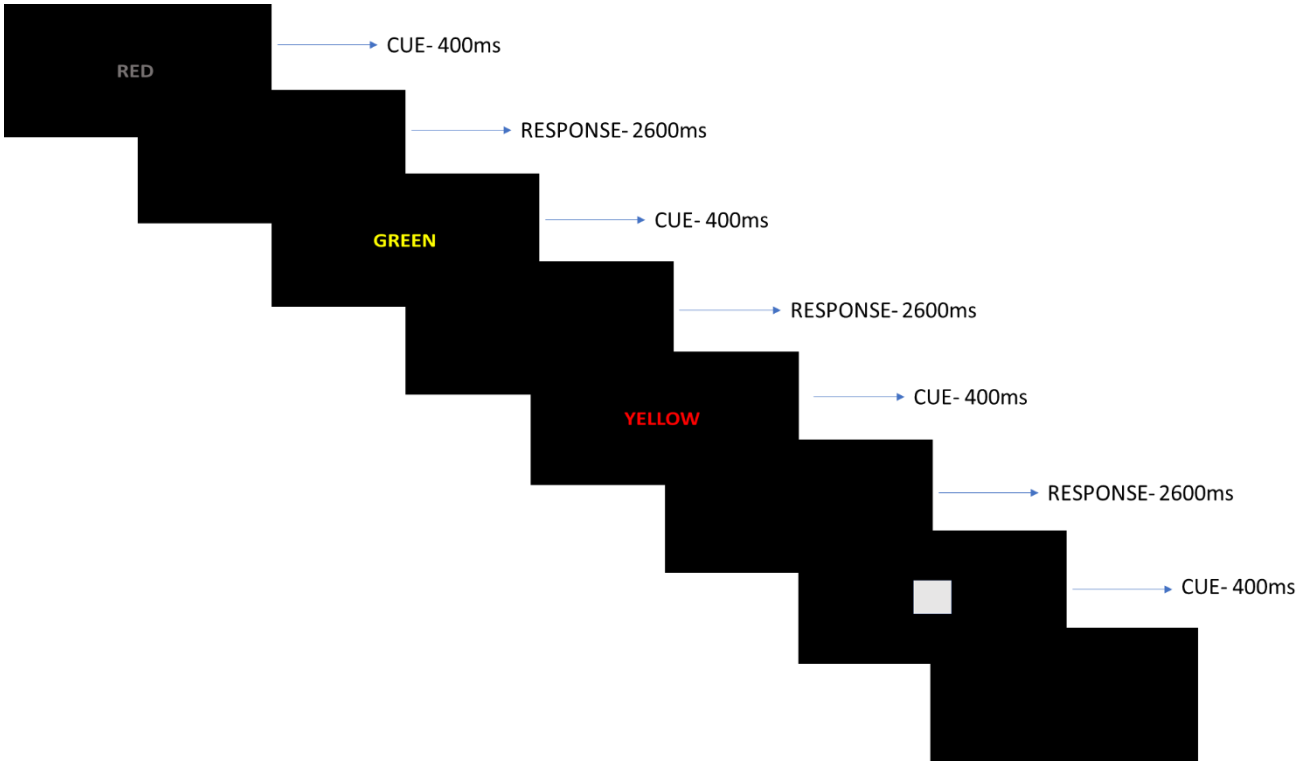


Figure 2.11 Representation of the Stroop task. The words RED, BLUE, GREEN, YELLOW and a white square are displayed in a randomized order every 3 seconds for 400ms in either coloured (incongruent cues) or grey ink (neutral cues) but never in the same colour as the written word (i.e., the word "red" displayed in red font). The cues were then followed by a response period displayed for 2600ms.

The participants are asked to respond as quickly and accurately as possible by pressing single marked keys which correspond with the various word/colour arrangements on a standard computer keyboard. The participant is asked to respond to the colour of the word and not the colour of the written word, except in the case where the word is in grey ink, to which the

participant is required to respond to the written word. The response to the colour of the word tests the participants' response inhibition and simultaneously tests reaction time (Stroop, 1935).

Incorporating the words written in grey ink, ensured that participants had to read and recognize the word cues and not only notice the colours, thereby invoking the Stroop effect (Stroop, 1935). The participants were asked not to speak the words but to respond to them by pressing the keys on the keyboard provided. For the white squares which appeared in the task, the participant was asked to mentally keep note of how many squares there were. The participant was asked to verbally recall the number of squares counted, thus giving an idea of the participant loading working memory. The behavioural data collected were extracted using E-prime and were cross-checked with the digital inputs to an EEG data file, **Figure 2.12** Acknowledge 4.1 (Biopac Systems Incorporated, 2012). The Behavioural data extracted included the number of correct responses, response time duration, errors of omission and commission.

2.10.4.1 Stroop task setup

The EEG setup and Stroop task were explained to the participant to ensure that they understood what was required. The EEG recording of the Stroop task from each participant was conducted in a room where the light was switched off and only partial light streamed through a small window above the door to the room. Each participant was seated in front of a 15-inch computer screen approximately 60cm away from the participant's face, with a mouse and keyboard within arm's reach. The keyboard keys 3, 4, 6 and 7 were appropriately labelled red, blue, green, and yellow. The participant was able to start the task by pressing the "enter" key when they were ready to start the task. Once the task was complete, the participant was asked to relax. The mental effort scale was handed to the participant for them to mark how much effort was applied to conduct the task. Only the researcher and participant were allowed in the room, to avoid any other external influences due to the sensitivity of the EEG.

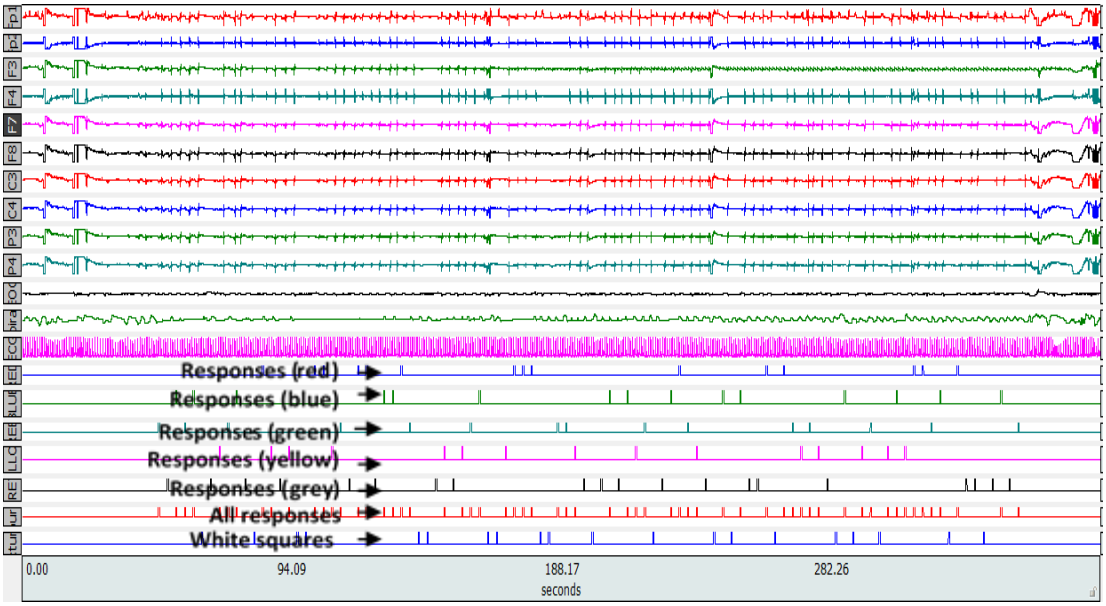


Figure 2.12 STROOP task full data set obtained from the Acqknowledge 4.1 software, indicating the duration of the STROOP task and the recording of seven digital channels used for this task. The participants' responses for the variable inter-stimuli intervals were recorded on digital channels 1 (red), 2 (blue), 3(green) and 4(yellow), digital channel 5(grey). Digital channel 6 represented all responses made and digital channel 7 represented the white squares seen throughout the task. All channels were collected at 500Hz. Behavioural data were collected through recorded through E-prime.

2.11 Electroencephalography setup

Prior to starting the EEG, the placement of the electrodes and tasks to be completed 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 from the forehead and on the side and below the right eye. Two sponge discs, used to support the Electrode Cap International electrode lycra cap (Electro-cap International inc, n.d.), were positioned on the forehead. Earrings were asked to be removed prior to the 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 Electrode Cap International electrode lycra cap was pulled onto the participant's 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 the electrode to the scalp or more gel was applied. Once all electrodes were producing excellent signals the EEG record was initiated, and the participant completed the REC, REO and cognitive tasks.

2.11.1 Electroencephalography data preparation for analysis

Preceding frequency and ERP extraction, the raw EEG data were corrected for EOG artefact using an automated independent component analysis within the data collection software package, Acqknowledge 4.1. Independent component analysis is based on a principle that statistically separates a mixed signal based on the assumption that the mixed signals are statistically independent (Biopac Systems Incorporated, 2012). The process results in two traces, one noisy trace and the other trace free of the specific noise removed. In this study, EOG artefact removal was conducted. It is important to apply independent component analysis for EOG artefact removal when extracting ERPs from a data set, due to eye blinking emitting a positive peak at 300 msec (Bonfiglio et al., 2009). All files which were EOG corrected were saved as a Matlab-coded file (extension .mat). Frequency bands and ERP waveforms were extracted using an automated Matlab-designed program (Matlab, Mathworks, MA, USA, developed in-house). The data will be bandpass filtered (FIR) with a Hamming window of 0.1-30Hz.

2.11.2 EEG Frequency band oscillations

The filtered EEG data from the resting conditions, resting eyes open and resting eyes closed, and relevant cognitive tasks will undergo Fast Fourier Transformation. Band frequencies that will be extracted include delta (δ, 0.1-4Hz), theta (θ, 4-7Hz), alpha (α, 7-14Hz), and beta (β, 15-30Hz) during resting conditions and the cognitive tasks. The extracted absolute power will be converted into relative band power (measured as %), to analyze group differences.

2.12 Event-related potential extraction

Event-related potentials will be extracted from three tasks; a continuous performance task (Williams, 2019), a cued target detection task (Fleur M. Howells et al., 2010) and the Stroop colour word conflict task (Hume et al., 2015). For each task, ERP waveforms extracted from

the pre-frontal (Fp_1, Fp_2) frontal (F_3 and F_4), central (C_3 and C_4), parietal lobes (P_3 and P_4) and occipital (O_3 and O_4) areas. The ERPs were extracted using an ERP extraction Matlab tool developed with a simple graphical user interface (GUI) (Matlab, Mathworks, MA, USA, developed in-house) (W. L. Martinez & Martinez, 2004). The ERP window setting was a 1000msec epoch measured 200msec before and 800msec after, the target stimulus. An artefact rejection limit of ±100μV was set for each extraction. This ensured the removal of an ERP with substantial distortion or artefact that may reduce the signal-to-noise ratio of the ERP waveform.

Grand mean average waveforms were generated to identify robust ERP components. For each ERP wave component, the amplitude (μV) and latency (ms) values were obtained. Robust ERP components were collected from the EEG data by creating grand averages of the ERP waveforms for each group (healthy controls, SCZ and MPD), and the data was plotted on an XY-lined scatter plot. The amplitude (μV) and latency (msec) values were extracted for each robustly identified ERP wave component. A visual inspection was conducted by plotting the participant data for each stimulus separately on a μV vs msec line graph. The visual inspection consisted of looking at each participant's data throughout the stimuli data extracted, to exclude participants with results which contained more than two sets of arbitrary data within each channel.

2.13 Statistical analysis

Statistical analysis was performed using the software package Statistica version 13 (Dell Inc, 2015). To determine the aims of the current thesis:

For the first aim, a group analysis was conducted to determine whether there were relative frequency activity differences for resting states; eyes open and eyes closed, between groups for (a) schizophrenia, methamphetamine-induced psychotic disorder, and healthy controls, and (b) Psychotic groups only separated by 1st generation antipsychotics (1st), 2nd generation antipsychotics (2nd), and not taking any antipsychotic medication (NONE). Then relationships were determined between population characteristics and resting state relative frequency.

For the second aim, group analysis was conducted to determine whether there were relative frequency activity differences for the continuous performance task and cued target detection task, between groups for (a) schizophrenia, methamphetamine-induced psychotic disorder and

healthy controls, and (b) psychotic groups only separated by 1st generation antipsychotics (1st), 2nd generation antipsychotics (2nd), and not taking any antipsychotic medication (NONE). Then relationships were determined between population characteristics and continuous performance tasks and cued target detection task relative frequency.

For the third aim, group analysis was conducted to determine whether there were P300 event-related potential waveform differences for the continuous performance task and cued target detection task, between groups for schizophrenia, methamphetamine-induced psychotic disorder, and healthy controls. Then relationships were determined between population characteristics and continuous performance task and cued target detection task P300 event-related potential.

For the fourth aim, group analysis was conducted to determine whether there were relative frequency activity and, N170 and P300 event-related potential differences for the STROOP task between groups for (a) schizophrenia, methamphetamine-induced psychotic disorder and healthy controls, and (b) psychotic groups only separated by 1st generation antipsychotics (1st), 2nd generation antipsychotics (2nd), and not taking any antipsychotic medication (NONE). Then relationships were determined between population characteristics and relative frequency activity and, N170 and P300 event-related potential differences for the STROOP task.

For the fifth aim, in this exploratory study, a group analysis was conducted to determine whether there were differences in the cytokine levels (IL-1β, IFN-γ, IL-12p70, IL-8, IL-10 and TNF-α) between groups for schizophrenia, methamphetamine-induced psychotic disorder and healthy controls. Then relationships were determined between cytokine levels and the population characteristics, relative frequency (resting states, continuous performance task, cued target detection task and STROOP task) and P300 event-related potential waveform (continuous performance task, cued target detection task and STROOP task).

The analysis of aims 1, 2 and 4, was achieved by first analyzing the distribution for each variable, using the 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 ($p<0.05$). Where appropriate, according to the data distribution, correlation analysis was performed using Pearson's or Spearman's rank order (Rho $>\pm0.6$ and p-value <0.01). The strength of the relationship was increased to ±0.6 Rho (Mukaka, 2012) and increased the probability of the relationship being repeated by lowering the p-value to 0.01 (Dahiru, 2008). Further, a one-way analysis of covariance (ANCOVA) was conducted to compare the effectiveness of the correlation where the data were significant, however, the analysis was limited to parametric data only.

The analysis of aims 3 and 5 was achieved by first analyzing the distribution for each variable, using the 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 ($p<0.05$). Where appropriate, according to the data distribution, correlation analysis was performed using Pearson's or Spearman's rank order (Rho $>\pm0.6$ and p-value <0.01).

3 Resting cortical arousal signatures in schizophrenia and methamphetamine-induced psychotic disorder

In this chapter, the differences in resting cortical arousal signatures for schizophrenia and methamphetamine-induced psychotic disorder were investigated.

Abstract

Introduction: Methamphetamine-induced psychotic disorder (MPD) is a psychotic disorder previously used as a pharmacologically induced model for schizophrenia. Schizophrenia (SCZ) is known to exhibit variations in electroencephalography (EEG) frequency activity, however, the question of whether MPD follows SCZ with similar variations in frequency activity needs to be investigated due to the current lack of information. The study of resting state oscillations is important to uncover the behavioural processes underlying normal and pathophysiological functioning. The purpose of this study was to identify differences in relative frequency between SCZ, MPD and socio-demographically matched controls (CON) in rest with eyes closed (REC) and rest with eyes open (REO), and to examine their potential associations of relative frequency activity with demographic and clinical symptom profiles and medications.

Methods: EEG was recorded from 104 individuals: SCZ (n=38), MPD (n=31), and CON (n=35), who completed two 3-minute tasks, REC and REO. Group differences were determined by ANOVA with Bonferroni post-hoc correction or multivariate Kruskal-Wallis test, dependent on data distribution. Associations were determined using Pearson's or Spearman's rank order correlation ($p<0.01$) where appropriate.

Results: Significant group differences were found when assessing REC and REO. First, SCZ reported reduced REC parietal ($p=0.011$) alpha and greater REC prefrontal theta ($p=0.021$), and greater REO central to occipital theta (C_3 $p=0.027$, C_4 $p=0.041$, P_3 $p=0.00046$, O_2 $p=0.049$) compared to CON. Second, MPD reported reduced right prefrontal REO delta ($p=0.035$) compared to CON, and prefrontal REC delta (Fp_1 $p=0.017$, Fp_2 $p=0.033$) was reduced compared to SCZ. Third, SCZ reported reduced REC prefrontal (Fp_1 $p=0.012$, Fp_2 $p=0.028$) and left central ($p=0.034$) beta, and reduced REC parietal ($p=0.021$), REC prefrontal ($p=0.045$) and REO ($p=0.025$) posterior alpha compared to MPD. Lastly, there were significant associations found in alpha drug use in SCZ (REO F_3 $r=-0.83$; $p=0.00035$, P_4 $r=-0.69$; $p=0.0084$) and MPD (REC Fp_2 $r=-0.63$; $p=0.000095$), beta for education in MPD (years of schooling (O_2 $r=0.60$; $p=0.00034$), and total years of formal education (O_2 $r=0.60$; $p=0.00028$)), and delta for SCZ (drug use F_3 $r=0.84$, $p=0.00029$; F_4 $r=0.71$, $p=0.0056$; P_4 $r=0.73$, $p=0.0046$;

O_2 r=0.75; p=0.0027), but only correlates for education and duration of methamphetamine use were found for theta.

Conclusion: This is the first study to show reduced frontal delta resting state activity in MPD compared to SCZ. We also found reduced anterior alpha and beta and reduced posterior alpha in SCZ during resting state and in addition their potential associations with clinical symptoms and prescribed medication. This study indicates decreased alpha and increased theta and beta activity during REC within these psychotic disorders. Psychotic disorders hold significant differences in REC and REO relative frequencies compared to CON. The data presented in the first directly compare relative frequency in SCZ and MPD and suggest that they are underpinned by different mechanisms in the pathogenesis of these two disorders.

3.1 Introduction

Electrophysiological abnormalities have been extensively studied in schizophrenia (SCZ) (Newson & Thiagarajan, 2019). Electroencephalography (EEG) measures real-time brain electrical activity, which can provide information about specific frequencies and has the potential to aid in diagnosis (Ranlund et al., 2014). Frequency oscillations can be organized into two systems that control brain function at the cognitive and sensory levels (Herrmann & Knight, 2001). Herrmann and Knight concluded that the oscillations observed during the resting state revealed an underlying relative level of consciousness of the person. Resting-state studies examine neural network activity and its association with regional brain areas (H.-L. S. Wang et al., 2015). Resting eyes closed (REC) and resting eyes open (REO) conditions lead the brain to switch between two different information processing states (Nakano, Kato, Morito, Itoi, & Kitazawa, 2013). The two processing states can be defined as exteroceptive for REO where attentional and ocular motive systems are activated, and interoceptive for REC where non-visual sensory systems are activated (Marx et al., 2003). The literature indicates that the study of resting state oscillations is important to uncover the behavioural processes underlying normal and pathophysiological functioning (Uhlhaas, Haenschel, Nikolić, & Singer, 2008).

In psychotic disorders, evidence of impairment within exteroceptive and interoceptive systems is often noted (Barch & Sheffield, 2014). However, most resting state studies limit their focus to a single psychotic disorder (Newson & Thiagarajan, 2019). To properly distinguish differences between psychotic disorders more than one disorder needs to be investigated (Newson & Thiagarajan, 2019). Methamphetamine-induced psychotic disorder (MPD) reliably displays a clinical symptom profile of SCZ and is often considered a pharmacological model

for SCZ (Featherstone et al., 2007; Wearne & Cornish, 2018b). After an initial diagnosis of MPD is made, if a psychotic episode is not preceded by the use of methamphetamine a diagnosis of SCZ is applied (American Psychiatric Association, 2013). Excessive synaptic concentrations of dopamine, norepinephrine and serotonin were found to result from methamphetamine intoxication (Newton et al., 2003; Wearne & Cornish, 2018b). However, the neurobiology which ultimately results in the presentation of MPD is not fully understood. Current evidence suggests functional and structural alterations of frontal, thalamic and striatal brain regions take place and lead to the presentation of MPD (Wearne & Cornish, 2019).

A prominent reported EEG frequency is alpha, with a significant number of studies suggesting that alpha power is reduced in SCZ during REO and REC, **Table 1**. The alpha frequency (8–13Hz) at rest indicates the current physiological state of being awake, relaxed, non-vigilant, and unfocused (Busch et al., 2009). Alpha frequency activity is present throughout the brain during resting and waking states and is stronger throughout the occipital area when the eyes are closed. Changes in alpha activity have been reported across REC and REO (Tan, Kong, Yang, Jin, & Li, 2013). This literature shows that a state of reduced alpha activity in REC is associated with an increase in alertness and attention-demanding processes (K. A. MacLean et al., 2009; M. H. MacLean, Arnell, & Cote, 2012). Furthermore, it is hypothesized that the decrease in alpha activity during REC indicates cortical idling and internal mental processing and social cognition (Knyazeva et al., 2008). During REO, alpha activity has been shown to decrease as a result of reduced processing of visual stimuli (Uhlhaas et al., 2008).

Research in SCZ has revealed visual perception and cognition impairments are associated with alpha-frequency activity (Ramsay, Lynn, Schermitzler, & Sponheim, 2021). During REO, SCZ presented with descending alpha activity in the frontal areas toward the posterior regions (J. W. Kim et al., 2015; Omori et al., 1995). Literature regarding REC frequency activity in SCZ has led to conflicting results. Some studies comparing SCZ to healthy controls (CON), have shown that SCZ-alpha activity increases during REC (Kam et al., 2013; Balaji Narayanan et al., 2014; Omori et al., 1995). Further, a study in never treated SCZ patients showed reduced alpha activity during REC (Omori et al., 1995). However, it was found that alpha was increased over the frontal and central regions (Balaji Narayanan et al., 2014) and in the posterior regions of the brain during REC (Laufs et al., 2003). A 2018 study found that SCZ had reduced alpha activity during a resting eyes-closed task compared to controls (Fleur M Howells et al., 2018). In a functional magnetic resonance imaging/EEG study, alpha was found to be reduced in SCZ compared to CON (Razavi et al., 2013). Further, an association was found between the default

mode network and alpha frequency in SCZ (Razavi et al., 2013). Another study examined differences between positive and negative forms of SCZ and found that both positive and negative forms of SCZ presented with a reduction in alpha activity compared to CON (Begić et al., 2000). It was found that increased alpha activity was detected during REO. The contradictory results found could be a result of comparing REC and REO as shown in (Kan, Croarkin, Phang, & Lee, 2017; L. Li, 2010) where lower alpha activity was found in REO.

EEG and symptom association studies have shown correlations between negative symptoms, assessed via the positive and negative symptom scale (PANSS) scale, and the alpha/ theta ratio across the frontotemporal region in SCZ (Wallwork, Fortgang, Hashimoto, Weinberger, & Dickinson, 2012). A 2018 study revealed no correlation between symptom severity to frequency of activity (Newson, 2018). In a second study, EEG activity was shown to be altered by antipsychotic medication (Blume, 2006). A third study found reduced alpha activity (Knott et al., 2001). Further significant associations were found between frequency activity and level of functioning, and the PANSS negative subscale (theta, alpha, and beta frequencies). The literature suggests that reduced alpha frequency activity in REC and increased alpha during REO is a prominent trait which could potentially be used to identify SCZ during resting conditions.

In addition to alpha frequency activity, theta frequency activity in SCZ has been commonly reported to be associated with different phases of the disorder (Shreekantiah Umesh, Tikka, Goyal, Nizamie, & Sinha, 2016). Theta frequency (4-8Hz) is increased during a test of visual images, hypnotic or hypoapoptic images, and light sleep. Theta frequency activity is more pronounced in the prefrontal cortex, somatosensory cortex, and visual cortex (Uhlhaas et al., 2008). Theta frequency activity in the frontal and midline areas of the brain is reduced when the default mode network is activated (Sanders, 2018). Current literature comparing SCZ to CON had varying results across REO and REC. Few studies have addressed theta activity during REO, however, it was noted that increased theta activity was detected in SCZ (Kan et al., 2017; L. Li, 2010). During REC, SCZ with negative symptoms showed increased theta activity over the frontal and parieto-occipital areas (Begić et al., 2000). The slowing of EEG activity in the frontal lobe had associations with altered working memory and planning in SCZ (Veiga et al., 2003). Other studies have found a positive correlation between increased theta activity and executive function, reasoning, and attention (Trammell et al., 2017). Further studies in SCZ showed increased theta activity during REC, for SCZ drug-naïve subjects, and chronic and first-episode patients (Shreekantiah Umesh et al., 2016). Further, widespread

increases in theta activity in psychotic patients prescribed antipsychotic medication (Knott et al., 2001). Conflicting results were found during REC when SCZ exhibited increased theta activity (Omori et al., 1995) and when SCZ was found to exhibit decreased theta activity (Goldstein et al., 2015). In addition, it has been found that theta activity is reduced in the frontal and lateral brain regions (Barry & De Blasio, 2017). More information is needed on SCZ theta frequency activity during REC as current literature on the topic is conflicting.

Beta activity, along with alpha and theta activity, plays a crucial role in cortical activation, which is often impaired in SCZ (Uhlhaas et al., 2008). Beta (13-30Hz) activity is associated with being present during wakefulness, alertness, concentration, problem-solving, and during rapid eye movement sleep. Beta activity has also been associated with cognitive processing, specifically, it is found when completing cognitive tasks involved in reward processing (Uhlhaas et al., 2008). Cortical activation was seen by an increase in beta activity (Gola, Kamiński, Brzezicka, & Wróbel, 2012). Beta activity is more common in cortical areas, including subcortical structures; thalamic nuclei, hippocampus, basilic ganglia and olfactory bulbs (Uhlhaas et al., 2008). A positive correlation between beta activity and accuracy on visual vigilance tasks has been found in the occipital-parietal areas in the brain (Gola et al., 2012). When investigating beta activity during REO, a reduction in beta activity was detected in SCZ (Kan et al., 2017; L. Li, 2010). During REC, SCZ had increased beta activity compared to controls (Kam et al., 2013; Razavi et al., 2013). Increased beta frequency activity was found in both positive and negative forms of SCZ compared to controls (Begić et al., 2000). However, no significant changes in beta activity were reported in REC and REO for SCZ (Tan et al., 2013). Most of the resting state studies reported low beta frequency amplitudes. However, as beta activity has been associated with cognitive processing, it could potentially be a good indicator for identifying SCZ.

The delta frequency (0-4Hz) is detected in phases of wakefulness and sleep, such as through meditation, inner concentration, prayer, and spiritual awareness. It has been suggested that delta activity is associated with the activation of cognitive and emotional processing and therefore should be increased during cognitive activation in the frontal, central and posterior brain areas (Güntekin & Başar, 2016). During REO, increased delta activity was found in the prefrontal and frontal regions (Kan et al., 2017). Increased delta activity during REC in SCZ was found in several studies, **Table 3.1**. During REC, it was found that delta activity was reduced in the frontal and lateral brain regions (Barry & De Blasio, 2017). In SCZ, delta frequency activity was found to be reduced during REC (Begić et al., 2000; Knyazev, 2012).

Research has shown decreased delta frequency activity in a negative form of SCZ, compared to CON (Begić et al., 2000). Further, increased delta activity for REC was found in SCZ compared to CON (Kam et al., 2013). The decrease in delta activity was unaffected by drug use as evidenced by the recruitment of untreated SCZ patients (J. W. Kim et al., 2015). According to the literature, reduced delta activity could be seen as a good indicator for SCZ.

Table 3.1 Schizophrenia electroencephalography resting state activity

			Frequency bands				
		Participants	**Delta**	**Theta**	**Alpha**	**Beta**	**Symptom correlates**
Resting eyes open condition							
Hanslmayr et al., 2013		26 SCZ 26 CON	SCZ > CON	-	-	-	
Howells et al., 2018	*	28 SCZ 29CON	SCZ > CON	-	SCZ < CON	-	
Omori et al., 1995		20 SCZ 20 CON	-	SCZ > CON	SCZ > CON	-	
Resting eyes closed condition							
Andreou et al, 2015		19 SCZ 23 CON	-	SCZ > CON	-	-	
Begić et al., 2000		25 SCZp 22 SCZn 50 CON	SCZp < CON SCZn > CON	SCZn > CON	SCZp < CON SCZn < CON	SCZp > CON SCZn > CON	
Garakh et al. 2015		32 SCZ 40 CON	-	SCZ > CON	SCZ < CON	-	
Goldstein et al., 2015		13 SCZ, 13 CON	SCZ < CON	SCZ < CON		-	
Howells et al., 2018	*	28 SCZ 29CON	SCZ > CON	-	SCZ < CON	-	
Kam et al., 2013		132 SCZ 136 CON	SCZ > CON	-	SCZ > CON	SCZ > CON	
Kim et al, 2015		90 SCZ 90 CON	SCZ > CON	SCZ > CON	SCZ < CON	-	
Knyazeva et al, 2008		14 SCZ 14 CON	SCZ < CON	SCZ < CON	SCZ < CON	-	Negative correlation between PANSS and alpha in SCZ
Narayanan et al, 2014		225 SCZ 200 CON	SCZ > CON	SCZ > CON	SCZ > CON	-	Negative correlation between PANSS and alpha in SCZ
Omori et al., 1995		20 SCZ 20 CON	-	SCZ > CON	SCZ > CON	-	
Razavi et al, 2013		11 SCZ 11 CON	SCZ > CON	SCZ > CON	SCZ < CON	SCZ > CON	
Shreekantiah-Umesh et al, 2016		20 SCZ 20 CON	-	SCZ > CON	-	-	
Veiga et al., 2003		25 SCZ 40 CON	SCZ > CON	SCZ > CON	-	-	

**Delta alpha ratio*
Abbreviations: healthy controls (CON), schizophrenia (SCZ), positive symptoms (SCZp), negative symptoms (SCZn)

Variations in EEG frequency activity in SCZ were considered, while investigations of potential variations in MPD are limited. Despite limited data being available on MPD, a handful of studies have investigated frequency alterations for resting state activity in methamphetamine use/dependence disorders and with a prescription of dexamphetamine, **Table 3.2**. For alpha, a study conducted on dexamphetamine showed reduced alpha frequency band activity compared to CON, however, the study noted no significant difference between REO and REC (Albrecht et al., 2016). The reduced alpha activity was found in MPD compared to CON (Khajehpour et al., 2019). An investigation of delta/alpha frequency during REO and REC found increased delta/alpha frequency activity in MPD during REO (Fleur M Howells et al., 2018). Although data on alpha frequency activity in MPD is limited, differences between MPD and CON are seen. However, differences in alpha activity between SCZ and MPD are yet to be determined.

Increased theta activity along with delta activity was previously shown to be associated with poor cognitive performance in methamphetamine-dependent individuals (Ceballos et al., 2009). Quantitative EEG studies have shown increased theta activity in methamphetamine dependant users compared to CON (Newton et al., 2004). In a study where non-psychotic participants were administered dexamphetamine, global theta frequency activity was reduced in REO, and REC (Albrecht et al., 2016). During REC, recently abstinent methamphetamine-dependent users had decreased theta frequency activity across the central brain areas (Shafiee-Kandjani et al., 2020). Decreased theta activity across methamphetamine-dependent users, individuals prescribed dexamphetamine and MPD, was a trend amongst the handful of studies found in current literature. The reduced theta activity in recently abstinent methamphetamine users shows that methamphetamine affects the brain in the long term, however, this needs further investigation.

Then for delta frequency activity in MPD, the delta band showed enhanced coupling values compared to CON (Khajehpour et al., 2019). Similarly to theta frequency activity, increased delta activity was previously shown to be associated with poor cognitive performance in methamphetamine-dependent individuals (Ceballos et al., 2009). In a study where non-psychotic participants were administered dexamphetamine, global delta frequency activity was reduced in both REO and REC (Albrecht et al., 2016). Methamphetamine-dependent users who abstained from use for 4 days had increased delta bands during REC (Newton et al., 2003). Literature is lacking on associations of delta frequency in MPD. However, literature has shown decreased delta frequency with methamphetamine abstinence, indicating that abstaining from methamphetamine could potentially increase cognitive performance (Salo et al., 2009).

Studies on beta frequency showed reduced activity in frontal regions but increased in parietal, occipital-temporal and occipital regions in response to dexamphetamine (Albrecht et al., 2016). Further, a 2019 study found decreased beta frequency activity in MPD compared to CON (Khajehpour et al., 2019). MPD showed enhanced beta oscillatory rhythm, which was most notable during REO although the interaction contrasts did not indicate strong differences between eye conditions. Current research shows that long-term use of methamphetamine can have irreversible structural and physiological alterations in neurotransmitter systems (Shafiee-Kandjani et al., 2020). However, the prescription of antipsychotic medication to patients exhibiting positive or negative symptoms of psychosis can be used to manage symptoms (Abekawa, Ito, Nakagawa, Nakato, & Koyama, 2008). As mentioned previously, beta activity during rest is often found to have lower amplitudes. The current literature needs more information on beta frequency activity at rest and whether there are differences between MPD and SCZ.

Table 3.2 Resting state activity for methamphetamine use/ dependence disorders and with prescription of dexamphetamine

		Frequency bands			
	Participants	**Delta**	**Theta**	**Alpha**	**Beta**
Resting eyes open condition					
Albrecht et al, 2016	14 dexamphetamine 14 CON	MPD < CON	MPD < CON	MPD < CON	MPD > CON posterior MPD < CON anterior
Howells et al., 2018	28 SCZ 24MPD	MPD > SCZ	-	MPD > SCZ	-
Resting eyes closed condition					
Albrecht et al, 2016	14 dexamphetamine 14 CON	MPD < CON	MPD < CON	MPD < CON	MPD > CON posterior MPD < CON anterior
Howells et al., 2018	24MPD 29CON	MPD > CON	-	MPD > CON	-
Khajehpour et al, 2019	36 MPD 24 CON	-	-	MPD < CON	MPD < CON
Newton et al, 2003	11 methamphetamine-dependent 11 CON	MPD > CON	MPD > CON	-	-
Newton et al, 2004	9 methamphetamine-dependent 10 CON	-	MPD > CON	-	-
Shafiee-Kandiani et al, 2020	18 patients with methamphetamine abstinence and 18 CON	MPD < CON	MPD < CON	-	-

Abbreviations: healthy controls (CON), methamphetamine induced-psychotic disorder (MPD), anterior applies to prefrontal, frontal and central regions, posterior applies to parietal and occipital regions

The purpose of this study was to identify differences in relative frequency activity in SCZ, MPD and CON during resting eyes closed (REC) and resting eyes open (REO). In addition, we investigated the potential associations of resting states with demographic variables and prescribed medication. To determine the relative frequency differences in SCZ, MPD and CON, we recorded EEG band frequency oscillations during resting conditions: REO and REC. We aimed to identify the relative frequency composition (alpha, theta, beta, and delta) of REO and REC EEG in SCZ, MPD and CON to help strengthen the current literature on the mechanisms of SCZ and MPD. We expected to report decreased alpha activity and increased theta activity during REC over frontal regions in psychotic disorders compared to CON. Then we expected to report increased alpha and decreased theta and beta activity during REO, strongly evident over parietal and occipital regions in the psychotic disorders compared to CON. Between psychotic groups, we expected differentiation in frequency activity, expecting SCZ to report greater theta activity over frontal regions and greater decreases in alpha activity globally during both resting conditions.

3.2 Method

3.2.1 Research participants

104 South African individuals, between the ages of 20 and 45 years, participated in this study: 38 with SCZ (8 females/30 males), 31 with MPD (7 females/24 males), and 35 healthy controls (CON: 15 females/20 males). The study was approved by the Health Sciences Research Ethics Committee, at the University of Cape Town (HREC Ref. No.: 479/2019). Western Cape Provincial and Hospital approval was also obtained. All research activities were conducted in accordance with the Declaration of Helsinki. All research participants provided voluntary informed consent.

Participants visited the laboratory twice. The first visit included the provision of informed consent and an assessment clinical interview. All participants underwent a Structured Clinical Interview for Diagnostic Systematic Manual- IV (SCID-DSM-IV), with modifications to include changes made in DSM-5. Control participants were excluded if there was a history of psychotic symptoms or a family history of psychotic disorder. Participants with a psychotic disorder were excluded if they did not meet the diagnostic criteria for the study conditions: for example, participants with schizoaffective disorder were excluded. Participants were also excluded if they were younger than 19 years or older than 40 years, had general medical conditions that required prescription medications, had an apparent learning disability, had major brain trauma/surgery, had any history of cardiovascular insult, individual or family history of epilepsy, medical implants or any metal within their person, for example, shrapnel.

Female participants were excluded if they were pregnant or lactating. Patients with SCZ were excluded if any of their episodes were considered to be related to the use of a substance. MPD included psychotic symptoms with onset during methamphetamine intoxication or withdrawal and did not persist beyond 1 month since the last use of methamphetamine, or evidence of an underlying ‘primary’ psychotic disorder not related to the use of methamphetamine. Evidence that the symptoms are better accounted for by a psychotic disorder that is not methamphetamine-induced included the following: the symptoms precede the onset of the methamphetamine use; the symptoms persist for a substantial period of time after the cessation of acute withdrawal or severe intoxication, or are substantially in excess of what would be expected given the amount of methamphetamine used or the duration of use; or there is other evidence that suggests the existence of an independent non-MPD (e.g. a history of recurrent non-methamphetamine- related episodes). Patients with MPD were excluded if it was unclear

if methamphetamine was causal to their symptoms or diagnosis, and if any of their psychotic episodes may have been related to another substance of abuse.

3.2.2 Study design

The second visit included a full morning of brain imaging. All EEGs were performed between 09h00-11h00, on a weekday. All clinical scales were performed on the same day and after the morning of brain imaging by trained clinical personnel.

Clinical rating scales included the Positive and Negative Syndrome Scale (PANSS); Calgary Depression Scale for Schizophrenia; Hamilton Rating Scale for Depression. Chlorpromazine equivalents were calculated from current medication regimes. Drug use history, nicotine, alcohol and methamphetamine were recorded using the Kreek-McHugh-Schluger-Kellogg scale (KMSK).

3.2.3 Electroencephalography

EEG recording of REO and REC was undertaken using a simple EEG montage that included prefrontal (Fp1 and Fp2), frontal (F3 and F4), central (C3 and C4), parietal (P3 and P4) and occipital (O1 and O2) electrodes. Standard 10/20 caps (Electro-Cap International, Inc.) were used, of either medium or large size depending on the head circumference of the participant. Participants were grounded peripherally, linked earlobe reference was applied, and electrooculography (EOG) was recorded. The EEG system used was the Biopac MP150 system with 100 C EEG amplifiers and an EOG amplifier (Biopac Systems, Inc.). Digital EEG data and analogue data, from E-prime, were collected via the MP150 system, with a sampling rate of 500Hz, and were visualised in real-time using Acq-Knowledge 4.1 (Biopac Systems, Inc.).

For EEG data processing, data were first eye blink corrected and movement corrected (EOG), using automated ICA EOG correction in Acqknowledge 4.1 (Biopac Systems, Inc.), and then bandpass filtered 0.1–30Hz and Fourier transformed, using an in-house Matlab GUI, to accommodate differences in participant electrical brain activity conduction. Relative (%) frequency bands power activity was extracted: delta (0.1–4.0Hz), theta (4–7Hz), alpha (7–14Hz) and beta (15–30Hz).

Resting states

Prior to obtaining EEG records, participants were familiarised with the different conditions: REO, and REC. For REO, using E-prime, a cross-hair, +, was presented on the screen and participants were asked to relax and look at the cross-hair. For REC ‘CLOSE EYES’ was

presented on the screen in front of them. Records of 3 min EEG were obtained for each of the resting-state conditions.

3.2.4 Statistical analysis

Statistical analysis was conducted using Statistica (Dell Inc, 2015). As EEG data is naturally skewed, an attempt was made to log10 transform the data which were non-parametric (Merrin & Floyd, 1992; Newton et al., 2003, 2004; Smulders, ten Oever, Donkers, Quaedflieg, & van de Ven, 2018). A second transformation attempt was conducted on the original data using the box-cox transform (Bicego & Baldo, 2016; Smulders et al., 2018). These and other transforms failed, which led to the use of the natural data obtained, applying parametric or non-parametric analysis dependent on data distribution.

To characterize our population, group differences in demographics (age on the day of testing, duration at school, tertiary education, total years of education, and handedness), clinical scale scores including the Positive and Negative Symptom Scale for Schizophrenia (PANSS) total score, PANSS positive symptom subscale, PANSS negative symptom subscale, PANSS general psychopathology subscale, duration of illness, drug use (methamphetamine, alcohol, tobacco, cannabis), and medication use (chlorpromazine equivalent dose), are reported between groups (CON, SCZ and MPD) and antipsychotic medication grouping (Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd).

A descriptive statistical analysis was applied to the data to determine normality using the Shapiro-Wilks 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. Parametric data underwent univariate one-way analysis of variance (ANOVA). When the ANOVA yielded significance, underwent post-hoc testing with Bonferroni correction to determine whether there were between-group differences ($p<0.05$). Non-parametric data 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 ($p<0.05$).

To determine group differences in relative frequency for the resting states (REC and REO) an analysis was conducted for (a) three groups (CON, SCZ and MPD) and to identify the differences within the (b) psychotic groups (SCZ, MPD) according to antipsychotic medication (Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic

medication (1st); prescribed 2nd generation antipsychotic (2nd). This was achieved by (1) analysing the distribution for each variable, using the Shapiro-Wilks test. Parametric data underwent univariate one-way repeated measures analyses of variance (ANOVA). When the ANOVA yielded significance, underwent post-hoc testing with Bonferroni correction to determine whether there were specific group differences ($p<0.05$). Non-parametric data 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) Where appropriate, according to the data distribution, correlation analysis was performed using Pearson's or Spearman's rank order (Rho $>\pm0.6$ and p-value <0.01) and (3) a one-way analysis of covariance (ANCOVA) was conducted to compare the effectiveness of the correlation where the data were significant, however, the analysis was limited to parametric data only.

3.3 Results

3.3.1 Participant demographics

A total of one hundred and four individuals, between the ages of 20 and 45 years, participated in this study: thirty-eight participants with a diagnosis of schizophrenia (SCZn=38; 8 females/30 males), thirty-one participants with a diagnosis of methamphetamine-induced psychotic disorder (MPDn=31; 7 females/24 males), as well as thirty-five socio-demographically matched control participants (CONn=35; 15 females/20 males), **Table 3.3**.

Years of education were found to differ: years of schooling ($H_{2,104}$=23.44; p<0.0001) where CON completed more than SCZ (p=0.00062) and MPD (p=0.00011); years of tertiary education ($H_{2,103}$=10.70; p=0.0047) where CON completed more than SCZ (p=0.024); total years of formal education ($H_{2,104}$=23.52; p<0.0001) where CON completed more than SCZ (p=0.000066) and MPD (p=0.00016), **Table 3.3**.

Within the psychotic groups, the duration of illness differed, where SCZ had held their psychiatric diagnosis longer than MPD ($H_{1,68}$=13.82; p=0.0002), and this was reflected in the number of psychotic episodes, where SCZ reported a greater number ($H_{1,69}$=6.12; p=0.013). Medication differences in psychotic groups were found for chlorpromazine equivalent dose was higher in SCZ than MPD ($H_{1,65}$=6.98; p=0.0082), then MPD reported fewer use of antipsychotic medication compared to SCZ (p=0.035), **Table 3.3**.

For clinical symptom scale scores, differences were found for the total and subscale scores of the Positive and Negative Syndrome Scale (PANSS) ($H_{2,102}$=52.28; p<0.0001), where scores were lower in CON compared to MPD (p<0.00015) and SCZ (p<0.0001), **Table 3.3**.

Methamphetamine use differences were limited to the psychotic groups (MPD and SCZ), due to the low reported use by our healthy controls. Finding the age of initial use ($H_{1,47}$=4.97; p=0.025) was earlier in MPD (p=0.026) and the duration of use ($F_{1,44}$=5.26; p=0.0089) was longer in MPD (p=0.014).

For lifetime use of drugs, as measured with KMSK, the methamphetamine score ($H_{2,104}$=49.33; p<0.0001) was higher in MPD compared to CON (p<0.0001) and SCZ (p=0.000040). The lifetime use of tobacco ($H_{2,104}$=6.77; p=0.033), heroine ($H_{2,104}$=16.78; p=0.00020) and cannabis ($H_{2,104}$=6.40; p=0.040) were found to differ by the group yet individual groups differences were not found **Table 3.3**.

Table 3.3 Research participant population characteristics

		Healthy control		Schizophrenia		Methamphetamine-induced psychotic disorder	
		n = 35 15 females/20 males		n = 38 8 females/30 males		n = 31 7 females/24 males	
		Median (min-max)		**Median (min-max)**		**Median (min-max)**	
Age (years)		30 (21-45)		29.5 (22-45)		28 (20-37)	
Handedness (ambidextrous: left: right)		2:1:32		0:1:37		0:1:28	
Education							
Years of schooling	[a]	12 (9-13)		10 (4-12)		10 (1-12)	
Years of tertiary education	[b]	0 (0-4)		0 (0-5)		0 (0-4)	
Total years of formal education	[a]	12 (9-16)		10.5 (4-17)		10 (1-16)	
Clinical history							
Duration of diagnosis (years)	[c]			7 (1.16-19)		3.75 (0.16-15)	
Number of psychotic episodes	[c]			3 (1-5)		2 (1-5)	
Clinical symptoms							
PANSS Total score	[d]	30 (30-35)		43.5 (30-91)		39 (30-97)	
PANSS Positive symptoms	[d]	7 (7-9)		11 (7-27)		8 (1-23)	
PANSS Negative symptoms	[d]	7 (7-8)		13.5 (7-28)		11 (7-45)	
PANSS General psychopathology	[d]	16 (16-19)		20 (16-45)		18 (16-37)	
Drug use							
Methamphetamine (used: not used)		2:33		15:23		31:0	
Age started using methamphetamine (years)	[e]	14-21		22.5 (15-36)		16 (12-34)	
Duration of methamphetamine use (months)	[f]	1-24		48 (5-144)		96 (10-228)	
Duration of methamphetamine abstinence (months)		*		9.23 (0.03-132)		0.84 (0.03-48)	
Lifetime drug use (KMSK)							
Alcohol (used: not used) score		25:10	7 (0-11)	22:16	5 (0-12)	20:11	7 (0-11)
Tobacco (used: not used) score	[g]	19:16	5 (0-13)	16:22	10.5 (0-13)	19:12	10 (0-13)
Cocaine (used: not used) score		3:32	0 (0-10)	26:12	0 (0-11)	26:5	0 (0-16)
Heroin (used: not used) score	[g]	0:35	0 (0-0)	5:33	0 (0-2)	9:22	0 (0-10)
Cannabis (used: not used) score	[g]	14:21	0 (0-14)	1:37	0 (0-14)	8:23	8 (0-14)
Methamphetamine (used: not used) score	[h]	4:31	0 (0-9)	15:23	0 (0-11)	28:30	10 (0-11)
Medication							
Chlorpromazine Equivalent Dose (mg)	[i]			300 (0-1100)		120 (0-750)	
Current prescribed antipsychotic medication				31		18	
1st Generation Antipsychotics	[j]			10		6	
(Haloperidol: Chlorpromazine: Fluanxol: Clopixol: Fluphenazine)				2:1:3:3:0		5:0:0:0:1	
2nd Generation Antipsychotics	[j]			23		13	
(Olanzapine: Risperidone: Clozapine: Quetiapine)				7:10:6:1		2:11:0:0	
Other medication				15		11	
Mood stabilizers							
Sodium valproate				8		5	
Anxiolytics							
Benzodiazepine: Diazepine				2:1		0:0	
Antidepressants							
Selective serotonin/ norepinephrine reuptake inhibitors (Fluoxetine: Tripilene: Citalopram)				3:1:0		0:0:0	
Anticholinergic							
Orphenadrine				4		5	

*[a] CON reported more years of schooling, and formal years of education compared to SCZ and MPD. [b] CON reported more years of tertiary education compared to SCZ [c] SCZ reported a longer diagnosis duration and more psychotic episodes compared to MPD. [d] CON reported lower scores for the PANSS scale total score, and its subscales compared to MPD and SCZ. [e] Methamphetamine use differences were limited to the psychotic groups due to the low number of CON reporting use of the drug, SCZ reported being older than MPD when first using methamphetamine and [f] SCZ reported a shorter duration of methamphetamine use compared to MPD. [g] Significant differences in lifetime drug use were found but not between groups for the KMSK tobacco, heroin and cannabis lifetime total scores. [h] MPD lifetime use of methamphetamine was greater compared to CON and SCZ. Medication use [i] SCZ reported a higher chlorpromazine equivalent dose compared to MPD and [j] MPD reported lower use of antipsychotic medication compared to SCZ. *CON duration of methamphetamine abstinence only 2 participants were reported using methamphetamine.*
Abbreviations: CON: Healthy controls; SCZ: Schizophrenia; MPD: Methamphetamine-induced psychotic disorder; PANSS: Positive and negative syndrome scale; KMSK: Kreek-McHugh-Schluger-Kellogg. Significance differences were reported at p<0,05

3.3.2 Resting eyes open relative delta activity

Group differences were found for REO delta over the right prefrontal electrode ($Fp_2(H_{2,102}=7.54$; p=0.023)) where MPD delta activity was lower compared to CON (p=0.035), **Table 3.4**.

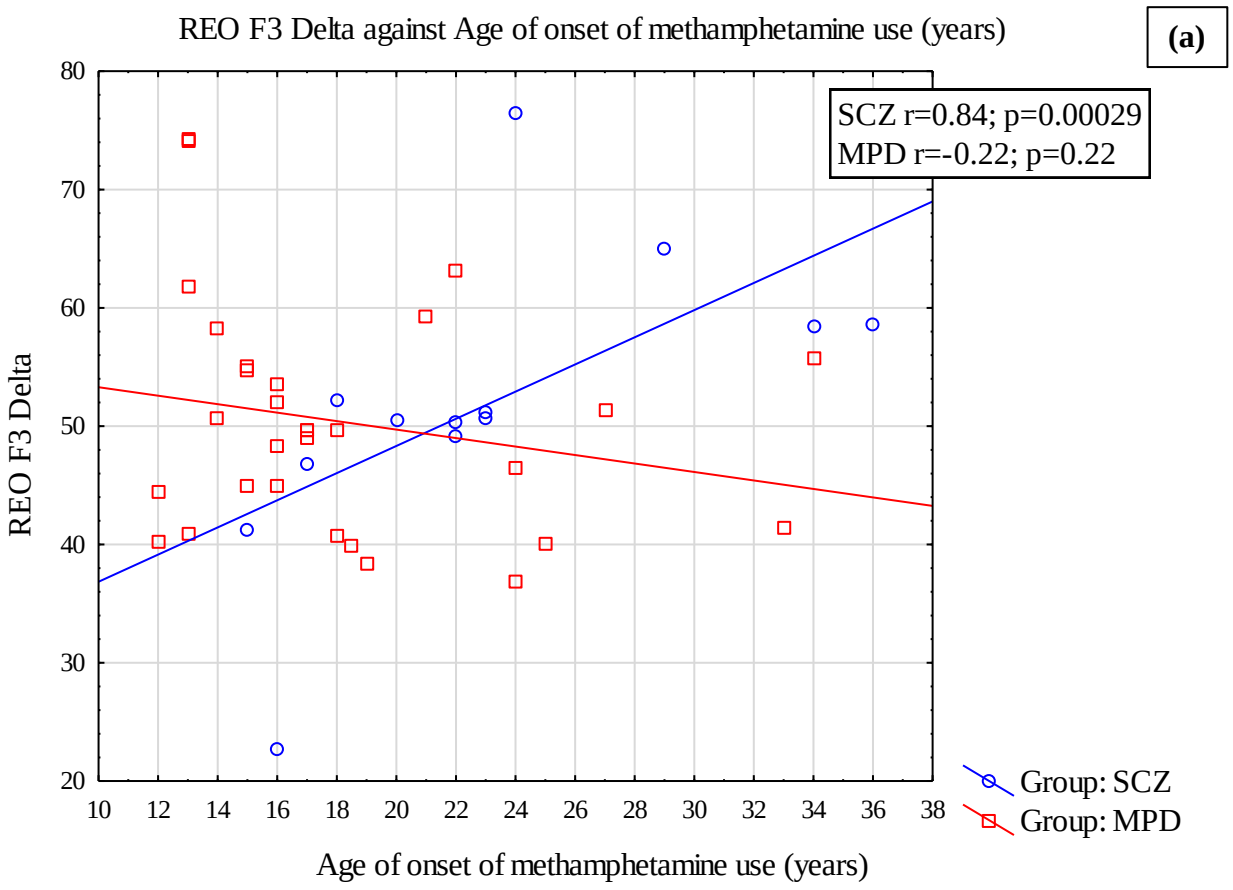
Table 3.4 Resting eyes open relative delta frequency activity

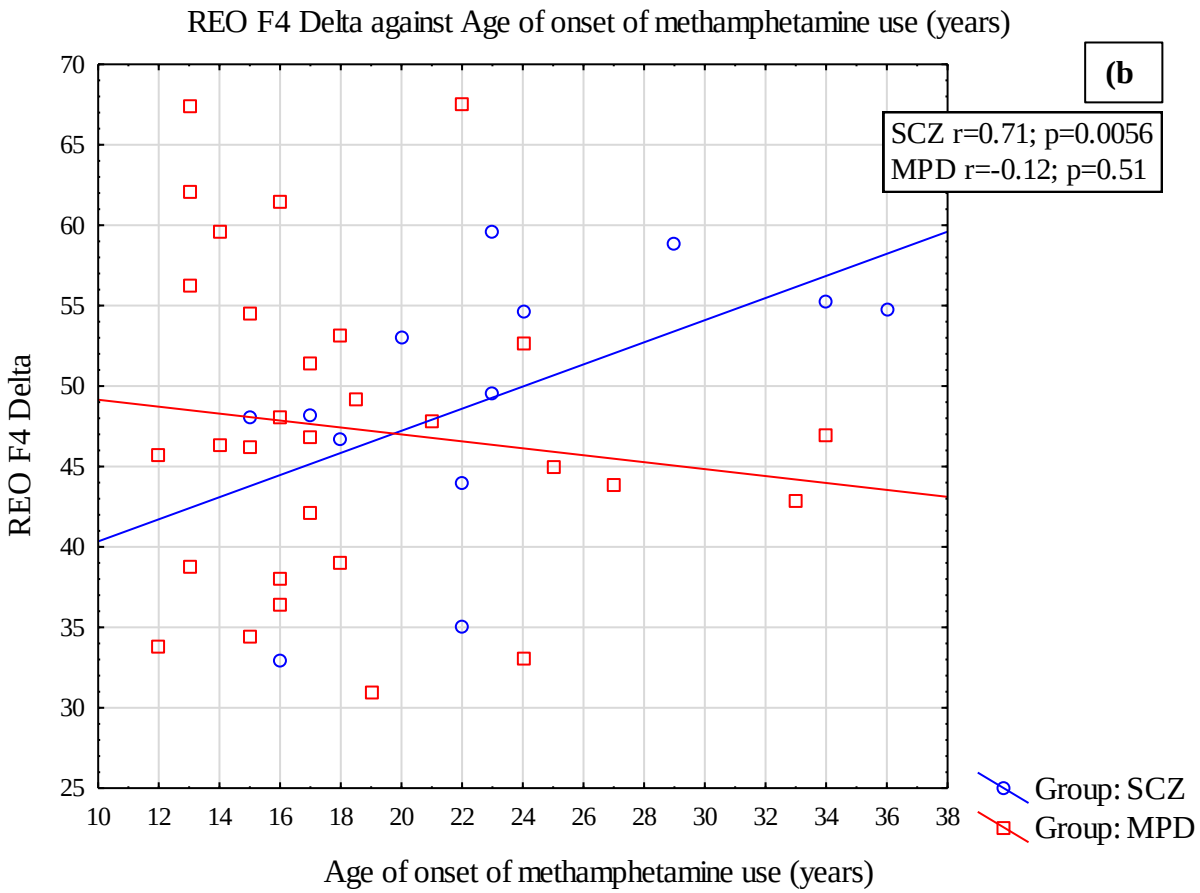
		Healthy control	**Schizophrenia**	**Methamphetamine-induced psychosis**		
		n = 35	n = 38	n = 31		
		15 females/20 males	8 females/30 males	7 females/24 males		
		Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test/ F test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	58.46 (43.59-68.48)	56.17(38.43-72.26)	55.83(38.33-74.37)	$F_{2,99}=1.04$; p=0.35	-
Right prefrontal cortex	**Fp_2**	57.98(31.67-81.59)	54.91(31.51-72.28)	48.84(32.88-75.25) *	$H_{2,102}=7.54$; p=0.023	MPD<CON p=0.035
Left frontal cortex	**F_3**	49.27(34.60-66.64)	51.05(16.33-76.40)	49.70(36.93-74.23)	$F_{2,99}=0.026$; p=0.97	-
Right frontal cortex	**F_4**	46.45(27.67-68.95)	48.10(15.78-64.22)	46.58(30.95-67.53)	$F_{2,99}=0.024$; p=0.97	-
Left central cortex	**C_3**	46.97(28.68-67.16)	50.32(22.57-69.68)	45.56(30.64-73.03)	$F_{2,99}=0.74$; p=0.47	-
Right central cortex	**C_4**	49.24(26.13-68.71)	52.33(24.67-79.31)	50.04(34.12-72.22)	$F_{2,99}=0.78$; p=0.46	-
Left parietal cortex	**P_3**	46.76(20.20-66.55)	47.22(27.50-67.06)	45.29(30.88-72.07)	$F_{2,99}=0.09$; p=0.91	-
Right frontal cortex	**P_4**	48.44(29.56-66.52)	52.47(23.64-76.63)	48.27(36.18-71.79)	$F_{2,99}=0.85$; p=0.43	-
Left occipital cortex	**O_1**	51.18(24.56-66.00)	50.91(24.07-73.83)	47.20(34.24-71.24)	$F_{2,99}=0.89$; p=0.41	-
Right occipital cortex	**O_2**	52.11(15.54-66.81)	50.42(37.70-70.89)	45.14(34.24-70.75)	$F_{2,99}=1.74$; p=0.17	-

****** *Methamphetamine-induced psychotic disorder (MPD) reported decreased delta activity during resting eyes closed (REC) compared to healthy controls (CON); Significance P<0, 05.*

Within the SCZ group those reported having used methamphetamine (n=15) their age of methamphetamine use onset positively correlated with REO delta activity for left and right frontal electrodes, through to the right parietal and occipital electrode ($F_3R_{spearman's(n=13)}=0.84$, p=0.00029; $F_4R_{spearman's(n=13)}=0.71$, p=0.0056; $P_4R_{spearman's(n=13)}=0.73$, p=0.0046; $O_2R_{Spearman's(n=13)=}0.75$; p=0.0027), **Figure 3.1**.

For patients not taking antipsychotics (n = 19 where, SCZn= 7; MPDn=13), REO right central delta activity negatively correlated with duration of tertiary education ($C_4R_{spearman's(n=19)}$= -0.72; p=0.00047), lifetime use of alcohol ($C_4R_{spearman's(n=19)}$=-0.69; p=0.00087) and cannabis ($C_4R_{spearman's(n=19)}$=-0.64; p=0.0026), **Figure 3.2**.


REO F3 Delta against Age of onset of methamphetamine use (years)
(a)
SCZ r=0.84; p=0.00029
MPD r=-0.22; p=0.22
REO F3 Delta
Age of onset of methamphetamine use (years)
Group: SCZ
Group: MPD


REO F4 Delta against Age of onset of methamphetamine use (years)
(b
SCZ r=0.71; p=0.0056
MPD r=-0.12; p=0.51
REO F4 Delta
Age of onset of methamphetamine use (years)
Group: SCZ
Group: MPD

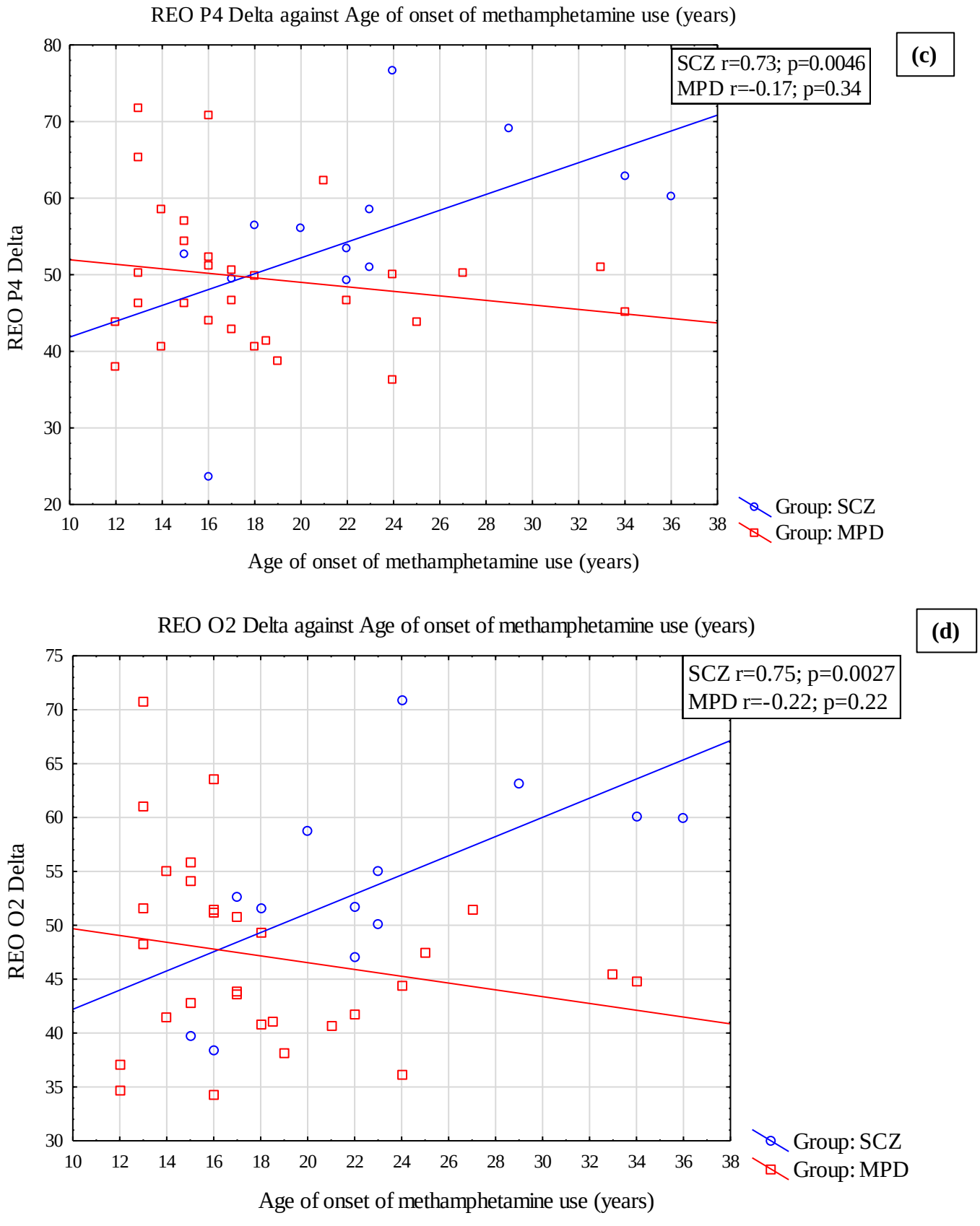
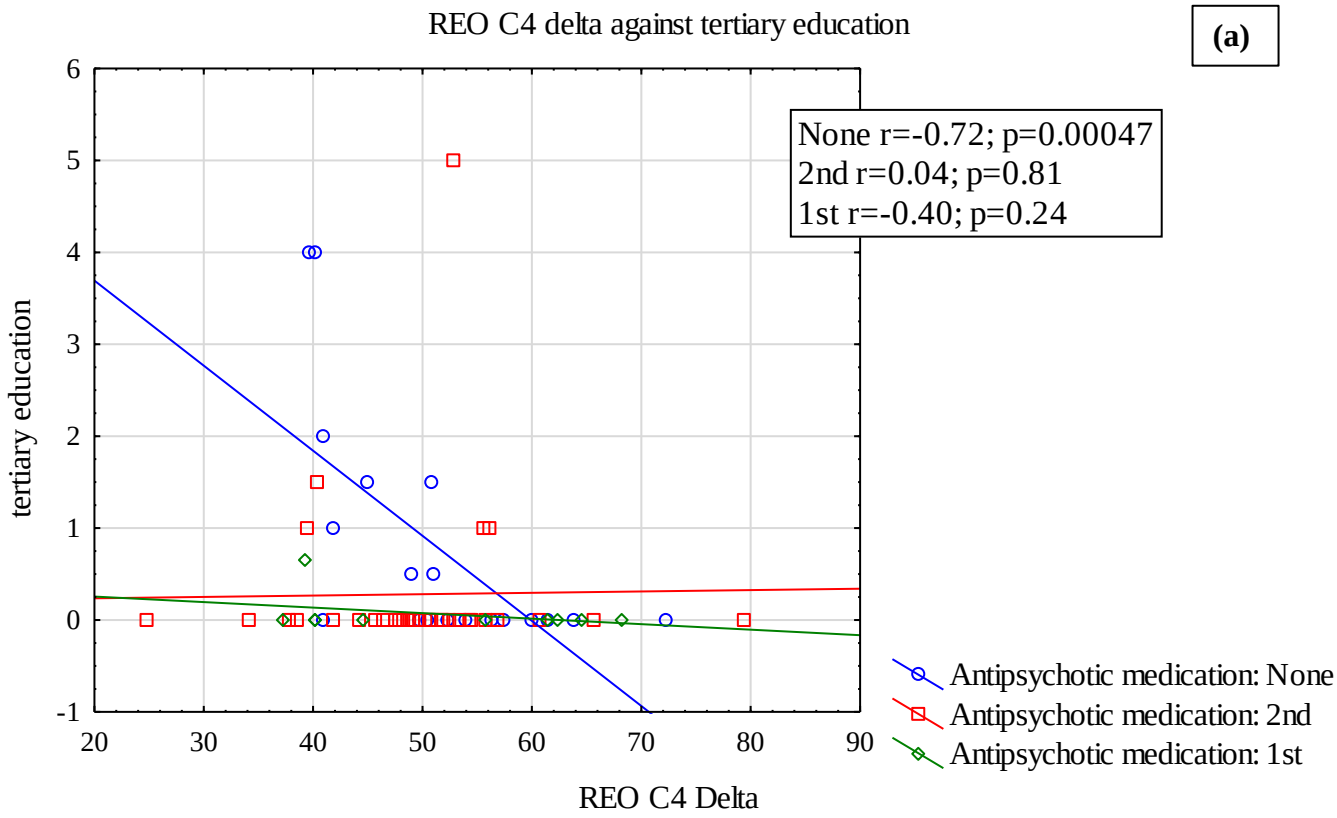
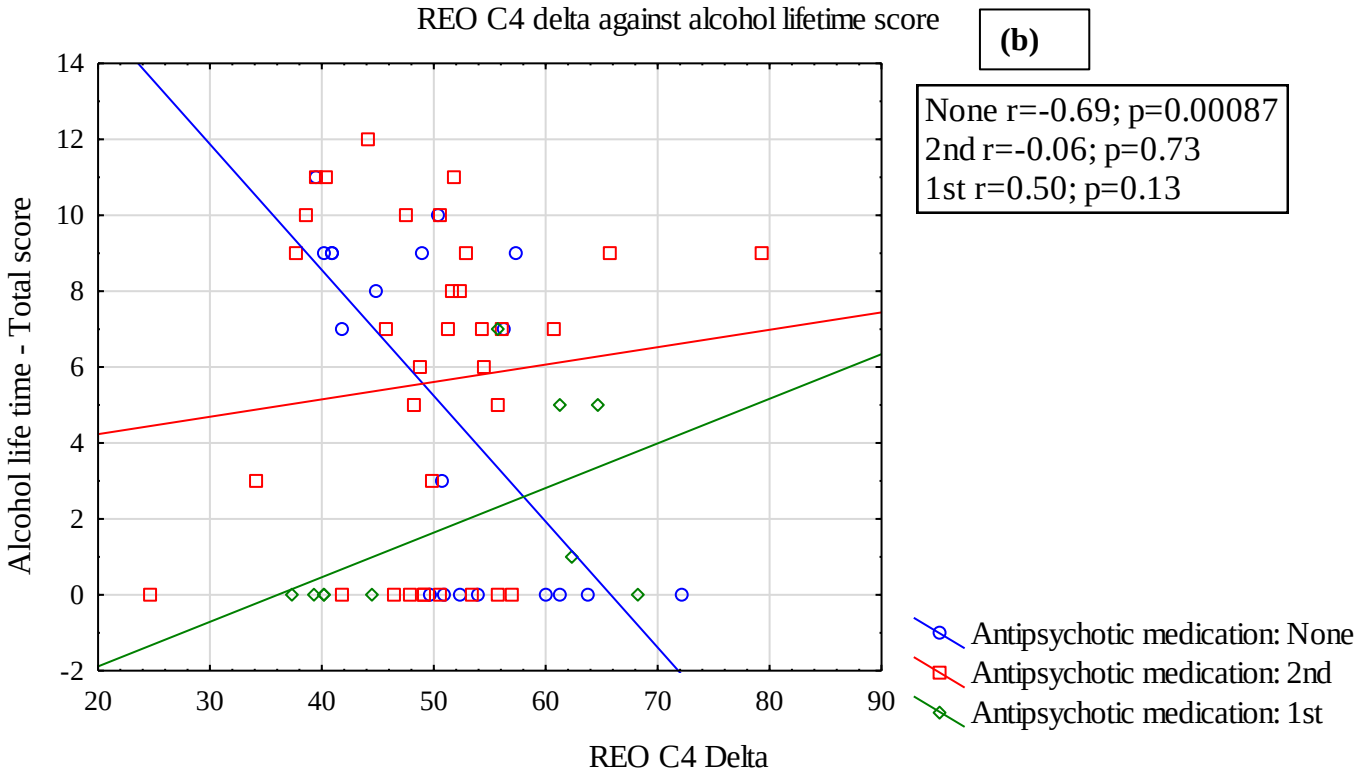


Figure 3.1 Relationships between resting eyes open condition relative delta frequency activity and the age of onset of methamphetamine use in years, where SCZ reported significant relationships for (a) left frontal (F3), (b) right frontal (F4), (c) right parietal (P4) and (d) right occipital (O2) electrodes. Schizophrenia (SCZ), Methamphetamine-induced psychotic disorder (MPD). Significance was reported for $p<0.01$ and Rho= $>\pm 0.60$.


REO C4 delta against tertiary education
(a)
None r=-0.72; p=0.00047
2nd r=0.04; p=0.81
1st r=-0.40; p=0.24
tertiary education
REO C4 Delta
Antipsychotic medication: None
Antipsychotic medication: 2nd
Antipsychotic medication: 1st


REO C4 delta against alcohol lifetime score
(b)
None r=-0.69; p=0.00087
2nd r=-0.06; p=0.73
1st r=0.50; p=0.13
Alcohol life time - Total score
REO C4 Delta
Antipsychotic medication: None
Antipsychotic medication: 2nd
Antipsychotic medication: 1st

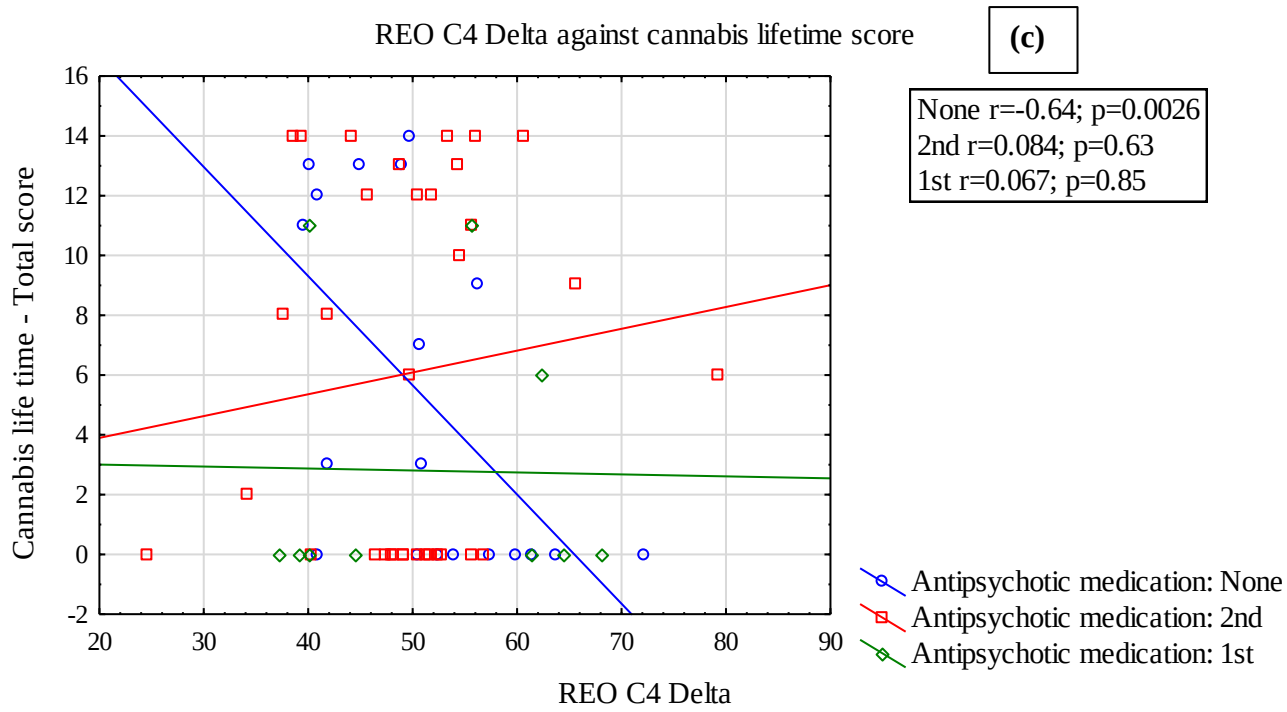
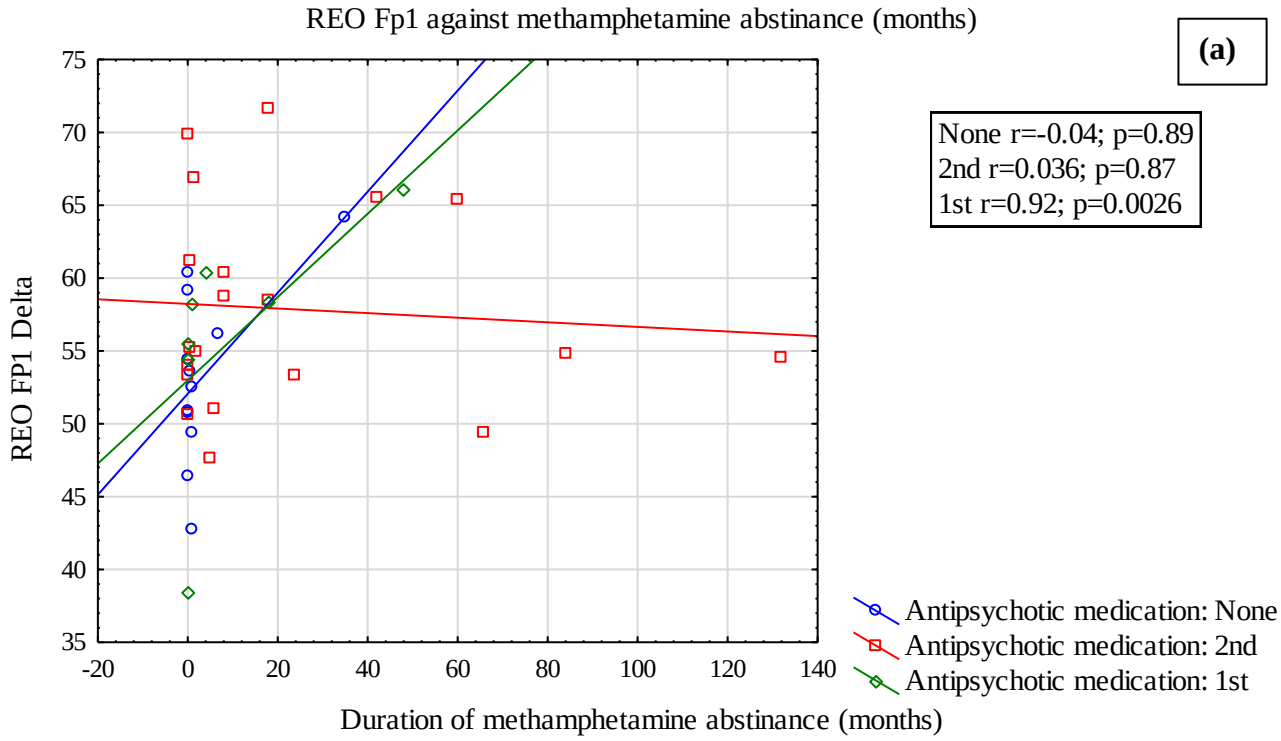
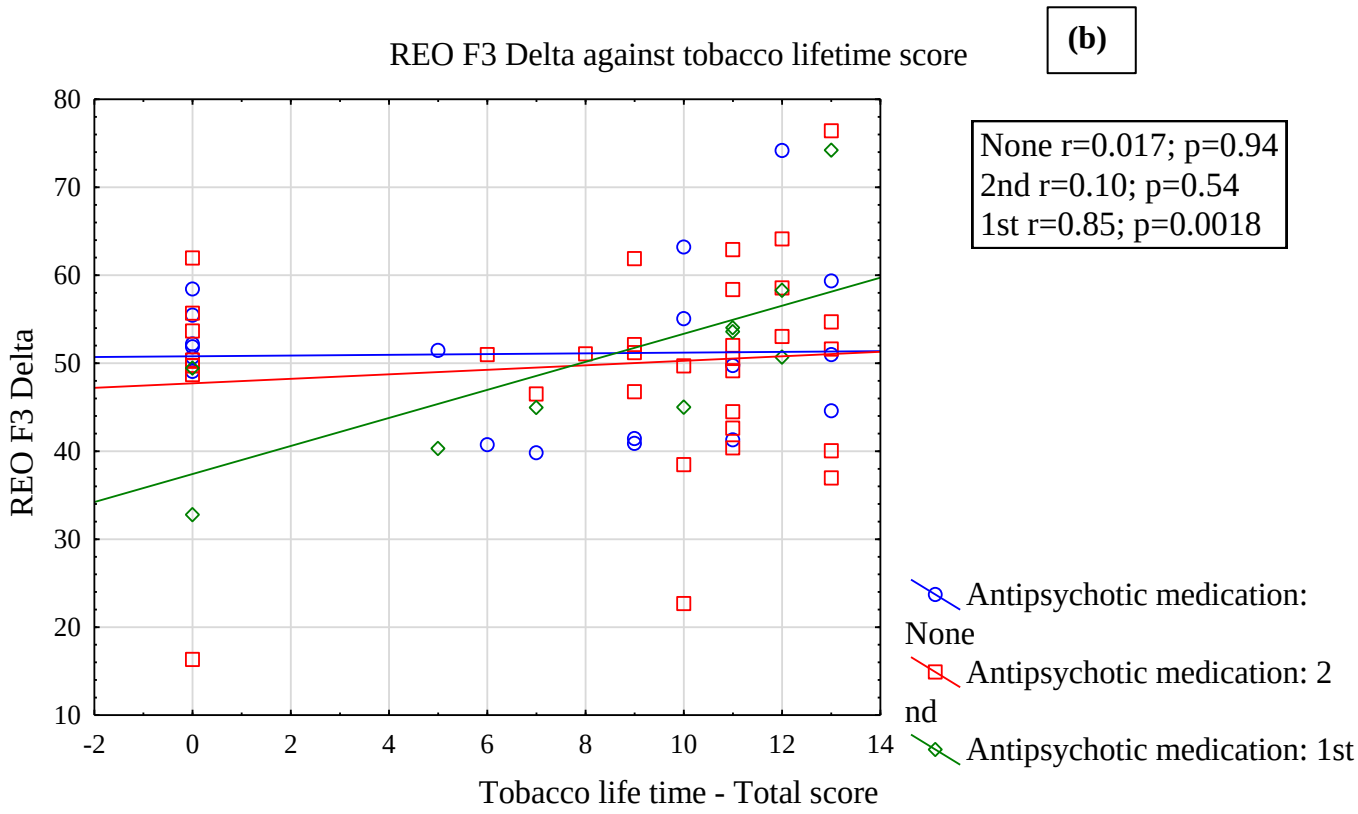
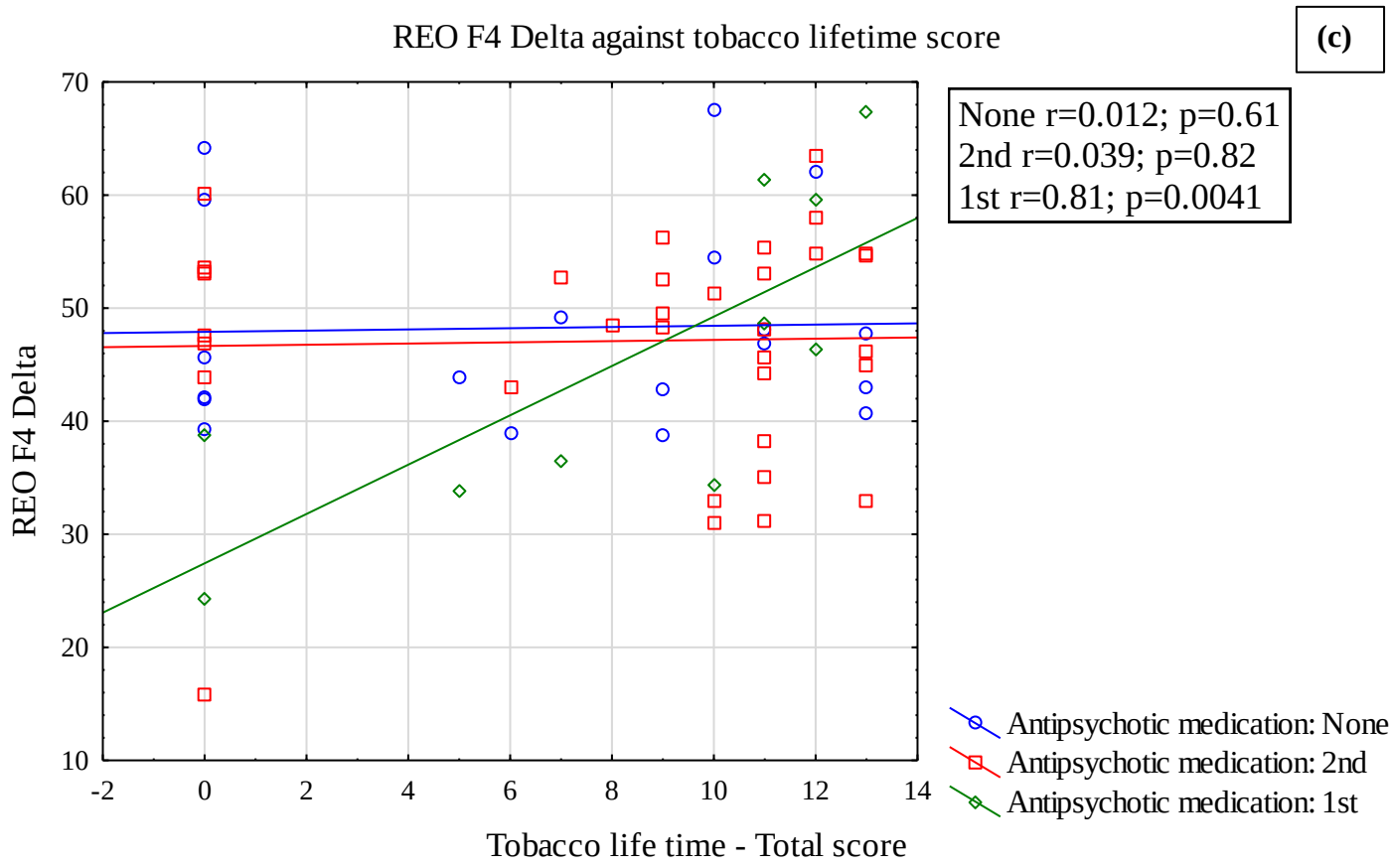


Figure 3.2 When patients were not taking antipsychotic medication right central (C_4) electrode relative delta activity during resting eyes open (REO) negatively correlated with (**a**) duration of tertiary education, (**b**) lifetime use of alcohol, and (**c**) lifetime use of cannabis. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= >±0.60.

For patients prescribed 1st generation antipsychotics (n = 7, where SCZn= 1; MPDn=6), REO left prefrontal delta activity positively correlated with duration of methamphetamine abstinence ($Fp_1R_{Spearman's(n=7)}=0.92$; p=0.0026). Then patients prescribed 1st generation antipsychotics (n = 10, where SCZn= 4; MPDn=6) lifetime use of tobacco positively correlated with REO left frontal delta activity ($F_3R_{Spearman's(n=10)}=0.85$; p=0.0018), REO right frontal delta activity ($F_4R_{Spearman's(n=10)}=0.81$; p=0.0041) and with REO right central delta activity ($C_4R_{Spearman's(n=10)}=0.81$; p=0.0041), **Figure 3.3**.


REO Fp1 against methamphetamine abstinance (months)
(a)
None r=-0.04; p=0.89
2nd r=0.036; p=0.87
1st r=0.92; p=0.0026
REO FP1 Delta
Duration of methamphetamine abstinance (months)
Antipsychotic medication: None
Antipsychotic medication: 2nd
Antipsychotic medication: 1st


REO F3 Delta against tobacco lifetime score
(b)
None r=0.017; p=0.94
2nd r=0.10; p=0.54
1st r=0.85; p=0.0018
REO F3 Delta
Tobacco life time - Total score
Antipsychotic medication: None
Antipsychotic medication: 2nd
Antipsychotic medication: 1st



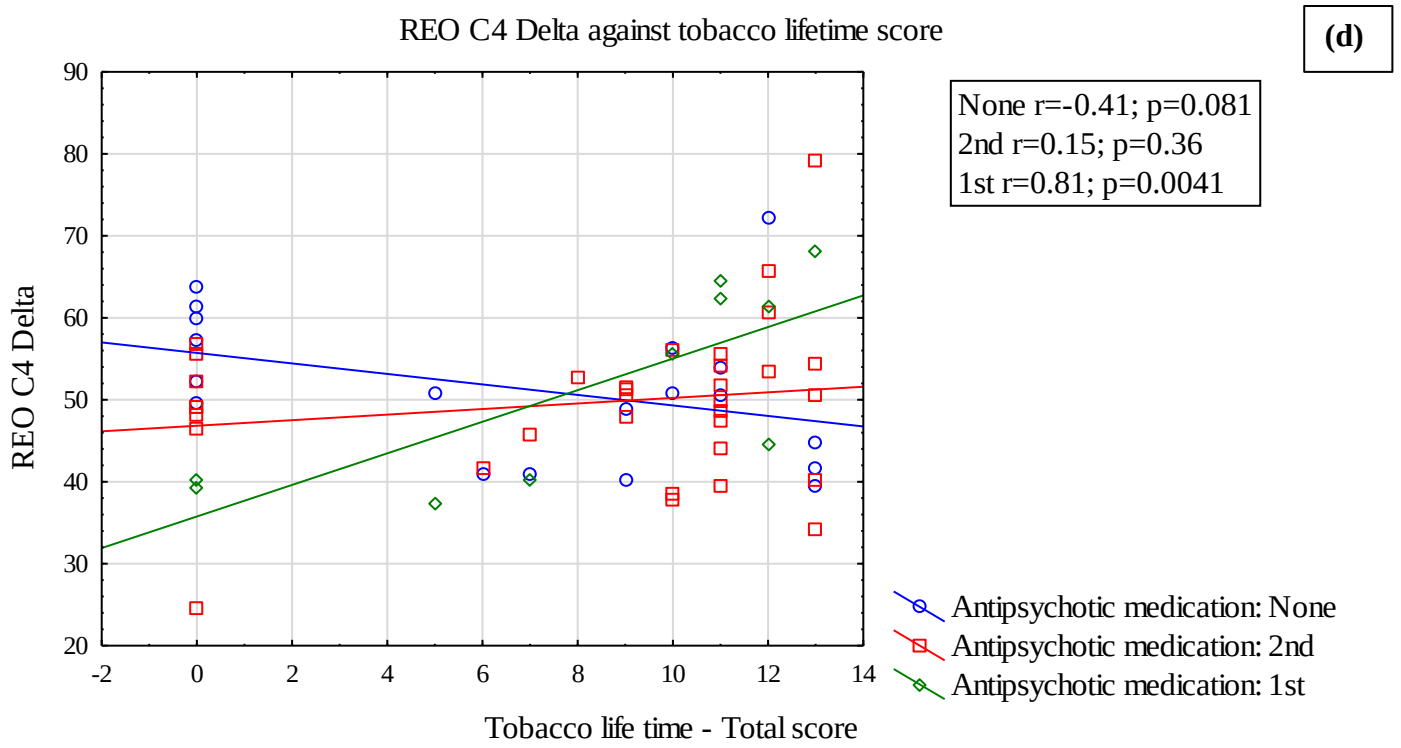


Figure 3.3 When patients were prescribed 1st generation antipsychotic medication: **(a)** left prefrontal (Fp_1) electrode relative delta activity during resting eyes open (REO) positively correlated with duration of methamphetamine abstinence; then lifetime use of tobacco positively correlated with (b) left frontal (F3), (c) right frontal (F4), and (d) right central (C4) electrodes. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm 0.60$.

3.3.3 Resting eyes closed relative to delta activity

REC delta showed group differences for the prefrontal cortices (Fp_1 ($F_{2,101}$=3.97; p=0.021), Fp_2 ($H_{2,104}$=6.46; p=0.039)) where MPD delta activity was less when compared to SCZ (Fp_1 p=0.017, Fp_2 p=0.033), **Table 3.5**. The only covariate which was found to interact with group differences was limited to analysis of the psychotic groups when classified by antipsychotic medication type (NONE, 1st, 2nd) on tertiary education (NONE; ($R_{Spearman's(n=20)}$=-0.63; p=0.0020)). There was a significant group difference in the duration of tertiary education for the left frontal relative delta (F_3 ($F_{2,61}$=3.66; p=0.031)); this did not however lead to any specific group differences.

Table 3.5 Resting eyes closed relative delta frequency activity

		Healthy control	**Schizophrenia**	**Methamphetamine-induced psychosis**		
		n = 35	n = 38	n = 31		
		15 females/20 males	8 females/30 males	7 females/24 males		
		Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test/ F test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	49.00(28.38-64.77)	51.10(37.03-73.85)	42.61(30.84-64.94) *	$F_{2,101}$=3.97; p=0.021	MPD<SCZ p=0.017
Right prefrontal cortex	**Fp_2**	45.01(28.39-70.46)	45.89(32.13-74.09)	38.18(25.51-65.26) *	$H_{2,104}$=6.46; p=0.039	MPD<SCZ p=0.033
Left frontal cortex	**F_3**	41.02(23.32-55.29)	40.80(25.23-67.63)	38.40(27.71-67.98)	$F_{2,101}$=0.84; p=0.65	
Right frontal cortex	**F_4**	37.57(14.74-52.76)	36.54(19.89-69.57)	34.65(20.76-67.05)	$H_{2,104}$=6.46; p=0.039	
Left central cortex	**C_3**	42.25(20.86-56.98)	41.91(23.19-67.56)	37.37(20.84-68.98)	$F_{2,101}$=1.71; p=0.18	
Right central cortex	**C_4**	40.14(22.91-57.37)	42.38(28.27-75.38)	38.02(22.62-67.47)	$H_{2,104}$=2.34; p=0.30	
Left parietal cortex	**P_3**	37.32(21.84-59.11)	39.91(18.11-71.18)	30.60(15.15-66.65)	$H_{2,104}$=4.53; p=0.10	
Right frontal cortex	**P_4**	39.76(24.57-54.77)	41.69(28.83-71.41)	37.42(23.00-70.22)	$H_{2,104}$=0.98; p=0.61	
Left occipital cortex	**O_1**	37.70(2.56-55.76)	40.13(21.40-70.65)	36.99(21.63-69.07)	$H_{2,104}$=1.45; p=0.48	
Right occipital cortex	**O_2**	38.63(20.57-58.93)	39.75(19.97-70.66)	36.37(19.65-68.05)	$H_{2,104}$=0.78; p=0.67	

***** *Methamphetamine-induced psychotic disorder (MPD) reported decreased delta activity during resting eyes closed (REC) compared to schizophrenia (SCZ); Significance P<0,05.*

For patients not taking antipsychotic medications (n = 20, where SCZn= 7; MPDn=13), REC left frontal relative delta activity negatively correlated with duration of tertiary education ($F_3R_{Spearman's(n=20)}$=-0.63; p=0.0020), **Figure 3.4**. Then patients not taking antipsychotic medications with a history of methamphetamine use (n = 14, where SCZn= 1; MPDn=13, their duration of methamphetamine use positively correlated with REC relative delta activity for the right central through to the right occipital cortical electrodes ($C_4R_{Spearman's(n=14)}$=0.76, p=0.0013; $P_4R_{Spearman's(n=14)}$=0.73, p=0.0029; $O_2R_{Spearman's(n=14)}$=0.70; p=0.0048), **Figure 3.5**.

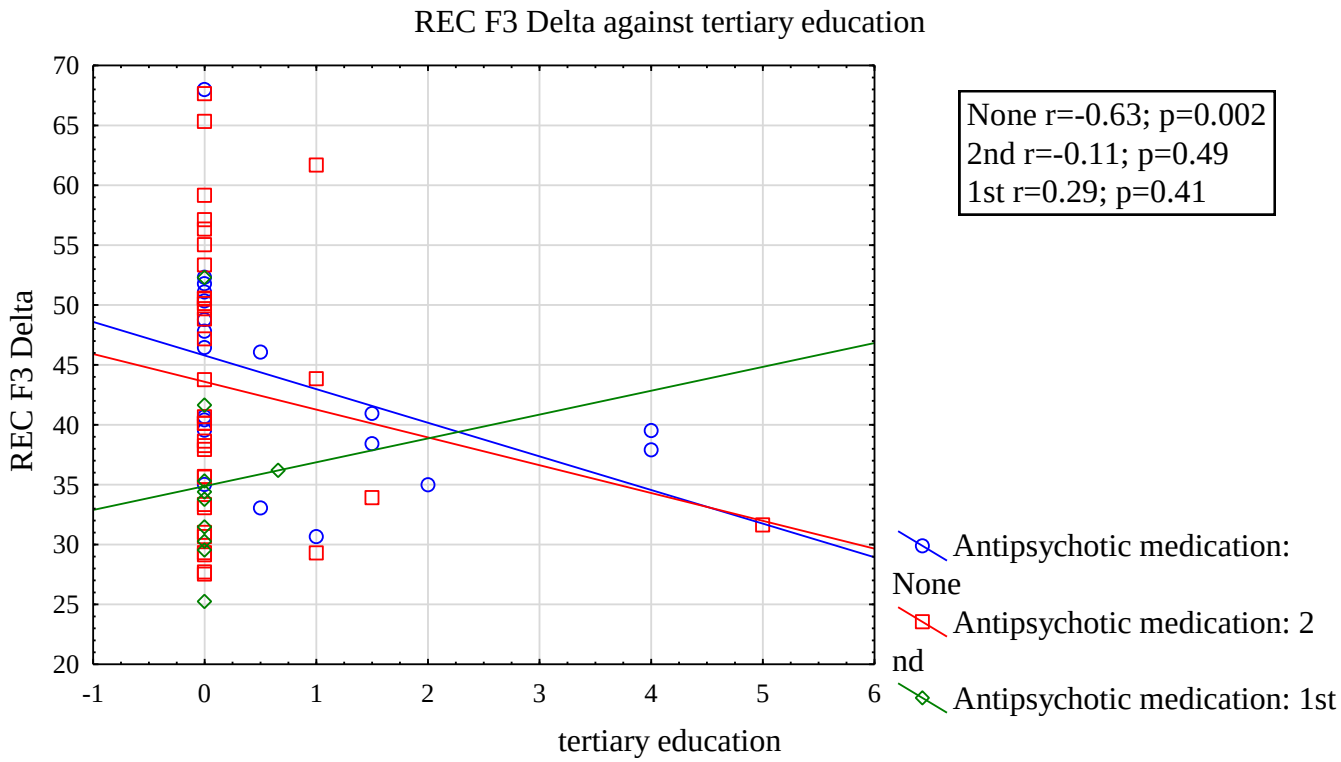
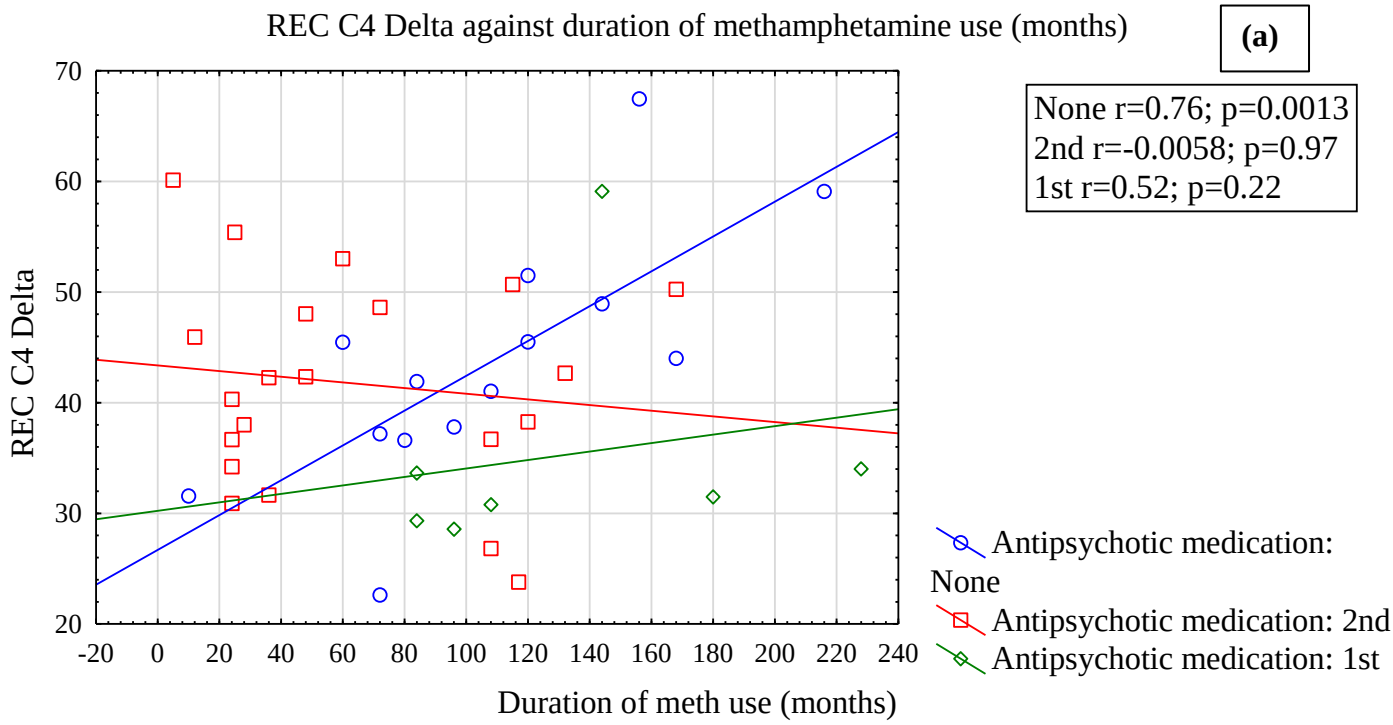


Figure 3.4 Resting eyes closed (REC) relative delta activity for the left frontal (F_3) electrode for patients not taking antipsychotic medication negatively correlated with duration of tertiary education. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm 0.60$.



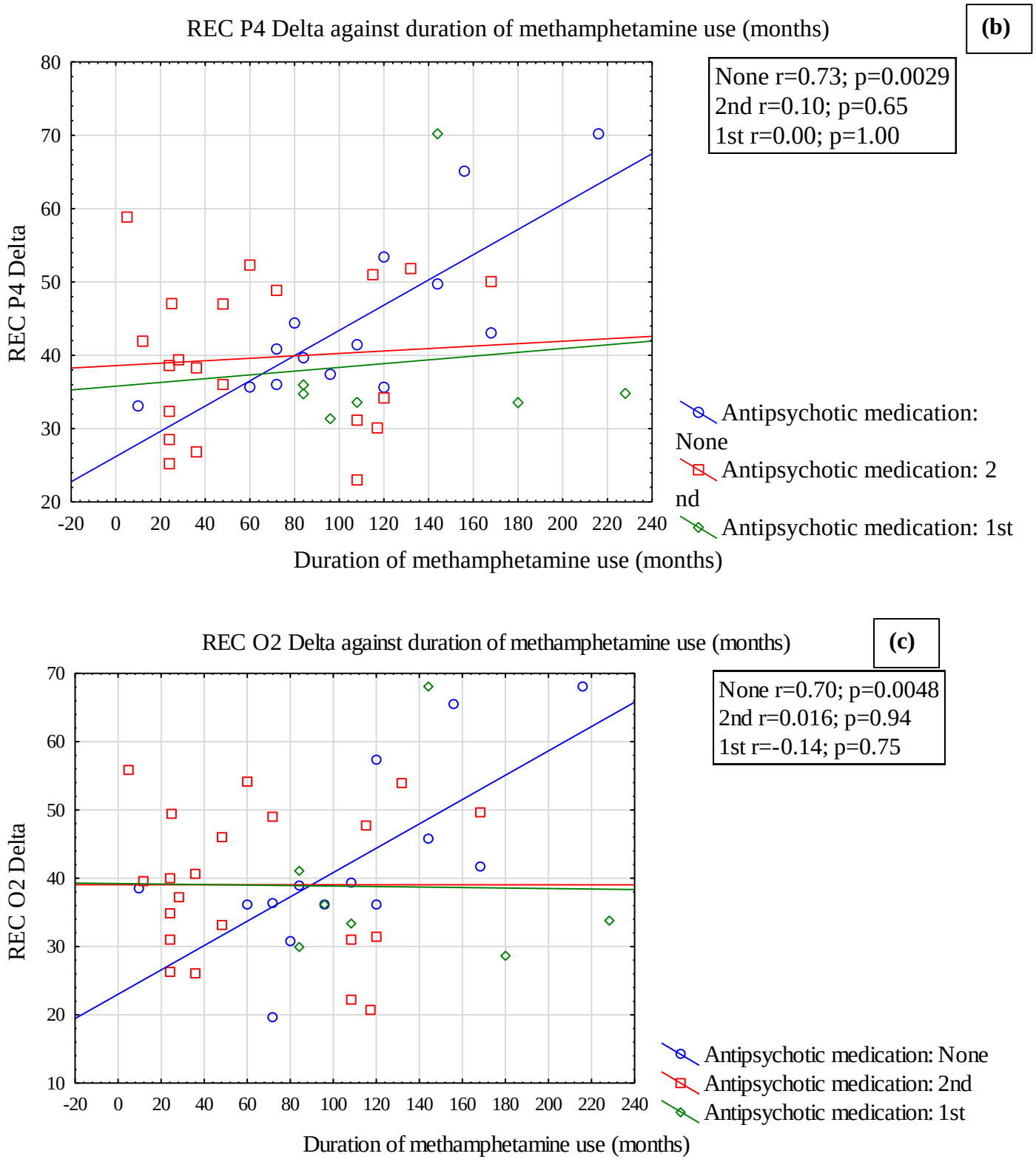


Figure 3.5 Resting eyes closed (REC) relative delta activity for patients not taking antipsychotic medication positively correlated with duration of methamphetamine use **(a)** right central (C_4), **(b)** right parietal (P_4) and **(c)** Right occipital (O_2) electrodes. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm0.60$.

3.3.4 Resting eyes open relative theta activity

REO Theta reported a group difference for the left and right central through to the occipital electrodes (C_3 ($H_{2.102}$=7.024; p=0.029), C_4 ($H_{2.102}$=6.63; p=0.036), P_3 ($H_{2.102}$=14.46; p=0.00070), O_2 ($H_{2.102}$=7.12; p=0.028)) where SCZ theta activity was greater compared to CON (C_3 p=0.027, C_4 p=0.041, P_3 p=0.00046, O_2 p=0.049), **Table 3.6**.

Table 3.6 Resting eyes open relative theta frequency activity

		Healthy control	**Schizophrenia**	**Methamphetamine-induced psychosis**		
		n = 35	n = 38	n = 31		
		15 females/20 males	8 females/30 males	7 females/24 males		
		Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test/ F test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	11.75 (7.08-16.19)	12.98(8.97-22.69)	12.91(7.34-19.69)	$H_{2.102}$=5.71; p=0.057	-
Right prefrontal cortex	**Fp_2**	12.34(3.69-17.69)	12.96(8.42-22.82)	13.36(8.90-19.45)	$H_{2.102}$=4.47; p=0.10	-
Left frontal cortex	**F_3**	11.47(7.47-15.71)	12.81(7.03-30.56)	11.76(6.05-18.37)	$H_{2.102}$=3.53; p=0.17	-
Right frontal cortex	**F_4**	11.67(7.56-16.07)	12.81(9.41-27.91)	12.06(6.21-16.58)	$H_{2.102}$=5.36; p=0.068	-
Left central cortex	**C_3**	11.29(8.11-18.25)	12.85(7.26-28.09) *	11.60(5.88-18.60)	$H_{2.102}$=7.024; p=0.029	SCZ>CON p=0.027
Right central cortex	**C_4**	11.43(6.60-20.07)	12.88(6.07-27.09) *	12.38(5.08-18.23)	$H_{2.102}$=6.63; p=0.036	SCZ>CON p=0.041
Left parietal cortex	**P_3**	10.78(7.05-16.25)	12.65(9.29-22.10) *	12.48(5.61-17.97)	$H_{2.102}$=14.46; p=0.00070	SCZ>CON p=0.00046
Right frontal cortex	**P_4**	11.16(6.89-15.67)	12.14(5.70-19.87)	12.29(5.23-17.74)	$F_{2.99}$=1.59; p=0.20	-
Left occipital cortex	**O_1**	11.36(8.13-14.83)	12.58(6.55-26.76)	12.17(6.00-18.69)	$H_{2.102}$=5.28; p=0.071	-
Right occipital cortex	**O_2**	11.19(5.28-14.94)	12.19(6.68-19.60) *	12.14(5.94-19.97)	$H_{2.102}$=7.12; p=0.028	SCZ>CON p=0.049

** Schizophrenia (SCZ) reported greater relative theta activity during resting eyes open (REO) compared to healthy controls (CON) Significance P<0,05.*

3.3.5 Resting eyes closed relative theta activity

REC Theta reported a group difference for the left prefrontal electrode (Fp_1 ($H_{2.104}$=8.57; p=0.013)) where SCZ relative theta activity was greater compared to CON (p=0.021), **Table 3.7.**

Table 3.7 Resting eyes closed relative theta frequency activity

		Healthy control	**Schizophrenia**	**Methamphetamine -induced psychosis**		
		n = 35	n = 38	n = 31		
		15 females/20 males	8 females/30 males	7 females/24 males		
		Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	9.88(7.21-15.34)	11.65(7.94-23.55) *	11.25(8.00-15.12)	$H_{2.104}$=8.57; p=0.013	SCZ>CON p=0.021
Right prefrontal cortex	**Fp_2**	10.65(5.90-15.13)	11.64(8.05-25.83)	12.31(8.26-18.45)	$H_{2.104}$=3.08; p=0.21	-
Left frontal cortex	**F_3**	11.36(6.81-20.05)	12.55(8.24-26.55)	11.85(8.00-16.26)	$H_{2.104}$=4.56; p=0.10	-
Right frontal cortex	**F_4**	11.32(7.16-16.19)	12.03(8.20-29.19)	11.21(8.24-21.47)	$H_{2.104}$=4.42; p=0.10	-
Left central cortex	**C_3**	11.08(7.03-19.16)	12.49(7.43-21.71)	11.48(6.80-19.67)	$H_{2.104}$=5.04; p=0.080	-
Right central cortex	**C_4**	11.32(6.05-16.99)	12.15(7.62-27.19)	11.89(7.89-17.02)	$H_{2.104}$=3.71; p=0.15	-
Left parietal cortex	**P_3**	10.75(7.18-16.90)	12.00(7.45-18.41)	11.01(7.41-19.89)	$H_{2.104}$=5.09; p=0.078	-
Right frontal cortex	**P_4**	10.84(6.70-18.56)	11.78(8.09-25.89)	11.32(7.49-17.18)	$H_{2.104}$=4.56; p=0.10	-
Left occipital cortex	**O_1**	10.77(6.73-15.35)	11.52(7.66-25.95)	11.44(7.02-19.97)	$H_{2.104}$=3.90; p=0.14	-
Right occipital cortex	**O_2**	11.14(7.04-17.28)	12.14(6.90-26.14)	12.28(7.03-17.94)	$H_{2.104}$=4.20; p=0.12	-

** Schizophrenia (SCZ) reported greater relative theta activity during resting eyes closed (REC) compared to healthy controls (CON). Significance P<0,05.*

For patients not taking antipsychotic medications (n = 20, where SCZn= 7; MPDn=13), REC left parietal relative theta activity negatively correlated with duration of tertiary education ($P_3R_{Spearman's(n=20)}$=-0.61; p=0.0040), **Figure 3.6.** Patients prescribed 1st generation antipsychotic medications with a history of methamphetamine use (n=14, where SCZn=1; MPDn=13), their duration of methamphetamine use positively correlated with REC relative theta activity for the left parietal cortical electrode ($P_3R_{Spearman's(n=14)}$=0.95, p=0.00080), **Figure 3.7.**

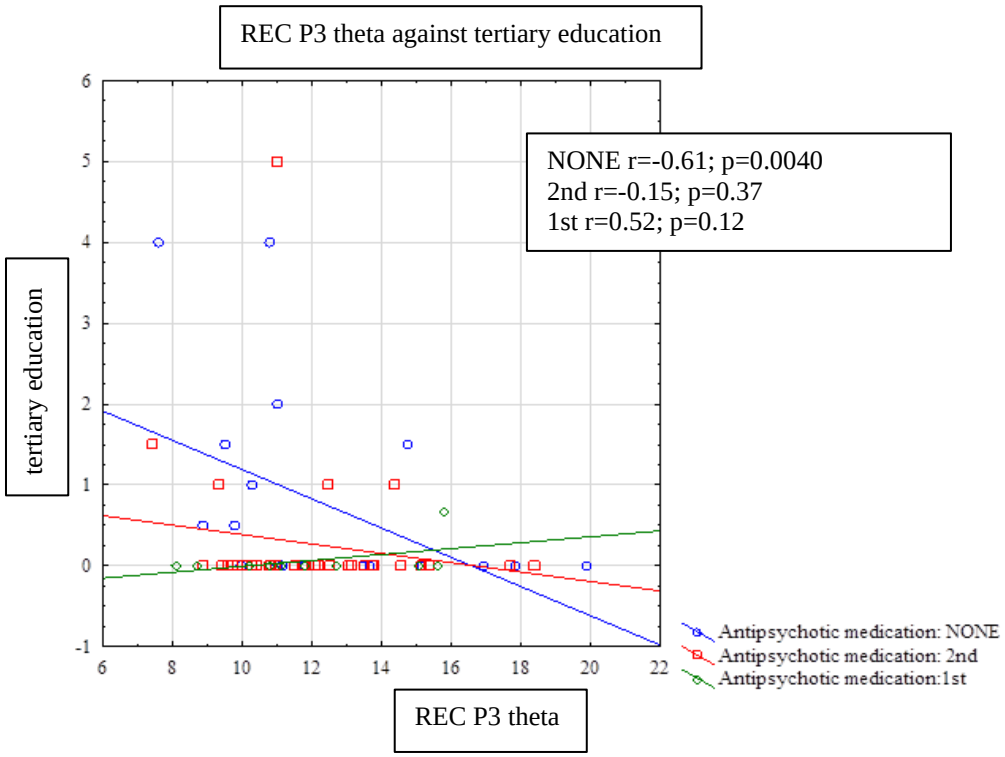


Figure 3.6 Resting eyes closed (REC) relative theta activity for patients prescribed 1st generation antipsychotic medication positively correlated with tertiary education left parietal (P3) electrodes. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for p<0.01 and Rho= >±0.60.

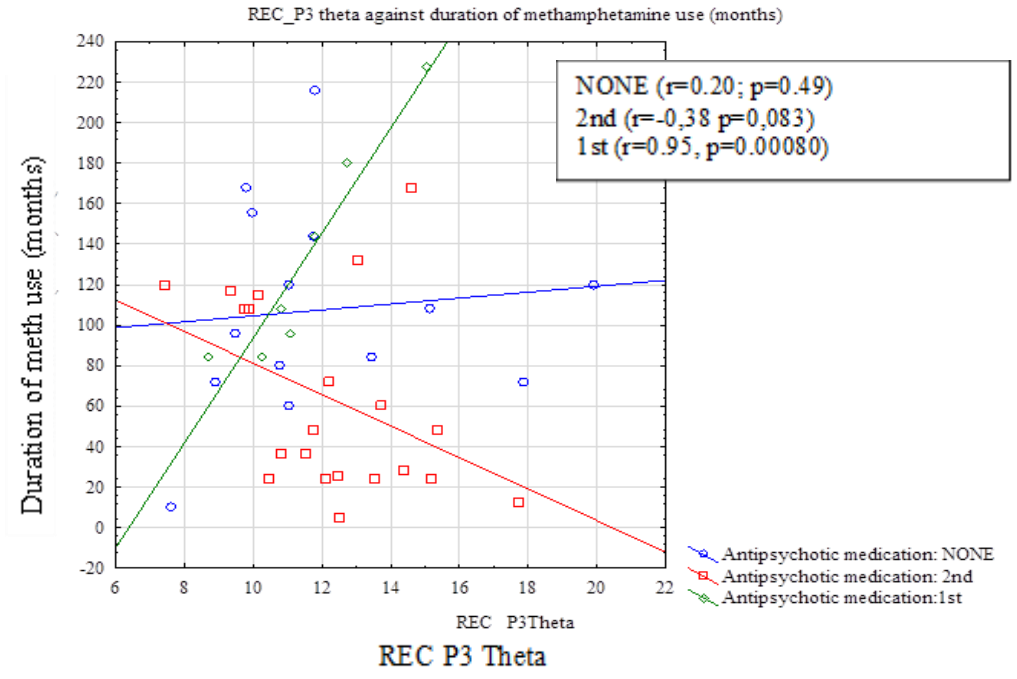


Figure 3.7 Resting eyes closed (REC) relative theta activity for patients prescribed 1st generation antipsychotic medication positively correlated with duration of methamphetamine use left parietal (P3) electrodes. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for p<0.01 and Rho= >±0.60.

3.3.6 Resting eyes open relative alpha activity

REO Alpha reported a group difference for the right parietal electrode (P_4 ($F_{2.99}$=4.94; p=0.0089)) where SCZ was smaller when compared to CON (p=0.024) and MPD (p=0.025). Then REO Alpha reported a group difference for the right prefrontal and right occipital electrodes (Fp_2 ($H_{2.104}$=8.57; p=0.013), O_2 ($H_{2.102}$=6.66; p=0.035), where SCZ relative alpha activity was smaller compared to MPD (O_2 p=0.033). Yet no specific group differences were found for the right prefrontal electrode, **Table 3.8**. The only covariate which was found was limited to the analysis of the psychotic groups when classified by group (SCZ and MPD). The right parietal electrode (P_4) relative alpha activity during REO correlated negatively with the age of methamphetamine use in years (SCZ; ($P_4R_{Spearman's(n=20)}$= -0.69; p=0.0084)). The inclusion of age of methamphetamine use in years reported a group difference for P_4 relative alpha (P_4 ($F_{1.40}$=7.60; p=0.0087)), resulting in SCZ reporting greater alpha activity compared to MPD (p=0.0037).

Table 3.8 Resting eyes open relative alpha frequency activity

		Healthy control	**Schizophrenia**	**Methamphetamine -induced psychosis**		
		n = 35	n = 38	n = 31		
		15 females/20 males	8 females/30 males	7 females/24 males		
		Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test/ F test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	14.51(9.43-22.16)	14.64(8.89-21.84)	15.55(8.89-21.80)	$F_{2.99}$=0.33; p=0.71	-
Right prefrontal cortex	**Fp_2**	14.69(6.43-24.056)	15.70(9.32-24.20) #	18.97(8.31-23.62)	$H_{2.102}$=6.55; p=0.037	ns
Left frontal cortex	**F_3**	18.35(11.01-28.30)	17.65(8.18-29.96)	17.76(8.83-23.02)	$H_{2.102}$=0.36; p=0.83	-
Right frontal cortex	**F_4**	18.61(10.43-32.18)	17.98(10.67-31.39)	19.34(10.10-29.49)	$H_{2.102}$=1.90; p=0.38	-
Left central cortex	**C_3**	17.76(11.16-31.57)	18.52(10.36-27.48)	18.56(9.20-29.33)	$H_{2.102}$=1.77; p=0.041	-
Right central cortex	**C_4**	18.76(11.29-33.74)	16.60(7.20-27.02)	18.43(9.500-28.58)	$F_{2.99}$=1.77; p=0.17	-
Left parietal cortex	**P_3**	18.01(12.14-32.09)	18.32(11.38-27.39)	20.07(9.88-28.41)	$F_{2.99}$=0.57; p=0.56	-
Right frontal cortex	**P_4**	18.49(11.48-33.70)	16.98(9.38-22.69) %	19.06(10.23-26.51)	$F_{2.99}$=4.94; p=0.0089	SCZ<CON p=0.024 SCZ<MPD p=0.025
Left occipital cortex	**O_1**	19.29(10.78-32.66)	17.45(10.63-28.32)	20.07(9.81-35.10)	$H_{2.102}$=5.89; p=0.052	-
Right occipital cortex	**O_2**	18.86(11.49-34.46)	18.15(11.43-23.37)*	19.55(10.20-34.65)	$H_{2.102}$=6.66; p=0.035	SCZ<MPD p=0.033

** Schizophrenia (SCZ) reported decreased relative alpha activity compared to methamphetamine-induced psychotic disorder (MPD), # Significant difference, yet no specific group difference % Schizophrenia (SCZ) reported decreased alpha frequency activity compared to healthy controls (CON) and methamphetamine-induced psychotic disorder (MPD); Significance P<0,05.*

In SCZ (n=13), the age of onset of methamphetamine use negatively correlated with REO alpha across the left frontal electrode and the right parietal electrode for REO alpha activity ($F_3R_{spearman's(n=13)}$=-0.83; p=0.00035, $P_4R_{spearman's(n=13)}$=-0.69; p=0.0084**)**, **Figure 3.8**.

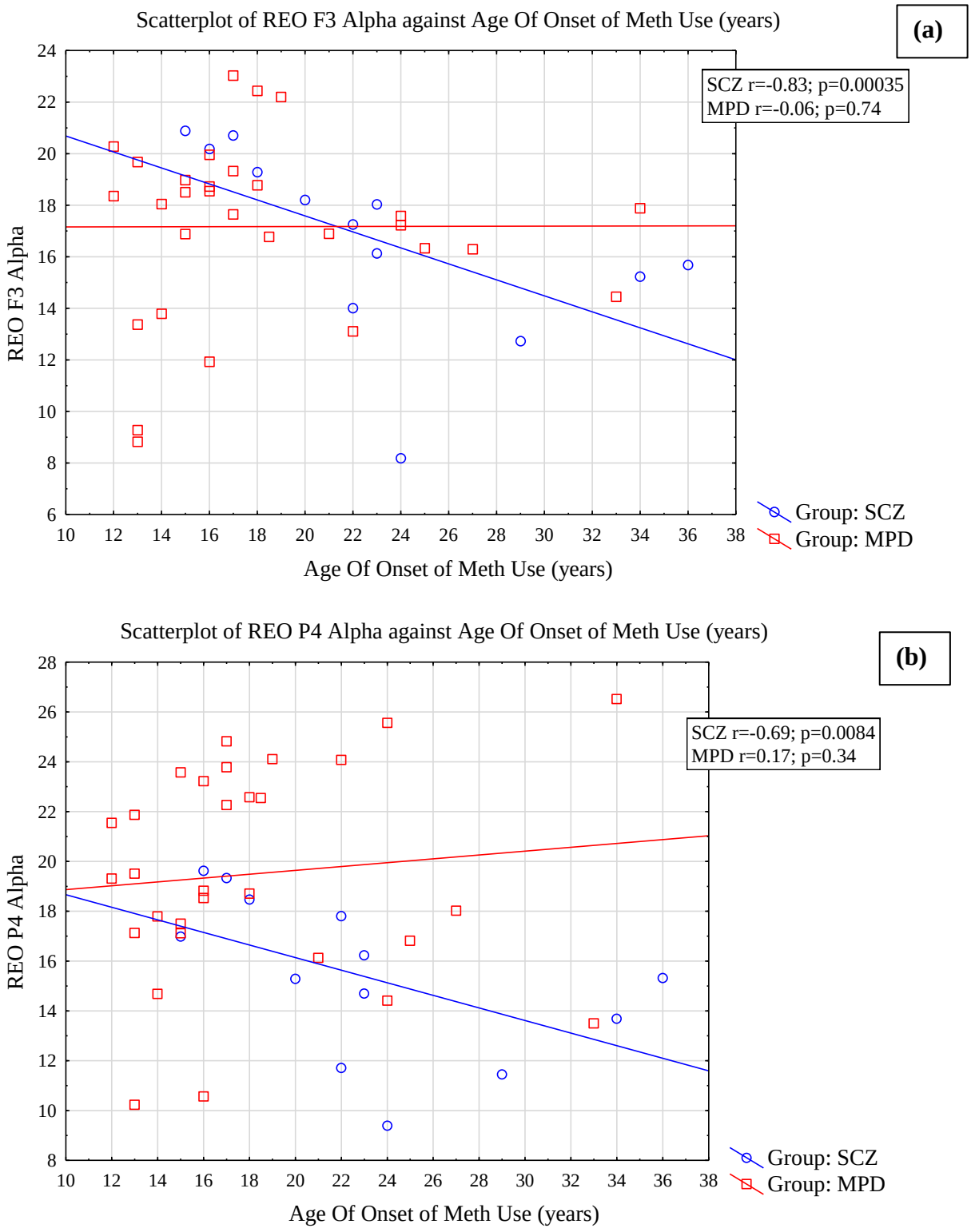


Figure 3.8 Resting eyes open (REO) relative alpha activity for the age of onset of methamphetamine use in years for Schizophrenia negatively correlated with **(a)** left frontal (F_3), and **(b)** right parietal (P_4) electrodes. Schizophrenia (SCZ); Methamphetamine-induced psychotic disorder (MPD). Significance was reported for $p<0.01$ and Rho= $>\pm 0.60$.

For patients not taking antipsychotic medications (n = 19, where SCZn= 7; MPDn=13), REO right central alpha positively correlated with tertiary education ($C_4R_{Spearman's(n=19)}$=0.63; p=0.0034), **Figure 3.9**. Patients not taking antipsychotic medications with a history of alcohol use (n = 19x, where SCZn= 7; MPDn=13) positively correlated with REO alpha activity for the right frontal, left and right central and the left parietal electrodes ($F_4R_{Spearman's(n=19)}$=0.27, p=0.0032; $C_3R_{Spearman's(n=19)}$=0.63, p=0.0032; $C_4R_{Spearman's(n=19)}$=0.62, p=0.0045; $P_3R_{Spearman's(n=19)}$=0.60; p=0.0064), **Figure 3.10.**

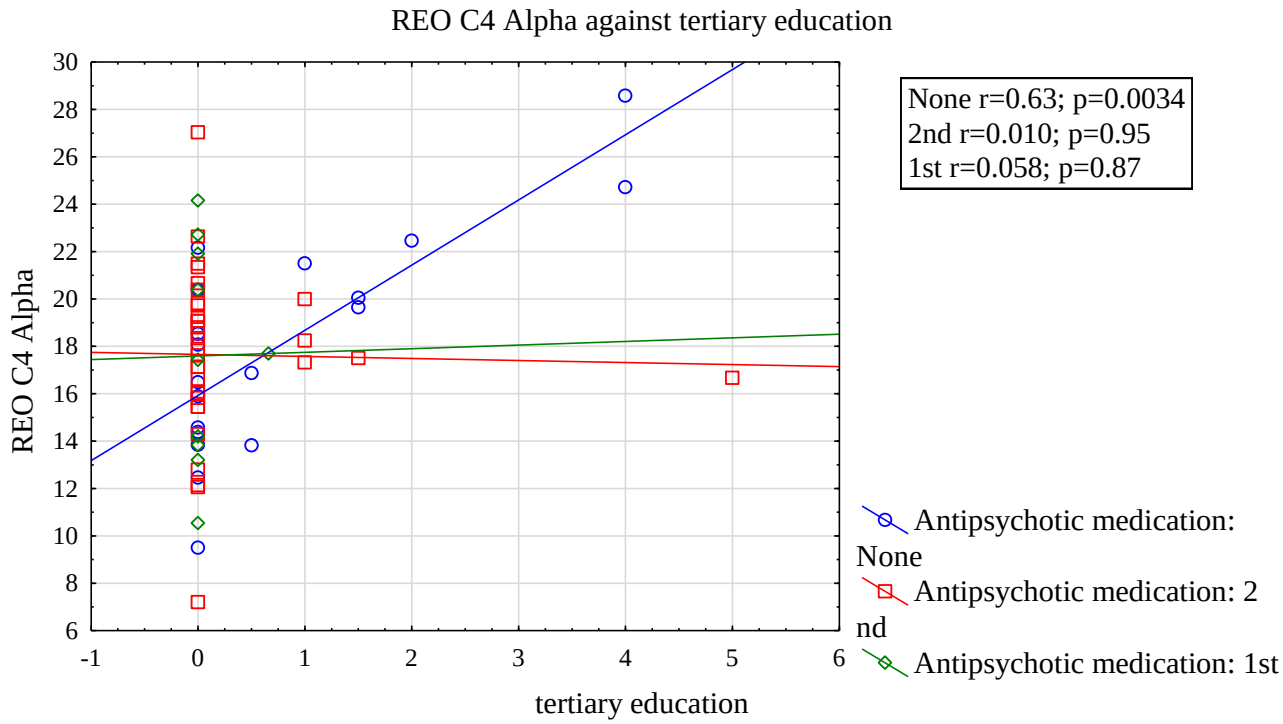
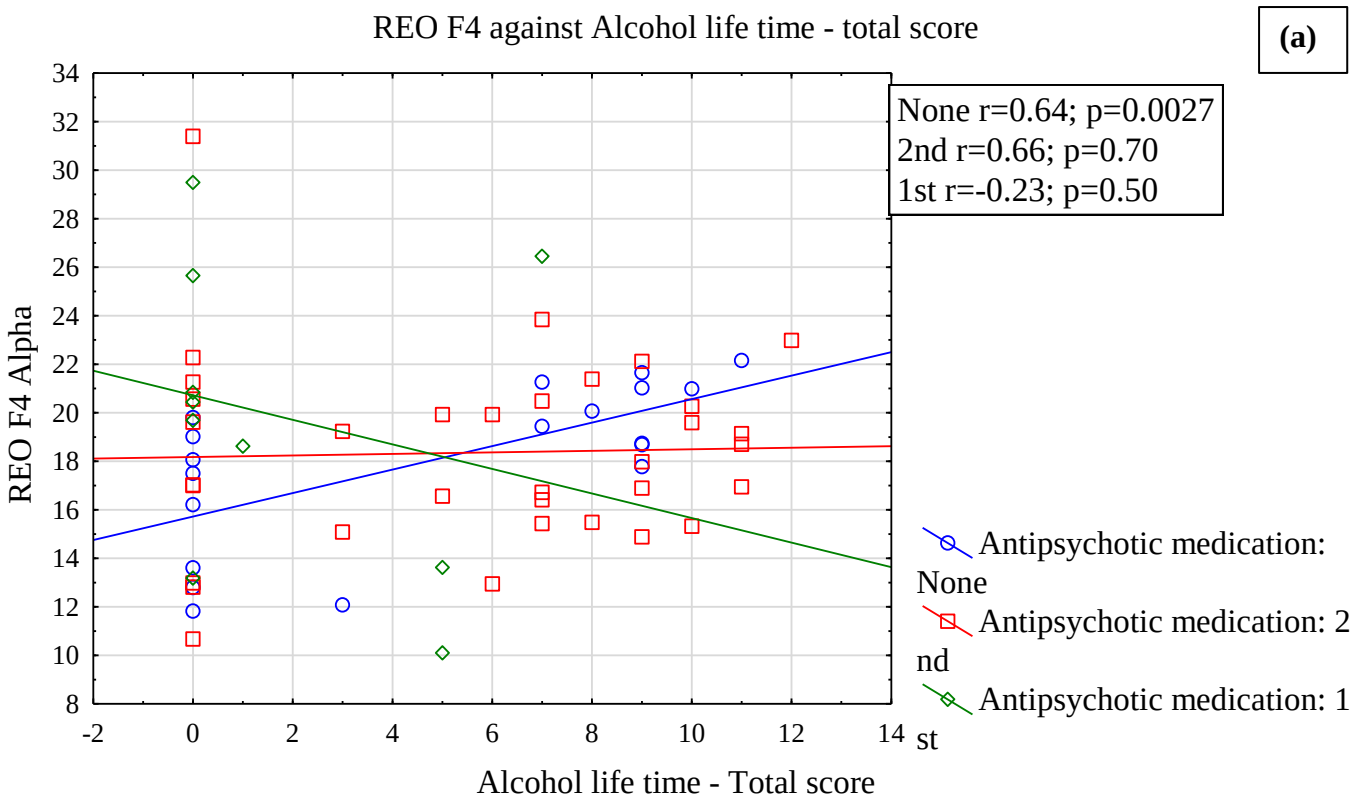
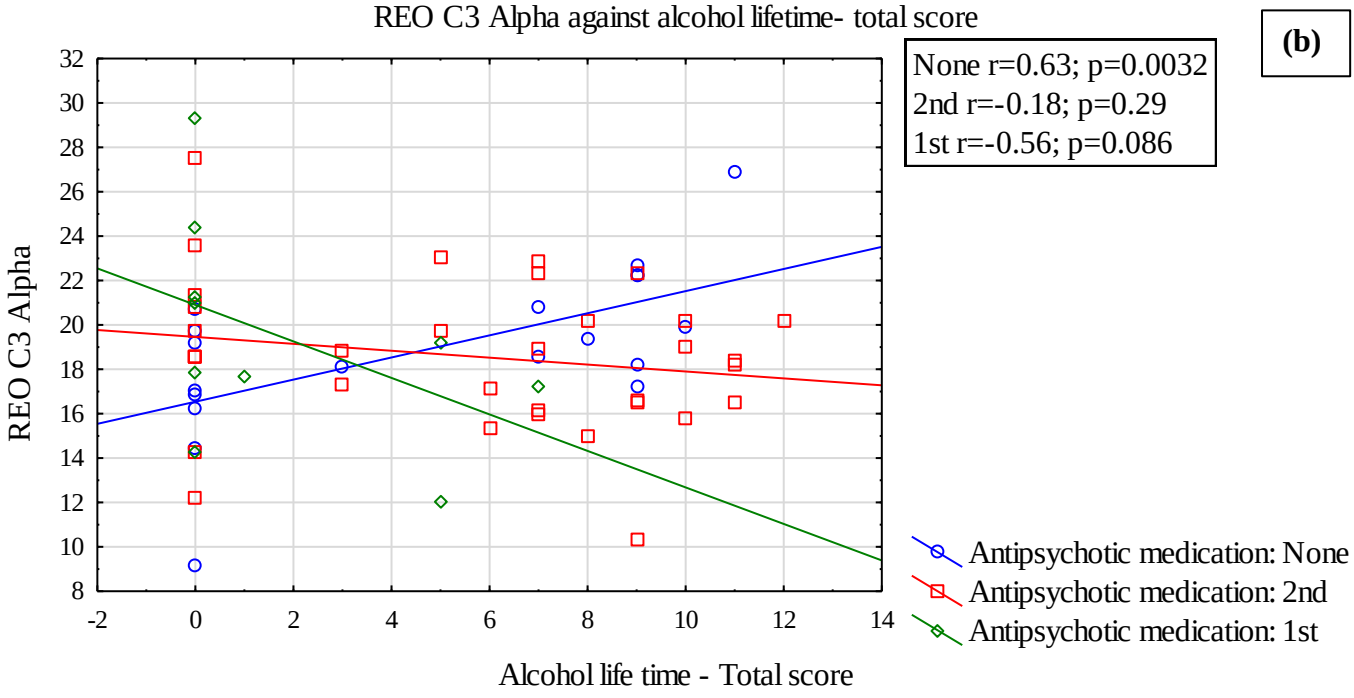


Figure 3.9 Resting eyes open (REO) relative alpha activity for the right central (C_4) electrode for patients not taking antipsychotic medication positively correlated with duration of tertiary education. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm0.60$.


REO F4 against Alcohol life time - total score
(a)
None r=0.64; p=0.0027
2nd r=0.66; p=0.70
1st r=-0.23; p=0.50
REO F4 Alpha
Alcohol life time - Total score
Antipsychotic medication: None
Antipsychotic medication: 2nd
Antipsychotic medication: 1st


REO C3 Alpha against alcohol lifetime- total score
(b)
None r=0.63; p=0.0032
2nd r=-0.18; p=0.29
1st r=-0.56; p=0.086
REO C3 Alpha
Alcohol life time - Total score
Antipsychotic medication: None
Antipsychotic medication: 2nd
Antipsychotic medication: 1st

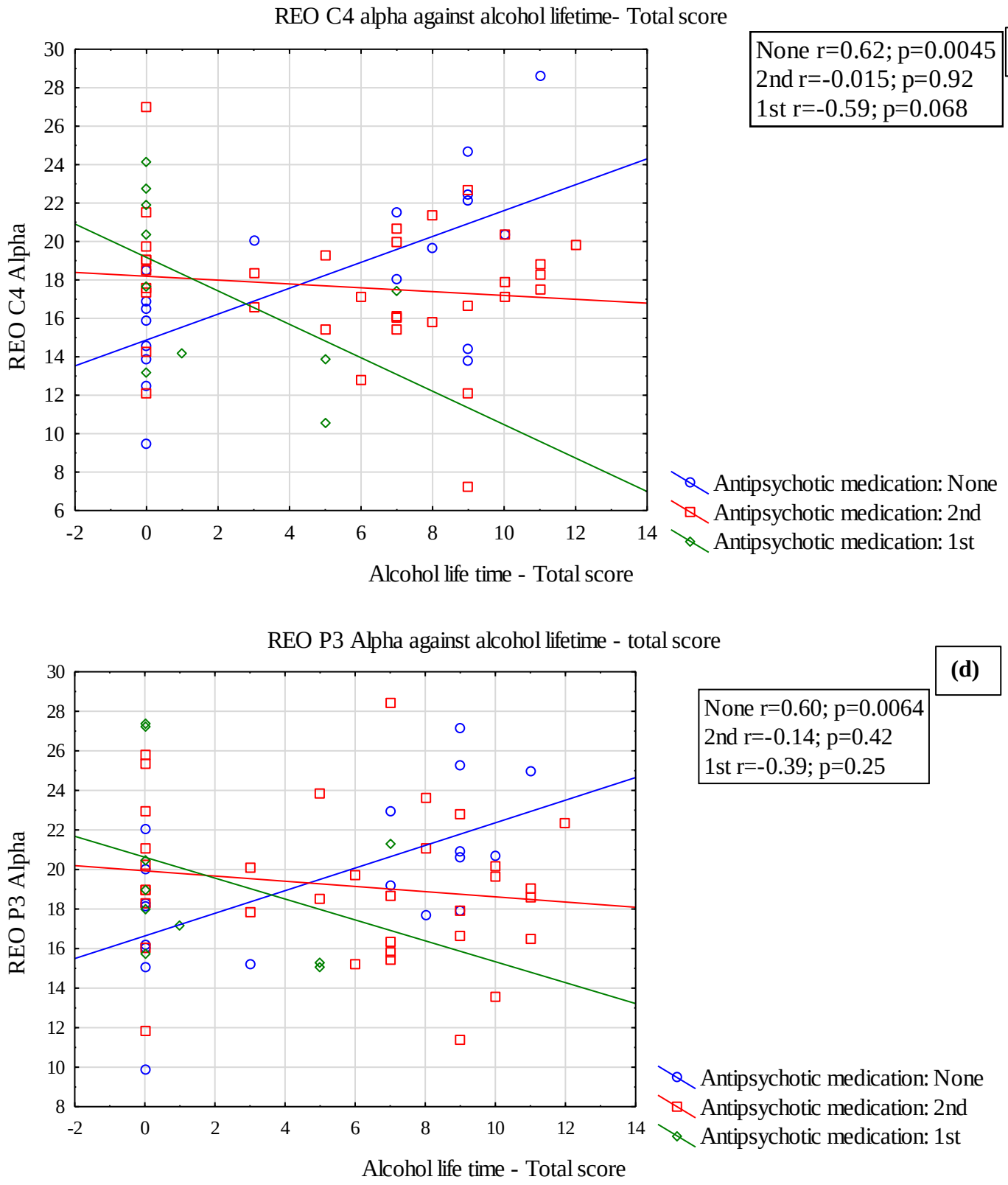


Figure 3.10 Resting eyes open (REO) relative alpha activity for the alcohol lifetime score for patients not taking antipsychotic medication positively correlated with **(a)** right frontal (F_4), **(b)** left central (C_3), **(c)** right central (C_4), and **(d)** left parietal (P_3) electrodes. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm 0.60$.

For patients prescribed 1st generation antipsychotics (n = 10, where SCZn= 4; MPDn=6), REO relative alpha activity for the left frontal electrode negatively correlated with lifetime use of tobacco ($F_3R_{Spearman's(n=10)}$=-0.91; p=0.00018), **Figure 3.11.**

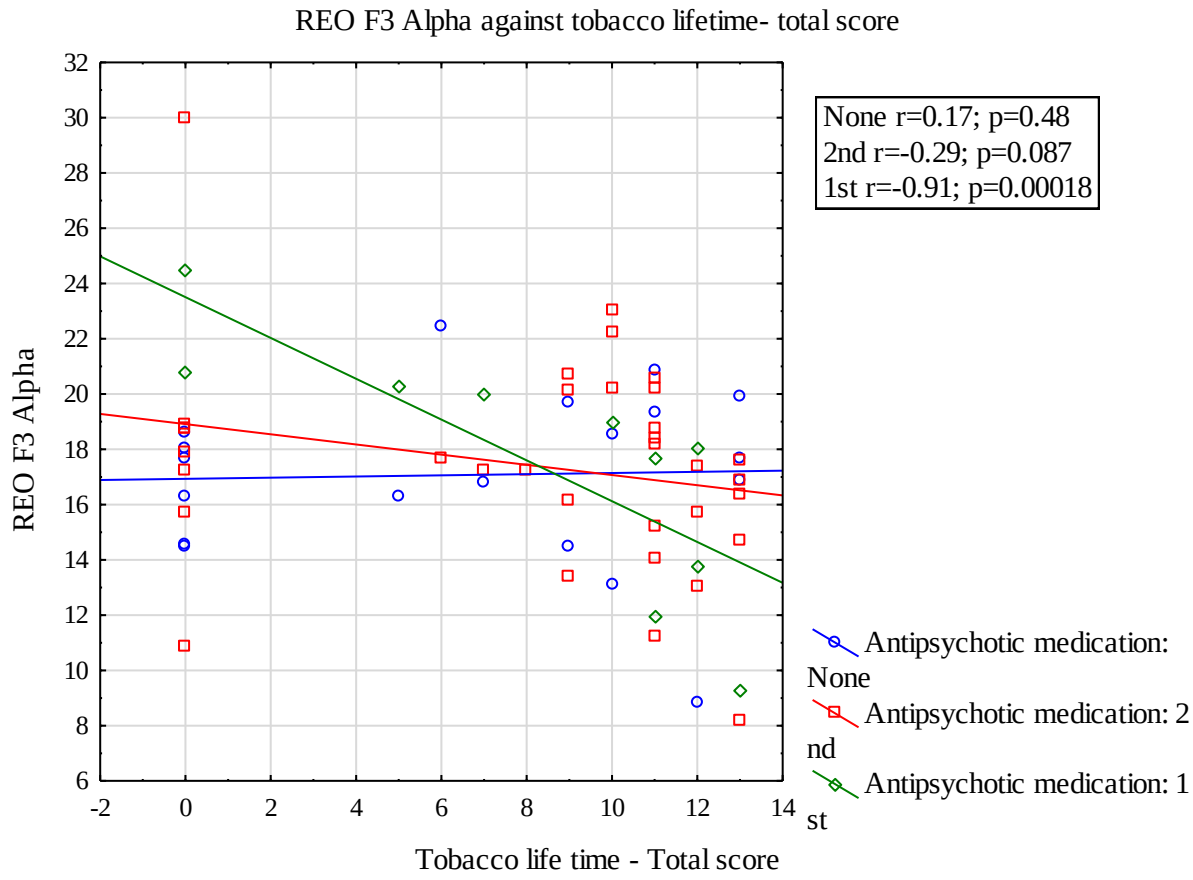


Figure 3.11 Resting eyes open (REO) relative alpha activity for the left frontal (F_3) electrode for patients prescribed 1st generation antipsychotic medication negatively correlated with the lifetime use of tobacco. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for p<0.01 and Rho= >±0.60.

3.3.7 Resting eyes closed relative alpha activity

REC relative alpha activity reported a group difference for the left and right parietal electrode (P_3 ($F_{2.101}$=4.55; p=0.012); P_4 ($F_{2.101}$=4.44; p=0.014)) where SCZ alpha activity was smaller compared to MPD (P_3 p=0.021) and CON (P_4 p=0.011). REC relative alpha activity also reported a group difference for the left prefrontal electrode (Fp_1 ($H_{2.104}$=6.56; p=0.037) where SCZ was smaller compared to MPD (p=0.045), **Table 3.9**. Covariate analysis was limited to the psychotic groups when classified by antipsychotic medication type (NONE, 1st, 2nd). Further limited to left parietal electrode (P_3) relative alpha activity during REC and total years of formal education (2nd $R_{spearman's(n=19)}$=0.60; p=0.00012). The inclusion of tertiary education reported a group difference for the left parietal relative delta (P_3 ($F_{2,61}$=3.55; p=0.034)), yet this did not lead to any specific group differences.

Table 3.9 Resting eyes closed relative alpha frequency activity

		Healthy control	Schizophrenia	Methamphetamine -induced psychosis		
		n = 35	n = 38	n = 31		
		15 females/20 males	8 females/30 males	7 females/24 males		
		Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test/ F test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	21.34(12.85-40.97)	18.28(8.33-28.89) *	22.16(12.21-36.55)	$H_{2.104}$=6.56; p=0.037	SCZ<CON p=0.045
Right prefrontal cortex	**Fp_2**	21.85(10.58-40.19)	19.70(7.83-29.03)	22.36(13.83-40.68)	$H_{2.104}$=5.10; p=0.078	-
Left frontal cortex	**F_3**	24.23(14.68-42.34)	21.34(12.08-35.72)	23.49(10.32-34.51)	$F_{2.101}$=0.99; p=0.37	-
Right frontal cortex	**F_4**	24.47(14.91-42.60)	20.71(9.28-36.26)	23.47(10.68-36.03)	$F_{2.101}$=2.22; p=0.11	-
Left central cortex	**C_3**	22.77(14.06-39.96)	21.50(9.88-35.95)	23.59(10.47-38.14)	$H_{2.104}$=0.96; p=0.61	-
Right central cortex	**C_4**	23.56(15.00-36.33)	21.25(7.60-37.46)	24.58(11.16-34.68)	$F_{2.101}$=1.57; p=0.21	-
Left parietal cortex	**P_3**	26.43(15.52-41.43)	21.55(8.52-37.69) *	25.64(11.80-43.14)	$F_{2.101}$=4.55; p=0.012	SCZ<MPD p=0.021
Right frontal cortex	**P_4**	26.54(14.17-42.95)	22.13(9.53-36.11) @	25.32(10.37-34.57)	$F_{2.101}$=4.44; p=0.014	SCZ<CON p=0.011
Left occipital cortex	**O_1**	28.73(15.33-47.55)	25.44(10.98-44.10)	26.14(11.68-44.09)	$F_{2.101}$=1.21; p=0.30	-
Right occipital cortex	**O_2**	27.27(13.35-42.62)	23.90(10.17-47.20)	26.33(10.56-46.94)	$F_{2.101}$=0.87; p=0.42	-

** Schizophrenia (SCZ) reported decreased alpha frequency activity compared to methamphetamine-induced psychotic disorder (MPD), @ Schizophrenia (SCZ) reported decreased alpha frequency activity compared to healthy controls (CON). Significance P<0,05.*

In MPD, the duration of methamphetamine use (n=31) was negatively correlated with REC alpha for the right prefrontal electrode (Fp_2($R_{spearman's(n=31)}$=-0.63; p=0.000095), **Figure 3.12**. Then, REC right occipital alpha activity positively correlated with years of schooling ($O_2R_{spearman's(n=31)}$=0.60; p=0.00034), and total years of formal education ($O_2R_{spearman's(n=31)}$=0.60; p=0.00028), **Figure 3.13**.

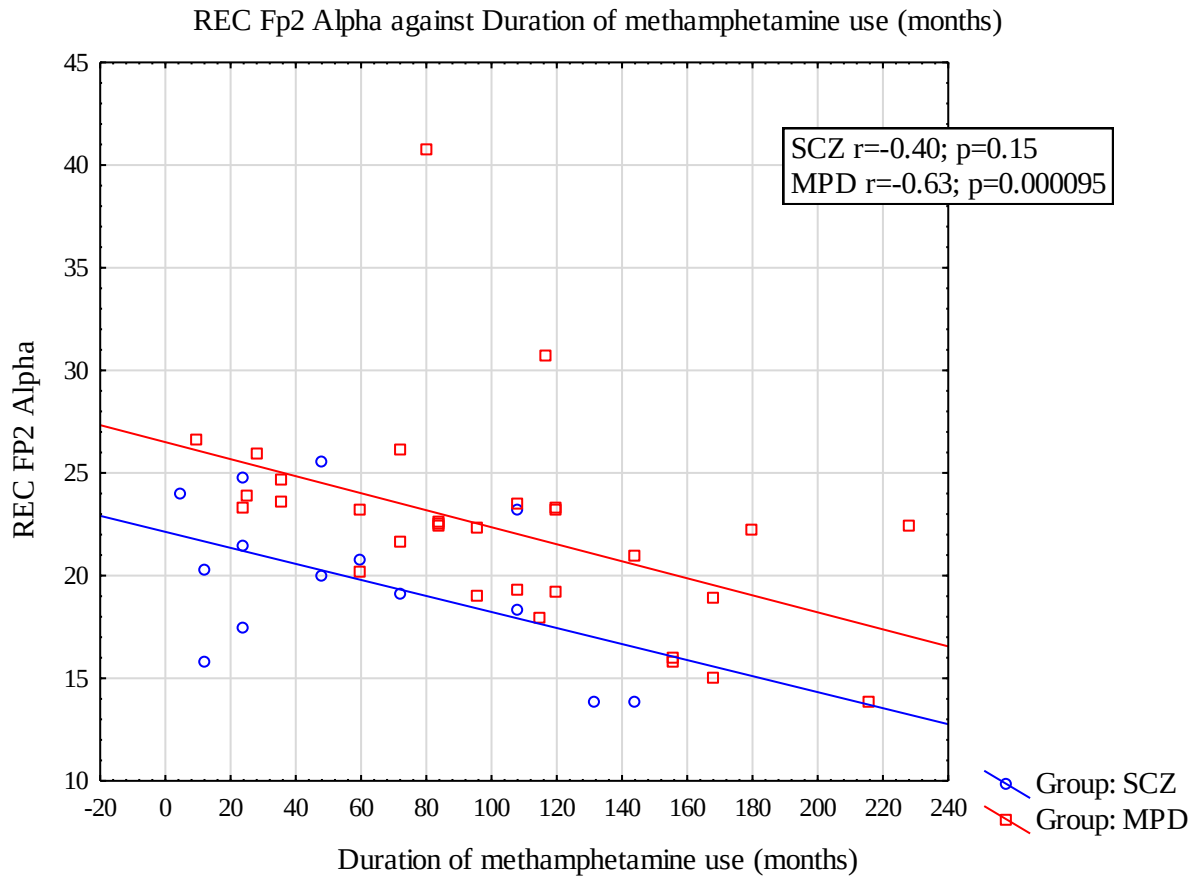


Figure 3.12 Resting eyes closed (REC) relative alpha activity for the right prefrontal (Fp_2) electrode for Methamphetamine-induced psychotic disorder negatively correlated with the duration of methamphetamine use. Schizophrenia (SCZ); Methamphetamine-induced psychotic disorder (MPD). Significance was reported for $p<0.01$ and Rho= $>\pm 0.60$.

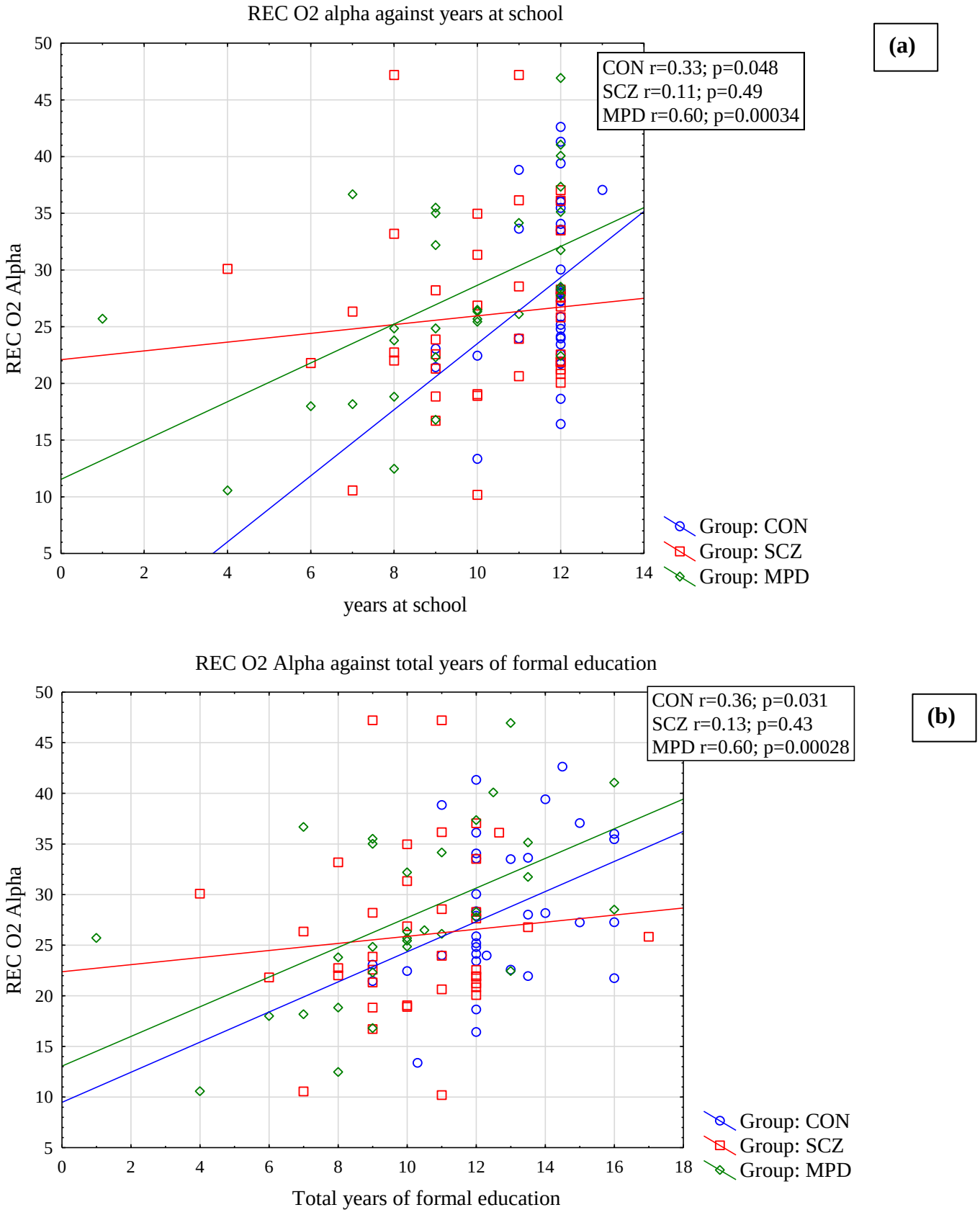


Figure 3.13 Resting eyes closed (REC) relative alpha activity for the right occipital electrode for Methamphetamine-induced psychotic disorder positively correlated with **(a)** years at school and **(b)** total years of formal education. Schizophrenia (SCZ); Methamphetamine-induced psychotic disorder (MPD), controls (CON). Significance was reported for $p<0.01$ and Rho= >±0.60.

For patients not taking antipsychotics (n = 20x, where SCZn= 7; MPDn=13): REC relative alpha activity for the left prefrontal cortical electrode positively correlated with lifetime use of alcohol ($Fp_1R_{Spearman's(n=20)}$=0.62; p=0.0033), and the right occipital cortical electrode positively correlated with the lifetime use of cannabis ($O_2R_{Spearman's(n=20)}$=0.60; p=0.0050), **Figure 3.14**; Then for patients not taking antipsychotic medication (n = 14, where SCZn= 1; MPDn=13), REC relative alpha activity negatively correlated with the right prefrontal through to the right parietal cortical electrodes for duration of methamphetamine use ($Fp_2R_{Spearman's(n=14)}$=-0.72; p=0.0036), ($C_4R_{Spearman's(n=14)}$=-0.68; p=0.0068), and ($P_4R_{Spearman's(n=14)}$=-0.67; p=0.0082), **Figure 3.15**; Then for patients not taking antipsychotic medication (n = 20, where SCZn= 7; MPDn=13, REC right occipital alpha activity positively correlated with duration of tertiary education for the right parietal and right occipital cortical electrodes ($P_4R_{spearman's(n=20)}$=0.65; p=0.0019; $O_2R_{spearman's(n=20)}$=0.68; p=0.00087), **Figure 3.16.**

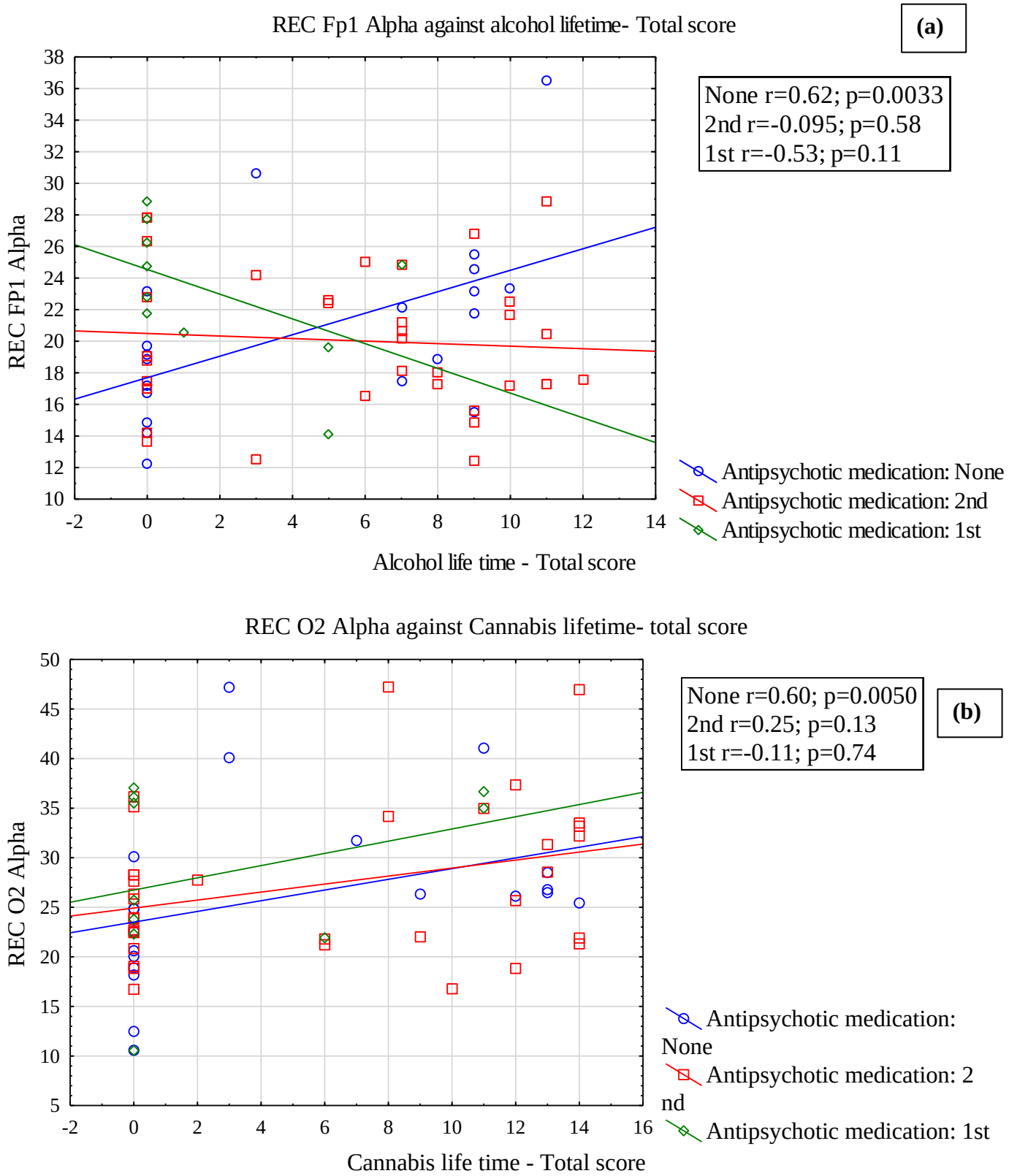
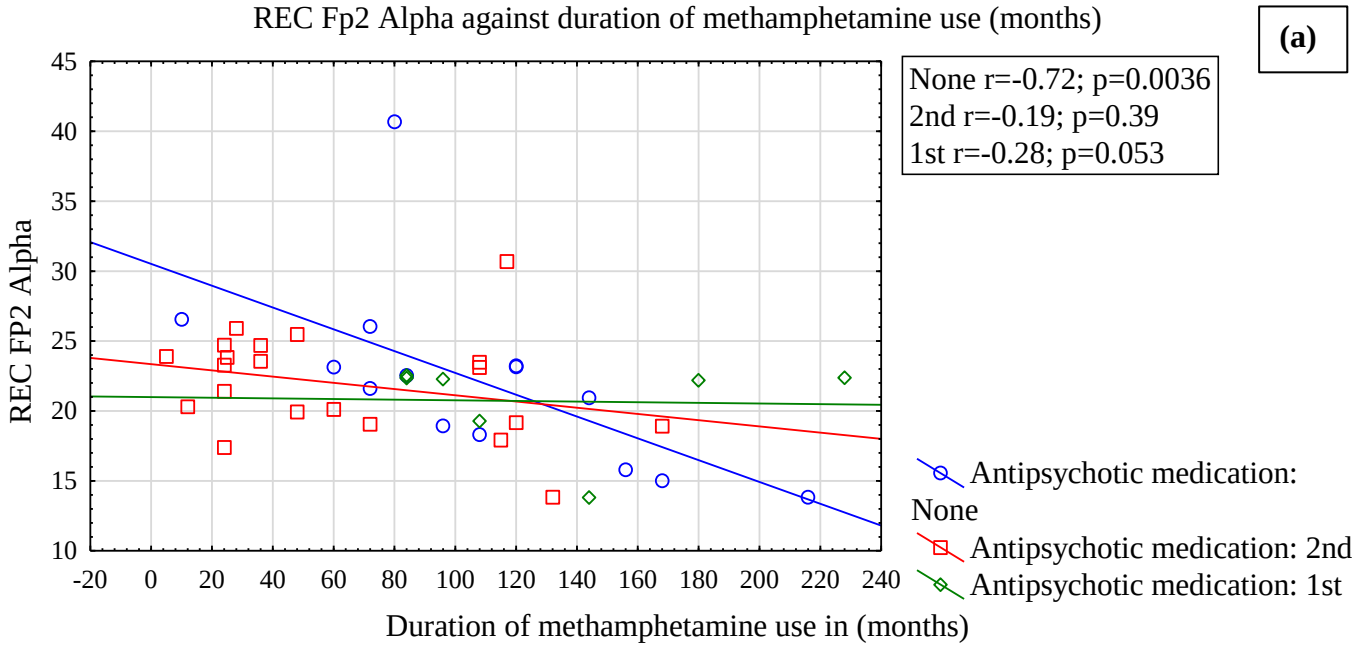
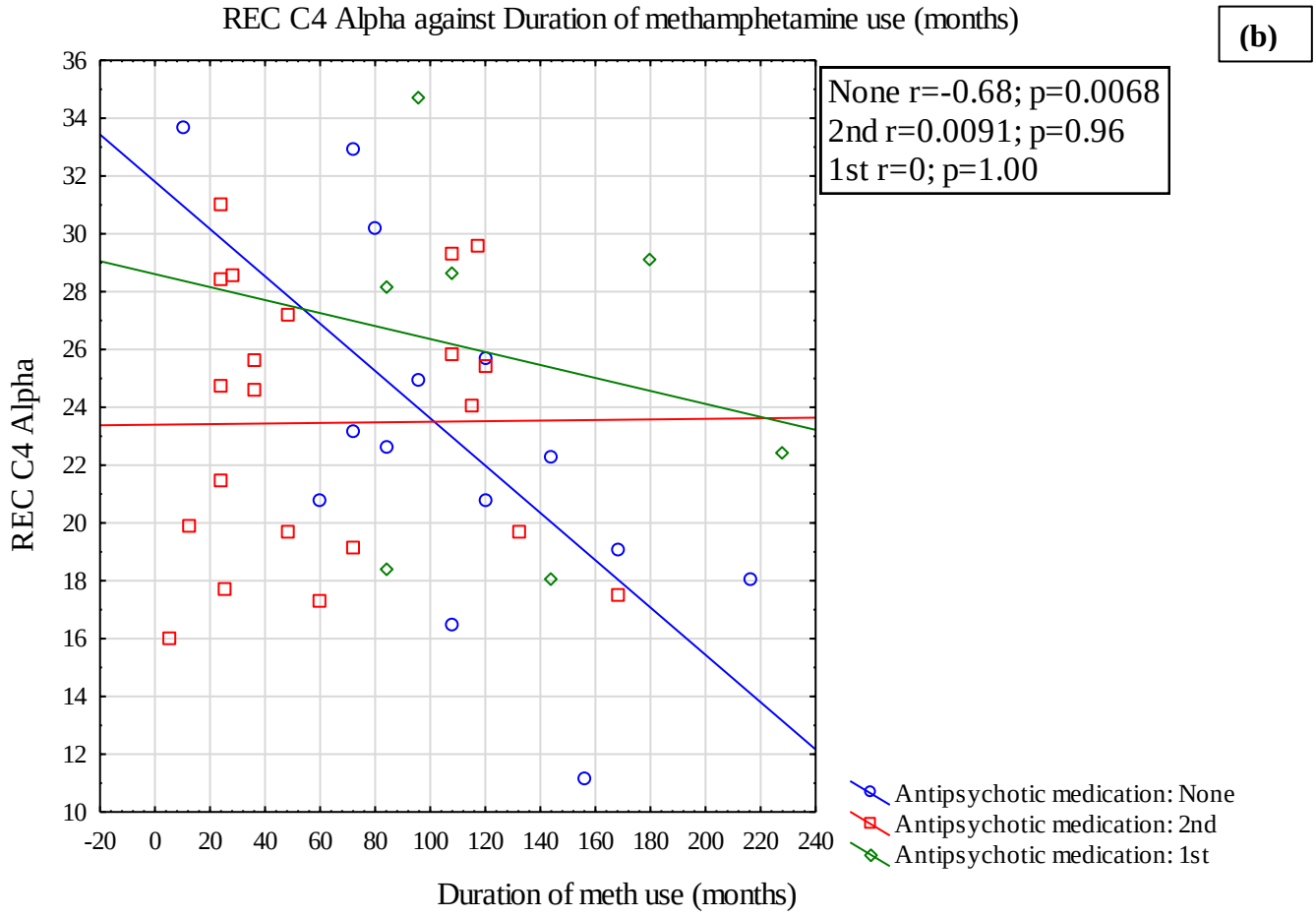


Figure 3.14 Resting eyes closed (REC) relative alpha activity for the lifetime use of alcohol for patients not taking antipsychotic medication positively correlated with **(a)** left prefrontal (Fp_1) electrode and REO relative alpha activity for the lifetime use of cannabis for patients not taking antipsychotic medication positively correlated with **(b)** right occipital (O_2) electrode. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm 0.60$.


REC Fp2 Alpha against duration of methamphetamine use (months)
(a)
None r=-0.72; p=0.0036
2nd r=-0.19; p=0.39
1st r=-0.28; p=0.053
REC FP2 Alpha
Duration of methamphetamine use in (months)
Antipsychotic medication: None
Antipsychotic medication: 2nd
Antipsychotic medication: 1st


REC C4 Alpha against Duration of methamphetamine use (months)
(b)
None r=-0.68; p=0.0068
2nd r=0.0091; p=0.96
1st r=0; p=1.00
REC C4 Alpha
Duration of meth use (months)
Antipsychotic medication: None
Antipsychotic medication: 2nd
Antipsychotic medication: 1st

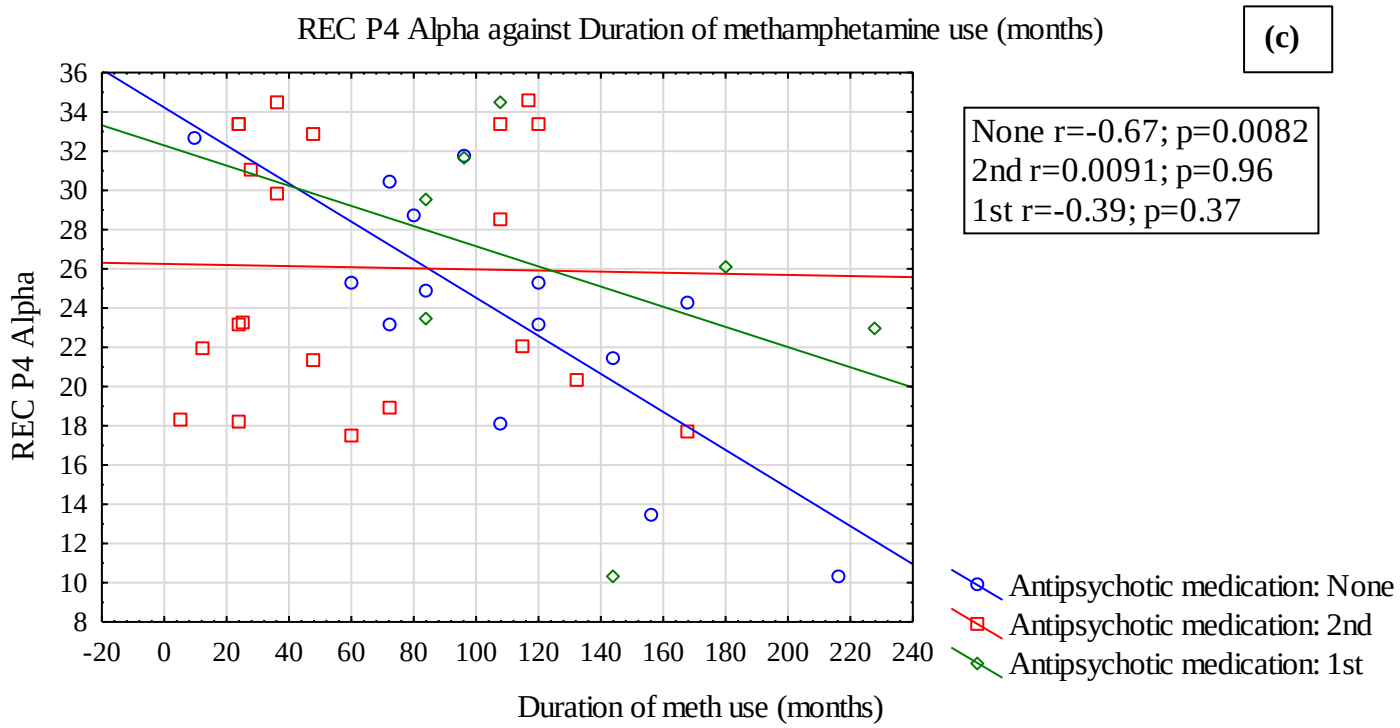


Figure 3.15 Resting eyes closed (REC) relative alpha activity for the duration of methamphetamine use for patients not taking antipsychotic medication negatively correlated with **(a)** right prefrontal (Fp_2), **(b)** right central (C_4), **(c)** right parietal (P_4) electrode. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm0.60$.

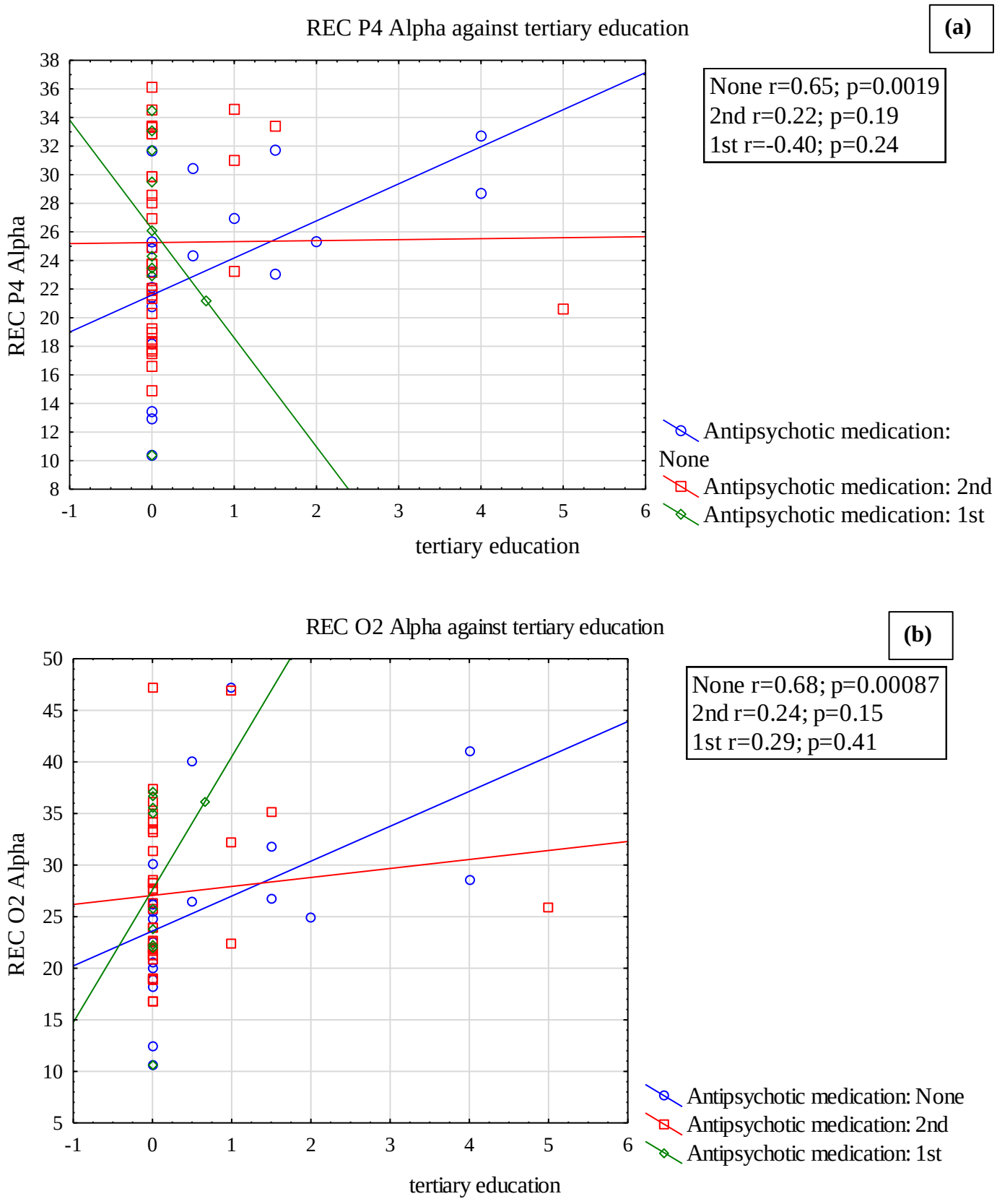


Figure 3.16 Resting eyes closed (REC) relative alpha activity for the duration of tertiary education for patients not taking antipsychotic medication positively correlated with **(a)** right parietal (P_4) and **(b)** right occipital (O_2) electrode. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm0.60$.

For patients prescribed 2nd generation antipsychotics (n = 35, where SCZn= 24; MPDn=11, REC alpha activity for the left parietal cortical electrode correlated positively with total years of formal education ($P_3R_{spearman's(n=35)}$=0.60, p=0.00012)**, Figure 3.17**.

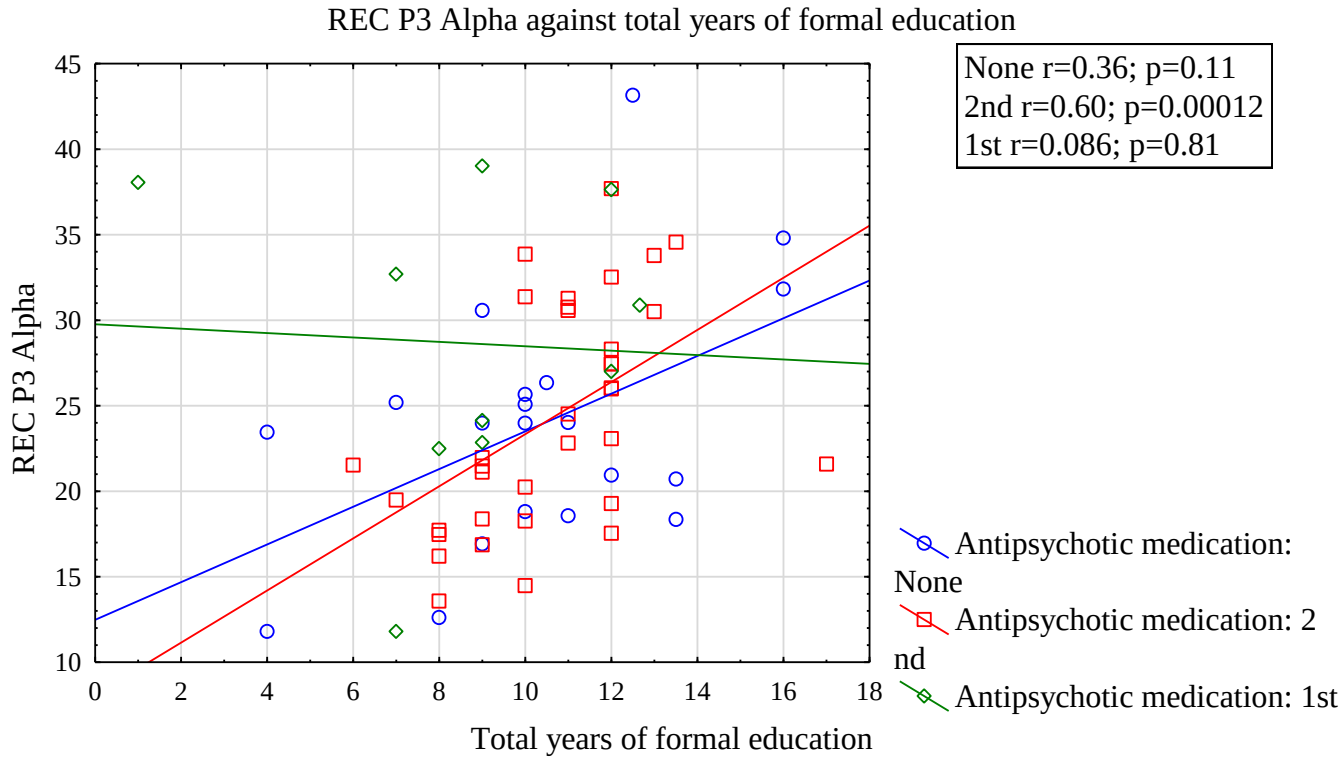


Figure 3.17 Resting eyes closed (REC) relative alpha activity for the left parietal (P_3) electrode for patients prescribed 2nd generation antipsychotic medication positively correlated with years of formal education. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for p<0.01 and Rho= >±0.60.

For patients prescribed 1st generation antipsychotics (n=7, where SCZn=1; MPDn=6), REC alpha activity for the left prefrontal cortical electrode correlated positively with duration of methamphetamine abstinence ($Fp_1R_{spearman's(n=7)}$=0.88, p=0.0073), **Figure 3.18**. Then for patients prescribed 1st generation antipsychotics (n=10, where SCZn=4; MPDn=6), REC alpha activity for the right frontal and left parietal cortical electrode correlated negatively with the number of psychotic episodes ($F_4R_{spearman's(n=10)}$=-0.81, p=0.0036; $P_3R_{spearman's(n=10)}$=-0.87, p=0.0010), **Figure 3.19**.

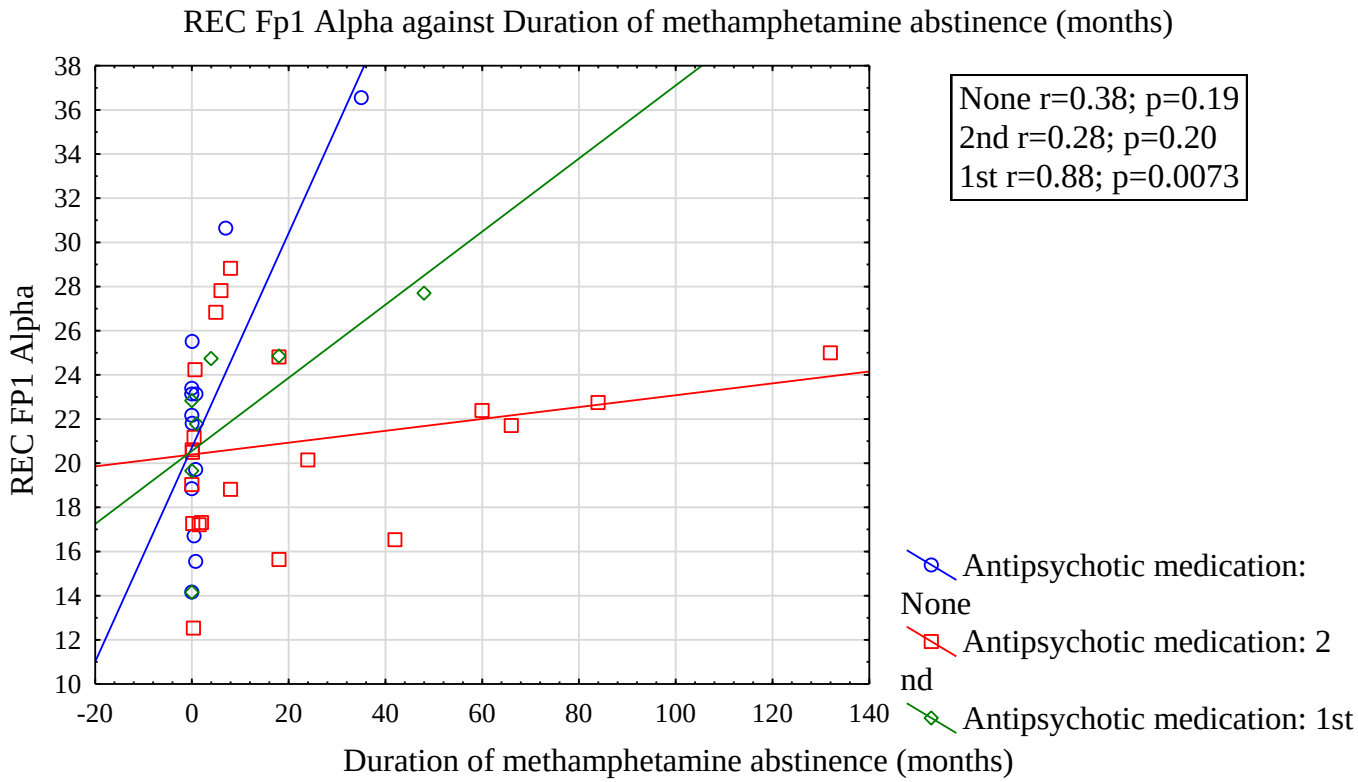


Figure 3.18 Resting eyes closed (REC) relative alpha activity for the left prefrontal (Fp_1) electrode for patients not taking antipsychotic medication positively correlated with duration of methamphetamine abstinence. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm 0.60$.

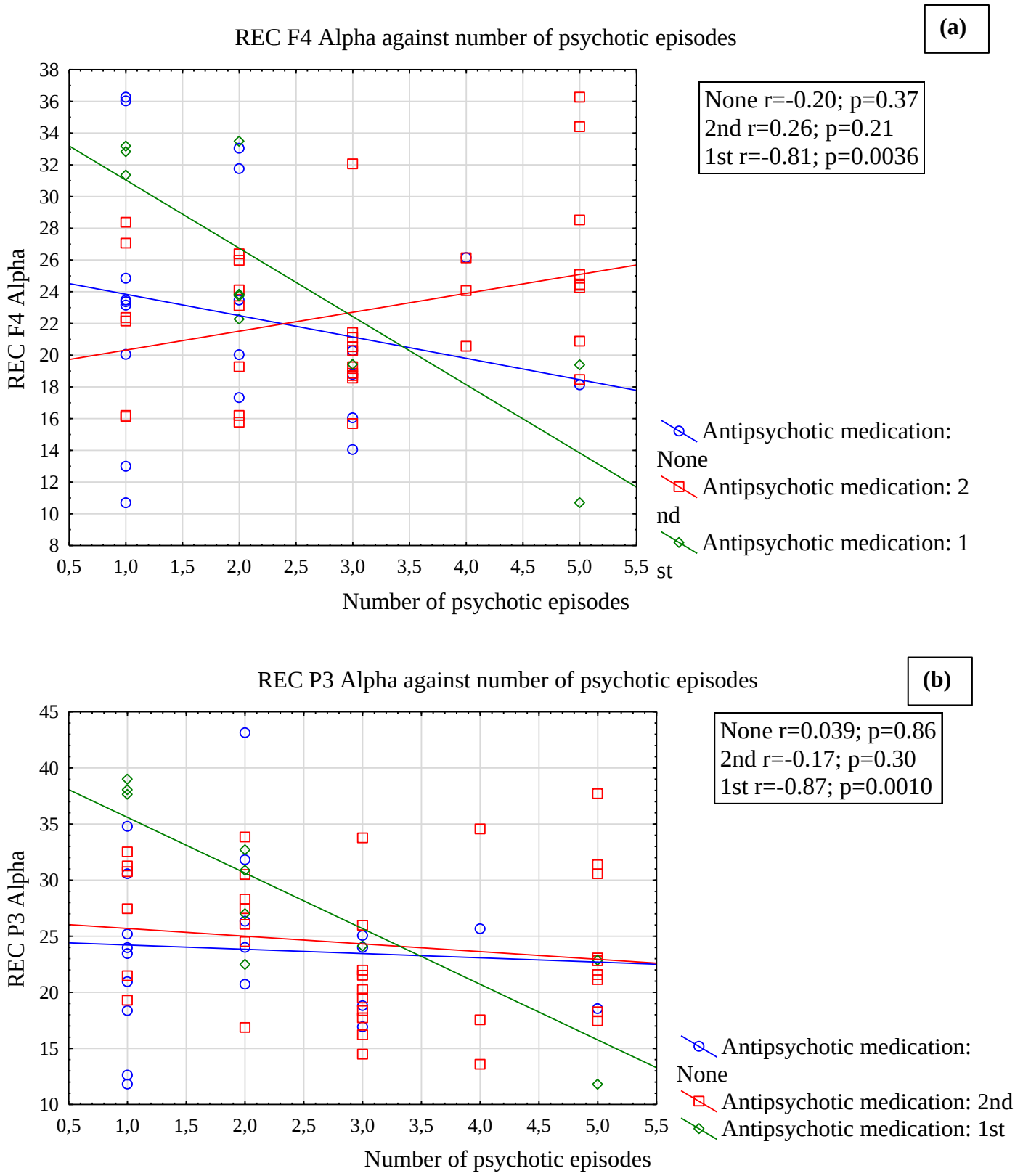


Figure 3.19 Resting eyes closed (REC) relative alpha activity for the number psychotic episodes patients prescribed 1st generation antipsychotic medication negatively correlated with **(a)** right frontal (F_4) **(b)** left parietal (P_3) electrode. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm 0.60$.

3.3.8 Resting eyes open relative beta activity

No group differences were found, however when potential co-variates were investigated the following differences were found, **Table 3.10**.

Covariates which were found to interact with group differences were limited to psychotic groups when classified by antipsychotic medication type (NONE, 1st, 2nd) on tertiary education (NONE $R_{spearman's(n=19)}$=0.64; p=0.0030). However, there was no significant group difference in the duration of tertiary education for C_4 relative beta.

The second covariate which was found to interact with group differences was limited to analysis of the psychotic groups when classified by antipsychotic medication type (NONE, 1st, 2nd) on lifetime cannabis total score (NONE $R_{spearman's(n=19)}$= 0.71; p=0.00055). However, there was no significant group difference in the duration of tertiary education for C_4 relative beta.

The third covariate which was found to interact with group differences was limited to analysis of the psychotic groups when classified by antipsychotic medication type (NONE, 1st, 2nd) on the positive and negative symptom scale total score (1st $R_{spearman's(n=19)}$= 0.78; p=0.0072). However, there was no significant group difference in the duration of tertiary education for Fp_1 relative beta.

Table 3.10 Resting eyes open relative beta frequency activity

		Healthy control	**Schizophrenia**	**Methamphetamine-induced psychosis**		
		n = 35	n = 38	n = 31		
		15 females/20 males	8 females/30 males	7 females/24 males		
		Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test/ F test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	14.87(7.28-25.83)	14.23(5.37-23.41)	14.75(5.72-28.50)	$F_{2.99}$=1.38; p=0.25	-
Right prefrontal cortex	**Fp_2**	17.42(14.01-8.27)	14.58(6.22-33.16)	19.49(7.39-32.70)	$H_{2.102}$=5.40; p=0.066	-
Left frontal cortex	**F_3**	20.28(9.24-33.99)	17.99(8.38-48.05)	20.54(6.00-35.16)	$H_{2.102}$=2.19; p=0.33	-
Right frontal cortex	**F_4**	22.12(8.57-42.73)	19.68(10.61-39.65)	22.09(10.60-38.37)	$H_{2.102}$=1.28; p=0.52	-
Left central cortex	**C_3**	21.82(8.05-36.46)	19.54(11.93-30.49)	20.98(6.95-40.90)	$H_{2.102}$=3.94; p=0.13	-
Right central cortex	**C_4**	20.22(8.47-37.28)	18.31(7.39-29.87)	19.18(7.32-37.80)	$F_{2.99}$=1.21; p=0.30	-
Left parietal cortex	**P_3**	21.58(9.46-51.67)	20.13(10.34-38.00)	20.52(7.31-36.82)	$H_{2.102}$=0.55; p=0.75	-
Right frontal cortex	**P_4**	19.87(7.60-32.56)	17.85(8.26-46.87)	18.95(7.18-28.16)	$H_{2.102}$=0.48; p=0.78	-
Left occipital cortex	**O_1**	18.85(9.46-36.59)	17.53(8.97-29.10)	18.86(8.24-29.35)	$H_{2.102}$=0.80; p=0.66	-
Right occipital cortex	**O_2**	18.65(8.37-44.70)	19.07(9.90-29.44)	19.62(8.26-29.20)	$H_{2.102}$=0.58; p=0.74	-

Non-parametric Kruskal Wallis (H-test) and parametric one-way analysis of variance (F-test), Significance P<0.05.

In SCZ (n=13), the age of methamphetamine use negatively correlated with REO relative beta activity for the left frontal and right occipital cortical electrodes ($F_3R_{spearman's(n=13)}$=-0.80, p=0.00079; O_2($R_{spearman's(n=13)}$=-0.73, p=0.0039), **Figure 3.20**.

For patients not taking antipsychotics (n=19, where SCZn=7; MPDn=13): REO beta activity right central and left occipital electrode positively correlated with years at a tertiary institution for ($C_4R_{Spearman's(n=19)=}0.64$; p=0.0030), ($O_1R_{Spearman's(n=19)=}0.61$; p=0.0053), **Figure 3.21**; REO beta activity right occipital electrode positively correlated with total years of formal education for ($O_2R_{Spearman's(n=19)=}0.64$; p=0.0028), **Figure 3.22**; REO beta activity positively correlated with the central through to the occipital cortical electrodes for lifetime cannabis score ($C_4R_{Spearman's(n=19)=}0.71$; p=0.00055), ($P_4R_{Spearman's(n=19)=-}0.62$; p=0.0046), and ($O_1R_{Spearman's(n=19)=-}0.67$; p=0.0015), **Figure 3.23.**

For patients prescribed 1st generation antipsychotics (n=10, where SCZn=4; MPDn=6): REO beta activity for the left prefrontal cortical electrode correlated positively for positive and negative symptom scale total score ($Fp_1R_{spearman's(n=10)}=0.78$; p=0.0072), **Figure 3.24**; REO beta activity for the right frontal cortical electrode correlated negatively for the lifetime tobacco total score ($F_4R_{spearman's(n=10)}=-0.94$; p=0.000046), **Figure 3.25**.

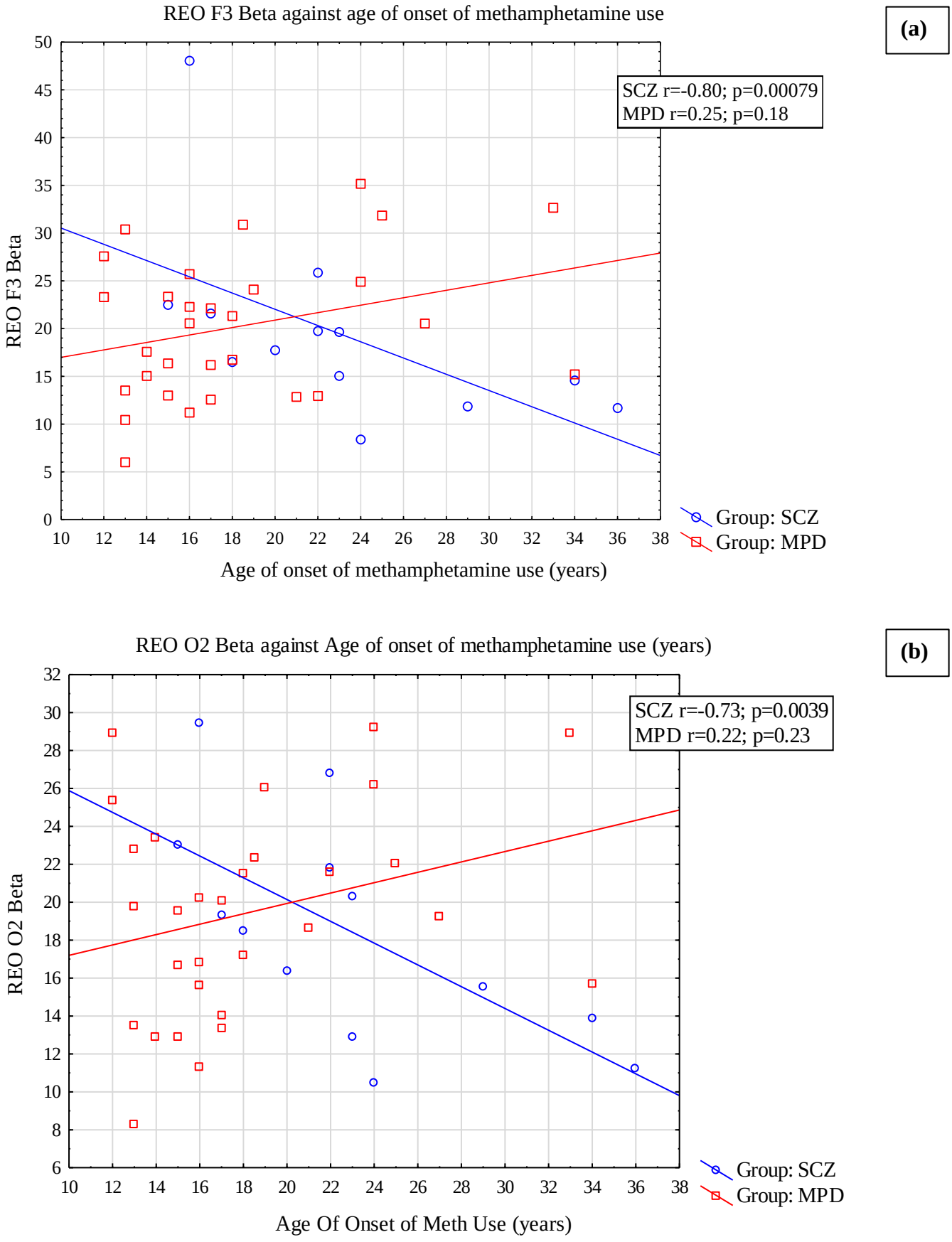


Figure 3.20 Resting eyes open (REO) relative beta activity for the age of onset of methamphetamine use Schizophrenia negatively correlated with **(a)** left frontal (F_3) **(b)** right occipital (O_2) electrodes. Schizophrenia (SCZ), Methamphetamine-induced psychotic disorder (MPD). Significance was reported for $p<0.01$ and Rho= $>\pm0.60$.

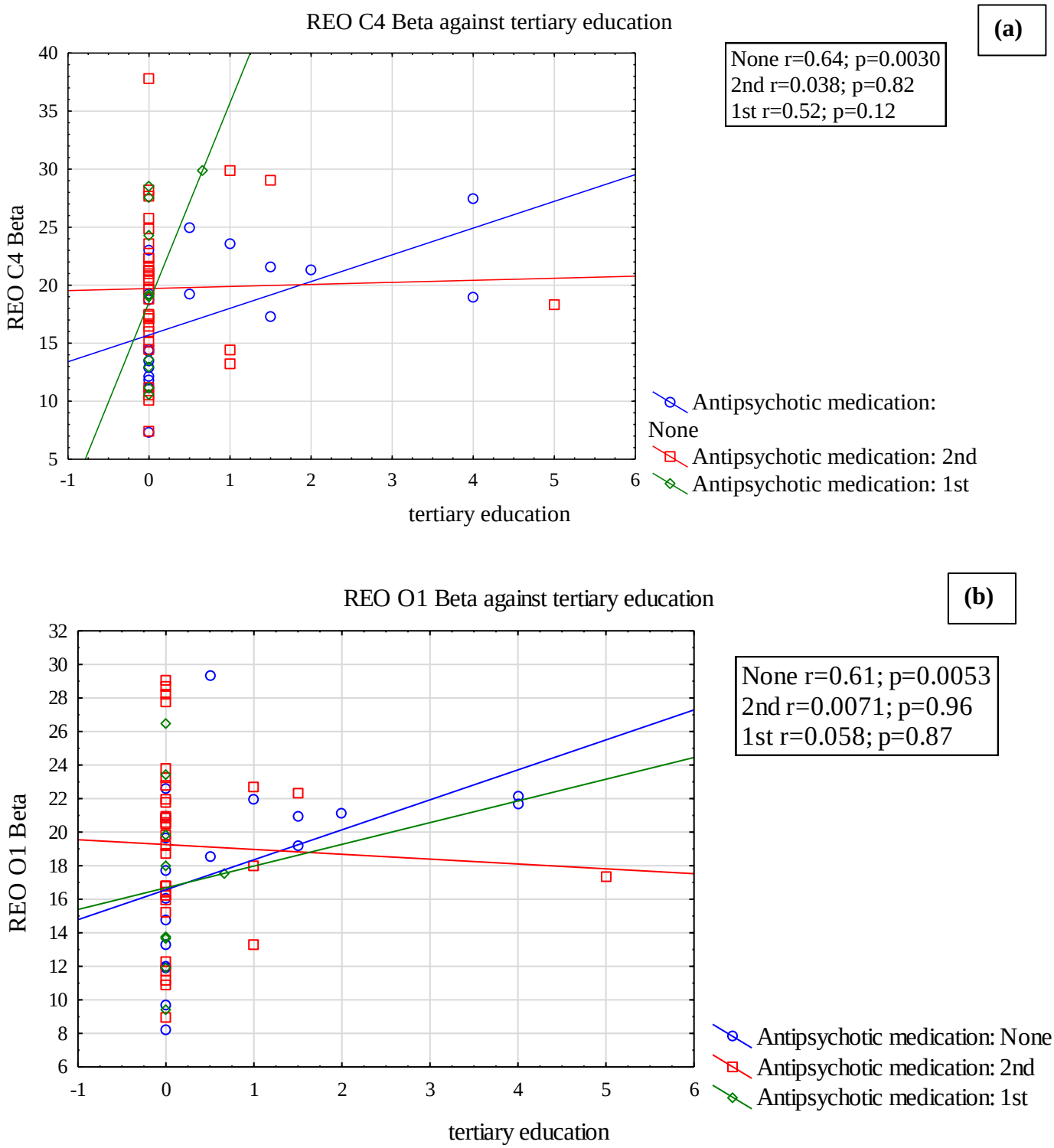


Figure 3.21 Resting eyes open (REO) relative beta activity for the duration of tertiary education for patients not taking antipsychotic medication negatively correlated with **(a)** right central (C_4) and **(b)** left occipital (O_1) electrode. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm0.60$.

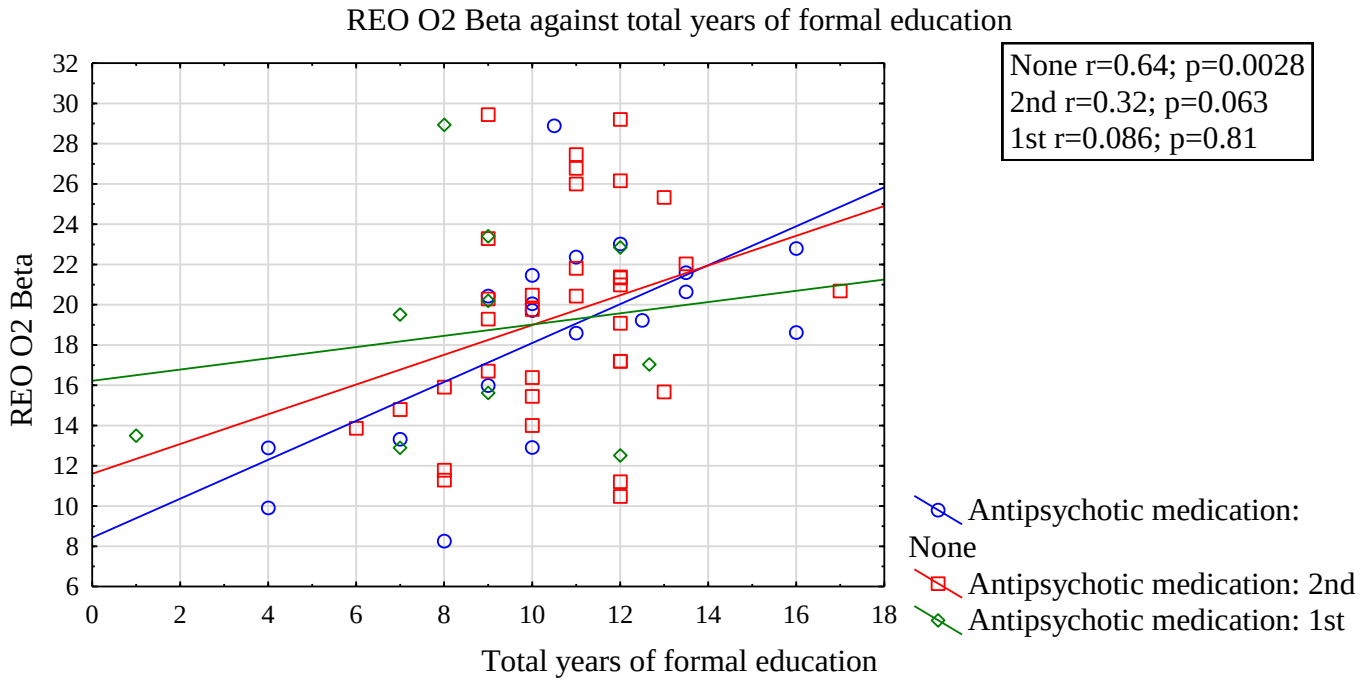
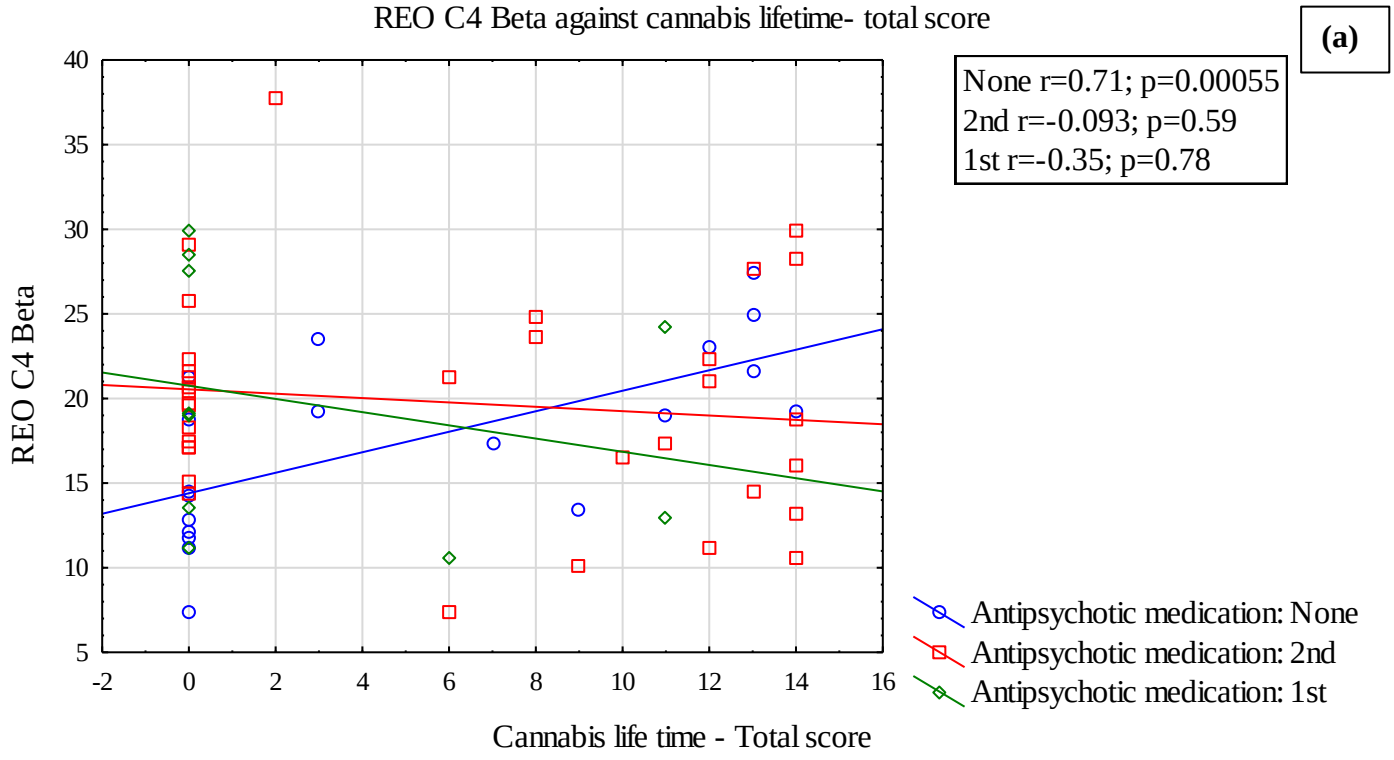


Figure 3.22 Resting eyes open (REO) relative beta activity for the right occipital (O_2) electrode for patients not taking antipsychotic medication negatively correlated with years of formal education. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm 0.60$.



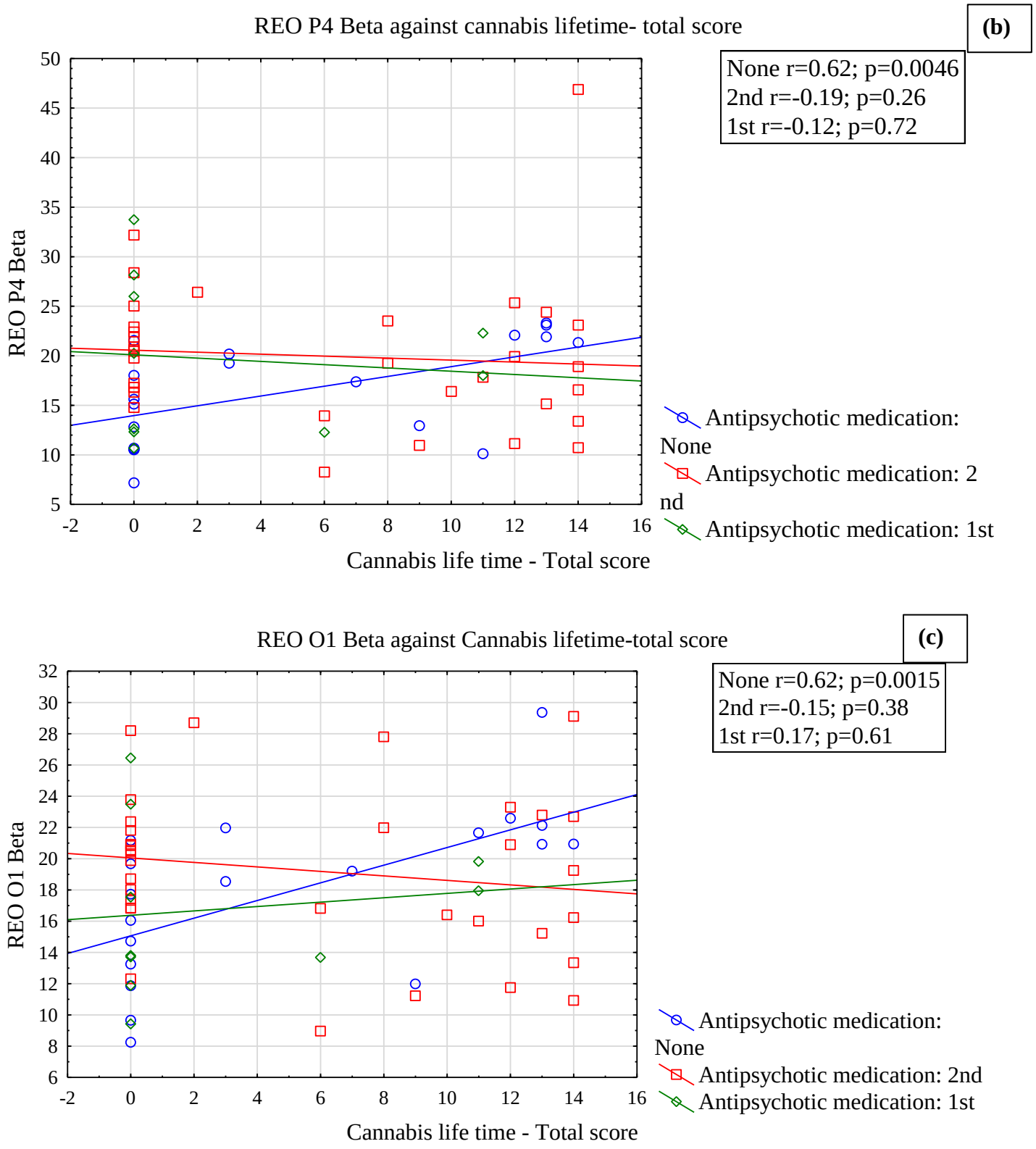


Figure 3.23 Resting eyes open (REO) relative beta activity for the lifetime cannabis total score patients not taking antipsychotic medication negatively correlated with **(a)** right central (C_4) **(b)** right parietal (P_4), **(c)** left occipital (O_1) electrode. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm 0.60$.

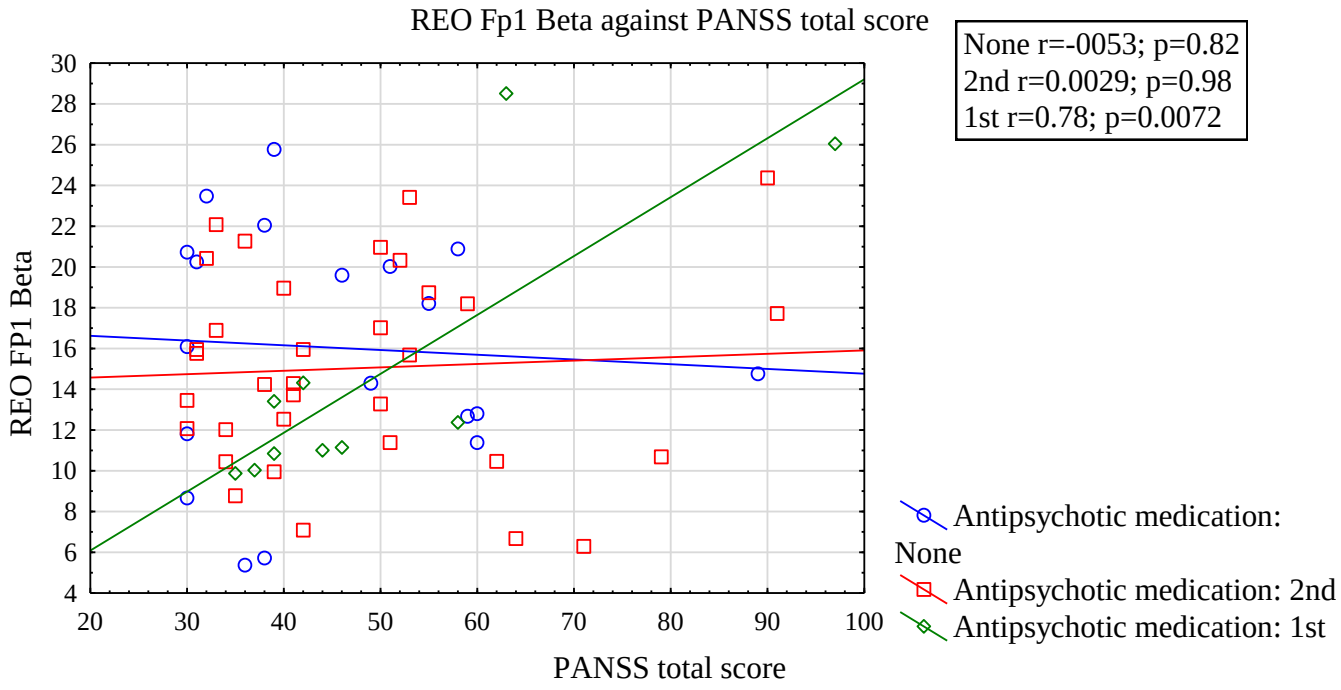


Figure 3.24 Resting eyes open (REO) relative beta activity for the left prefrontal (Fp_1) electrode for patients prescribed 1st generation antipsychotic medication negatively correlated with the positive and negative symptom scale total score. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= >±0.60.

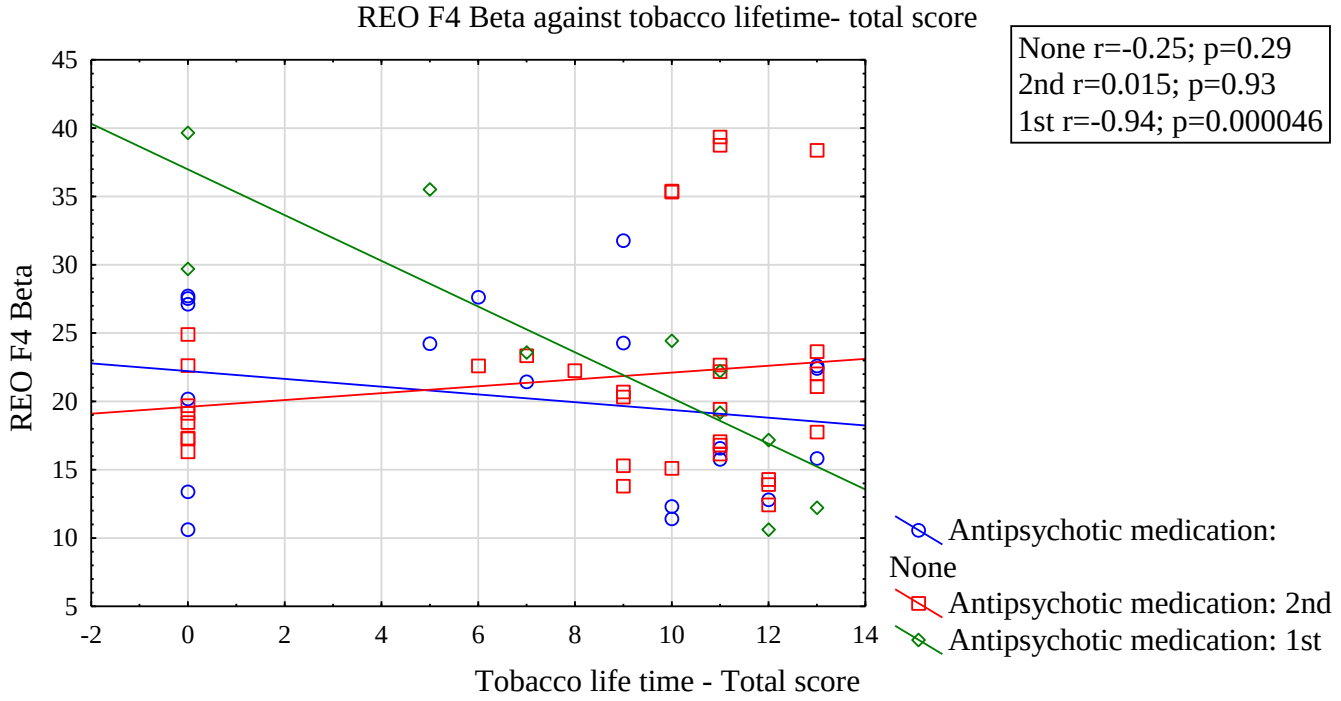


Figure 3.25 Resting eyes open (REO) relative beta activity for the right frontal (F_4) electrode for patients prescribed 1st generation antipsychotic medication negatively correlated with the lifetime tobacco total score. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= >±0.60.

3.3.9 *Resting eyes closed relative beta activity*

REC beta reported a group difference for the left and right prefrontal and left central electrodes (Fp_1 ($H_{2.104}$=8.30; p=0.015); Fp_2 ($H_{2.104}$=6.92; p=0.031); C_3 ($H_{2.104}$=6.52; p=0.038)) where SCZ relative beta activity was smaller compared to MPD (Fp_1 p=0.012, Fp_2 p=0.028, C_3 p=0.034), **Table 3.11**.

Table 3.11 Resting eyes closed relative beta frequency activity

		Healthy control	**Schizophrenia**	**Methamphetamine -induced psychosis**		
		n = 35	n = 38	n = 31		
		15 females/20 males	8 females/30 males	7 females/24 males		
		Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H-test)**	**Post hoc**
Left prefrontal cortex	**Fp_1**	18.07(11.49-45.72)	16.37(9.62-30.51) *	22.35(9.63-34.91)	$H_{2.104}$=8.30; p=0.015	SCZ<MPD p=0.012
Right prefrontal cortex	**Fp_2**	21.56(10.07-45.88)	18.60(9.40-36.73) *	25.43(9.41-31.60)	$H_{2.104}$=6.92; p=0.031	SCZ<MPD p=0.028
Left frontal cortex	**F_3**	20.93(13.50-46.70)	19.47(10.56-43.60)	23.86(11.05-42.91)	$H_{2.104}$=3.20; p=0.20	-
Right frontal cortex	**F_4**	24.81(13.43-51.02)	24.38(9.58-44.93)	25.20(9.59-45.91)	$H_{2.104}$=0.93; p=0.62	-
Left central cortex	**C_3**	22.68(12.91-46.36)	21.28(10.27-35.73) *	24.85(10.27-55.27)	$H_{2.104}$=6.52; p=0.038	SCZ<MPD p=0.034
Right central cortex	**C_4**	22.83(11.51-50.88)	20.22(9.38-35.72)	22.58(10.92-43.75)	$H_{2.104}$=3.81; p=0.14	-
Left parietal cortex	**P_3**	23.81(11.90-49.72)	23.82(9.46-43.05)	26.57(10.79-45.54)	$H_{2.104}$=1.11; p=0.57	-
Right frontal cortex	**P_4**	20.74(12.25-47.01)	19.49(8.07-48.28)	21.74(8.07-39.21)	$H_{2.104}$=0.66; p=0.71	-
Left occipital cortex	**O_1**	21.43(11.02-43.63)	20.89(7.90-34.05)	20.90(7.90-39.28)	$H_{2.104}$=0.87; p=0.64	-
Right occipital cortex	**O_2**	21.25(11.49-42.59)	20.76(8.81-33.19)	21.10(8.82-40.25)	$H_{2.104}$=0.39; p=0.81	-

****** SCZ reported decreased delta frequency activity compared to MPD; Non-parametric Kruskal Wallis (H-test), Significance P<0.05.*

For patients not taking antipsychotics (n=20, where SCZn=7; MPDn=13); REC relative beta activity for the left prefrontal electrode negatively correlated with the general psychopathology subscale of the positive and negative symptom scale ($Fp_1R_{Spearman's(n=20)}$=-0.63; p=0.0029), **Figure 3.26**; REC relative beta activity right central electrode positively correlated with years of tertiary education ($C_4R_{Spearman's(n=20)}$=0.69; p=0.00066), with total years of formal education ($C_4R_{Spearman's(n=20)}$=0.60; p=0.0045) and lifetime use of cannabis ($C_4R_{Spearman's(n=20)}$=0.73; p=0.00020)**, Figure 3.27.**

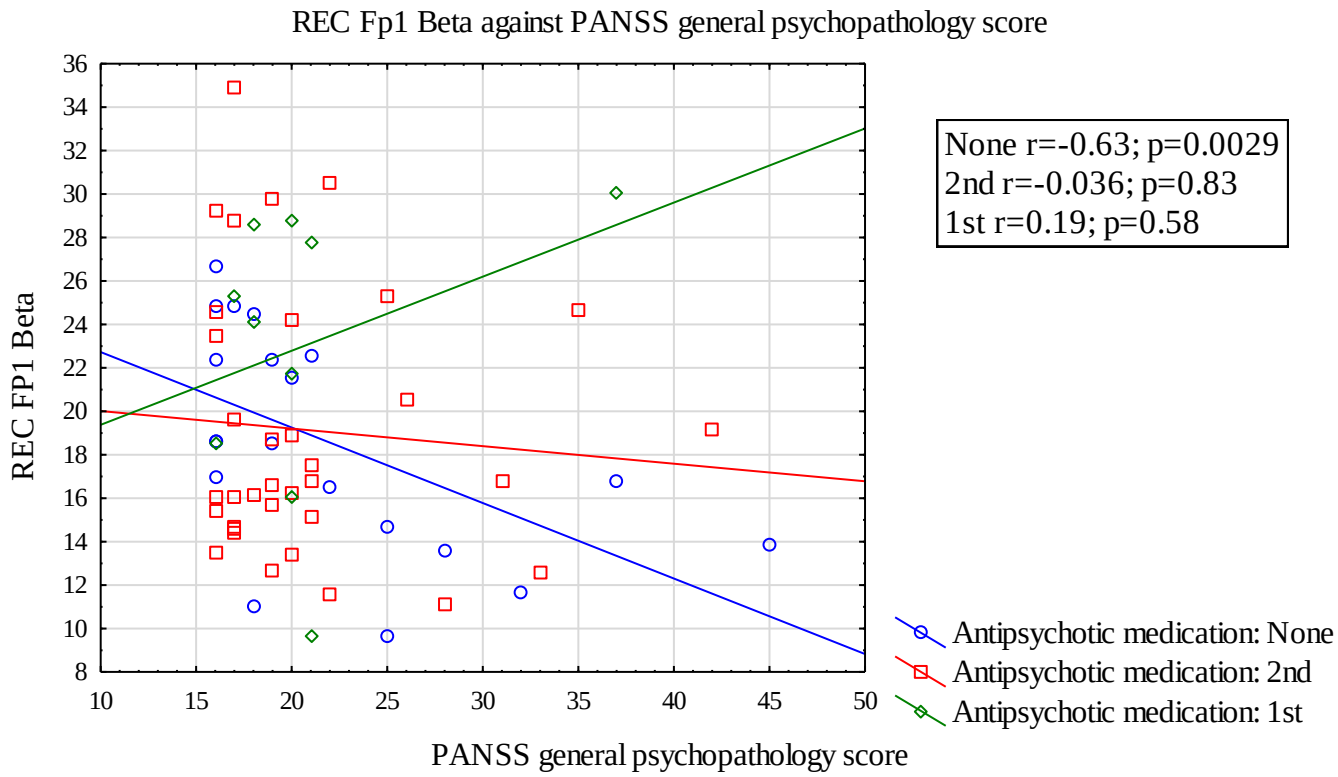
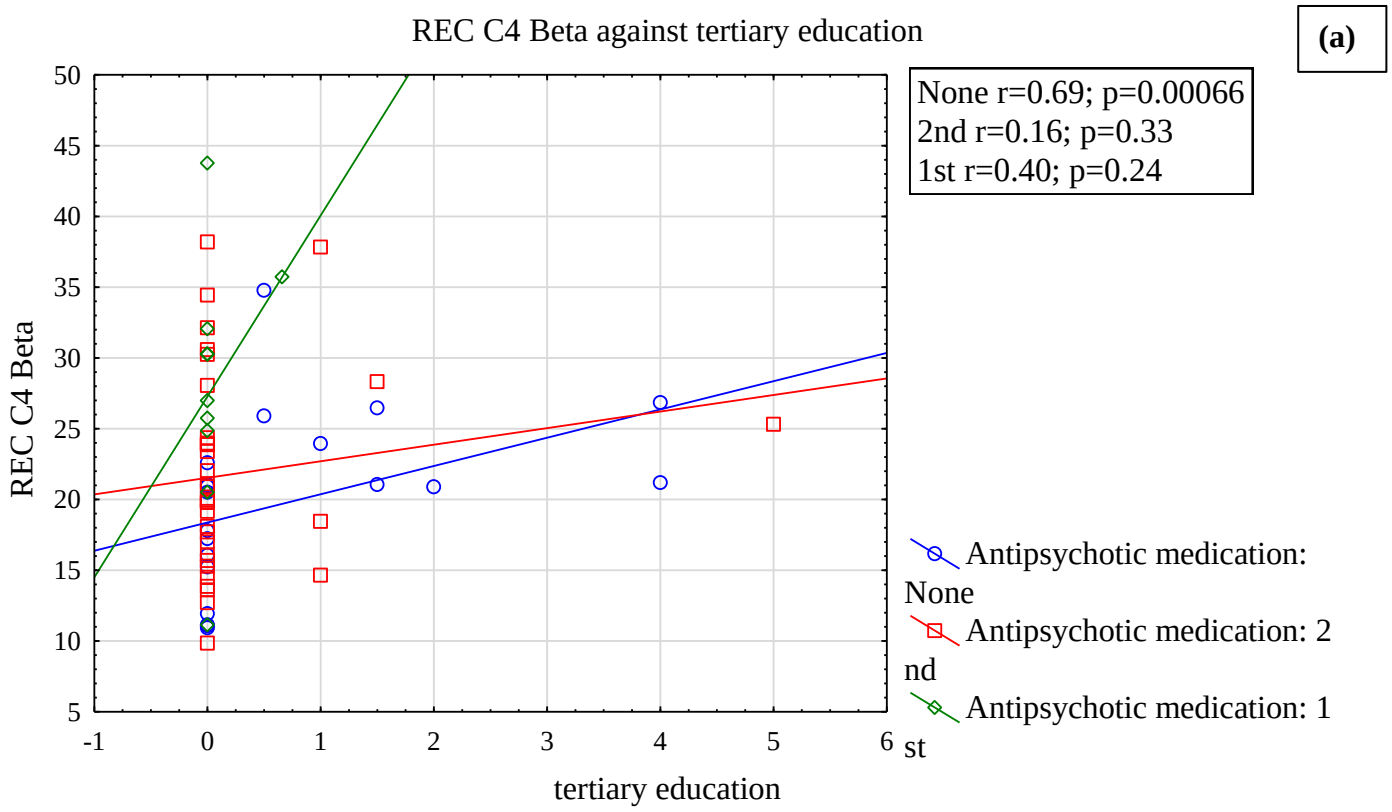


Figure 3.26 Resting eyes closed (REC) relative beta activity for the left prefrontal (Fp_1) electrode for patients not taking antipsychotic medication negatively correlated with the general psychopathology subscale of the positive and negative symptom scale. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm 0.60$.



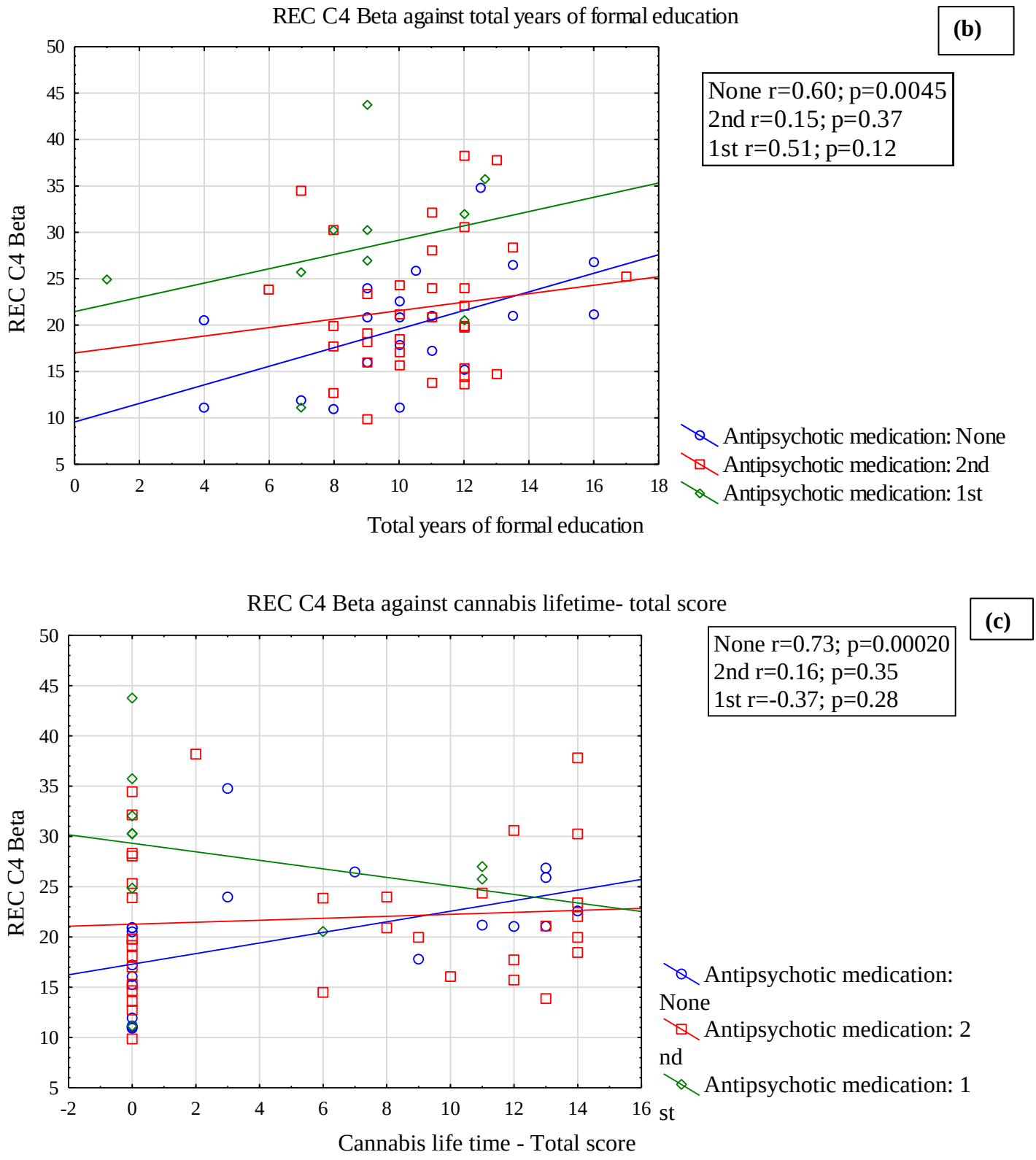


Figure 3.27 Resting eyes closed (REC) relative right central electrode (C_4) beta activity for the antipsychotic medication positively correlated with **(a)** duration of tertiary education, **(b)** total years of formal education and **(c)** lifetime use of cannabis. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm0.60$.

3.4 Discussion

The present study examined relative frequency activity during resting eyes closed (REC) and resting eyes open (REO) in SCZ, MPD and CON, and in addition their potential associations with clinical symptoms and prescribed medication. Our main findings are as follows; first, our study presented decreased alpha and increased theta and beta activity during REC within the psychotic disorders. Second, we reported an increase in theta activity during REO for SCZ, however for MPD delta activity was reduced. Third, as expected in both REO and REC alpha activity was reduced in the psychotic disorders. These results indicate impaired behavioural processing and pathological functioning in psychotic disorders.

Delta

This study complements the current literature on MPD and shows reduced delta frequency in MPD compared to CON during REO (Albrecht et al., 2016) and reduced REC delta activity in MPD compared to SCZ (Shafiee-Kandjani et al., 2020). MPD often suffer from cognitive deficits associated with structural abnormalities. These structural abnormalities have been found to be a result of methamphetamine use and have been specifically noted across anterior brain regions (Thompson et al., 2004). Previous studies have shown abnormalities in the anterior cingulate cortex, prefrontal cortex, and parietal cortex in methamphetamine-dependent individuals (Chang, Alicata, Ernst, & Volkow, 2007a). In our study we reported associations of methamphetamine use where the age of onset of methamphetamine use positively correlated with frontal and parietal electrodes in SCZ, indicating an association with cognitive and emotional processing (Güntekin & Başar, 2016). Further, a positive correlation was found between the prefrontal delta of REO and the duration of methamphetamine abstinence in patients prescribed first-generation antipsychotics. Literature has shown that patients prescribed first-generation antipsychotics showed improved cognitive control (Nestor, Ghahremani, Monterosso, & London, 2011). Tobacco use was positively correlated with anterior REO delta in patients taking first-generation antipsychotics. In the literature, SCZ was reported to have increased tobacco smoking which was shown to be associated with the use of haloperidol, a first-generation antipsychotic (Jiloha, 2008). Further, increased alcohol and tobacco use was found to be common in SCZ and MPD due to a reduction in impulse control (Patkar et al., 2002). Nicotine aids in regulating the mesolimbic system by increasing dopamine

levels in the prefrontal cortex. An increase in dopamine in the prefrontal cortex reduces positive and negative symptoms.

Alpha

In our study, REC alpha relative frequency activity was smaller in the prefrontal region in SCZ compared to CON. Furthermore, when compared to MPD, SCZ had reduced posterior alpha activity. An increase in alpha activity over the parietal-occipital area in REC was found to be associated with a reduction of visual processing (K. A. MacLean et al., 2009; M. H. MacLean et al., 2012). This reduction in alpha activity was also shown to be associated with patients prescribed antipsychotic medication (Knott et al., 2001). In SCZ, a negative correlation between REO frontal and parietal alpha activity and the age of onset of methamphetamine use was reported. Tobacco scores negatively correlated with REO frontal, central and parietal alpha in patients taking 1st generation antipsychotics. As mentioned, tobacco use could be a mechanism used to counteract extrapyramidal side effects of the medication (Jiloha, 2008). REO posterior alpha positively correlated with alcohol in patients not taking antipsychotic medication. These results indicate that the resting state functional networks are altered by the use of alcohol and tobacco (Vergara, Liu, Claus, Hutchison, & Calhoun, 2017). For education, a positive correlation with posterior REC alpha activity was found in MPD, and in patients prescribed 2nd generation antipsychotics and patients not taking antipsychotics. According to literature, low doses of amphetamines can help improve cognitive functioning, however, it is also known that large doses of amphetamines can cause impaired cognitive functioning (Hart et al., 2012). The duration of methamphetamine use negatively correlated with REC prefrontal alpha in MPD and patients not taking antipsychotic medication. However, in patients prescribed 1st generation antipsychotics, REC prefrontal alpha was positively correlated with methamphetamine abstinence. In literature, prefrontal activation in methamphetamine-abstinent individuals was associated with cognitive control (Nestor et al., 2011). This positive association found between methamphetamine abstinence and patients prescribed 1st generation antipsychotics could indicate that cognitive control and processing within the somatosensory network are improving with the use of 1st generation antipsychotic medication. REC frontal and parietal alpha activity negatively correlated with the number of psychotic episodes in patients taking 1st generation antipsychotic medication. In drug use, our study revealed REC posterior alpha positively correlated with cannabis in patients not taking antipsychotics. In current literature, the duration of cannabis use was found to reduce alpha activity in posterior

regions (Ceballos et al., 2009). Lastly, REC prefrontal alpha was positively correlated with alcohol in patients not taking antipsychotic medication.

Beta

Beta activity was found to be associated with cognitive processing during the completion of cognitive tasks and is found in low amplitudes during resting state tasks (Gola et al., 2012; Uhlhaas et al., 2008). In our study, patients not taking antipsychotic medication positively correlated with posterior REO beta activity for education and cannabis use. Similar results were found in REC where education and cannabis positively correlated with beta activity in patients not taking antipsychotics. Further, a positive correlation was found for REO prefrontal beta and PANSS total score in patients taking 1st generation antipsychotic medication, however, a negative correlation was noted for patients not taking antipsychotic medication REC prefrontal beta activity for PANSS general. These results indicate that 1st generation antipsychotics reduced symptoms and improved cognitive functioning in SCZ and MPD (A. Guerin, 2019).

Theta

REO central through to occipital and REC prefrontal theta frequency activity was greater in SCZ compared to CON. These results align with current literature presenting increased theta activity over the frontal region in REO (Kan et al., 2017; L. Li, 2010), and over the frontal, parietal and occipital regions (Begić et al., 2000). Although no significant correlation was found for theta in REO, during REO theta negatively correlated with education over the parietal area in patients not taking antipsychotic medication. This indicates patients not taking antipsychotics negatively impacted education as seen by low numbers of total years of education seen in psychotic patients.

Limitations of the study include the lack of testing individuals for methamphetamine use on the morning of the EEG scan, including those individuals going through withdrawal for not having methamphetamine for several hours. Future studies should include unmedicated SCZ patients and those who have not used methamphetamine to identify whether the reduced alpha in SCZ compared to MPD holds, as this could potentially be a marker to help distinguish SCZ from MPD. By increasing the cohort, the addition of genetic markers can be included to identify differences in SCZ and MPD. Further, an investigation into the associations between the genetic markers and EEG frequency activity can be investigated.

To conclude, the lack of literature on resting state activity in MPD shows the novelty of this study. We identified differences in relative frequency activity in SCZ, MPD and CON during REC and REO, and in addition their potential associations with clinical symptoms and prescribed medication. Our study opposes current literature and presents decreased alpha and increased theta and beta activity during REC within psychotic disorders. Psychotic disorders hold significant differences in REO and REC relative frequencies compared to healthy controls. The data presented in this study provides insight into frequency variation in MPD.

In the next chapter, I will be discussing cortical processing in schizophrenia and methamphetamine-induced psychotic disorder during the continuous performance task and the cued target detection task. This will show the differences in arousal during the resting state and the completion of cognitive tasks. Further investigating cortical activity during the cognitive tasks in schizophrenia and methamphetamine-induced psychotic disorder will help in understanding the mechanisms involved in these psychotic disorders.

4 Cortical processing of the continuous performance task and cued-target detection task within schizophrenia and methamphetamine-induced psychotic disorder

This chapter discusses the cortical processing and arousal in schizophrenia and methamphetamine-induced psychotic disorder during cognitive tasks. This chapter also investigates the association medication has on relative frequency of the continuous performance task and cued target detection task by grouping medication use in schizophrenia and methamphetamine induced-psychotic disorder according to those not taking antipsychotic medication (NONE), those taking first-generation antipsychotics (1^{st}) and those taking second-generation antipsychotics (2^{nd}).

Abstract

Introduction: Schizophrenia (SCZ) and other psychotic disorders generally present with cognitive impairments including in attention, however cortical processing measured through electroencephalographic frequency activity during the recording of cognitive tasks is currently lacking in methamphetamine induced-psychotic disorder (MPD). We aimed to investigate differences in cognitive performance and frequency activity (alpha, beta, theta, and delta), and identify relationships between frequency activity and population characteristics in healthy controls (CON), SCZ, and MPD, and between SCZ and MPD via medication grouping.

Methods: EEG was recorded from 104 individuals: SCZ (n=38), MPD (n=31), and CON (n=35), who completed two cognitive tasks, a continuous performance task (CPT-5 minutes) and cued target detection task (CTD-6:20 minutes). Group differences were determined by ANOVA with Bonferroni post-hoc correction or multivariate Kruskal-Wallis test, dependent on data distribution. Associations were determined using Pearson's or Spearman's rank order correlation ($p<0.01$) where appropriate.

Results: SCZ and MPD had poor behavioural responses ($p<0.05$) for the CPT and CTD compared to controls. Increased central and parietal theta activity during the CPT was noted in MPD compared to SCZ (C_3 p=0.0091, P_3 p=0.0072), however, no significant group differences were noted in CTD. Associations were found for CPT where omissions negatively correlated with alpha frequency activity in SCZ (Fp_2 r=-0.62, p=0.000045) and in patients not taking antipsychotics (C_4 r= -0.62; p=0.0068; P_4 r= -0.62; p=0.0071; O_1 r= -0.607; p=0.0097. For CTD, congruent cue omissions negatively correlated with alpha activity (Fp_1 r=-0.62, p=0.00057) in MPD, and double cue correct response reaction time negatively correlated with

theta activity (Fp_1 $r_=$-0.62, p=0.0056) in patients not taking antipsychotics, and right posterior beta activity positively correlated with double cue omissions P_4 r=0.86; p=0.0055; O_2 r=0.85; p=0.0071). In patients not taking antipsychotics, PANSS clinical scale scores positively correlated with parietal theta in CPT ($p<0.01$). Lastly in SCZ, frontal delta positively correlated with patients using methamphetamine and those who have abstained.

Conclusion: Both SCZ and MPD reported poor performance across both cognitive tasks compared to CON. This is consistent with previous work, although it is the first study to directly compare cortical processing linked to attention in MPD. Further studies are needed to understand the attention mechanisms underlying MPD and whether methamphetamine permanently alters cognitive functioning long-term.

4.1 Introduction

Attention networks within psychotic disorders are often impaired (A. Martinez et al., 2015). Attention is reported as a psychological process which includes detecting and orienting to stimuli, executive functioning and alertness (Posner & Petersen, 1990). Attention can also be referred to as a set of brain networks which determines or influences the processing of other brain networks for consciousness and observable behaviour (Fan et al., 2009; Posner & Petersen, 1990; Raz, 2004). Three attention networks are known to exist; alerting, orienting and executive control, and were found to be independent across brain networks (Fan et al., 2009). The alerting attentional network provides the capacity to increase vigilance to impeding stimuli. Two types of alerting attentional networks are known; tonic which refers to wakefulness and arousal, and phasic which refers to the readiness to attend to a target stimulus (Raz, 2004). Orienting an attentional network refers to the selection of specific information. There are two types of orienting attentional networks; exogenous refers to the sudden alerting of a target stimulus via a cue, and endogenous refers to the individual searching for the target within the visual field. Lastly, executive control refers to the detection and resolving of conflict resolution (Fan et al., 2009).

Attention is described as an operational series arranged from central cortical goals and tasks in the prefrontal cortex to the mid-level translation of goals in the dorsal brain and then to peripheral representations in the posterior cortex (Tamber-Rosenau & Marois, 2016). Imaging studies have shown associations between metabolic activity and attention performance (Sarter, Givens, & Bruno, 2001). The anterior network was found to be connected to the posterior network through connections in the parietal lobe and the frontal lobes (Riccio, Reynolds, Lowe,

& Moore, 2002b). Attention mechanisms are assigned to the frontal and parietal regions of the brain (Lückmann, Jacobs, & Sack, 2014).

Attention and working memory were found to be essential for cognitive control and goal-directed behaviour (Slotboom et al., 2017). With attention being a behavioural and cognitive process, there are several neural networks which can be accessed via the completion of different tasks. Two different attentional processes are involved in detecting the target stimuli in attention-based tasks; the dorsal (sustained) and ventral (salient) attentional networks (Jonathan K. Wynn et al., 2015). Sustained attention is the ability to maintain focus on a specific stimulus within a task (Featherstone et al., 2007). Sustained attention is based on the mindfulness theory which states that any errors created within a sustained attention task are a result of an internal shift from focus to thoughts (Helton et al., 2009). Sustained attention represents a basic attentional function that determines the efficiency of the "higher" aspects of selective and divided attention, and of the cognitive capacity in general (Sarter et al., 2001).

Arousal changes are generally measured via electroencephalography (EEG) to access attentional performance, from which behavioural data can be extracted to measure attention (Sarter et al., 2001; Villano et al., 2017). EEG is defined as a measure of real-time electrical brain activity which can provide information about specific frequencies being produced for diagnostic purposes (Ranlund et al., 2014). The brain activity recorded is also referred to as oscillations, which is defined as the number of cycles per second or the frequency activity (alpha, beta, theta, or delta) and amplitudes reflecting the neural firing power (Sanders, 2018). The frequency bands representing brain activity are an indication of neural processing mechanisms (Behzadnia, Ghoshuni, & Chermahini, 2017).

Schizophrenia (SCZ), a mental disorder, presents with severe visual processing deficits in response to stimuli which activate the magnocellular/dorsal pathway (A. Martinez et al., 2015). Changes in dopamine transmission within the thalamus and striatum have been associated with a decline in cognitive performance, including working memory, and visual attention (Koob & Volkow, 2010; Weinstein et al., 2017). Furthermore, reduced dopamine concentrations in the prefrontal cortex have been associated with impaired working memory and negative symptoms in SCZ (Gibert-Rahola & Villena-Rodriguez, 2014; Riccio et al., 2002b). These cognitive function impairments were also found in substance use-related disorders such as methamphetamine-induced psychotic disorder (MPD). Methamphetamine use disorder has previously been shown to have cognitive deficits as a result of a reduction in dopamine

concentration (T. Chen et al., 2020), and has been associated with deficits in impulse control, working memory, decision-making, attention and motor coordination (Halpin et al., 2014).

Current literature on frequency activity within methamphetamine use, abuse and psychotic disorder when completing attention-based tasks is currently lacking. In MPD, methamphetamine use, and meth-dependent disorders present with frontal lobe atrophy (Coutinho, Flynn, Burdo, Mervis, & Fox, 2008). When comparing current literature, no differences were found for SCZ and MPD in tasks related to verbal memory, working memory, motor speed, verbal fluency, attention, information processing speed, executive functioning and total cognitive ability (Wearne & Cornish, 2018b). However, opposing results for cognitive impairments such as executive functioning, attention and working memory were found to be less in MPD compared to SCZ (Ezzatpanah et al., 2014). Understanding the processes underlying the cause of cognitive dysfunction/impairment in SCZ and MPD will be of importance in identifying the mechanisms which aid in the development of the disorders (Elvevåg, 2002).

Behavioural correlates have previously been shown to support attention and aid in understanding cognitive impairments (Karhson, Mock, & Golob, 2015). Neuromodulator circuitry can influence behavioural performance in attention-demanding tasks (Knudsen, 2014). Two cognitive tasks which were included in this study to address attention, are the continuous performance task (CPT) and the cued target detection task (CTD). The continuous performance task (CPT) is a known measure of sustained attention (Behzadnia et al., 2017; Smid, De Witte, Homminga, & Van Den Bosch, 2006). The CPT task generally contains a cueing process, target, and non-stimuli. Whereas the CTD was designed to determine divergent attention refers to an individual's attention being diverted. The CTD task used in the present study is a derivative of the Posner's exogenous covert orienting task (Hayward & Ristic, 2013). The task was designed to measure the covert reflexive attentional ability while looking at a fixed central solid circle. The CTD focuses on assessing attention, more specifically divergent attention. The incorporation of invalid cues during the CTD, allows for the orienting attentional network to be active (Fan et al., 2009). The CPT correct number of responses was recorded as an indication of attention (Riccio et al., 2002b). However, further studies revealed omission errors (targets not responded to), commission errors (responses to stimuli other than the target) and the number of correct responses are all an indication of attention. Frontal cortex damage including lesions in the parietal area can result in decreases in the correct number of responses and increased reaction time (Rueckert & Grafman, 1996, 1998; Sarter et al., 2001). Patients

with legions in the frontal lobes were found to have increased reaction time (RT) and more incorrect responses than CON (Rueckert & Grafman, 1996). Furthermore, patients with parietal legions had increased RT and more incorrect responses compared to CON (Rueckert & Grafman, 1998). Investigations into the effects of medication on behavioural performance have voiced contradictory results. Some studies have found medication to have negative effects on cognition in SCZ patients using medication and those who were not using medication (Rehse et al., 2016). However, few studies have reported the neural circuitry involved in attention, especially within MPD (Knudsen, 2014).

Alpha frequency (8-13Hz) is hypothesized to have a central role in the visual perceptual process and to have a further role in cognitive functioning such as attention, working memory, and problem-solving (Ramsay et al., 2021). Alpha frequency was proposed to mediate top-down cognitive control (M. Murphy & Öngür, 2019). Further research has found that altered alpha and theta activity in the frontal regions of the brain has been linked to impaired cognitive processing and working memory (Mitra et al., 2017). Alpha frequency activity has also been identified as an anticipating mechanism to suppress distractor stimuli (Fu et al., 2001). This increased alpha frequency activity was noted across the parietal-occipital area during the presentation of cues. Posterior alpha has been associated with cognitive processing and attentional demands (Zhao et al., 2018). The mechanisms of engagement and disengagement of attention affect the power of alpha activity within the parietal area (Fu et al., 2001). For SCZ, alpha activity was found to decrease in the prefrontal region when compared to CON during a degraded stimulus CPT (Ramsay et al., 2021). Altered alpha activity found in psychotic disorders can help to delineate psychotic disorders compared to controls.

Research assessing frequency association with cognitive functioning has found theta frequency waves to be more prominent during cognitive tasks (Best, Gale, Tran, Haque, & Bowie, 2017; Puma, Matton, Paubel, Raufaste, & El-Yagoubi, 2018). Theta frequency (4-8Hz) is present during a test of visual imagery, hypnotic or hypoapoptic imagery and light sleep, and is associated with decreased drowsiness, alertness, and cognitive impairment. Theta activity is more prominent in the prefrontal cortex, somatosensory cortex and visual cortex (Uhlhaas et al., 2008). Further research has found that altered theta activity in the frontal regions of the brain has been linked to impaired cognitive processing and working memory (Mitra et al., 2017). Reduced theta activity is linked to an increase in vigilance and attention-demanding processes (K. A. MacLean et al., 2009; M. H. MacLean et al., 2012). In CON, an increased theta frequency activity was associated with increased cognitive workload (Puma et al., 2018).

SCZ presented with increased theta activity over the frontal and parieto-occipital areas (Begić et al., 2000). Increased theta activity in the frontal lobe had associations with altered working memory and planning in SCZ (Veiga et al., 2003). A positive correlation was found between increased theta activity and executive functioning, reasoning and attention (Bonelli & Cummings, 2007; Trammell et al., 2017), and it was also found that theta activity decreases during tasks which require a response (Shreekantiah Umesh et al., 2016). A few studies have investigated frequency alterations in substance use and dependence disorders. Theta alterations in methamphetamine-dependent users have been linked to a range of cognitive deficits (Newton et al., 2003). Increased theta activity was previously shown to be associated with poor performance in methamphetamine-dependent individuals (Ceballos et al., 2009). Overall, altered theta activity may represent a trait marker for diagnosing neurocognitive deficits in SCZ (Andreou et al., 2015).

Beta frequency activity (13–30Hz) is more frequent across cortical areas including the subcortical structures; thalamic nuclei, hippocampus, basil ganglia and olfactory bulb (Uhlhaas et al., 2008). Beta activity has also been associated with cognitive processing, specifically, it is found when completing cognitive tasks involved in reward processing (Uhlhaas et al., 2008). A positive correlation between beta activity and accuracy for visual vigilance tasks was found across the occipital-parietal areas in the brain (Gola et al., 2012). The increased beta activity was noted within the frontal region which suggests increased alertness and attentiveness to the environment (Riccio et al., 2002b). Furthermore, literature revealed that increased beta activity, activated in the prefrontal cortex, was associated with the presentation of a trial ending during a cognitive task (Schmidt et al., 2019). A reduction of delta activity across the frontal, central and posterior brain areas during cognitive activation could indicate a possible electrophysiological marker for SCZ and other cognitive disorders (Güntekin & Başar, 2016).

The ability of SCZ to maintain attention during a cognitive task has previously been studied, however, attention-based studies are lacking in MPD. We aimed to investigate whether there are group differences in attention during a cognitive task between (a) CON, SCZ, and MPD and (b) antipsychotic medication grouping (Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd)). This included differences in (1) cognitive performance while completing the CPT and CTD, and (2) relative frequency activity (alpha, beta, theta, and delta) during cueing and target processing. (3) Few studies have investigated the relationship between frequency activity of the CPT and CTD with the population characteristics, and cognitive

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. This will enhance our understanding of the electrophysiology of these disorders, and potentially distinguish neural circuitry activation signatures which are unique to psychotic disorders.

4.2 Method

4.2.1 Research participants

104 South African individuals, between the ages of 20 and 45 years, participated in this study: 38 with SCZ (8 females/30 males), 31 with MPD (7 females/24 males), and 35 healthy controls (CON: 15 females/20 males). The study was approved by the Health Sciences Research Ethics Committee, at the University of Cape Town (HREC Ref. No.: 479/2019). Western Cape Provincial and Hospital approval was also obtained. All research activities were conducted in accordance with the Declaration of Helsinki. All research participants provided voluntary informed consent.

Participants visited the laboratory twice. The first visit included the provision of informed consent and an assessment clinical interview. All participants underwent a Structured Clinical Interview for Diagnostic Systematic Manual- IV (SCID-DSM-IV), with modifications to include changes made in DSM-5. Control participants were excluded if there was a history of psychotic symptoms or a family history of psychotic disorder. Participants with a psychotic disorder were excluded if they did not meet the diagnostic criteria for the study conditions: for example, participants with schizoaffective disorder were excluded. Participants were also excluded if they were younger than 19 years or older than 40 years, had general medical conditions that required prescription medications, had an apparent learning disability, had major brain trauma/surgery, had any history of cardiovascular insult, individual or family history of epilepsy, medical implants or any metal within their person, for example, shrapnel.

Female participants were excluded if they were pregnant or lactating. Patients with SCZ were excluded if any of their episodes were considered to be related to the use of a substance. MPD included psychotic symptoms with onset during methamphetamine intoxication or withdrawal and did not persist beyond 1 month since the last use of methamphetamine, or evidence of an underlying ‘primary’ psychotic disorder not related to the use of methamphetamine. Evidence that the symptoms are better accounted for by a psychotic disorder that is not methamphetamine-induced included the following: the symptoms precede the onset of the methamphetamine use; the symptoms persist for a substantial period of time after the cessation

of acute withdrawal or severe intoxication, or are substantially in excess of what would be expected given the amount of methamphetamine used or the duration of use; or there is other evidence that suggests the existence of an independent non-MPD (e.g. a history of recurrent non-methamphetamine- related episodes). Patients with MPD were excluded if it was unclear if methamphetamine was causal to their symptoms or diagnosis, and if any of their psychotic episodes may have been related to another substance of abuse.

4.2.2 Study design

The second visit included a full morning of brain imaging. All EEGs were performed between 09h00-11h00, on a weekday. All clinical scales were performed on the same day and after the morning of brain imaging by trained clinical personnel.

Clinical rating scales included the Positive and Negative Syndrome Scale (PANSS); Calgary Depression Scale for Schizophrenia; Hamilton Rating Scale for Depression. Chlorpromazine equivalents were calculated from current medication regimes. Drug use history, nicotine, alcohol and methamphetamine were recorded using the Kreek-McHugh-Schluger-Kellogg scale (KMSK).

4.2.3 Electroencephalography

EEG recording of REO and REC was undertaken using a simple EEG montage that included prefrontal (Fp1 and Fp2), frontal (F3 and F4), central (C3 and C4), parietal (P3 and P4) and occipital (O1 and O2) electrodes. Standard 10/20 caps (Electro-Cap International, Inc.) were used, of either medium or large size depending on the head circumference of the participant. Participants were grounded peripherally, linked earlobe reference was applied, and electrooculography (EOG) was recorded. The EEG system used was the Biopac MP150 system with 100 C EEG amplifiers and an EOG amplifier (Biopac Systems, Inc.). Digital EEG data and analogue data, from E-prime, were collected via the MP150 system, with a sampling rate of 500Hz, and were visualised in real-time using Acq-Knowledge 4.1 (Biopac Systems, Inc.).

For EEG data processing, data were first eye blink corrected and movement corrected (EOG), using automated ICA EOG correction in Acqknowledge 4.1 (Biopac Systems, Inc.), and then bandpass filtered 0.1–30Hz and Fourier transformed, using an in-house Matlab GUI, to accommodate differences in participant electrical brain activity conduction. Relative (%) frequency bands power activity was extracted: delta (0.1–4.0Hz), theta (4–7Hz), alpha (7–14Hz) and beta (15–30Hz).

Continuous performance task

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 are presented with 60 trials with three consecutive S's, the presentation of the third S requires a behavioural response. In addition, 40 single S's or trick S's are embedded in the task with 300 inter-stimuli letters. The trick stimulus was presented to distract the participant from the presentation of the three consecutive S's. The task contains 20 letters of the alphabet and excluded the vowels, A, E, I, O, and U as well as the letter X. Each letter was presented for 500msec with a 100 msec inter-stimulus interval before the next stimulus. However, the participant can shorten the presentation of the third S if a response is given before the 500msec time limit. Once the task was complete, the participant was asked to relax. The mental effort scale was handed to the participant for them to mark how much effort was applied to conduct the task. The behavioural data collected, were extracted using E-prime and were cross-checked with the digital inputs to an EEG data file Acknowledge 4.1 (Biopac Systems, Inc.). The behavioural data extracted included the number of correct responses, response time duration, errors of omission and commission.

Cued-target detection task

The cued target detection task (CTD) focuses on assessing attention, more specifically divergent attention. The CTD requires participants to focus on a solid grey circle in the centre of the computer screen. An outline of a grey rectangle was positioned on either side of the central cue, which remains throughout the cognitive task. The participant is required to respond to the presentation of a square within either of the rectangles. For this task, there are four conditions: (1) congruent cue and stimulus presentation; (2) incongruent cue and stimulus presentation; (3) double cue and stimulus presentation; and (4) no cue and stimulus presentation. The cues are presented for 500 msec and the stimulus is presented for 500 msec. The inter-stimulus interval is variable throughout the task, with durations of 500, 1000, or 1500 msec. The CTD has 64 congruent stimuli; 16 incongruent stimuli; 16 double-cue stimuli; and 16 no-cue stimuli. The ERP waveform windows we are expecting to see due to their link with attention are the P100, P150, N170 and P300. Behaviourally, the reaction time, correct detection, omission errors and commission errors will be extracted and analysed.

4.2.4 Statistical analysis

Statistical analysis was conducted using Statistica (Dell Inc, 2015). To determine group differences in relative frequency for the CPT and CTD, and cognitive performance, an analysis was conducted for (a) three groups (CON, SCZ and MPD) and (b) psychotic groups (SCZ, MPD) according to antipsychotic medication (Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). For correlation analysis, the demographics (age on the day of testing, duration at school, tertiary education, and total years of education), 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, duration of illness, drug use (methamphetamine, alcohol, tobacco, cannabis), and medication use (chlorpromazine equivalent dose) were included.

First, an analysis of distribution was conducted for each variable, using the 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 between-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 ($p < 0.05$). Where appropriate, according to the data distribution, correlation analysis was performed using Pearson's or Spearman's rank order (Rho $>\pm0.6$ and p-value <0.01). A further ANCOVA statistical analysis was conducted on parametric data.

4.3 Results

4.3.1 Participant demographics

A total of one hundred and four individuals, between the ages of 20 and 45 years, participated in this study: thirty-eight participants with a diagnosis of schizophrenia (SCZn=38; 8 females/30 males), thirty-one participants with a diagnosis of methamphetamine-induced psychotic disorder (MPDn=31; 7 females/24 males), as well as thirty-five socio-demographically matched control participants (CONn=35; 15 females/20 males).

Cognitive performance differences were found for CPT: correct responses ($H_{2,100}$=16.13; p=0.00030) where more correct responses were reported in CON compared to SCZ (p=0.00031) and MPD (p=0.017); the number of omissions ($H_{2,100}$=6.32; p=0.042) where SCZ

reported more omissions compared to CON (p=0.049); trick S responses ($H_{2,100}$=9.89; p=0.0071) where trick S responses were more in SCZ compared to CON (p=0.024), **Table 4.1**.

Cognitive performance differences were found for CTD: incongruent omissions ($H_{2,100}$=8.75; p=0.012) where SCZ reported more omissions compared to CON (p=0.033); incongruent correct responses ($H_{2,100}$=7.06; p=0.029) where SCZ reported fewer correct responses compared to CON (p=0.031); congruent correct responses ($H_{2,100}$=6.039; p=0.048) where SCZ reported fewer correct responses compared to CON (p=0.044); double cue correct responses ($H_{2,100}$=7.44; p=0.024) where SCZ reported fewer correct responses compared to CON (p=0.023); no cue correct responses ($H_{2,100}$=7.28; p=0.026) where SCZ reported fewer responses compared to CON (p=0.039); then double cue omissions ($H_{2,100}$=6.96; p=0.0307) and no cue omissions ($H_{2,100}$=4.38; p=0.11) were found to differ by group yet individual groups differences were not found, **Table 4.2**.

Table 4.1 CPT task behavioural data

	Control	**Schizophrenia**	**Methamphetamine-induced psychosis**	**ANOVA (H test/ F test)**	**Post-Hoc**
	n = 35	n = 38	n = 31		
	15 females/20 males	8 females/30 males	7 females/24 males		
CPT task	**Median (min-max)**	**Median (min-max)**	**Median (min-max)**		
Correct responses	47(3-59)	24,5(3-57)	31(3-59)	$H_{2,100}$=9.89; p=0.0071	SCZ>CON p=0.024
Average reaction time	296,31(137,55-429,82)	298,85(110,10-486,33)	288(104,33-434,89)	$H_{2,100}$=16.13; p=0.00030	SCZ<CON p=0.00031 MPD<CON p=0.017
Errors of commission	4(0-58)	10,5(0-74)	9(0-56)	$H_{2,100}$=0.62; p=0.72	-
Errors of omission	4(0-23)	11(0-57)	9(0-38)	$H_{2,100}$=5.67; p=0.058	-
Trick S responses	0(0-11)	0,5(0-34)	0(0-25)	$H_{2,100}$=6.32; p=0.042	SCZ>CON p=0.049

Non-parametric Kruskal Wallis (H-test), Significance P<0, 05.

Table 4.2 CTD task behavioural data

	Control	**Schizophrenia**	**Methamphetamine-induced psychosis**	**ANOVA (H test/ F test)**	**Post-Hoc**
	n = 35	n = 38	n = 31		
	15 females/20 males	8 females/30 males	7 females/24 males		
CTD task	**Median (min-max)**	**Median (min-max)**	**Median (min-max)**		
CTD Incongruent errors of omission	0(0-13)	1(0-16)	0(0-10)	$H_{2,100}$=8.75; p=0.012	SCZ>CON p=0.033
CTD Incongruent errors of commission	0(0-8)	0(0-10)	0(0-8)	$H_{2,100}$=3.47; p=0.17	-
CTD Incongruent correct responses	16(2-16)	14(0-16)	15(6-16)	$H_{2,100}$=7.06; p=0.029	SCZ<CON p=0.031
CTD Incongruent average reaction time	529,68(373-689,14)	523,21(124-672,09)	527,31(422,71-636,16)	$H_{2,99}$=0.38; p=0.82	-
CTD Congruent errors of omission	2(0-38)	6(0-64)	3(1-33)	$H_{2,100}$=5.65; p=0.059	
CTD Congruent errors of commission	0(0-32)	0(0-41)	0(0-31)	$H_{2,100}$=3.58; p=0.16	-
CTD Congruent correct responses	62(14-64)	55(0-63)	60,5(25-63)	$H_{2,100}$=6.039; p=0.048	SCZ<CON p=0.044
CTD Congruent average reaction time	479,69(370,23-616,86)	453,24(244-604,66)	424,04(364,60-615,38)	$H_{2,99}$=4.45; p=0.10	-
CTD Double cue errors of omission	1(0-10)	2(0-16)	1(0-12)	$H_{2,100}$=6.96; p=0.0307	ns
CTD Double cue errors of commission	0(0-7)	0(0-8)	0(0-8)	$H_{2,100}$=1.69; p=0.42	-
CTD Double cue correct responses	15(3-16)	14(0-16)	14,5(4-16)	$H_{2,100}$=7.44; p=0.024	SCZ<CON p=0.023
CTD Double cue average reaction time	513,31(398,62-660,33)	502,53(170-663,33)	476,75(387-652,75)	$H_{2,99}$=2.87; p=0.23	-
CTD No cue errors of omission	1(0-12)	1(0-16)	1(0-10)	$H_{2,100}$=4.38; p=0.11	-
CTD No cue errors of commission	0(0-8)	0(0-9)	0(0-8)	$H_{2,100}$=6.405; p=0.0406	ns
CTD No cue correct responses	15(0-16)	14(0-16)	15(6-16)	$H_{2,100}$=7.28; p=0.026	SCZ<CON p=0.039
CTD No cue average reaction time	513,12(0-687,5)	498,65(282-686,83)	486,22(388,26-698,5)	$H_{2,99}$=2.86; p=0.23	-

Ns no significance between groups after post-hoc. Non-parametric Kruskal Wallis (H-test), Significance P<0, 05.

4.3.2 Continuous performance task relative delta activity

No significant group differences were found for CPT delta, **Table 4.3**.

Table 4.3 Continuous performance task relative delta frequency activity

		Control	**Schizophrenia**	**Methamphetamine-induced psychosis**		
		n = 35	n = 38	n = 31		
		15 females/20 males	8 females/30 males	7 females/24 males		
		Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test/ F test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	54.04(36.09-69.88)	51.30(38.52-66.20)	52.06(36.09-71.97)	$F_{2.100}$=0.52; p=0.59	-
Right prefrontal cortex	**Fp_2**	48.34(31.65-76.67)	47.75(32.12-65.95)	49.72(32.10-67.16)	$H_{2.103}$=0.039; p=0.98	-
Left frontal cortex	**F_3**	43.48(31.44-69.03)	50.33(28.96-63.40)	47.03(29.54-73.26)	$F_{2.100}$=0.43; p=0.64	-
Right frontal cortex	**F_4**	40.59(22.47-66.25)	40.80(22.38-77.24)	44.02(24.45-72.15)	$H_{2.103}$=3.40; p=0.18	-
Left central cortex	**C_3**	41.78(22.38-69.64)	44.05(24.25-59.82)	45.63(25.23-67.71)	$F_{2.100}$=0.43; p=0.65	-
Right central cortex	**C_4**	43.04(27.85-70.29)	51.41(29.08-64.42)	49.07(26.47-73.24)	$F_{2.100}$=0.89; p=0.41	-
Left parietal cortex	**P_3**	38.66(26.79-69.98)	39.62(20.96-74.49)	46.29(21.77-69.07)	$F_{2.100}$=0.89; p=0.41	-
Right frontal cortex	**P_4**	45.95(30.32-71.25)	46.77(29.59-63.40)	46.84(30.95-73.40)	$F_{2.100}$=0.40; p=0.66	-
Left occipital cortex	**O_1**	45.17(31.54-68.53)	46.67(27.10-69.81)	49.27(32.29-65.98)	$F_{2.100}$=0.55; p=0.57	-
Right occipital cortex	**O_2**	45.40(23.51-69.55)	46.97(24.96-63.31)	47.82(29.77-73.18)	$F_{2.100}$=0.37; p=0.69	-

Non-parametric Kruskal Wallis (H-test), Significance P<0, 05.

In patients taking 2nd generation antipsychotics (n=22 where SCZn=10; MPDn=12), CPT left prefrontal delta activity positively correlated with duration of methamphetamine abstinence ($Fp_1R_{spearman's(n=22)}$= 0.61; p=0.0025), **Figure 4.1**. CPT left central delta activity negatively correlated with age of onset of methamphetamine use ($C_3R_{spearman's(n=22)}$=-0.62; p=0.0017), **Figure 4.2**.

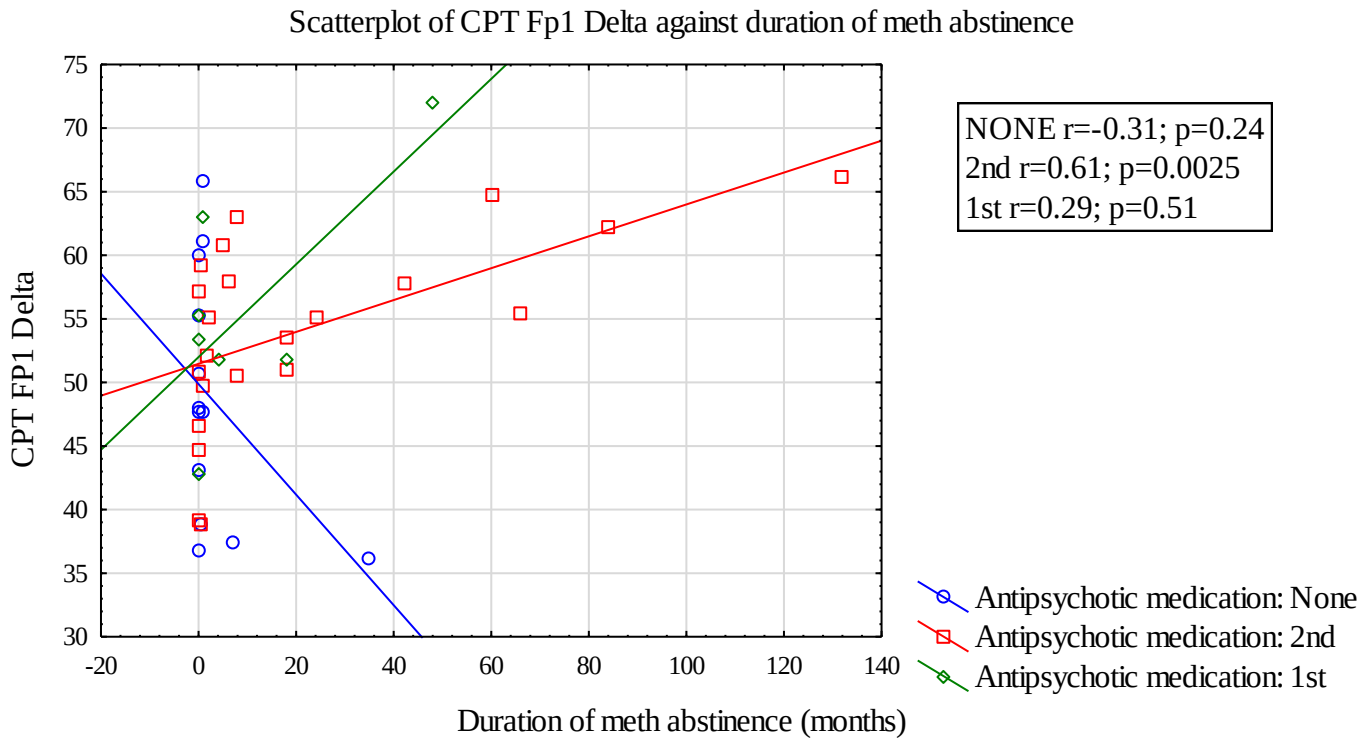


Figure 4.1 Patients prescribed 2nd generation antipsychotic medication left prefrontal (Fp_1) electrode relative delta activity during continuous performance task (CPT) positively correlated with methamphetamine abstinence. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm 0.60$.

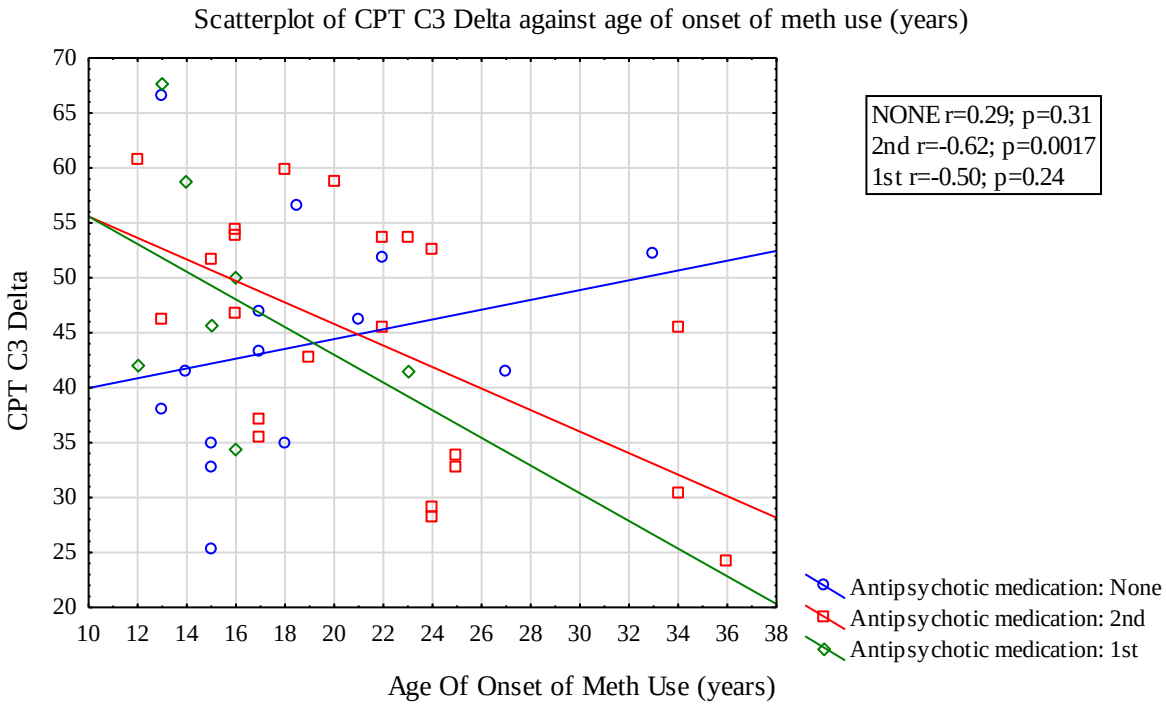


Figure 4.2 Patients prescribed 2nd generation antipsychotic medication left central (C_3) electrode relative delta activity during continuous performance task (CPT) negatively correlated with age of onset of methamphetamine use. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm 0.60$.

4.3.3 Cued target detection task relative delta activity

No significant group differences were found for CTD delta, **Table 4.4**.

Table 4.4 Cued target detection task relative delta frequency activity

		Healthy control	**Schizophrenia**	**Methamphetamine-induced psychosis**		
		n = 35	n = 38	n = 31		
		15 females/20 males	8 females/30 males	7 females/24 males		
		Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test/ F test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	53.97(38.06-70.44)	52.67(26.36-67.12)	50.24(31.24-74.84)	$F_{2.94}$=1.89; p=0.15	-
Right prefrontal cortex	**Fp_2**	49.43(31.32-67.64)	51.97(29.77-67.01)	46.22(31.54-72.93)	$H_{2.97}$=2.12; p=0.34	-
Left frontal cortex	**F_3**	46.60(32.17-63.67)	47.61(22.54-60.04)	44.22(31.58-72.68)	$F_{2.94}$=0.025; p=0.97	-
Right frontal cortex	**F_4**	42.73(18.62-58.85)	43.06(18.40-59.79)	40.93(24.28-68.82)	$F_{2.94}$=0.057; p=0.94	-
Left central cortex	**C_3**	42.43(23.02-64.55)	45.15(20.20-58.34)	43.04(22.87-72.10)	$F_{2.94}$=0.34; p=0.70	-
Right central cortex	**C_4**	46.60(32.59-76.07)	50.79(22.50-60.58)	44.97(30.44-72.18)	$F_{2.94}$=0.31; p=0.72	-
Left parietal cortex	**P_3**	39.24(23.73-62.29)	44.79(18.05-56.50)	39.23(22.92-71.71)	$F_{2.94}$=0.30; p=0.73	-
Right frontal cortex	**P_4**	43.33(30.96-64.00)	47.23(22.51-58.29)	43.81(33.22-70.53)	$F_{2.94}$=0.052; p=0.94	-
Left occipital cortex	**O_1**	43.02(26.98-64.05)	49.52(22.80-59.01)	44.09(30.36-70.04)	$F_{2.94}$=0.43; p=0.65	-
Right occipital cortex	**O_2**	43.41(20.93-69.11)	47.06(22.64-60.10)	44.26(31.80-72.49)	$F_{2.94}$=0.23; p=0.78	-

Non-parametric Kruskal Wallis (H-test) and parametric one-way analysis of variance (F-test), Significance P<0.05.

For MPD (n=28), CTD left prefrontal delta activity positively correlated with the KMSK methamphetamine total score ($Fp_1R_{spearman's(n=28)}$= 0.61; p=0.00047), **Figure 4.3**.

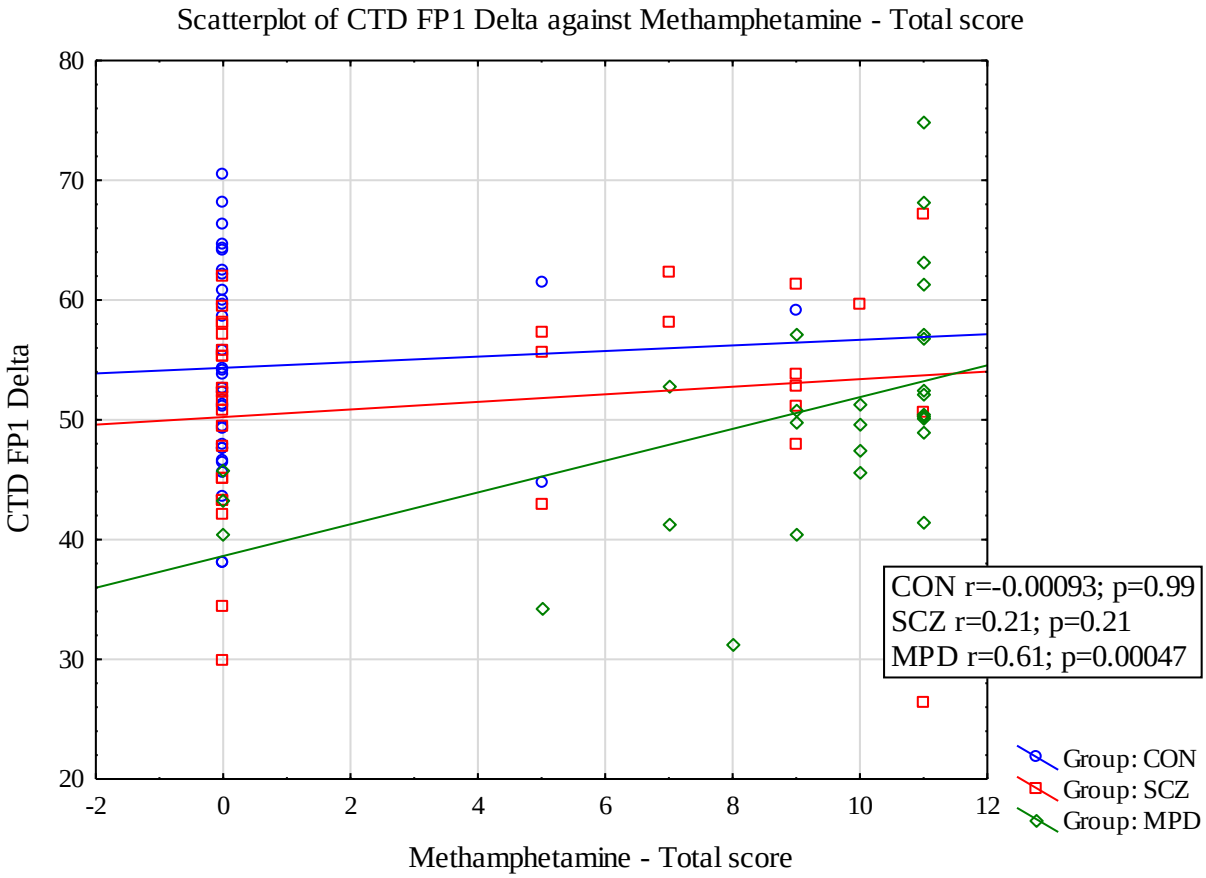


Figure 4.3 Cued target detection task (CTD) relative delta activity for the left prefrontal (Fp_1) electrode for MPD positively correlated with methamphetamine lifetime score. Healthy controls (CON); Schizophrenia (SCZ); Methamphetamine-induced psychotic disorder (MPD). Significance was reported for $p<0.01$ and Rho= $>\pm0.60$.

For patients with a history of methamphetamine use, for patients not taking antipsychotic medications (n=13 where, SCZn= 1; MPDn=12), their methamphetamine abstinence positively correlated with CTD relative delta activity for the right prefrontal cortical electrode ($Fp_2R_{Spearman's(n=13)}$=0.73, p=0.00041), **Figure 4.4**.

For patients taking 2nd generation antipsychotics (n=19 where, SCZn=10; MPDn=9), duration of methamphetamine use positively correlated with CTD relative delta activity for the right prefrontal cortical electrode ($Fp_2R_{Spearman's(n=19)}$=0.62, p=0.0044), **Figure 4.5**.

In patients taking 1st generation antipsychotics (n=8 where, SCZn=4; MPDn=4), the PANSS negative subscale negatively correlated with the CTD left central delta activity ($C_3R_{spearman's(n=8)}$=-0.94; p=0.00039), **Figure 4.6**.

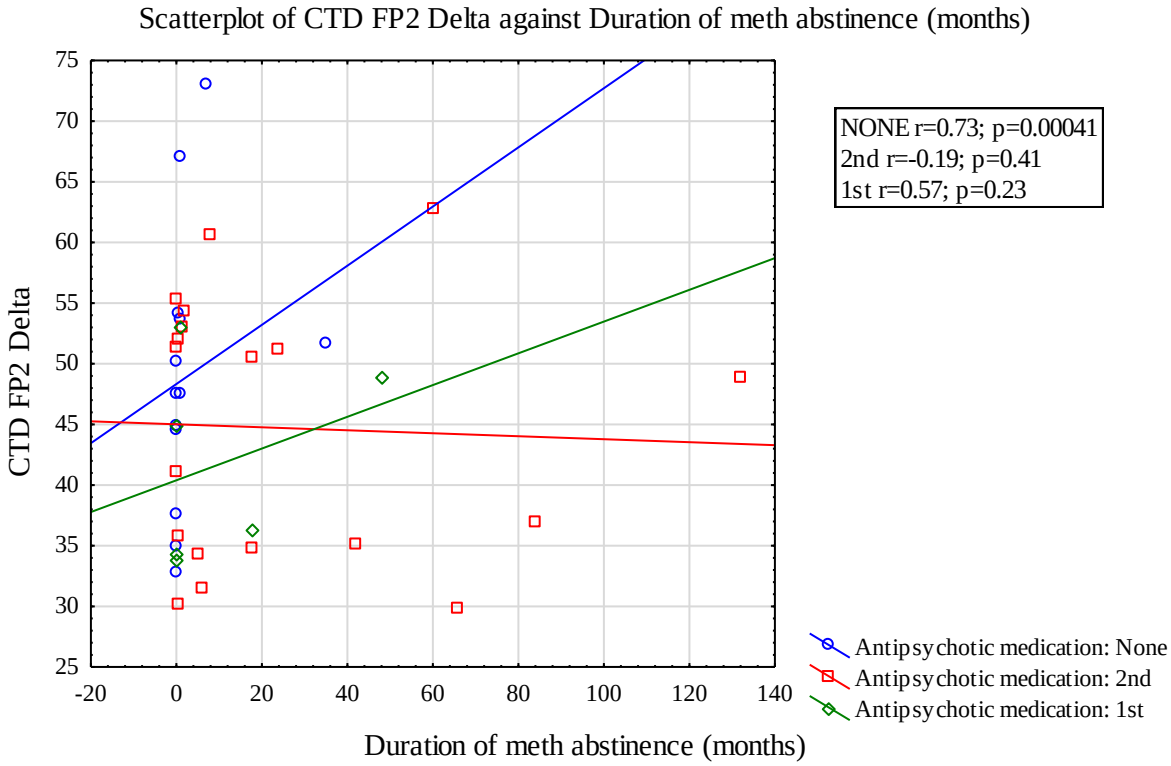


Figure 4.4 Cued target detection task (CTD) relative delta activity for the right prefrontal (Fp_2) electrode for patients not taking antipsychotic medication positively correlated with methamphetamine abstinence. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm 0.60$.

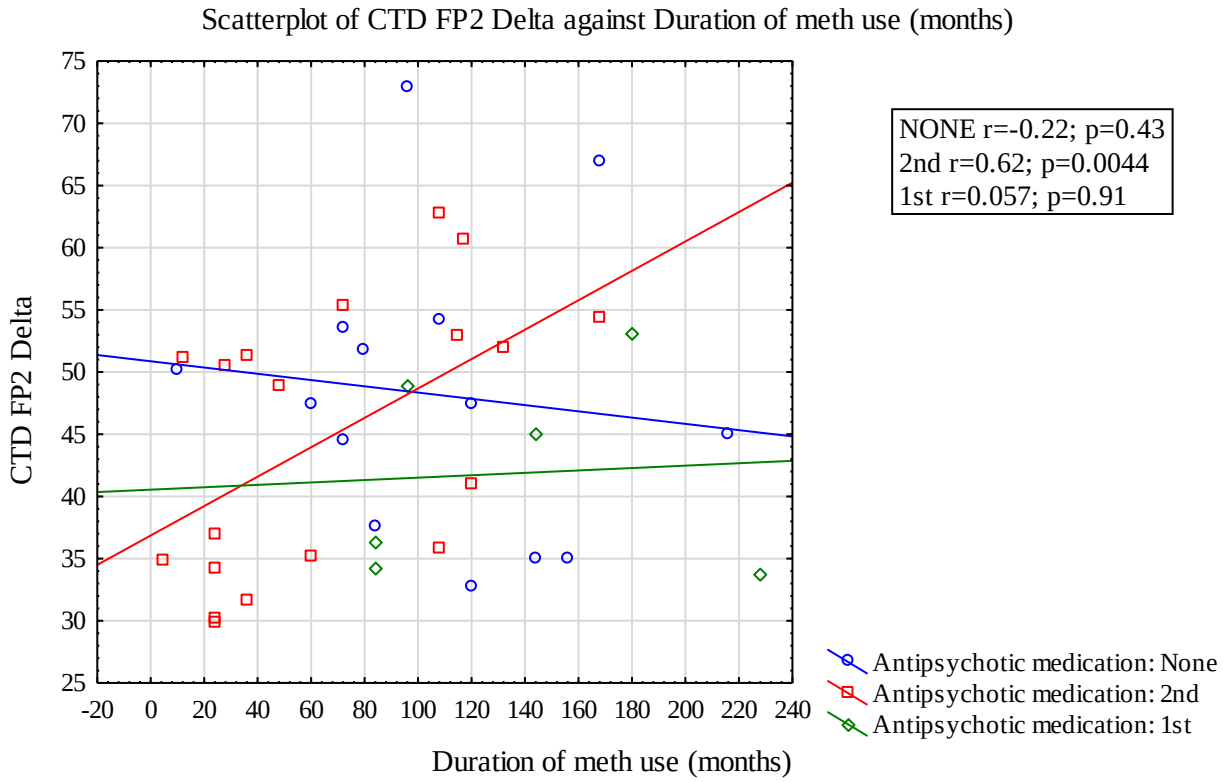


Figure 4.5 Cued target detection task (CTD) relative delta activity for the right prefrontal (Fp_2) electrode for patients prescribed 2nd generation antipsychotic medication positively correlated with duration of methamphetamine use. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm 0.60$.

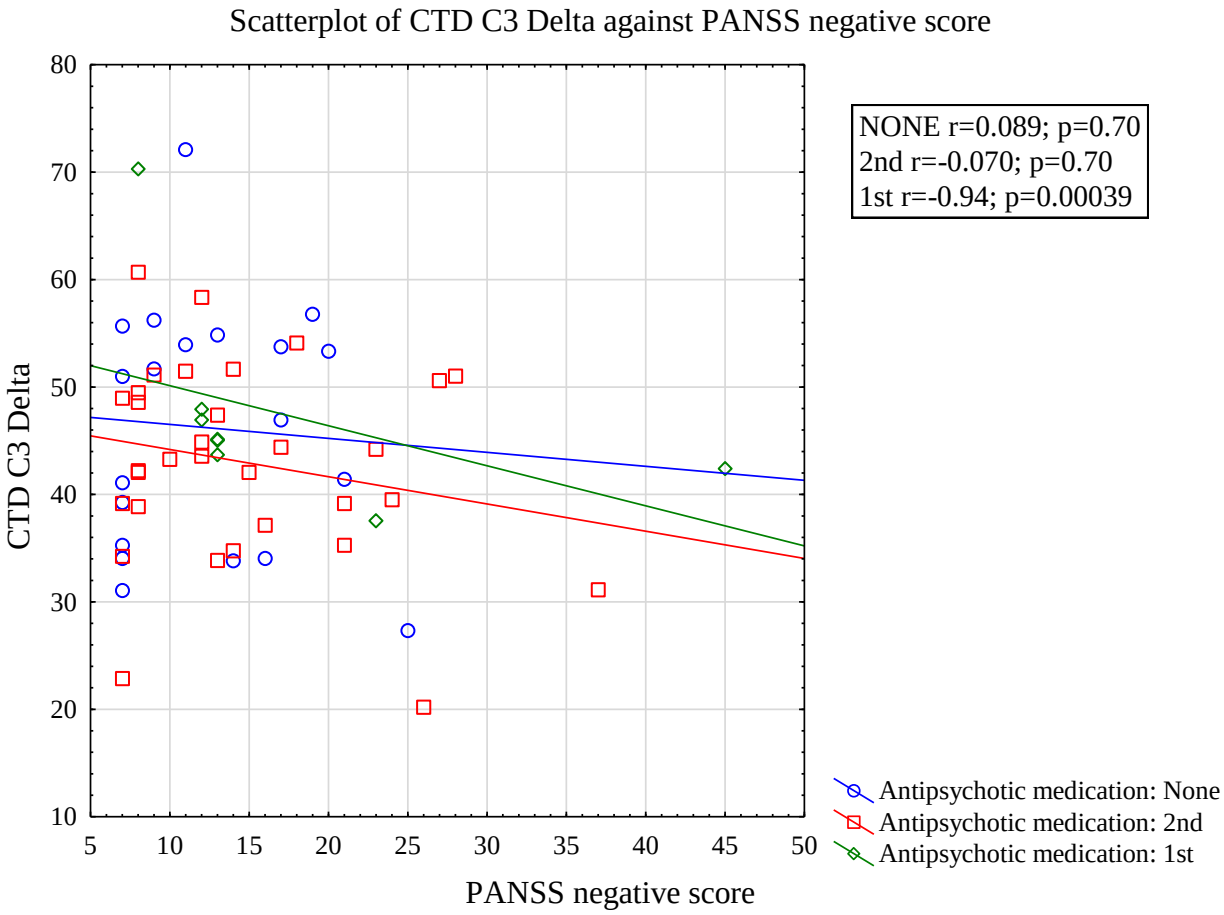


Figure 4.6 Cued target detection task (CTD) relative delta activity for the left central (C_3) electrode for patients prescribed 1st generation antipsychotic medication negatively correlated with PANSS negative scores. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm 0.60$.

4.3.4 Continuous performance task relative theta activity

CPT Theta reported a group difference for the left prefrontal, central and parietal electrodes (Fp_1 ($H_{2.103}$=6.072; p=0.048), C_3 ($H_{2.103}$=9.062; p=0.0108), P_3 ($H_{2.103}$=9.41; p=0.0090)) where no between groups significance was found, and where MPD theta activity was lower compared to SCZ (C_3 p=0.0091, P_3 p=0.0072), **Table 4.5**.

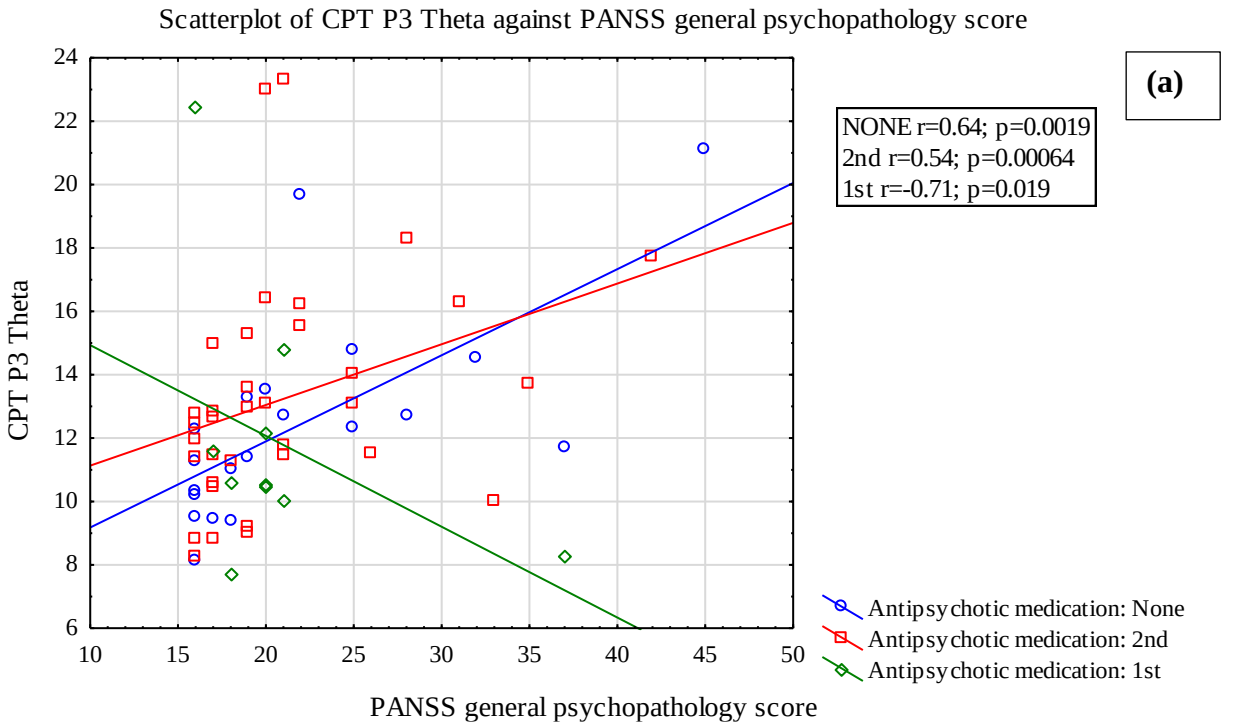
Table 4.5 Continuous performance task relative theta frequency activity

		Healthy control	**Schizophrenia**	**Methamphetamine-induced psychosis**		
		n = 35	n = 38	n = 31		
		15 females/20 males	8 females/30 males	7 females/24 males		
		Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	12.27(7.90-23.56)	13.34(9.77-28.53)	11.94(7.82-16.95)	$H_{2.103}$=6.072; p=0.048	%
Right prefrontal cortex	**Fp_2**	12.67(6.48-31.97)	13.35(11.09-29.46)	12.83(7.48-16.98)	$H_{2.103}$=5.59; p=0.061	-
Left frontal cortex	**F_3**	12.17(8.96-30.13)	12.12(9.51-25.67)	11.82(7.65-16.17)	$H_{2.103}$=3.60; p=0.16	-
Right frontal cortex	**F_4**	12.20(7.34-32.03)	13.32(7.88-26.38)	11.89(7.24-19.33)	$H_{2.103}$=5.62; p=0.060	-
Left central cortex	**C_3**	11.77(7.91-27.77)	12.90(9.28-25.25)	10.93(7.14-18.32) *	$H_{2.103}$=9.062; p=0.0108	SCZ>MPD p=0.0091
Right central cortex	**C_4**	11.89(7.68-25.38)	12.44(8.45-29.37)	12.08(6.30-19.61)	$H_{2.103}$=1.75; p=0.41	-
Left parietal cortex	**P_3**	11.36(7.45-29.45)	13.10(8.15-29.02)	11.26(7.68-16.30) *	$H_{2.103}$=9.41; p=0.0090	SCZ>MPD p=0.0072
Right frontal cortex	**P_4**	11.65(8.16-24.89)	12.67(9.10-25.19)	11.26(7.68-16.30)	$H_{2.103}$=4.87; p=0.087	-
Left occipital cortex	**O_1**	12.25(7.49-25.55)	12.76(5.77-26.69)	11.92(7.22-16.17)	$H_{2.103}$=5.029; p=0.080	-
Right occipital cortex	**O_2**	12.28(8.24-25.53)	12.83(7.79-27.91)	12.16(8.15-16.27)	$H_{2.103}$=2.70; p=0.25	-

****** Methamphetamine-induced psychotic disorder (MPD) reported greater relative theta activity during continuous performance task (CPT) compared to Schizophrenia (SCZ) % with no significance between groups after post-hoc testing. Non-parametric Kruskal Wallis (H-test) and parametric one-way analysis of variance (F-test), Significance P<0.05.*

For patients not taking antipsychotic medications (n=20 where, SCZn=7; MPDn=13), CPT left parietal relative theta activity positively correlated with PANSS total ($P_3R_{Spearman's(n=20)}$=0.64; p=0.0019) and PANSS general ($P_3R_{Spearman's(n=20)}$=0.74; p=0.00015), **Figure 4.7**.

For patients prescribed 1st generation antipsychotic medications (n=10 where, SCZn=4; MPDn=6), CDS score positively correlated with CPT relative theta activity for the left frontal cortical electrode ($F_3R_{Spearman's(n=10)}$=0.81, p=0.0037), **Figure 4.8**.



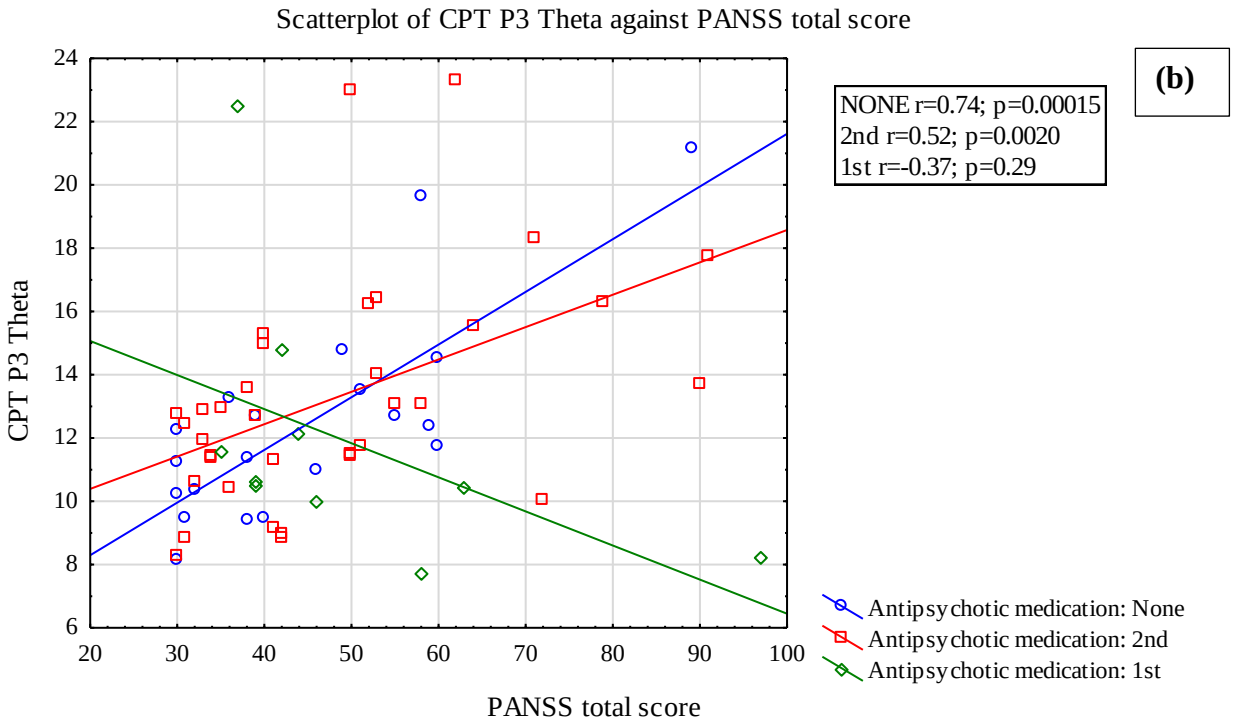


Figure 4.7 Continuous performance task (CPT) relative theta activity for the left parietal (P_3) electrode for patients not taking antipsychotic medication positively correlated with (a) PANSS total scores and (b) PANSS general scores. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance reported for $p<0.01$ and Rho= $>\pm 0.60$

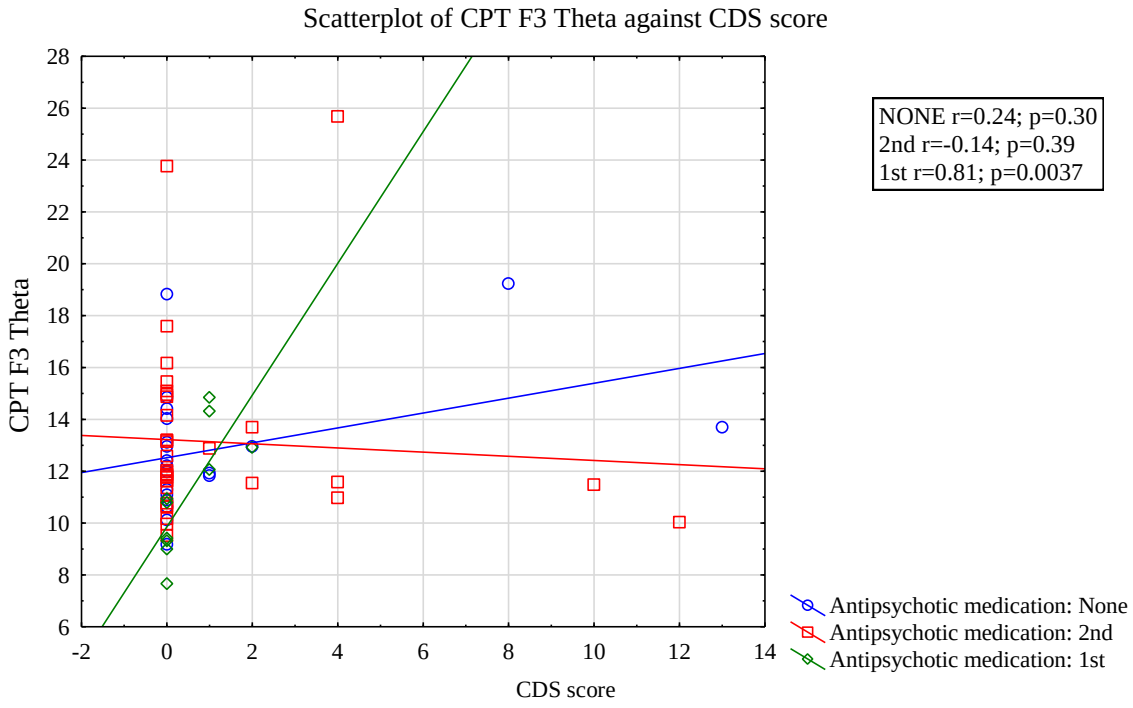


Figure 4.8 Continuous performance task (CPT) relative theta activity for the left frontal (F_3) electrode for patients prescribed 1st generation antipsychotic medication positively correlated with the CDS score. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance reported for p<0.01 and Rho= >±0.60

4.3.5 Cued target detection task relative theta activity

No significant group differences were found for CTD Theta**, Table 4.6.**

Table 4.6 Cued target detection task relative theta frequency activity

		Healthy control	**Schizophrenia**	**Methamphetamine-induced psychosis**		
		n = 35	n = 38	n = 31		
		15 females/20 males	8 females/30 males	7 females/24 males		
		Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	11.94(8.79-20.47)	12.57(8.33-24.73)	12.05(7.13-18.42)	$H_{2,97}$=2.97; p=0.22	-
Right prefrontal cortex	**Fp_2**	12.63(6.96-21.91)	13.14(8.43-23.50)	13.11(8.68-17.95)	$H_{2,97}$=1.26; p=0.53	-
Left frontal cortex	**F_3**	12.07(8.94-19.14)	12.73(8.35-26.07)	11.66(7.31-21.04)	$H_{2,97}$=4.73; p=0.093	-
Right frontal cortex	**F_4**	12.56(7.73-23.26)	12.66(7.76-25.07)	13.08(7.49-25.49)	$H_{2,97}$=0.26; p=0.87	-
Left central cortex	**C_3**	12.02(8.03-19.38)	12.90(8.38-25.30)	12.08(6.57-25.37)	$H_{2,97}$=2.10; p=0.34	-
Right central cortex	**C_4**	12.17(7.99-20.07)	12.60(8.42-26.12)	12.14(6.75-20.84)	$H_{2,97}$=1.52; p=0.46	-
Left parietal cortex	**P_3**	12.36(8.92-21.61)	12.36(7.35-24.78)	11.73(6.16-25.55)	$H_{2,97}$=1.10; p=0.57	-
Right frontal cortex	**P_4**	11.86(9.09-19.05)	12.31(8.63-26.07)	12.10(7.26-22.15)	$H_{2,97}$=1.46; p=0.48	-
Left occipital cortex	**O_1**	11.56(8.57-19.79)	12.70(9.24-25.90)	12.00(7.77-19.56)	$H_{2,97}$=2.98; p=0.22	-
Right occipital cortex	**O_2**	11.61(6.60-19.82)	12.39(8.43-25.96)	11.62(7.61-20.26)	$H_{2,97}$=3.43; p=0.17	-

Non-parametric Kruskal Wallis (H-test). Significance P<0,05.

For patients not prescribed antipsychotic medication (n=18 where, SCZn=7; MPDn=11), double cue correct responses reaction time negatively correlated with CTD relative theta activity for the left prefrontal cortical electrode ($Fp_1R_{Spearman's(n=18)}$=-0.62, p=0.0056), **Figure 4.9**.

For patients prescribed 1st generation antipsychotic medications (n=8 where, SCZn=12; MPDn=6), duration of psychotic disorder use positively correlated with CTD relative theta activity for the right prefrontal cortical electrode ($Fp_2R_{Spearman's(n=8)}$=0.904, p=0.0020), **Figure 4.10**; CDS scale positively correlated with the right frontal cortical electrode ($F_4R_{Spearman's(n=8)}$=0.86, p=0.0054), **Figure 4.11**, and age on the day of testing positively correlated with the left occipital cortical electrode ($O_1R_{Spearman's(n=8)}$=0.86, p=0.0052), **Figure 4.12.**

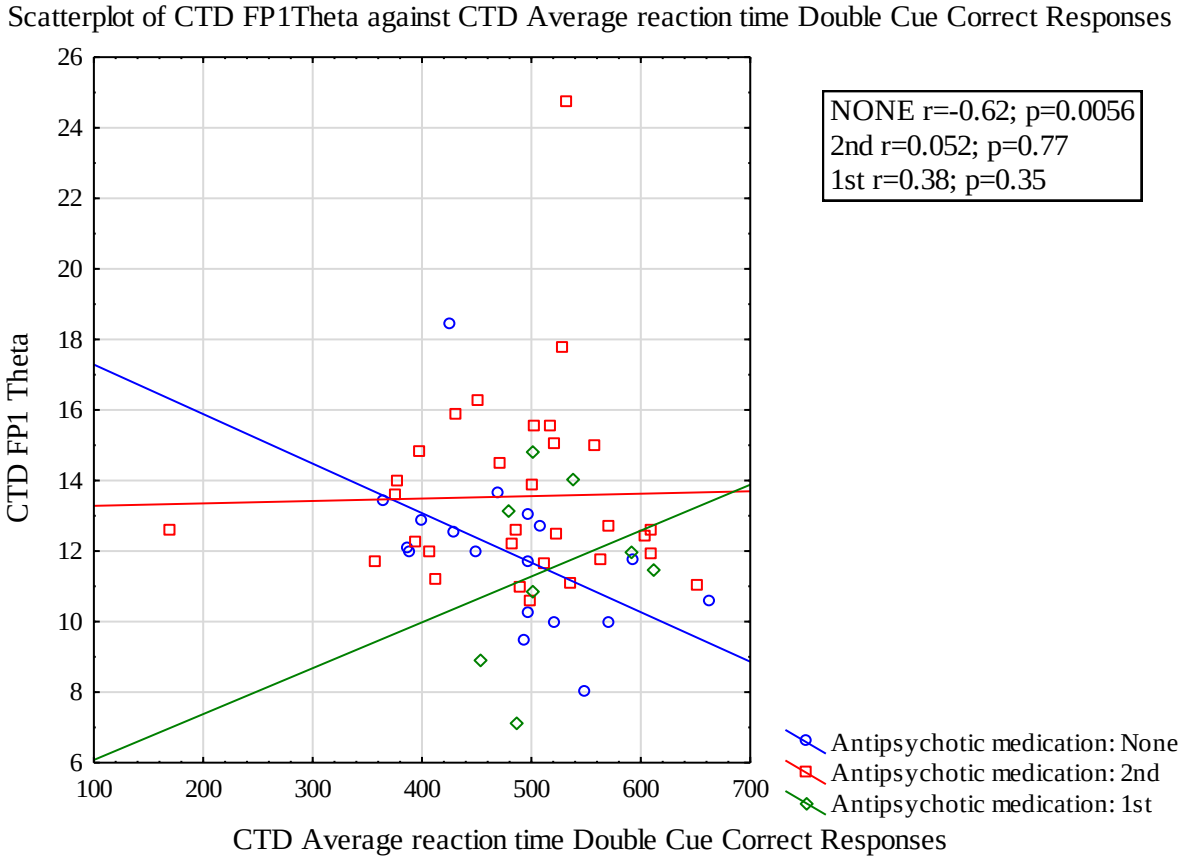


Figure 4.9 Cued target detection task (CTD) relative theta activity left prefrontal (Fp_1) electrode for patients not taking antipsychotic medication negatively correlated with double cue correct response reaction time. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm0.60$.

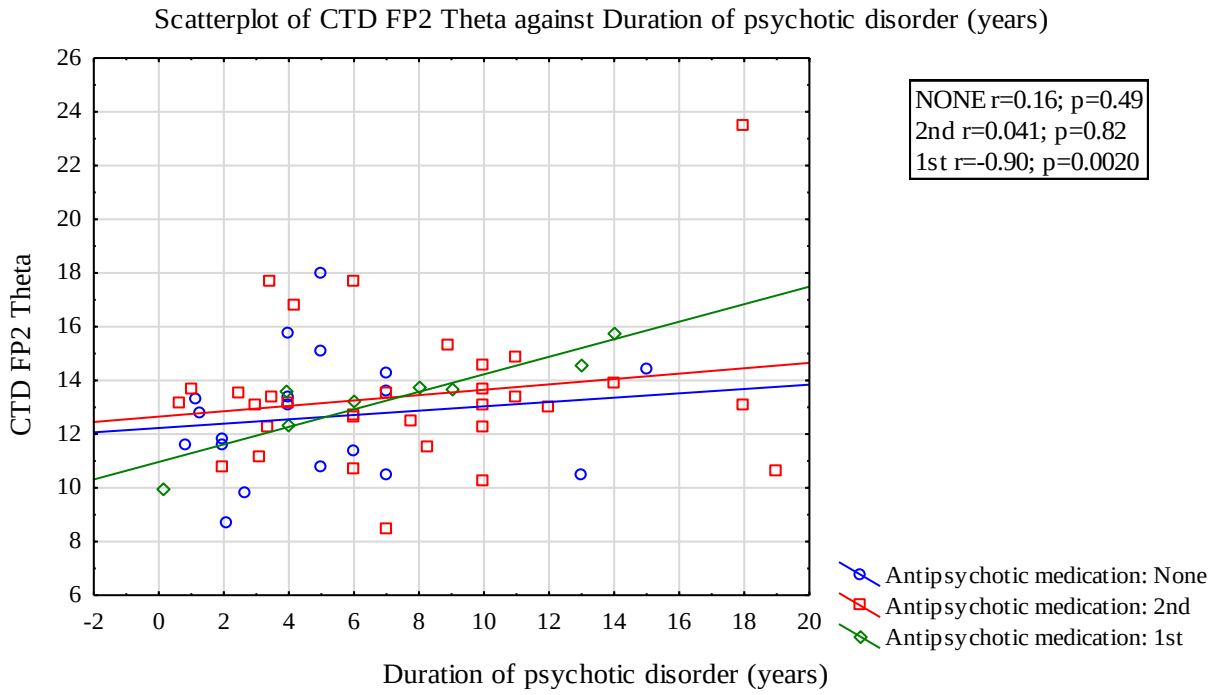


Figure 4.10 Cued target detection task (CTD) relative theta activity right prefrontal (Fp_2) electrode for patients prescribed 1st generation antipsychotic medication positively correlated with duration of psychotic disorder. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= >±0.60.

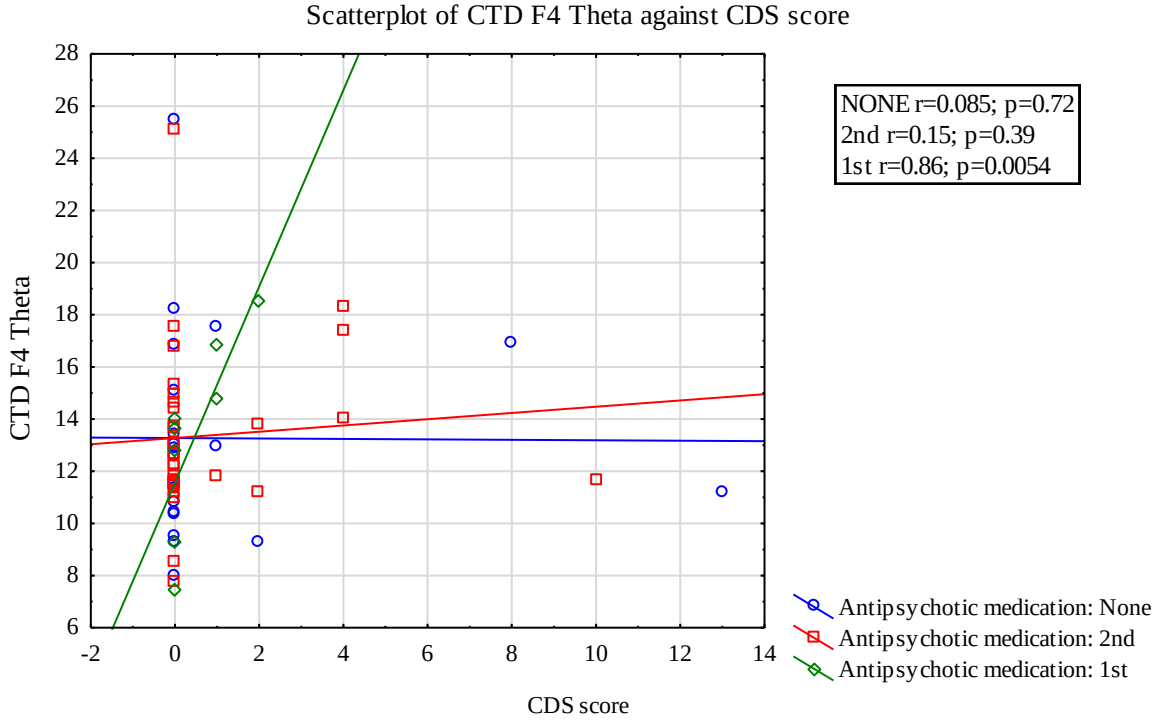


Figure 4.11 Cued target detection task (CTD) relative theta activity right frontal (F_4) electrode for patients prescribed 1st generation antipsychotic medication positively correlated with the Calgary depression rating scale (CDS) score. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= >±0.60.

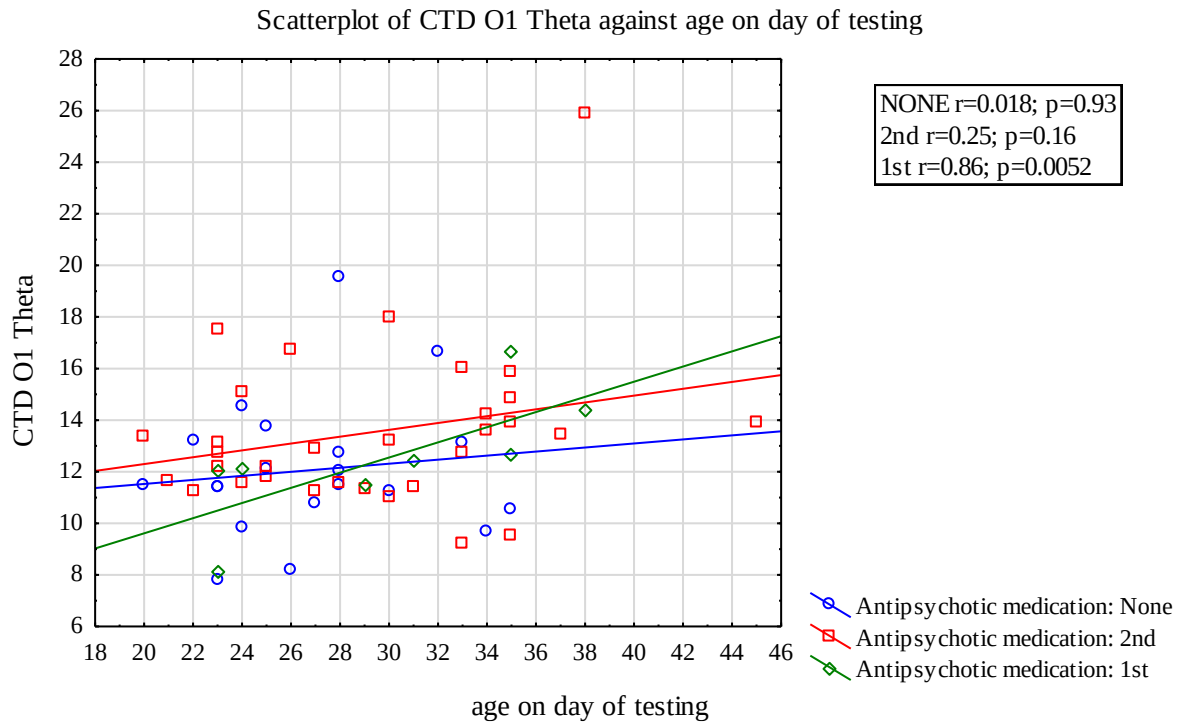


Figure 4.12 Cued target detection task (CTD) relative delta activity for the left occipital (O_1) electrode for patients not taking antipsychotic medication negatively correlated with age on the day of testing. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance reported for p<0.01 and Rho= >±0.60

4.3.6 Continuous performance task relative alpha activity

No significant group differences were found for CPT Alpha, **Table 4.7**.

Table 4.7 Continuous performance task relative alpha frequency activity

		Healthy control	**Schizophrenia**	**Methamphetamine-induced psychosis**		
		n = 35	n = 38	n = 31		
		15 females/20 males	8 females/30 males	7 females/24 males		
		Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test/ F test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	14.56(10.42-19.13)	15.86(12.13-25.94)	16.90(8.41-25.10)	$H_{2.103}$=2.51; p=0.28	-
Right prefrontal cortex	**Fp_2**	16.91(7.78-25.76)	17.26(10.59-24.72)	18.86(11.41-25.27)	$H_{2.103}$=0.95; p=0.62	-
Left frontal cortex	**F_3**	18.01(11.39-26.55)	17.78(12.21-30.26)	17.71(8.28-25.48)	$F_{2.100}$=0.49; p=0.60	-
Right frontal cortex	**F_4**	19.42(10.08-30.49)	19.76(7.44-32.41)	18.22(9.43-27.12)	$F_{2.100}$=0.65; p=0.52	-
Left central cortex	**C_3**	19.39(10.72-32.00)	18.32(14.53-31.49)	18.22(11.10-29.70)	$H_{2.103}$=0.59; p=0.74	-
Right central cortex	**C_4**	19.60(11.06-27.57)	18.03(13.34-30.40)	18.73(8.64-28.20)	$F_{2.100}$=0.13; p=0.87	-
Left parietal cortex	**P_3**	20.12(11.01-30.74)	21.11(7.90-32.67)	18.80(10.12-35.44)	$F_{2.100}$=1.43; p=0.24	-
Right frontal cortex	**P_4**	20.53(10.13-31.17)	18.94(13.80-30.20)	19.86(8.81-31.31)	$F_{2.100}$=0.15; p=0.85	-
Left occipital cortex	**O_1**	20.64(10.48-29.80)	18.43(10.10-30.41)	19.36(12.70-31.20)	$F_{2.100}$=0.21; p=0.80	-
Right occipital cortex	**O_2**	20.10(10.56-28.95)	18.25(13.31-29.79)	20.38(9.01-30.61)	$F_{2.100}$=0.50; p=0.60	-

Non-parametric Kruskal Wallis (H-test) and parametric one-way analysis of variance (F-test), Significance P<0.05.

In SCZ (n=14), the duration of methamphetamine abstinence negatively correlated with CPT alpha for the right occipital electrode ($O_2R_{spearman's(n=14)}$=-0.73; p=0.0029), **Figure 4.13**. Behaviourally omissions negatively correlated with the right prefrontal cortical electrode ($Fp_2R_{Spearman's(n=36)}$=-0.62, p=0.000045)**, Figure 4.14**.

In patients not taking antipsychotics (n=17 where, SCZn=6; MPDn=11), omissions negatively correlated with the CPT alpha for the right central ($C_4R_{Spearman's(n=17)}$= -0.62; p=0.0068), right parietal ($P_4R_{Spearman's(n=17)}$= -0.62; p=0.0071) and left occipital cortical electrodes ($O_1R_{Spearman's(n=17)}$= -0.607; p=0.0097), **Figure 4.15**.

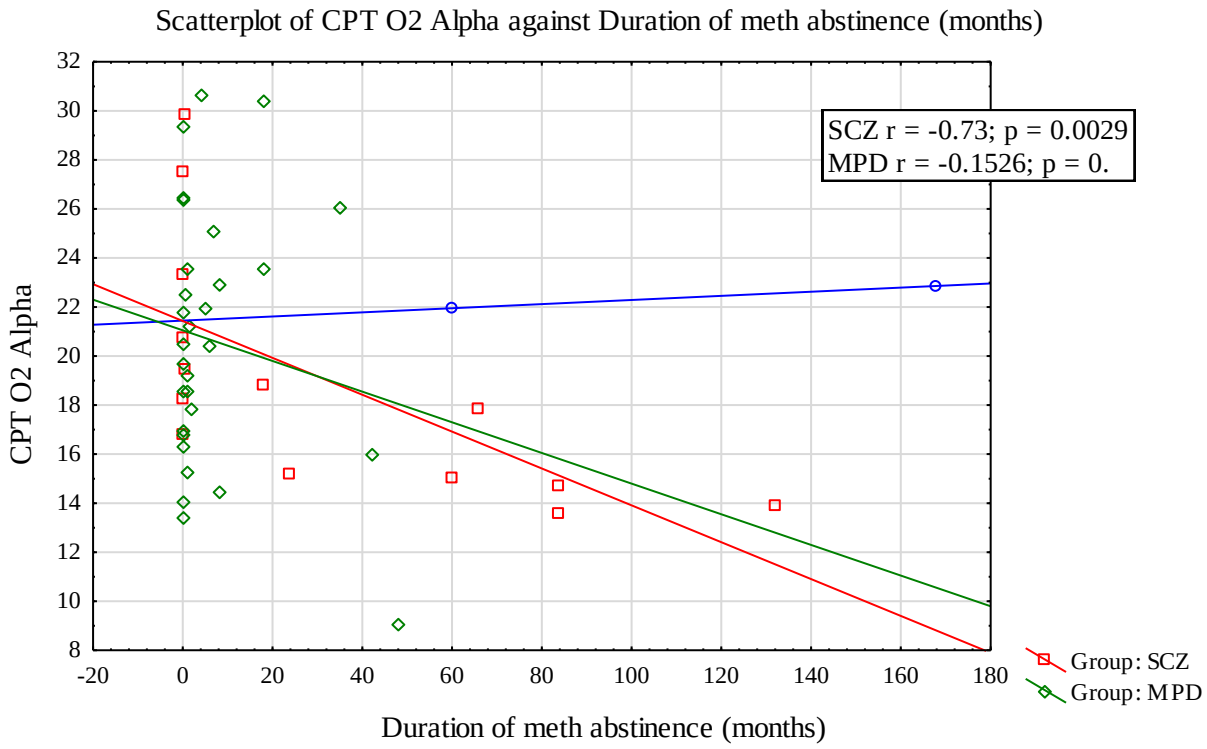


Figure 4.13 Continuous performance task (CPT) relative alpha activity for the duration of methamphetamine abstinence in months for Schizophrenia negatively correlated with the right occipital (O_2) electrode. Schizophrenia (SCZ); Methamphetamine-induced psychotic disorder (MPD). Significance was reported for $p<0.01$ and Rho= >±0.60.

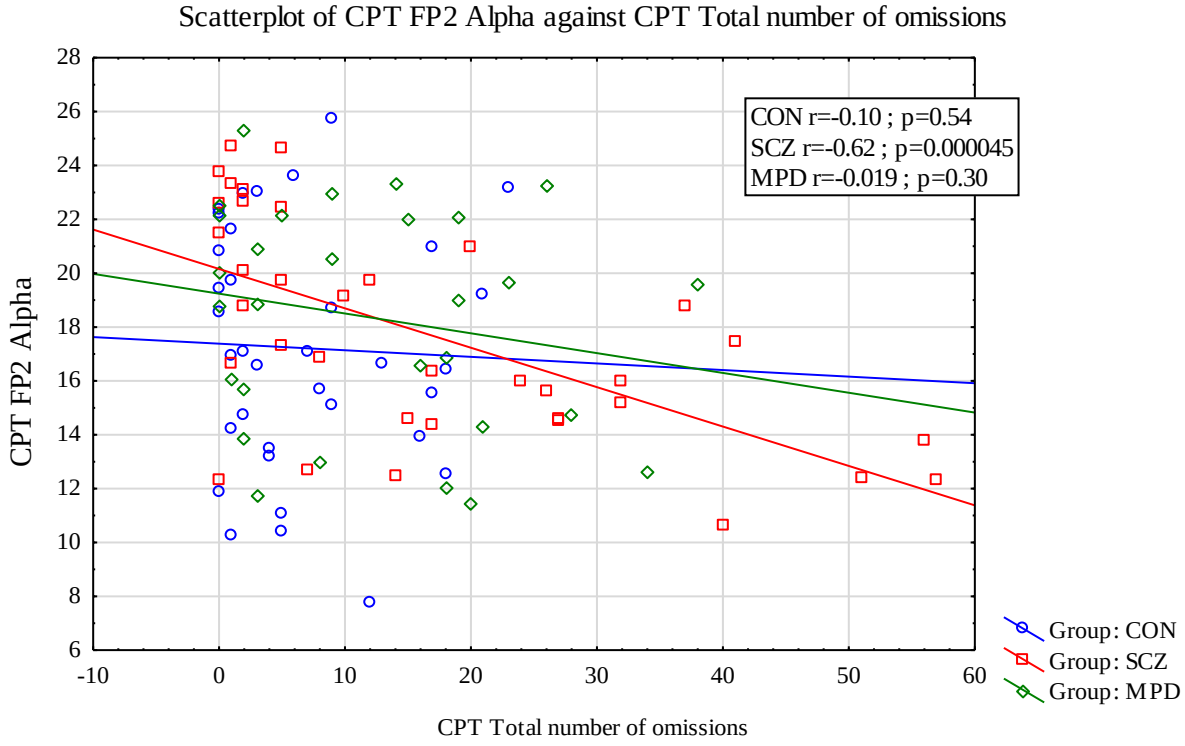


Figure 4.14 Continuous performance task (CPT) relative alpha activity for the total number of omissions for Schizophrenia negatively correlated with the right occipital (Fp_2) electrode. Schizophrenia (SCZ); Methamphetamine-induced psychotic disorder (MPD). Significance was reported for $p<0.01$ and Rho= >±0.60.

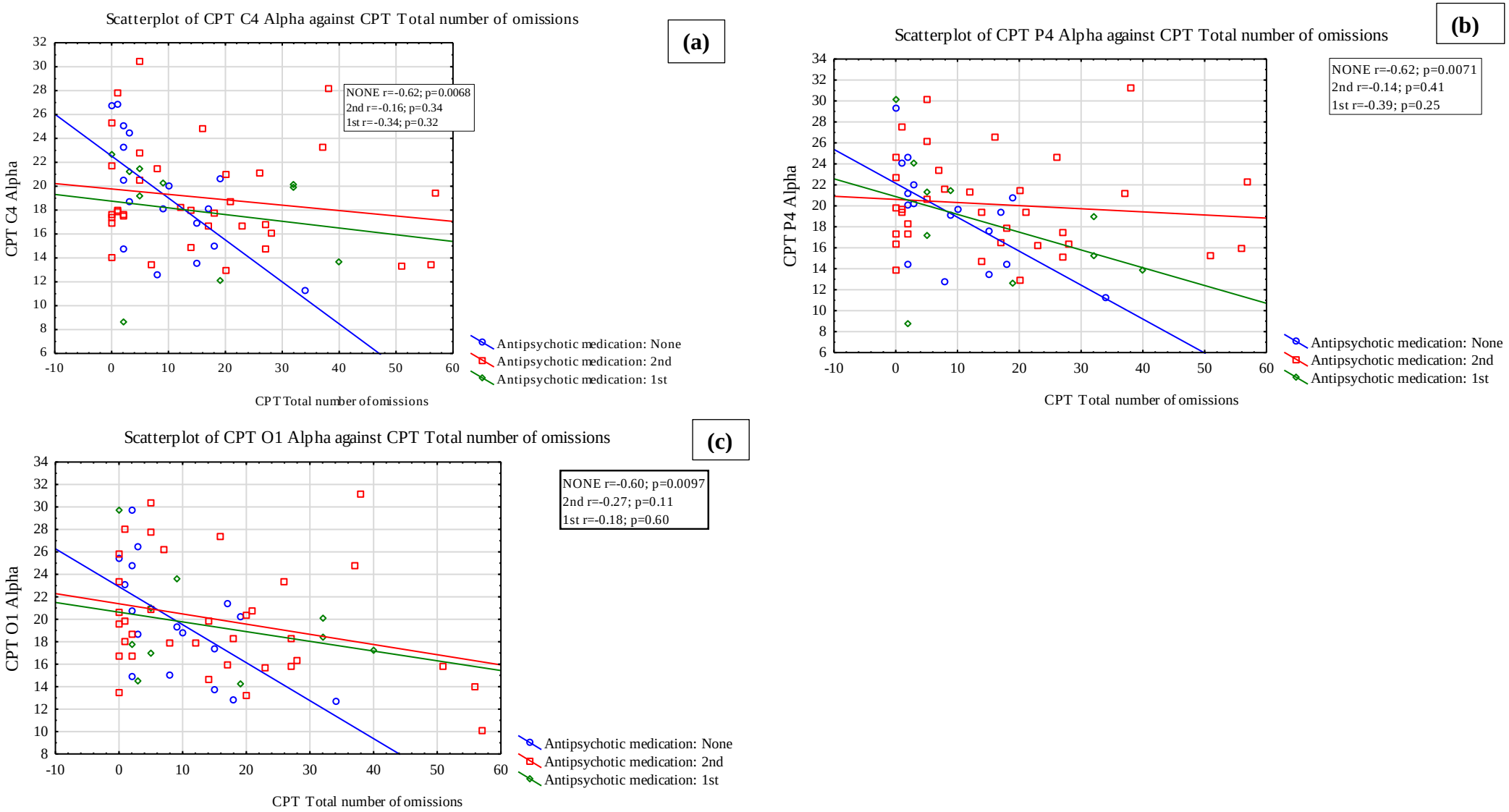


Figure 4.15 Continuous performance task (CPT) for patients not taking antipsychotic medication negatively correlated with the total number of omissions for relative delta **(a)** right central (C_4), **(b)** right parietal (P_4) and **(c)** left occipital (O_1) cortical electrodes. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm0.60$.

4.3.7 Cued target detection task relative alpha activity

No significant group differences were found for CTD relative alpha activity, **Table 4.8**.

Table 4.8 Cued target detection task relative alpha frequency activity

		Healthy control	**Schizophrenia**	**Methamphetamine-induced psychosis**		
		n = 35	n = 38	n = 31		
		15 females/20 males	8 females/30 males	7 females/24 males		
		Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test/ F test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	15.33(8.89-25.13)	16.62(8.76-34.04)	17.73(8.70-24.30)	$H_{2.97}$=4.17; p=0.12	-
Right prefrontal cortex	**Fp_2**	17.41(10.52-23.98)	17.56(9.17-32.20)	18.83(8.56-24.28)	$H_{2.97}$=1.83; p=0.40	-
Left frontal cortex	**F_3**	17.51(12.39-28.46)	19.02(13.12-35.97)	18.93(9.32-29.75)	$H_{2.97}$=0.47; p=0.78	-
Right frontal cortex	**F_4**	18.28(12.18-28.72)	19.41(12.54-37.71)	20.23(10.37-29.77)	$H_{2.97}$=0.23; p=0.88	-
Left central cortex	**C_3**	17.90(11.73-26.24)	18.73(13.58-36.50)	19.80(10.00-38.01)	$H_{2.97}$=0.94; p=0.95	-
Right central cortex	**C_4**	18.63(9.06-28.04)	18.12(12.36-35.83)	19.62(10.03-29.31)	$F_{2.94}$=0.054; p=0.94	-
Left parietal cortex	**P_3**	20.18(12.91-27.66)	20.06(13.24-37.42)	21.56(9.84-35.71)	$H_{2.97}$=0.26; p=0.87	-
Right frontal cortex	**P_4**	20.95(12.63-30.42)	19.17(14.82-35.97)	21.92(10.18-30.82)	$F_{2.94}$=0.20; p=0.81	-
Left occipital cortex	**O_1**	20.49(11.36-35.83)	19.53(12.55-36.02)	21.15(9.77-30.36)	$H_{2.97}$=0.85; p=0.65	-
Right occipital cortex	**O_2**	21.08(10.84-32.82)	19.24(13.24-35.91)	21.57(9.14-32.83)	$F_{2.94}$=0.16; p=0.84	-

Non-parametric Kruskal Wallis (H-test) and parametric one-way analysis of variance (F-test), Significance P<0.05.

In MPD (n=26), congruent omissions negatively correlated with CTD alpha for the left prefrontal cortical electrode ($Fp_1R_{Spearman's(n=26)}$=-0.62, p=0.00057)**, Figure 4.16**.

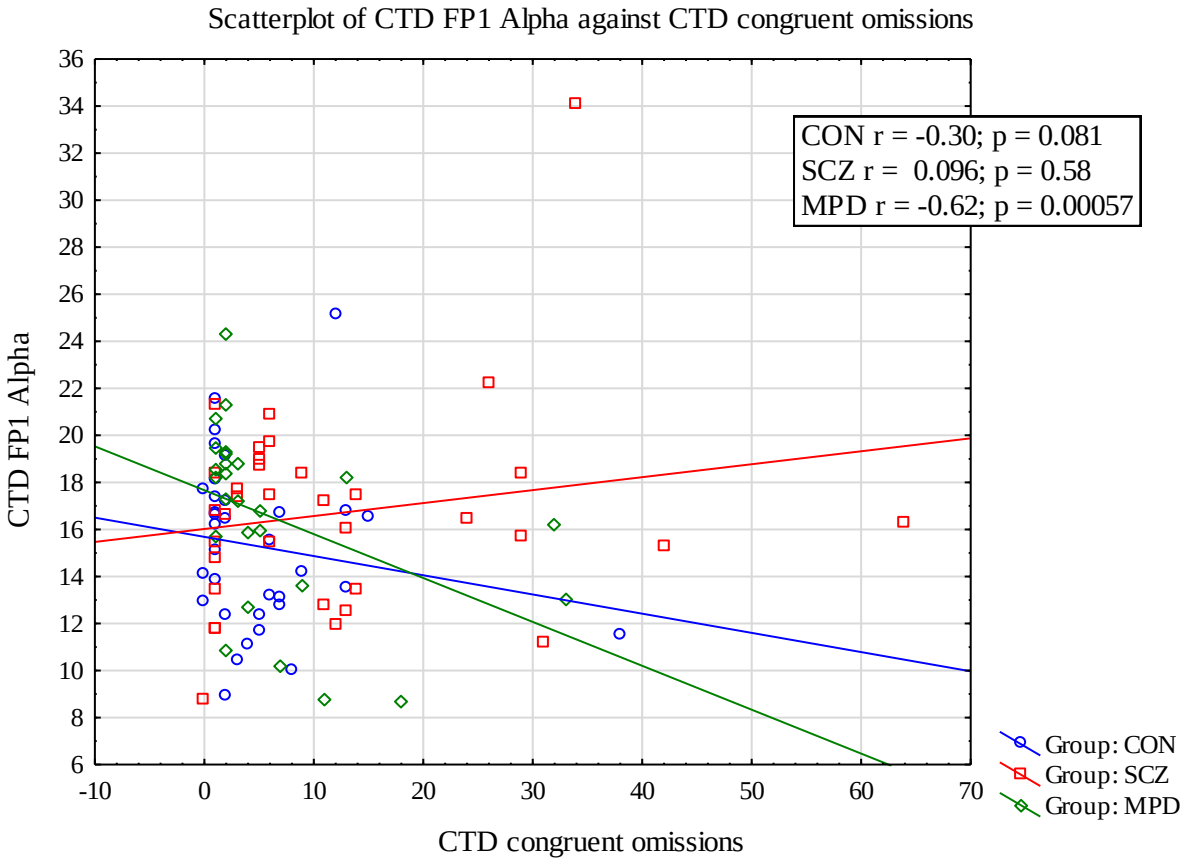


Figure 4.16 Cued target detection task (CTD) relative alpha activity for the total number of congruent omissions for MPD negatively correlated with the left prefrontal (Fp_1) electrode. Schizophrenia (SCZ); Methamphetamine-induced psychotic disorder (MPD). Significance was reported for $p<0.01$ and Rho= >±0.60.

Patients taking 1st generation antipsychotic medications (n=8 where, SCZn=4; MPDn=4) with a history of tobacco use negatively correlated with CTD alpha activity for the right central and the left parietal electrodes ($C_4R_{Spearman's(n=8)}$=-0.86, p=0.0052; $P_3R_{Spearman's(n=8)}$=-0.98; p=0.000004), **Figure 4.17.** Behaviourally double cue correct responses reaction time positively correlated with the right frontal cortical electrode ($F_4R_{Spearman's(n=8)}$=0.85; p=0.0065), **Figure 4.18**.

In patients taking 2nd generation antipsychotic medications (n=19 where, SCZn=10; MPDn=9), CTD right prefrontal alpha negatively correlated with duration of methamphetamine use ($Fp_2R_{Spearman's(n=19)}$=-0.63; p=0.0034), **Figure 4.19**.

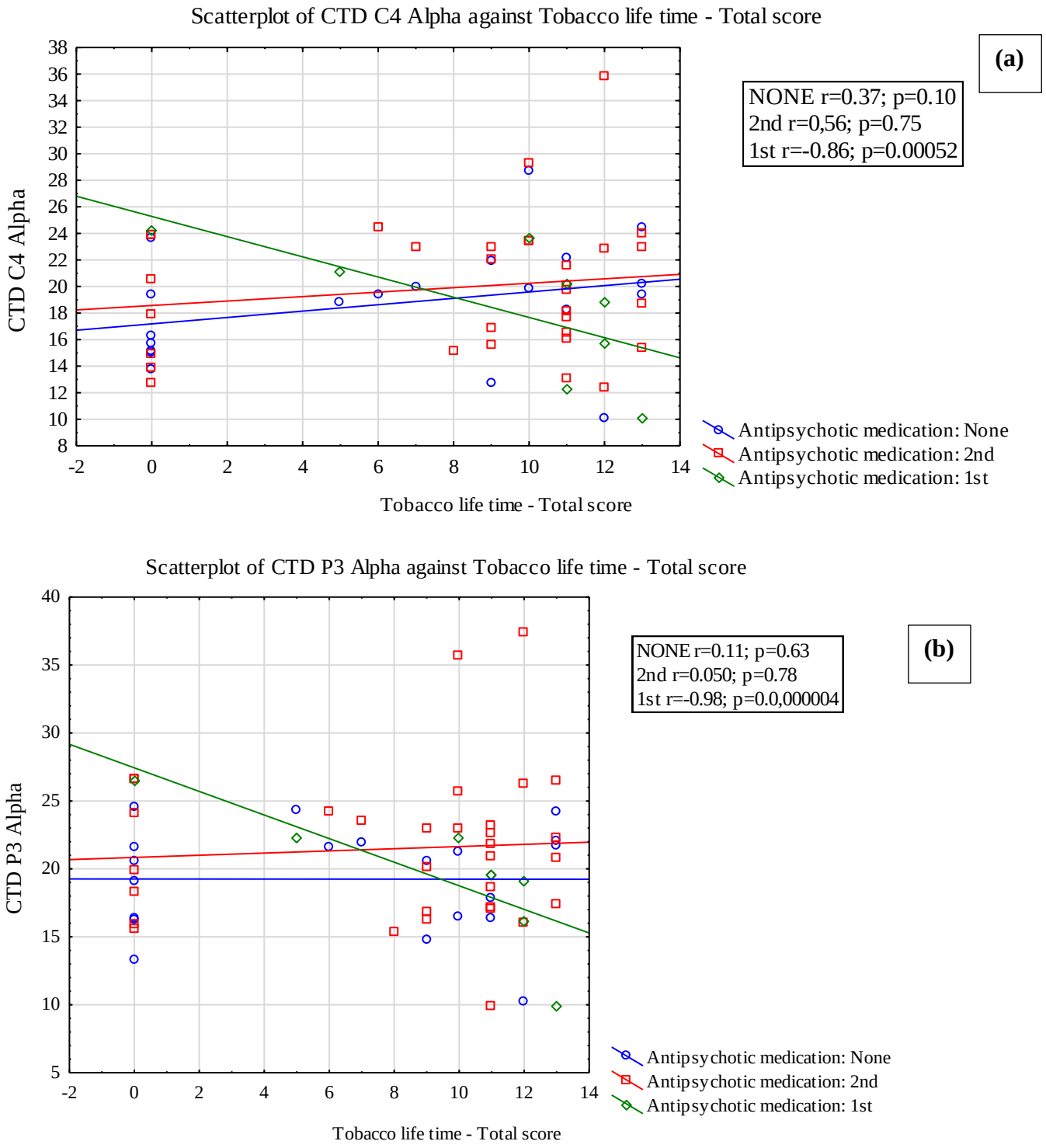


Figure 4.17 Cued target detection task (CTD) relative alpha activity for the **(a)** right central (C_4) and **(b)** left parietal (P3) electrode for patients not taking antipsychotic medication negatively correlated with the tobacco lifetime score. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance reported for $p<0.01$ and Rho= $>\pm 0.60$.

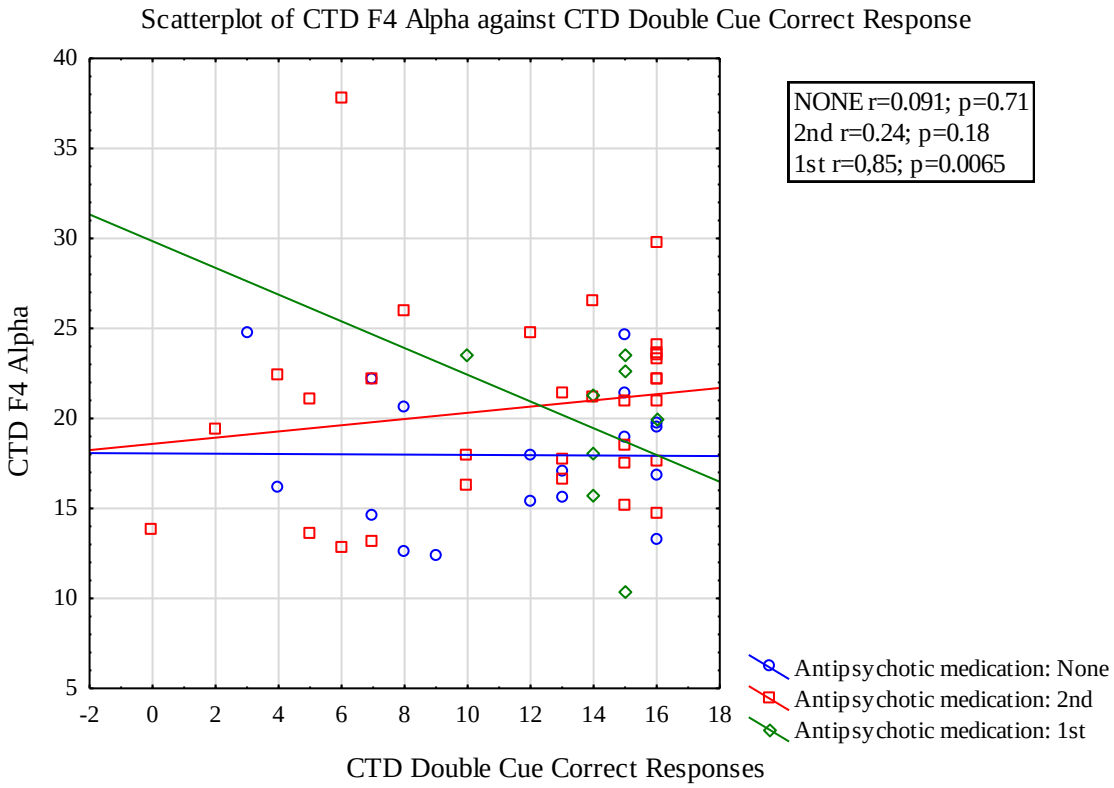


Figure 4.18 Cued target detection task (CTD) relative alpha activity for the double cue correct responses for patients prescribed 1st generation antipsychotic medication positively correlated with the left parietal electrode Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for p<0.01 and Rho= >±0.60.

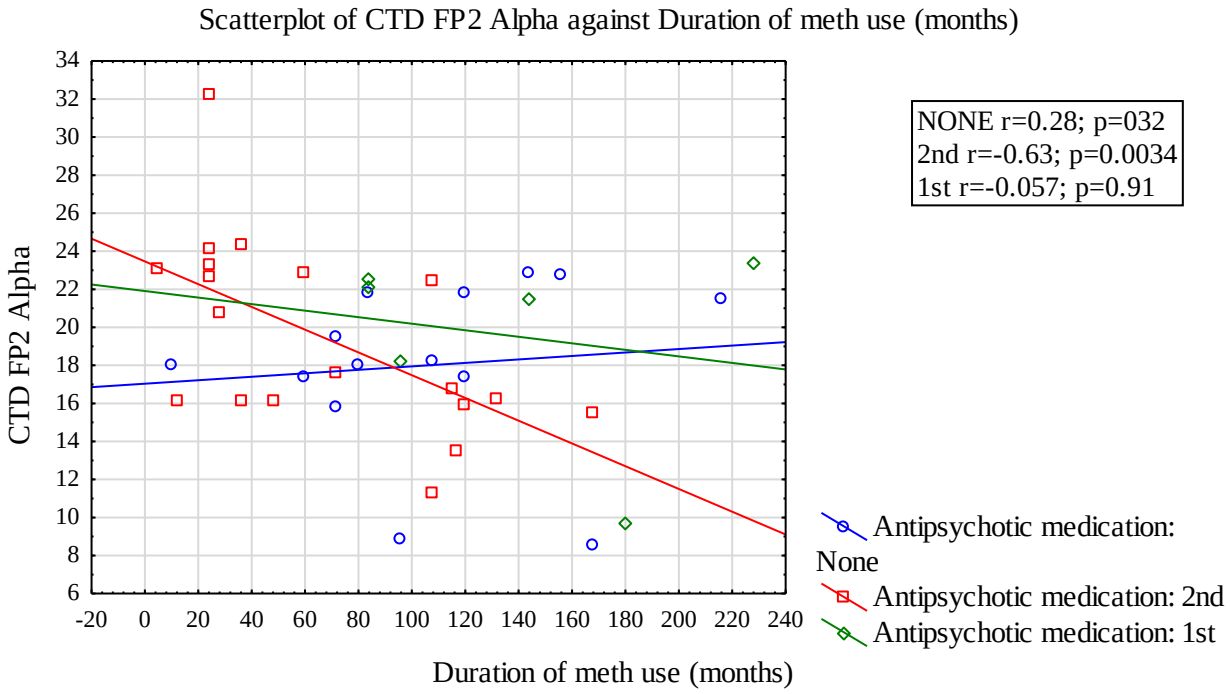


Figure 4.19 Cued target detection task (CTD) relative alpha activity for the right prefrontal (Fp_2) electrode for patients not taking antipsychotic medication positively correlated with duration of methamphetamine use. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for p<0.01 and Rho= >±0.60.

4.3.8 Continuous performance task relative beta activity

No significant group differences were found for CPT relative beta activity, **Table 4.9**.

Table 4.9 Continuous performance task relative beta frequency activity

		Healthy control	**Schizophrenia**	**Methamphetamine-induced psychosis**		
		n = 35	n = 38	n = 31		
		15 females/20 males	8 females/30 males	7 females/24 males		
		Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test/ F test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	18.78(7.16-35.59)	16.10(9.64-33.84)	18.11(10.68-31.10)	$H_{2.103}$=1.27; p=0.52	-
Right prefrontal cortex	**Fp_2**	20.35(7.49-33.02)	18.81(11.05-33.51)	22.09(10.01-30.33)	$H_{2.103}$=1.35; p=0.50	-
Left frontal cortex	**F_3**	21.28(7.96-39.92)	17.83(12.40-33.87)	20.61(9.45-36.16)	$F_{2.100}$=0.56; p=0.57	-
Right frontal cortex	**F_4**	24.80(14.90-41.01)	21.13(7.42-43.52)	22.80(8.49-41.25)	$H_{2.103}$=4.26; p=0.11	-
Left central cortex	**C_3**	24.84(7.53-38.71)	21.45(13.91-32.89)	22.27(10.47-42.23)	$H_{2.103}$=4.59; p=0.10	-
Right central cortex	**C_4**	21.55(6.82-38.29)	17.56(11.53-34.54)	20.45(9.00-41.27)	$F_{2.100}$=2.52; p=0.084	-
Left parietal cortex	**P_3**	26.11(7.38-38.41)	22.99(9.45-43.87)	23.11(10.63-48.70)	$H_{2.103}$=3.20; p=0.20	-
Right frontal cortex	**P_4**	20.74(8.11-29.13)	17.80(11.81-35.38)	19.36(9.05-32.35.85)	$F_{2.100}$=0.63; p=0.53	-
Left occipital cortex	**O_1**	20.76(9.56-32.13)	17.85(11.34-34.83)	19.41(10.43-32.60)	$F_{2.100}$=1.37; p=0.25	-
Right occipital cortex	**O_2**	21.81(7.52-41.82)	18.28(11.74-34.95)	20.13(9.35-35.53)	$F_{2.100}$=1.77; p=0.17	-

Non-parametric Kruskal Wallis (H-test) and parametric one-way analysis of variance (F-test), Significance P<0.05.

In patients not taking antipsychotics (n=14 where, SCZn=1; MPDn=13), the duration of methamphetamine use negatively correlated with CPT relative beta activity for the left frontal cortical electrode ($F_3R_{spearman's(n=14)}$=-0.702, p=0.0050), **Figure 4.20**.

In patients taking 1st generation antipsychotic medication (n=10 where, SCZn=4; MPDn=6), PANSS positive subscale scores positively correlated with the CPT relative beta activity for the right occipital cortical electrode ($O_2R_{spearman's(n=10)}$=0.78, p=0.0069), **Figure 4.21**.

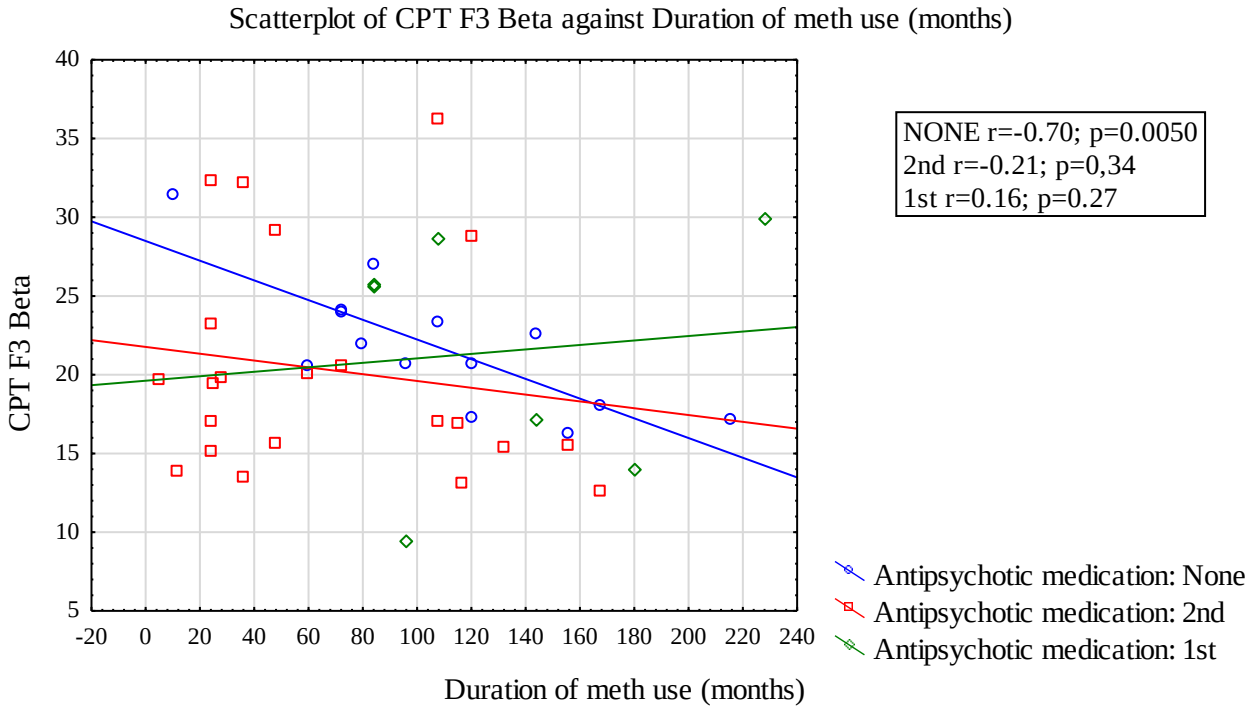


Figure 4.20 Continuous performance task (CPT) relative beta activity for the duration of methamphetamine use in months for patients not taking antipsychotic medication negatively correlated with left frontal (F_3) electrode. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm 0.60$.

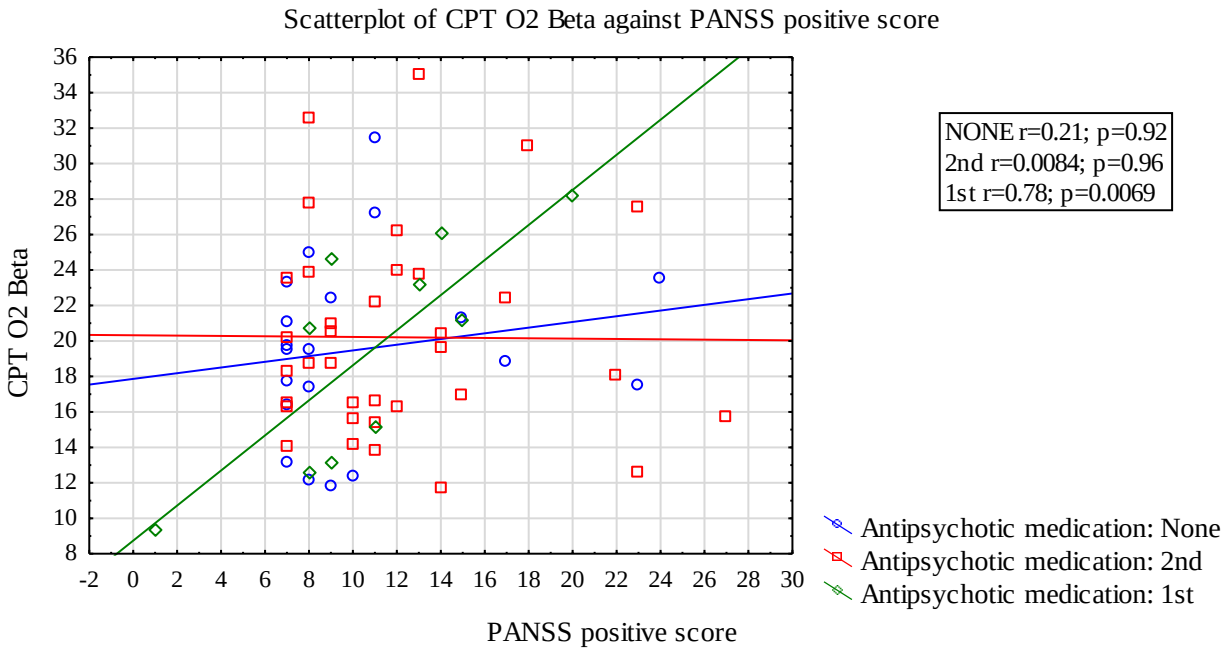


Figure 4.21 Continuous performance task (CPT) relative beta activity for the right occipital (O_2) electrode for patients not taking antipsychotic medication positively correlated with the PANSS positive score. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm 0.60$.

4.3.9 Cued target detection task relative beta activity

No significant group differences were found for CTD beta, **Table 4.10**.

Table 4.10 Cued target detection task relative beta frequency activity

		Healthy control	**Schizophrenia**	**Methamphetamine-induced psychosis**		
		n = 35	n = 38	n = 31		
		15 females/20 males	8 females/30 males	7 females/24 males		
		Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test/ F test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	17.95(8.85-26.19)	18.08(9.42-41.01)	19.10(8.42-34.57)	$H_{2.97}$=2.92; p=0.23	-
Right prefrontal cortex	**Fp_2**	22.13(8.95-38.37)	18.44(9.47-36.24)	23.57(9.51-31.03)	$H_{2.97}$=2.83; p=0.24	-
Left frontal cortex	**F_3**	22.66(12.70-32.88)	19.69(10.31-38.79)	21.75(9.49-35.11)	$F_{2.94}$=0.87; p=0.42	-
Right frontal cortex	**F_4**	25.83(15.19-47.66)	23.29(12.62-44.09)	24.39(9.61-42.36)	$F_{2.94}$=0.42; p=0.65	-
Left central cortex	**C_3**	25.44(9.89-44.15)	20.86(10.47-38.56)	24.24(9.42-36.96)	$F_{2.94}$=1.95; p=0.14	-
Right central cortex	**C_4**	22.51(6.85-33.78)	18.33(9.82-38.92)	22.65(9.64-36.49)	$F_{2.94}$=1.56; p=0.21	-
Left parietal cortex	**P_3**	26.93(9.95-41.06)	21.04(12.42-46.96)	25.69(9.85-46.06)	$H_{2.97}$=3.05; p=0.21	-
Right frontal cortex	**P_4**	22.14(9.87-32.81)	19.66(11.25-39.11)	20.80(10.05-32.24)	$F_{2.94}$=0.22; p=0.80	-
Left occipital cortex	**O_1**	22.42(11.93-32.92)	19.40(12.82-39.08)	21.08(11.98-30.70)	$F_{2.94}$=1.42; p=0.24	-
Right occipital cortex	**O_2**	22.71(11.38-44.83)	20.61(12.32-39.01)	21.87(10.40-30.31)	$H_{2.97}$=2.89; p=0.23	-

Non-parametric Kruskal Wallis (H-test) and parametric one-way analysis of variance (F-test), Significance P<0.05.

For patients taking 1st generation antipsychotic medication (n=20 where, SCZn=7; MPDn=13); CTD relative beta activity right occipital electrode positively correlated with PANSS positive subscale ($O_2R_{Spearman's(n=8)}$=0.87; p=0.0045), **Figure 4.22**, the PANSS negative subscale positively correlated with the CTD relative beta activity for the left prefrontal ($Fp_1R_{Spearman's(n=8)}$=0.84; p=0.0079) left frontal ($F_3R_{Spearman's(n=8)}$=0.84; p=0.0079) and right frontal ($F_4R_{Spearman's(n=8)}$=0.96; p=0.000067) electrodes, **Figure 4.23**. Behaviourally double cue omissions positively correlated with right parietal ($P_4R_{Spearman's(n=8)}$=0.86; p=0.0055) and right occipital ($O_2R_{Spearman's(n=8)}$=0.85; p=0.0071) cortical electrodes, **Figure 4.24.**

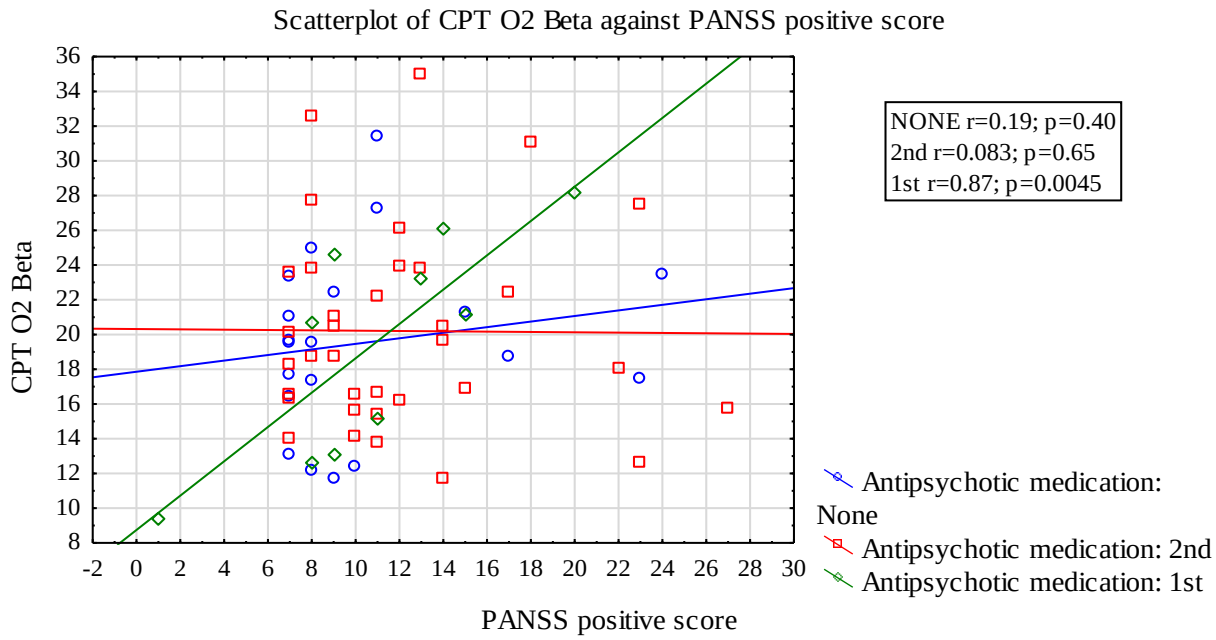


Figure 4.22 Cued target detection task (CTD) relative beta activity for the right occipital (O_2) electrode for patients not taking antipsychotic medication positively correlated with the PANSS positive score. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm 0.60$.

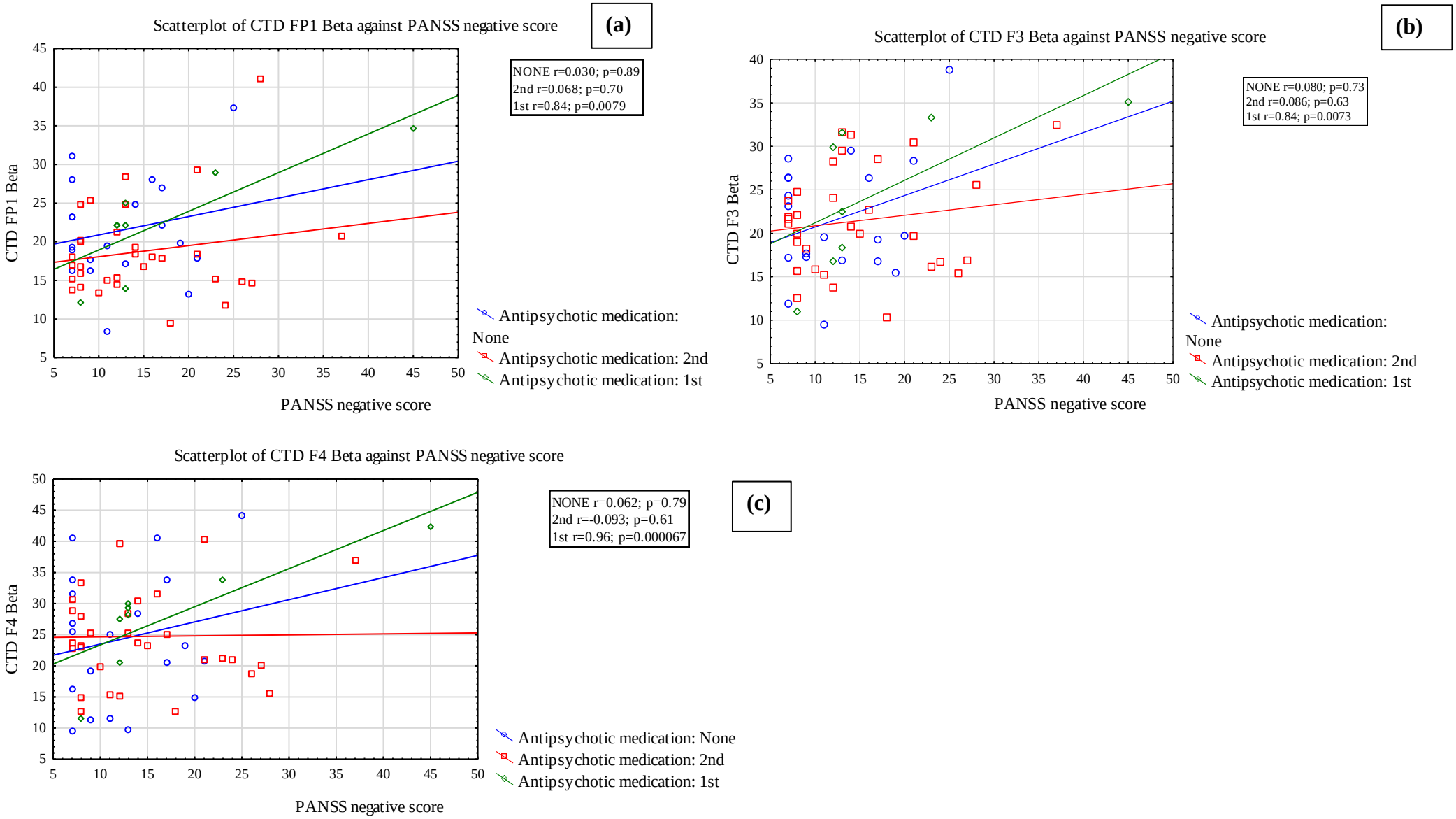
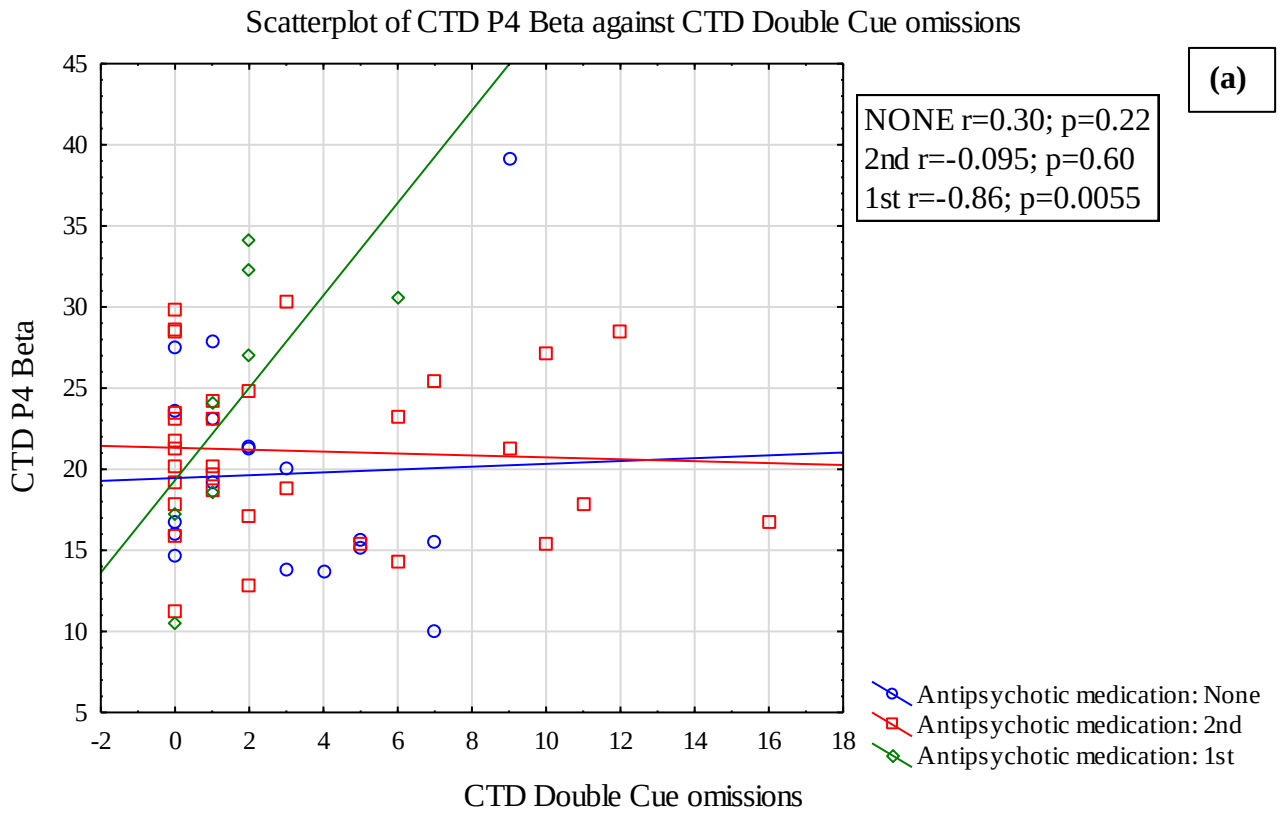


Figure 4.23 PANSS negative subscale score positively correlated with the Cued target detection task (CTD) relative beta activity for the **(a)** left prefrontal (Fp_1), **(b)** left frontal (F_3), **(c)** and right frontal (F_4) electrodes. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm0.60$.



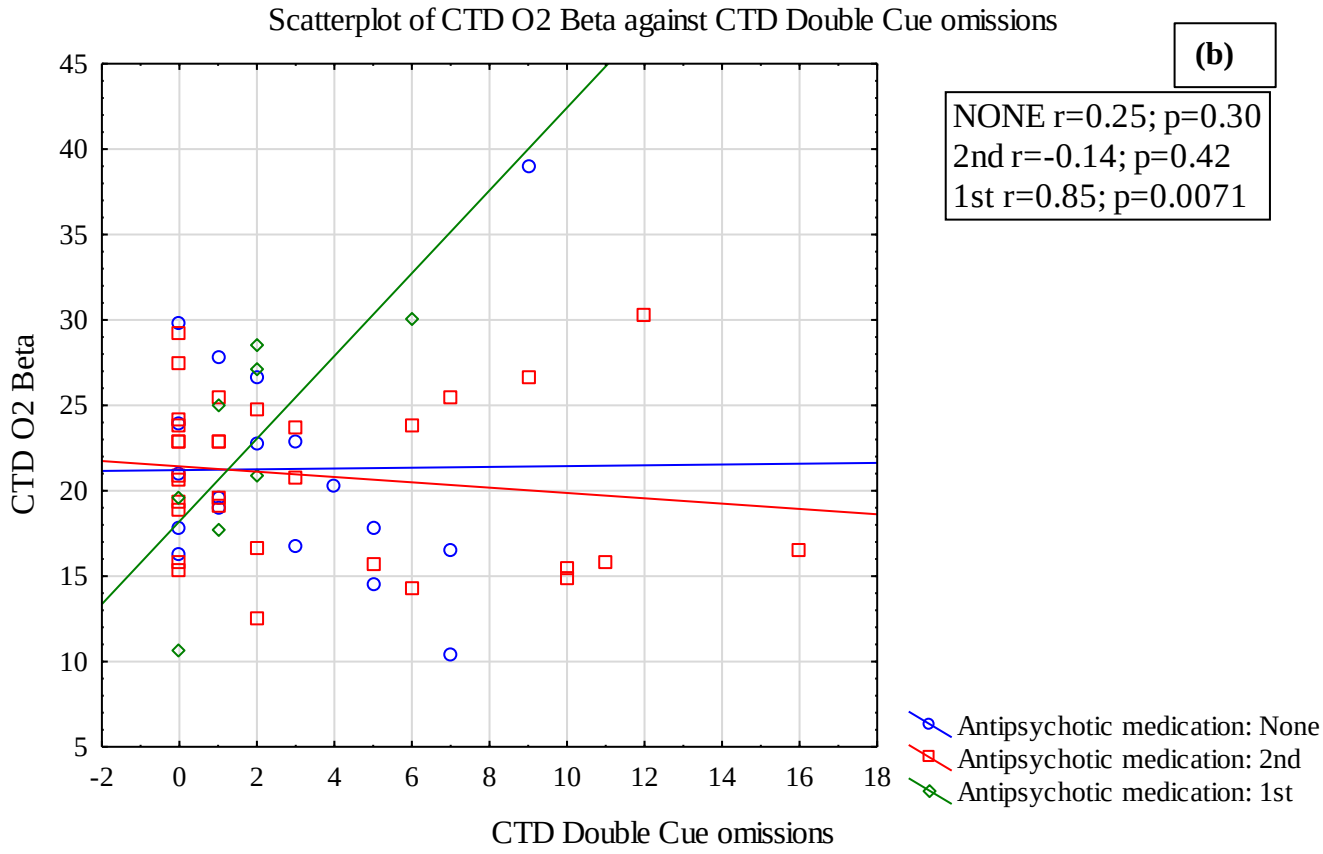


Figure 4.24 Cued target detection task (CTD) double cue omissions for patients prescribed 1st generation antipsychotic medication positively correlated with the **(a)** right parietal (P_4), **(b)** and right occipital (O_2) cortical electrodes. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= >±0.60.

4.4 Discussion

The main findings in the present study were: (1) SCZ and MPD reported poor performance across both cognitive tasks, as seen by the reduction in correct responses and increased number of omissions and trick S responses when compared to CON. Further increased left central and parietal theta activity during the CPT was noted in MPD compared to SCZ, however, no significant group differences were noted for CTD across SCZ, MPD and CON. (2) Significant associations were found for CPT where omissions negatively correlated with alpha frequency activity in patients not taking antipsychotics. For CTD, frontal alpha and theta activity negatively correlated with double cue correct responses, and the right posterior beta frequency activity positively correlated with double cue omissions. Then for both cognitive tasks, clinical scale scores positively correlated with frontal theta in CTD and parietal theta in CPT. Tobacco use negatively correlated with left parietal alpha frequency activity in patients prescribed 1st generation antipsychotics. Lastly, a positive correlation was found for patients using methamphetamine and those who are abstinent, with frontal delta in both cognitive tasks.

Behavioural

For the CPT, MPD theta activity was found to be lower when compared to SCZ. The presentation of reduced theta activity indicates cognitive decline within MPD patients. However, for the prescription of 1st generation antipsychotic medications, age on the day of testing positively correlated with CTD theta left occipital cortical electrode. This increased theta activity within patients has previously been found to be associated with cognitive functioning impairments (Trammell et al., 2017). These cognitive functioning impairments can be seen through the behavioural data collected during the completion of cognitive tasks.

Omissions during a cognitive task were referenced to the attention given to the specific task which needed to be completed. In our study omissions negatively correlated with the CPT alpha left prefrontal cortical electrode in MPD, and with the CPT alpha right prefrontal cortical electrode in SCZ. The increased prefrontal alpha is indicative of cognitive impairment in patient groups compared to CON. For patients taking 1st generation antipsychotic medication double cue omissions positively correlated with CTD beta right parietal and right occipital cortical electrodes. The literature revealed beta frequency activity is associated with the planning and execution of motor control, which requires the ability to ignore distractor stimuli

(Wiesman, Koshy, Heinrichs-Graham, & Wilson, 2020). Patients exhibited lower beta frequency activity compared to controls indicating that although patients were prescribed 1st generation antipsychotic medication, cognition was still poorer in the patient group. Further, for patients prescribed 1st generation antipsychotics double cue correct responses positively correlated with CTD alpha right frontal cortical electrode and for patients not prescribed antipsychotic medication, double cue correct responses negatively correlated with CTD theta left prefrontal cortical electrode. Patients exhibited an increase in alpha and theta frequency activity over the frontal brain region indicating a possible increase in attention to attend to the cue. These behavioural results indicate reduced cognitive performance in patients compared to CON.

Medication use

Clinically our study revealed significant differences for patients being prescribed 1st generation antipsychotic medication. It is important to note that literature has revealed that patients prescribed 1st generation antipsychotics and anticholinergics can have adverse effects on cognitive functioning, and therefore cause cognitive impairments (Hill et al., 2010). As reported in our study, patients were found to have increased theta activity within the frontal brain regions during the completion of the CTD task. The duration of the psychotic disorder was found to positively correlate with the CTD theta right prefrontal cortical electrode. Then, associations were found for CTD beta which positively correlated with the PANSS negative subscale for the left prefrontal, bilateral frontal electrodes but negatively correlated with the CTD left central delta activity. Negative symptoms were found to have a key role in identifying cuing and cognitive interference during cognitive-related tasks (D.-W. W. Kim et al., 2013). In patients taking 1st generation antipsychotic medication, PANSS positive subscale scores positively correlated with CPT and CTD beta right occipital cortical electrode. The increased beta activity was noted within the frontal region which suggests increased alertness and attentiveness to the environment (Riccio et al., 2002b).

Substance involvement

Substance involvement was previously shown to have adverse effects on cognitive functioning. In our study, the age of onset of methamphetamine use in patients prescribed 2nd generation antipsychotics had a negatively correlated with the CPT left central delta activity. Then for MPD, CTD left prefrontal delta activity positively correlated with the KMSK methamphetamine total score. It was expected that MPD reported increased use of substance

use (McKetin, Lubman, Baker, Dawe, & Ali, 2013). For the duration of methamphetamine use in patients not taking antipsychotics, a negative correlation was noted with CPT relative beta activity for the left frontal cortical electrode. And for patients taking 2nd generation antipsychotics duration of methamphetamine use positively correlated with CTD relative delta activity and negatively with CTD relative alpha activity for the right prefrontal cortical electrode. The activation of the prefrontal cortex during methamphetamine use was found to be associated with a reduction in cognitive control (Nestor et al., 2011). In our study, a handful of individuals had abstained from methamphetamine use. We assessed whether an association for duration of methamphetamine abstinence was present, and results showed a negative correlation with CPT alpha in SCZ for the right occipital electrode, a positive correlation with CPT delta in patients prescribed 2nd generation antipsychotics for the left prefrontal electrode and lastly a positive correlation with CTD delta in patients not taking antipsychotics for the right prefrontal cortical electrode. It was found that despite patients abstaining from methamphetamine use, cognitive deficits were found to persist long after methamphetamine use had been stopped (Scott et al., 2007). In our study, SCZ was shown to be prescribed more 1st generation antipsychotic medication. The use of tobacco while taking first-generation antipsychotic medication negatively affected alpha activity within the posterior brain region. This is seen by the decrease in alpha activity during CTD. Literature has shown alpha frequency activity increases across the posterior brain region during cuing paradigms (Benedek, Schickel, Jauk, Fink, & Neubauer, 2014; Klimesch, 2021).

Limitations of the study are the lack of computer skills from several individuals, as a result of never being given the opportunity to learn or not having access to a computer. A limitation of measuring sustained attention is the increase in mental fatigue which can result in a decrease in attention over time (Reteig et al., 2019). Our study included patients currently on a medication regime and future work should include a control group of patients prescribed medication and those who are unmedicated. Further, studies should include mapping the EEG data to brain structure through structural brain imaging or a combination of fMRI and EEG studies.

Conclusion: Both SCZ and MPD reported poor performance across both cognitive tasks compared to CON. This is consistent with previous work, although it is the first study to directly compare cortical processing linked to attention in MPD. Further studies are needed to understand the attention mechanisms underlying MPD and whether methamphetamine permanently alters cognitive functioning long-term.

In the current chapter, I discussed electroencephalographic relative frequency activity in schizophrenia, methamphetamine-induced psychotic disorder, and healthy controls, where I addressed attentional networks and cortical processing in the continuous performance task and the cued target detection task. I found poor cognitive functioning in patient groups compared to controls across both cognitive tasks. In line with this work, in the next chapter, I investigated the P300 event-related potential waveform in the cued target detection task and continuous performance task which further investigates attention mechanisms in schizophrenia and methamphetamine-induced psychotic disorder.

5 P300 differences of the continuous performance task and cued-target detection task within schizophrenia and methamphetamine-induced psychotic disorder

In the previous chapter, I included two tasks, the continuous performance task and the cued target detection task which focused on cortical arousal during the completion of cognitive tasks. In this study, we will go one step further and investigate attention in schizophrenia and methamphetamine-induced psychotic disorder where we extracted the P300 event-related potential waveform.

Abstract

Introduction: Psychotic disorders generally present with cognitive impairments including attention. Cognitive impairments, specifically attention can be assessed by investigating the P300 event-related potential (ERP) waveform, which is a representation of cortical updating. The P300 ERP waveform is widely studied in schizophrenia (SCZ) during cognitive tasks, however, literature on the methamphetamine-induced-psychotic disorder (MPD) is currently lacking. We aimed to investigate differences in attention via the P300 event-related potential waveform and its relationship with drug use, clinical scales, and population characteristics between healthy controls (CON), SCZ, and MPD, and between SCZ and MPD via medication grouping.

Method: EEG was recorded from 104 individuals: SCZ (n=38), MPD (n=31), and CON (n=35), who completed two cognitive tasks, a continuous performance task (CPT-5 minutes) and cued target detection task (CTD-6:20 minutes). Group differences were determined by ANOVA with Bonferroni post-hoc correction or multivariate Kruskal-Wallis test, dependent on data distribution. Associations were determined using Pearson's or Spearman's rank order correlation ($p<0.01$) where appropriate.

Results: Group differences were reported where the CPT target P300 amplitude was attenuated for MPD (Fp_1 $p=0.021$, C_3 $p=0.039$) compared to CON. P300 latency was found to be delayed for the CPT distractor cue in SCZ (F_4 $p=0.0092$, P_3 $p=0.035$) and CTD no cue in MPD (Fp_1 $p=0.039$) compared to CON. Correlates found for the CPT target P300 latency indicated methamphetamine use in SCZ negatively correlated with the frontal amplitude ($r=-0.73$; $p=0.0029$) and positively correlated with the right parietal ($r=0.77$; $p=0.0012$) but positively

correlated with the right prefrontal latency (r=0.69; p=0.0056). For CTD incongruent P300 latency a negative correlation was found for the parietal region and age of onset of methamphetamine use in SCZ (r=-0.87; p=0.00084). Lastly, a positive correlation was found for the prefrontal CTD incongruent P300 latency and alcohol use in CON (r=0.604; p=0.0037).

Conclusion: The P300 amplitude was attenuated within the frontal-parietal regions for SCZ and frontal regions for MPD, indicating impaired cognitive functioning within the psychotic disorders. This result is in line with current literature showing attenuated P300 amplitude in SCZ. Correlates were found between methamphetamine use for the frontal CPT and CTD P300 amplitude and latency, indicating a reduction in attention and cognitive control in SCZ and MPD. Lastly, methamphetamine affected an individual's ability to focus. Further studies are needed to understand the mechanisms underlying attention in MPD and whether methamphetamine affects cognitive function long-term.

5.1 Introduction

Methamphetamine use disorder has previously been shown to have cognitive deficits as a result of chronic methamphetamine use (T. Chen et al., 2020). When comparing current literature, conflicting results were reported for cognitive impairments in methamphetamine-induced psychotic disorder (MPD) and schizophrenia (SCZ), a mental disorder which presents with severe visual processing deficits (A. Martinez et al., 2015). Executive functioning, attention and working memory were found to be less severe in MPD compared to SCZ (Ezzatpanah et al., 2014). Attention is reported as a psychological process which includes detecting and orienting to stimuli, executive functioning and alertness (Posner & Petersen, 1990). Attention mechanisms are assigned to the frontal and parietal regions of the brain (Lückmann et al., 2014), and any structural changes within those regions may suggest cognitive impairment (Qiu, Tang, Chan, Sun, & He, 2014). Electroencephalography (EEG) can be used to assess attention and cognitive performance through the extraction of event-related potential waveforms (ERP) (Sarter et al., 2001; Villano et al., 2017).

The P300 ERP is thought to represent cortical updating processes (Sur & Sinha, 2009) and is said to be a cognitive ERP (Dias et al., 2011). The P300 ERP waveform is a large-amplitude, positive deflection that occurs approximately 300 msec after a response is made during a task. The P300 waveform has been studied in a variety of visual and auditory tasks in healthy control and individuals with various mental disabilities (Ethridge et al., 2015). The P300 has been widely studied in SCZ, where interesting findings about cortical processing within the affected

individuals have been revealed (Oribe et al., 2013; Roth, Roesch-Ely, Bender, Weisbrod, & Kaiser, 2007). Roth and colleagues found increased P300 ERP latency variability in the frontal midline area and an increase in P300 ERP amplitude in the parietal midline area. Their results support the concept of increased cortical activity from frontal to parietal regions (Roth et al., 2007). Oribe and colleagues investigated the differences in prodromal phase SCZ and SCZ compared to CON, where they found reduced P300 ERP amplitudes and delayed P300 latencies in prodromal phase SCZ and SCZ compared to CON. Further Oribe and colleagues noted an association between decreased P300 amplitude and an increase in severity of positive symptoms in prodromal phase SCZ (Oribe et al., 2013). The SCZ P300 waveform is characterised by an attenuated amplitude and delayed latency in response to target stimuli when compared to healthy controls. The attenuated amplitudes are often seen as a result of psychotic and negative symptoms of SCZ (Ethridge et al., 2015). When comparing MPD to SCZ, P300 amplitude was found to be attenuated in SCZ, however, no P300 latency differences were found. This difference in P300 amplitude between SCZ and MPD is likely linked to differences in the neural pathology of each psychotic disorder (Chun et al., 2013; Turetsky et al., 2007). The results provided for P300 abnormalities are useful in understanding cortical processing and disease risk in SCZ and many other psychiatric disorders.

Attempts to understand the underlying mechanisms of cognitive dysfunction in psychotic disorders are continual in the clinical research setting and by use of animal models (Emilien et al., 1999; Harvey, 2011; Weiss et al., 2002). Sadly, cognitive dysfunction in psychotic illnesses is not treated with current medication regimes (Featherstone et al., 2007). Duration of antipsychotic treatment and high doses of antipsychotic medication has been shown to aid in the decline of cognitive function (Rehse et al., 2016), however, this was more apparent with the use of first-generation antipsychotics versus second-generation antipsychotics (Hill et al., 2010). With second-generation antipsychotics, the dosage of the antipsychotic medication was lower and was more efficient in treating negative symptoms and improving cognitive impairment (Sampaio et al., 2017). The improvement in cognitive functioning with the use of second-generation antipsychotics, specifically olanzapine and risperidone (Weickert & Goldberg, 2005), was reported in patients diagnosed with SCZ (Weiss et al., 2002). Most patients who are receiving managed treatment can live productive life without significant cognitive impairment (Harvey, 2011).

Frontal cortex damage including lesions of the parietal area can result in decreases in the correct number of responses and increased reaction time (Rueckert & Grafman, 1996, 1998; Sarter et

al., 2001). Patients with legions in the frontal lobes were found to have increased reaction time (RT) and more incorrect responses than CON (Rueckert & Grafman, 1996). Furthermore, patients with parietal legions had increased RT and more incorrect responses compared to CON (Rueckert & Grafman, 1998). Investigations into the effects of medication on cognition have voiced contradictory results. Some studies have found first-generation antipsychotics to have negative effects on cognition in SCZ patients using medication and those who were not using medication (Rehse et al., 2016). However, few studies have reported the neural circuitry involved in attention, especially within MPD (Knudsen, 2014).

As described above, the ability of SCZ to maintain attention during a cognitive task has previously been studied. However, studies on attention networks in MPD and SCZ are limited. Therefore, in this study we aimed to investigate attention networks, with two cognitive tasks; the continuous performance task (CPT) and the cued target detection task (CTD). With this study, we aim to determine electrophysiological differences between SCZ, MPD and CON, and, to evaluate whether the CPT distractor (trick S) influences the overall electrophysiological response to the target. In this study, we investigated the associations present within the P300 ERP waveform and the population characteristics (i.e., demographics, medication, methamphetamine use, etc) to identify the relationships that are apparent across study groups and determine whether there are unique associations between SCZ and MPD. This will enhance our neurobiological understanding of these disorders, and potentially distinguish neural circuitry activation signatures which are unique to psychotic disorders.

5.2 Method

5.2.1 Research participants

104 South African individuals, between the ages of 20 and 45 years, participated in this study: 38 with SCZ (8 females/30 males), 31 with MPD (7 females/24 males), and 35 healthy controls (CON: 15 females/20 males). The study was approved by the Health Sciences Research Ethics Committee, at the University of Cape Town (HREC Ref. No.: 479/2019). Western Cape Provincial and Hospital approval was also obtained. All research activities were conducted in accordance with the Declaration of Helsinki. All research participants provided voluntary informed consent.

Participants visited the laboratory twice. The first visit included the provision of informed consent and an assessment clinical interview. All participants underwent a Structured Clinical Interview for Diagnostic Systematic Manual- IV (SCID-DSM-IV), with modifications to

include changes made in DSM-5. Control participants were excluded if there was a history of psychotic symptoms or a family history of psychotic disorder. Participants with a psychotic disorder were excluded if they did not meet the diagnostic criteria for the study conditions: for example, participants with schizoaffective disorder were excluded. Participants were also excluded if they were younger than 19 years or older than 40 years, had general medical conditions that required prescription medications, had an apparent learning disability, had major brain trauma/surgery, had any history of cardiovascular insult, individual or family history of epilepsy, medical implants or any metal within their person, for example, shrapnel.

Female participants were excluded if they were pregnant or lactating. Patients with SCZ were excluded if any of their episodes were considered to be related to the use of a substance. MPD included psychotic symptoms with onset during methamphetamine intoxication or withdrawal and did not persist beyond 1 month since the last use of methamphetamine, or evidence of an underlying 'primary' psychotic disorder not related to the use of methamphetamine. Evidence that the symptoms are better accounted for by a psychotic disorder that is not methamphetamine-induced included the following: the symptoms precede the onset of the methamphetamine use; the symptoms persist for a substantial period of time after the cessation of acute withdrawal or severe intoxication, or are substantially in excess of what would be expected given the amount of methamphetamine used or the duration of use; or there is other evidence that suggests the existence of an independent non-MPD (e.g. a history of recurrent non-methamphetamine- related episodes). Patients with MPD were excluded if it was unclear if methamphetamine was causal to their symptoms or diagnosis, and if any of their psychotic episodes may have been related to another substance of abuse.

5.2.2 Study design

The second visit included a full morning of brain imaging. All EEGs were performed between 09h00-11h00, on a weekday. All clinical scales were performed on the same day and after the morning of brain imaging by trained clinical personnel.

Clinical rating scales included the Positive and Negative Syndrome Scale (PANSS); Calgary Depression Scale for Schizophrenia; Hamilton Rating Scale for Depression. Chlorpromazine equivalents were calculated from current medication regimes. Drug use history, nicotine, alcohol and methamphetamine were recorded using the Kreek-McHugh-Schluger-Kellogg scale (KMSK).

5.2.3 Electroencephalography

EEG recording of REO and REC was undertaken using a simple EEG montage that included prefrontal (Fp1 and Fp2), frontal (F3 and F4), central (C3 and C4), parietal (P3 and P4) and occipital (O1 and O2) electrodes. Standard 10/20 caps (Electro-Cap International, Inc.) were used, of either medium or large size depending on the head circumference of the participant. Participants were grounded peripherally, linked earlobe reference was applied, and electrooculography (EOG) was recorded. The EEG system used was the Biopac MP150 system with 100 C EEG amplifiers and an EOG amplifier (Biopac Systems, Inc.). Digital EEG data and analogue data, from E-prime, were collected via the MP150 system, with a sampling rate of 500Hz, and were visualised in real-time using Acq-Knowledge 4.1 (Biopac Systems, Inc.).

For EEG data processing, data were first eye blink corrected and movement corrected (EOG), using automated ICA EOG correction in Acqknowledge 4.1 (Biopac Systems, Inc.), and then bandpass filtered 0.1–30Hz and Fourier transformed, using an in-house Matlab GUI, to accommodate differences in participant electrical brain activity conduction. Relative (%) frequency bands power activity was extracted: delta (0.1–4.0Hz), theta (4–7Hz), alpha (7–14Hz) and beta (15–30Hz).

Continuous performance task

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 are presented with 60 trials with three consecutive S's, the presentation of the third S requires a behavioural response. In addition, 40 single S's or trick S's are embedded in the task with 300 inter-stimuli letters. The trick stimulus was presented to distract the participant from the presentation of the three consecutive S's. The task contains 20 letters of the alphabet and excluded the vowels, A, E, I, O, and U as well as the letter X. Each letter was presented for 500msec with a 100 msec inter-stimulus interval before the next stimulus. However, the participant can shorten the presentation of the third S if a response is given before the 500msec time limit. Once the task was complete, the participant was asked to relax. The mental effort scale was handed to the participant for them to mark how much effort was applied to conduct the task. The behavioural data collected, were extracted using E-prime and were cross-checked with the digital inputs to an EEG data file Acknowledge

4.1 (Biopac Systems, Inc.). The behavioural data extracted included the number of correct responses, response time duration, errors of omission and commission.

Cued-target detection task

The cued target detection task (CTD) focuses on assessing attention, more specifically divergent attention. The CTD requires participants to focus on a solid grey circle in the centre of the computer screen. An outline of a grey rectangle was positioned on either side of the central cue, which remains throughout the cognitive task. The participant is required to respond to the presentation of a square within either of the rectangles. For this task, there are four conditions: (1) congruent cue and stimulus presentation; (2) incongruent cue and stimulus presentation; (3) double cue and stimulus presentation; and (4) no cue and stimulus presentation. The cues are presented for 500 msec and the stimulus is presented for 500 msec. The inter-stimulus interval is variable throughout the task, with durations of 500, 1000, or 1500 msec. The CTD has 64 congruent stimuli; 16 incongruent stimuli; 16 double-cueing stimuli; and 16 no-cue stimuli. The ERP waveform windows we are expecting to see due to their link with attention are the P100, P150, N170 and P300. Behaviourally, the reaction time, correct detection, omission errors and commission errors will be extracted and analysed.

5.2.4 Statistical analysis

Statistical analysis was conducted using Statistica (Dell, 2016). To determine group differences for the P300 ERP waveform in cognitive tasks (CPT and CTD) an analysis was conducted for three groups (CON, SCZ and MPD). For correlation analysis, the demographics (age on the day of testing, duration at school, tertiary education, and total years of education), 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, duration of illness, drug use (methamphetamine, alcohol, tobacco, cannabis), and medication use (chlorpromazine equivalent dose) were included.

An analysis of distribution for each variable, using the 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 between-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 ($p<0.05$). Where

appropriate, according to the data distribution, correlation analysis was performed using Pearson's or Spearman's rank order (Rho $\geq \pm 0.6$ and p-value <0.01).

5.3 Results

5.3.1 Participant demographics

A total of one hundred and four individuals, between the ages of 20 and 45 years, participated in this study: thirty-eight participants with a diagnosis of schizophrenia (SCZn=38; 8 females/30 males), thirty-one participants with a diagnosis of methamphetamine-induced psychotic disorder (MPDn=31; 7 females/24 males), as well as thirty-five socio-demographically matched control participants (CONn=35; 15 females/20 males).

5.3.2 Continuous performance task target P300 amplitude event-related potential waveform

Group differences were reported for the CPT target left prefrontal, left central and right frontal electrodes (Fp_1 ($F_{2.100}$=3.82; p=0.025), C_3 ($H_{2.100}$=7.062; p=0.029), F_4 ($H_{2.103}$=7.33; p=0.025)) where MPD P300 amplitude was attenuated compared to CON (Fp_1 p=0.021, C_3 p=0.039). Yet no specific group differences were found post-hoc for the right frontal electrode, **Table 5.1**.

Table 5.1 Continuous performance task target P300 amplitude event-related potential waveform

			Healthy control	Schizophrenia	Methamphetamine-induced psychosis		
			n = 35	n = 38	n = 31		
			15 females/20 males	8 females/30 males	7 females/24 males		
			Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test/ F test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	A	7.78(-4.79-22.21)	7.20(-4.05-22.58)	4.27(-8.55-12.57) *	$F_{2.100}$=3.82; p=0.025	MPD<CON p=0.021
Right prefrontal cortex	**Fp_2**	A	5.28(-2.41-19.29)	7.32(-9.53-56.75)	7.00(-8.22-45.51)	$H_{2.92}$=1.61; p=0.44	-
Left frontal cortex	**F_3**	A	5.43(-1.36-18.68)	4.83(-4.06-18.85)	4.80(-1.51-18.10)	$H_{2.103}$=1.84; p=0.39	-
Right frontal cortex	**F_4**	A	3.94(-0.74-19.34)	2.14(-1.68-10.81)	1.38(-7.08-16.92) %	$H_{2.103}$=7.33; p=0.025	%
Left central cortex	**C_3**	A	5.31(-2.12-20.86)	3.52(-4.51-15.78)	2.69(-1.78-13.67) *	$H_{2.100}$=7.062; p=0.029	MPD<CON p=0.039
Right central cortex	**C_4**	A	6.91(-1.71-22.42)	4.76(-3.80-14.74)	3.80(-4.15-13.31)	$H_{2.103}$=1.71; p=0.42	-
Left parietal cortex	**P_3**	A	2.73(-5.21-14.18)	2.14(-6.83-27.69)	1.35(-4.11-16.72)	$H_{2.103}$=2.94; p=0.22	-
Right frontal cortex	**P_4**	A	6.31(-3.24-16.47)	3.69(-4.71-16.17)	3.50(-16.27-13.98)	$H_{2.103}$=4.68; p=0.095	-
Left occipital cortex	**O_1**	A	4.60(-6.16-15.38)	2.86(-5.96-12.13)	4.21(-11.69-10.81)	$F_{2.100}$=1.35; p=0.26	-
Right occipital cortex	**O_2**	A	4.55(-3.03-15.08)	3.95(-6.38-12.03)	5.49(-11.55-10.29)	$F_{2.100}$=0.83; p=0.43	-

***** *Methamphetamine-induced psychotic disorder (MPD) reported attenuated CPT target P300 amplitude compared to controls (CON) % no significance between groups after post-hoc testing. Non-parametric Kruskal Wallis (H-test) and parametric one-way analysis of variance (F-test), Significance P<0.05.*

5.3.3 Continuous performance task target P300 latency event-related potential waveform

No significant group differences were found for CPT target P300 latency, **Table 5.2**.

Table 5.2 Continuous performance task target P300 latency event-related potential waveform

			Healthy control	Schizophrenia	Methamphetamine-induced psychosis		
			n = 35	n = 38	n = 31		
			15 females/20 males	8 females/30 males	7 females/24 males		
			Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	T	382(200-498)	352(200-498)	380(200-498)	$H_{2.103}$=0.97; p=0.61	-
Right prefrontal cortex	**Fp_2**	T	370(200-498)	348(200-498)	350(200-498)	$H_{2.103}$=0.78; p=0.67	-
Left frontal cortex	**F_3**	T	384(200-498)	310(200-498)	336(200-498)	$H_{2.103}$=3.33; p=0.18	-
Right frontal cortex	**F_4**	T	360(200-498)	346(200-498)	362(200-498)	$H_{2.103}$=0.52; p=0.77	-
Left central cortex	**C_3**	T	364(200-498)	358(200-498)	358(200-498)	$H_{2.100}$=2.85; p=0.86	-
Right central cortex	**C_4**	T	402(200-498)	326(200-498)	376(200-498)	$H_{2.103}$=4.74; p=0.093	-
Left parietal cortex	**P_3**	T	374(300-498)	396(300-498)	392(300-498)	$H_{2.103}$=3.15; p=0.20	-
Right frontal cortex	**P_4**	T	408(300-498)	374(300-498)	364(300-498)	$H_{2.103}$=2.51; p=0.28	-
Left occipital cortex	**O_1**	T	428(300-498)	406(300-498)	400(300-498)	$H_{2.103}$=0.20; p=0.90	-
Right occipital cortex	**O_2**	T	426(300-498)	396(300-498)	386(300-498)	$H_{2.103}$=2.63; p=0.26	-

Non-parametric Kruskal Wallis (H-test), Significance P<0.05.

For SCZ (n=14), duration of methamphetamine use (months) negatively correlated with the CPT target right prefrontal ($Fp_2R_{spearman's(n=14)}$=-0.73; p=0.0029) and positively correlated with the right parietal ($P_4R_{spearman's(n=14)}$=0.77; p=0.0012) P300 latency, **Figure 5.1**. Then, CPT target right prefrontal P300 latency positively correlated with methamphetamine abstinence ($Fp_2R_{spearman's(n=14)}$=0.69; p=0.0056), **Figure 5.2**.

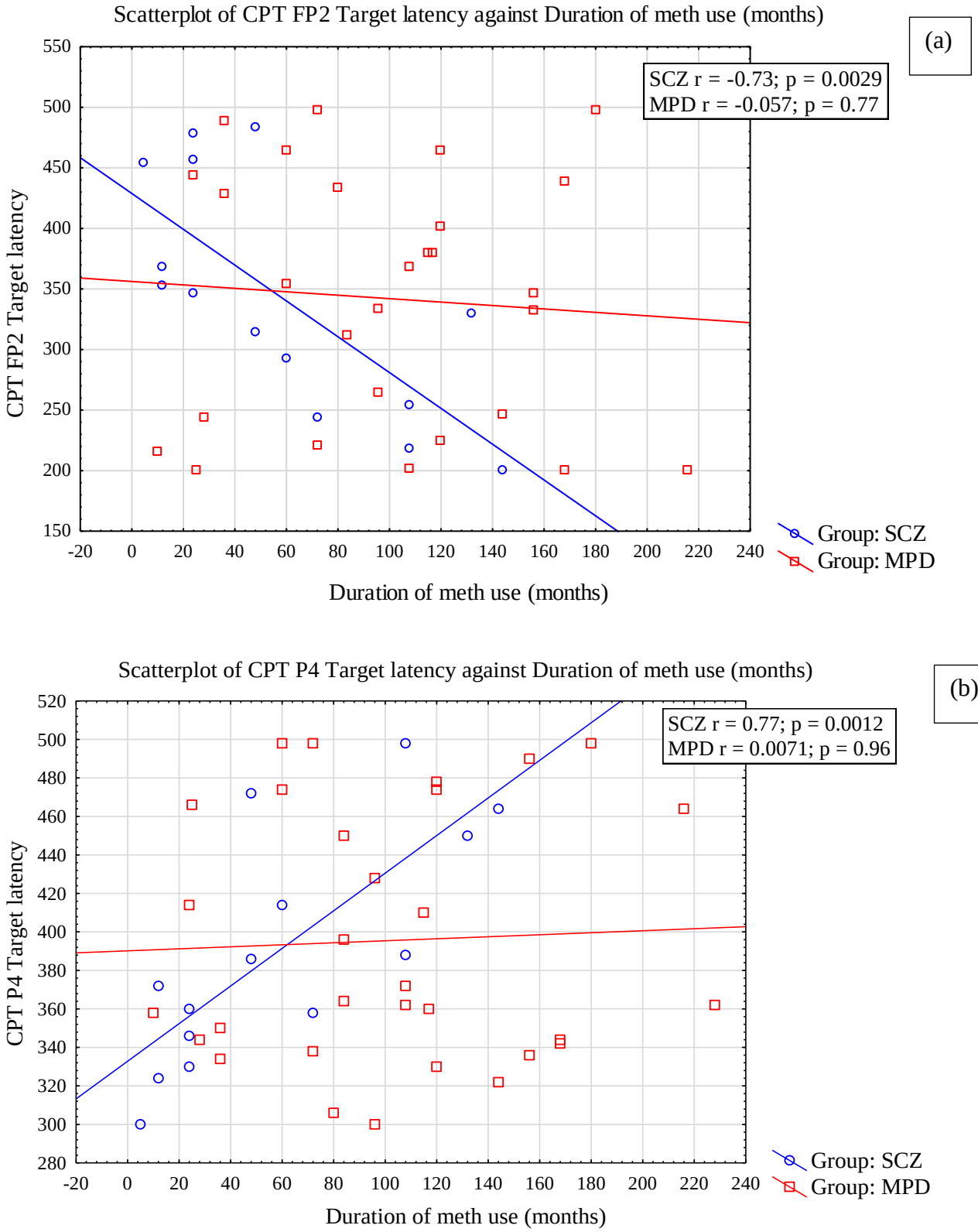


Figure 5.1 Continuous performance task (CPT) target, duration of methamphetamine use (months) **(a)** negatively correlated with the CPT target right prefrontal (Fp_2) and **(b)** positively correlated with the CPT right parietal (P_4) P300 latency. Healthy controls (CON); Schizophrenia (SCZ); Methamphetamine-induced psychotic disorder (MPD). Significance was reported for $p<0.01$ and Rho= $>\pm 0.60$.

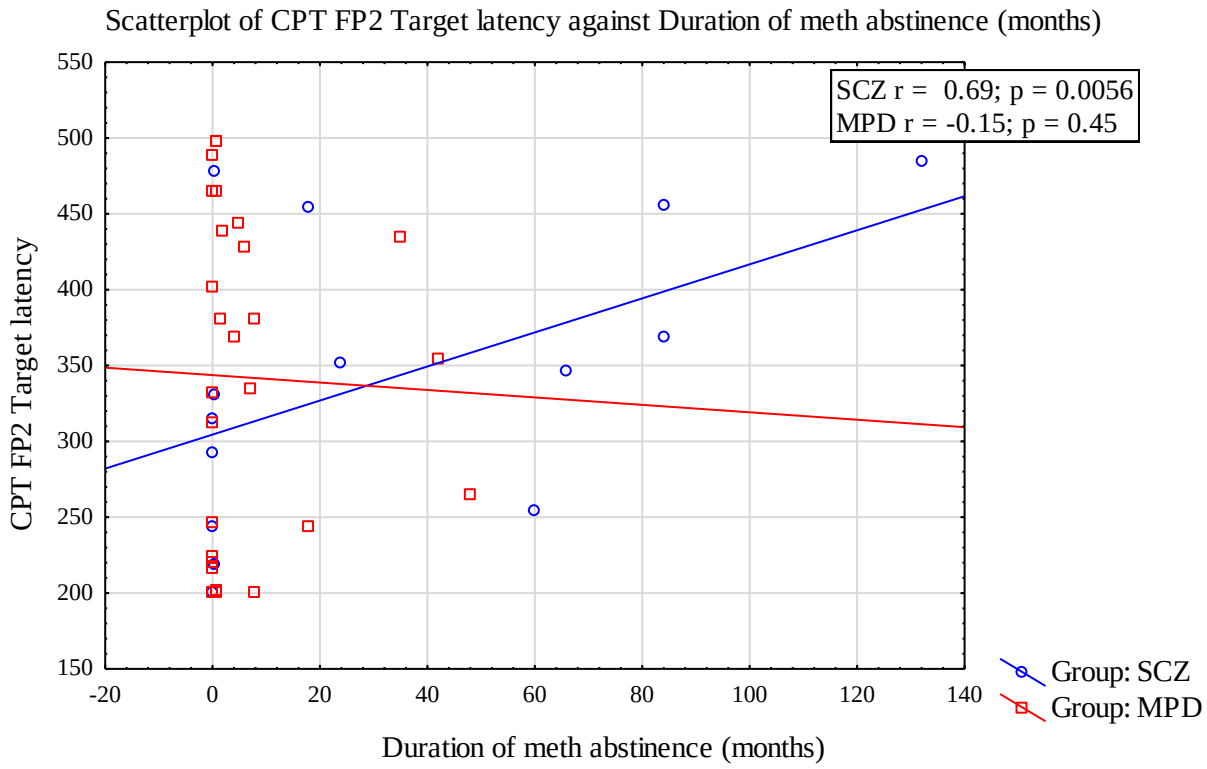


Figure 5.2 Continuous performance task (CPT) target, methamphetamine abstinence positively correlated with the right prefrontal (Fp2) P300 latency. Schizophrenia (SCZ); Methamphetamine-induced psychotic disorder (MPD). Significance was reported for p<0.01 and Rho= >±0.60.

5.3.4 Continuous performance task trick S P300 amplitude event-related potential waveform

No significant group differences were found for the CPT trick S P300 amplitude, **Table 5.3**.

Table 5.3 Continuous performance task trick S P300 amplitude event-related potential waveform

			Healthy control	**Schizophrenia**	**Methamphetamine-induced psychosis**		
			n = 35	n = 38	n = 31		
			15 females/20 males	8 females/30 males	7 females/24 males		
			Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	A	5.32(-2.37-19.03)	4.17(-3.54-21.19)	4.01(-4.64-18.67)	$H_{2.96}$=1.51; p=0.46	-
Right prefrontal cortex	**Fp_2**	A	4.72(0.40-11.70)	3.44(-4.56-32.42)	3.41(0.23-18.65)	$H_{2.73}$=3.26; p=0.19	-
Left frontal cortex	**F_3**	A	4.96(-0.33-21.99)	4.17(-1.90-13.51)	3.41(-3.46-14.09)	$H_{2.96}$=2.51; p=0.28	-
Right frontal cortex	**F_4**	A	2.13(-0.17-13.15)	2.18(-1.85-13.16)	1.41(-0.52-20.40)	$H_{2.99}$=1.68; p=0.43	-
Left central cortex	**C_3**	A	2.52(-0.56-11.09)	3.96(-0.92-11.30)	3.30(0.06-21.26)	$H_{2.89}$=2.64; p=0.26	-
Right central cortex	**C_4**	A	3.74(-0.54-16.65)	3.44(-1.27-15.59)	3.04(-1.88-23.11)	$H_{2.102}$=0.78; p=0.67	-
Left parietal cortex	**P_3**	A	2.06(-0.60-9.32)	2.48(0.21-15.01)	1.88(-0.65-17.01)	$H_{2.94}$=1.84; p=0.39	-
Right frontal cortex	**P_4**	A	4.26(-2.32-15.86)	3.68(-3,01-16.05)	4.20(-0.95-17.82)	$H_{2.99}$=0.13; p=0.93	-
Left occipital cortex	**O_1**	A	3.88(-2.41-14.52)	3.29(-5.26-17.06)	4.02(-0.47-14.66)	$H_{2.103}$=0.027; p=0.98	-
Right occipital cortex	**O_2**	A	4.00(-2.47-17.87)	3.55(-1.91-14.34)	2.72(-3.82-14.17)	$H_{2.103}$=1.70; p=0.42	-

Non-parametric Kruskal Wallis (H-test), Significance P<0.05.

5.3.5 Continuous performance task trick S P300 latency event-related potential waveform

CPT trick S P300 latency reported a group difference for the right frontal and left parietal electrodes (F_4 ($H_{2.99}$=8.76; p=0.012), P_3 ($H_{2.94}$=6.87; p=0.032)) where SCZ P300 latency was delayed compared to CON (F_4 p=0.0092, P_3 p=0.035), **Table 5.4**.

Table 5.4 Continuous performance task trick S P300 latency event-related potential waveform

			Healthy control	**Schizophrenia**	**Methamphetamine-induced psychosis**		
			n = 35	n = 38	n = 31		
			15 females/20 males	8 females/30 males	7 females/24 males		
			Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test/ F test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	T	314(200-498)	309(202-498)	300(210-498)	$H_{2.96}$=0.50; p=0.77	-
Right prefrontal cortex	**Fp_2**	T	322(240-468)	316(200-498)	296(212-4728)	$F_{2.70}$=0.98; p=0.37	-
Left frontal cortex	**F_3**	T	328(200-488)	346(224-498)	318(200-490)	$H_{2.96}$=0.32; p=0.85	-
Right frontal cortex	**F_4**	T	295(214-498)	361(204-498) *	358(224-494)	$H_{2.99}$=8.76; p=0.012	SCZ>CON p=0.0092
Left central cortex	**C_3**	T	345(212-498)	364(226-488)	396(214-496)	$H_{2.89}$=1.70; p=0.42	-
Right central cortex	**C_4**	T	290(202-498)	291(208-498)	336(216-498)	$H_{2.102}$=3.81; p=0.14	-
Left parietal cortex	**P_3**	T	398(306-494)	444(318-494) *	398(300-496)	$H_{2.94}$=6.87; p=0.032	SCZ>CON p=0.035
Right frontal cortex	**P_4**	T	389(300-498)	422(300-498)	366(300-496)	$H_{2.99}$=5.79; p=0.055	-
Left occipital cortex	**O_1**	T	402(300-498)	410(300-496)	422(300-496)	$H_{2.103}$=0.97; p=0.61	-
Right occipital cortex	**O_2**	T	396(300-498)	412(300-498)	418(300-496)	$H_{2.103}$=0.89; p=0.63	-

****** Schizophrenia (SCZ) reported attenuated P300 amplitude during the presentation of the CPT trick S compared to controls (CON). Non-parametric Kruskal Wallis (H-test) and parametric one-way analysis of variance (F-test), Significance P<0.05.*

5.3.6 Cued target detection task congruent P300 amplitude event-related potential waveform

CTD congruent P300 amplitude reported a group difference for the left frontal electrodes (F_3 ($H_{2.90}$=6.49; p=0.038)) where SCZ P300 amplitude was increased compared to CON (F_3 p=0.033), **Table 5.5.**

Table 5.5 Cued target detection task congruent P300 amplitude event-related potential waveform

			Healthy control	Schizophrenia	Methamphetamine-induced psychosis		
			n = 35	n = 38	n = 31		
			15 females/20 males	8 females/30 males	7 females/24 males		
			Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	A	2.55(-5.63-11.91)	4.45(-0.99-12.92)	1.91(-4.26-16,43)	$H_{2.82}$=5.32; p=0.069	-
Right prefrontal cortex	**Fp_2**	A	3.11(-3.89-13.80)	4.14(-0.79-23.29)	4.20(-1.95-14.46)	$H_{2.67}$=1.38; p=0.50	-
Left frontal cortex	**F_3**	A	0.71(-3.44-21.13)	2.91(-0.94-17.56) *	2.49(-2.00-9.59)	$H_{2.90}$=6.49; p=0.038	SCZ>CON p=0.033
Right frontal cortex	**F_4**	A	2.04(-2.00-14.73)	2.19(-0.17-11.70)	2.89(-1.14-7.87)	$H_{2.76}$=1.11; p=0.57	-
Left central cortex	**C_3**	A	1.34(-5.80-8.88)	2.67(-1.08-12.99)	2.76(-1.52-11.70)	$H_{2.81}$=4.71; p=0.094	-
Right central cortex	**C_4**	A	2.68(-3.20-13.66)	2.98(-1.99-21.45)	2.77(-3.24-14.54)	$H_{2.87}$=0.28; p=0.86	-
Left parietal cortex	**P_3**	A	3.32(-0.58-13.61)	2.84(-0.26-15.07)	3.24(-1.59-8.65)	$H_{2.83}$=0.98; p=0.61	-
Right frontal cortex	**P_4**	A	3.55(-3,21-8.44)	3.31(-2.60-17.72)	4.44(-0.78-11.28)	$H_{2.86}$=1.95; p=0.37	-
Left occipital cortex	**O_1**	A	54.15(-0,18-19.59)	4.63(-1.31-19.31)	3.60(0.25-12.51)	$H_{2.93}$=1.32; p=0.51	-
Right occipital cortex	**O_2**	A	4,10(-0.19-9.23)	4.65(-1.12-20.11)	4.06(-0.94-12.22)	$H_{2.93}$=1.85; p=0.39	-

***** *Schizophrenia (SCZ) reported increased CTD congruent P300 amplitude compared to healthy controls (CON). Non-parametric Kruskal Wallis (H-test) and parametric one-way analysis of variance (F-test), Significance P<0.05.*

For MPD (n=19), chlorpromazine equivalent negatively correlated with the right frontal CTD congruent P300 amplitude ($F_4R_{Spearman's(n=19)}$=-0.81, p=0.000021), **Figure 5.3**.

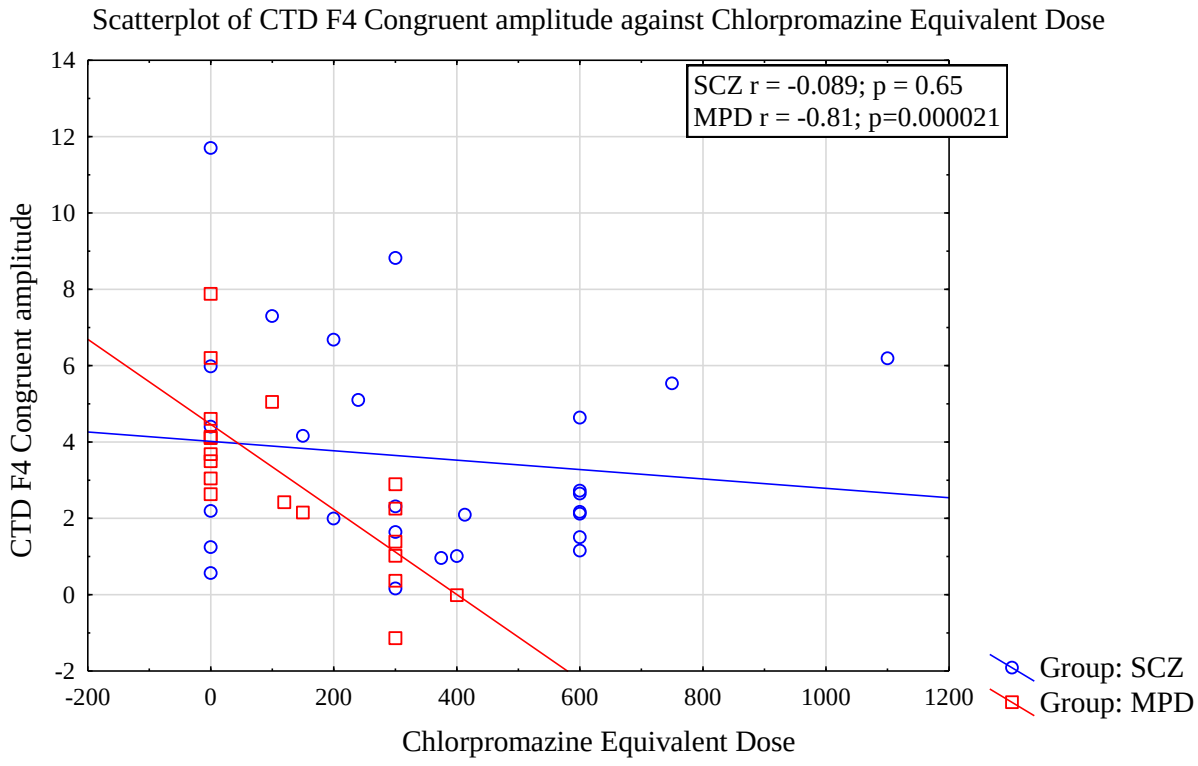


Figure 5.3 Cued target detection task (CTD) congruent P300 amplitude left prefrontal (Fp_1) electrode for MPD negatively correlated with the chlorpromazine equivalent dose. Healthy controls (CON); Schizophrenia (SCZ); Methamphetamine-induced psychotic disorder (MPD). Significance was reported for p<0.01 and Rho= >±0.60.

5.3.7 Cued target detection task congruent P300 latency event-related potential waveform

No significant group differences were found for CTD congruent P300 latency, **Table 5.6**.

Table 5.6 Cued target detection task congruent P300 latency event-related potential waveform

			Healthy control n = 35 15 females/20 males	Schizophrenia n = 38 8 females/30 males	Methamphetamine-induced psychosis n = 31 7 females/24 males		
			Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	T	440(400-698)	458(402-698)	458(400-698)	$H_{2.82}$=1.53; p=0.46	-
Right prefrontal cortex	**Fp_2**	T	478(400-698)	476(400-698)	522(400-698)	$H_{2.67}$=0.14; p=0.92	-
Left frontal cortex	**F_3**	T	470(400-698)	484(400-698)	478(406-698)	$H_{2.90}$=0.21; p=0.89	-
Right frontal cortex	**F_4**	T	591(400-698)	558(400-698)	576(402-698)	$H_{2.76}$=1.28; p=0.52	-
Left central cortex	**C_3**	T	545(418-698)	517(422-698)	494(430-698)	$H_{2.81}$=1.76; p=0.41	-
Right central cortex	**C_4**	T	514(416-698)	528(400-696)	516(414-698)	$H_{2.87}$=0.82; p=0.66	-
Left parietal cortex	**P_3**	T	558(492-698)	564(460-684)	557(432-698)	$H_{2.83}$=1.64; p=0.44	-
Right frontal cortex	**P_4**	T	536(400-698)	488(442-692)	515(416-698)	$H_{2.86}$=1.54; p=0.46	-
Left occipital cortex	**O_1**	T	526(400-698)	484(410-698)	502(400-698)	$H_{2.93}$=2.94; p=0.22	-
Right occipital cortex	**O_2**	T	528(400-698)	478(400-698)	498(400-698)	$H_{2.93}$=3.15; p=0.20	-

Non-parametric Kruskal Wallis (H-test) and parametric one-way analysis of variance (F-test), Significance P<0.05.

5.3.8 Cued target detection task double cue P300 amplitude event-related potential waveform

CTD double cue P300 amplitude reported a group difference for the left frontal and left and right central electrodes (F_3 ($F_{2.90}$=6.49; p=0.038), C_3 ($F_{2.90}$=6.49; p=0.038), C_4 ($F_{2.90}$=6.49; p=0.038)) where CON P300 amplitude was increased compared to SCZ (F_3 p=0.015) and MPD (C_3 p=0.00043, C_4 p=0.031), **Table 5.7.**

Table 5.7 Cued target detection task double cue P300 amplitude event-related potential waveform

			Healthy control n = 35 15 females/20 males	Schizophrenia n = 38 8 females/30 males	Methamphetamine induced psychosis n = 31 7 females/24 males		
			Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test/ F test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	A	4.17(-2.31-12.23)	7.71(-1.28-25.41)	5.26(-3.38-17.65)	$H_{2.80}$=5.14; p=0.076	-
Right prefrontal cortex	**Fp_2**	A	6.28(-0.59-14.01)	11.12(-10.38-24.47)	8.67(-1.18-21.42)	$F_{2.66}$=0.95; p=0.39	-
Left frontal cortex	**F_3**	A	3.00(-4.23-11.30)	6.44(-2.05-24.40) *	6.56(-10.46-20.93)	$H_{2.79}$=8.30; p=0.015	SCZ<CON p=0.015
Right frontal cortex	**F_4**	A	3.51(0.86-7.96)	3,93(-4.51-31.49)	4.50(-1.80-17.17)	$H_{2.84}$=0.87; p=0.64	-
Left central cortex	**C_3**	A	2.51(-1.50-9.53)	4.10(-0.39-25.10)	6.66(-5.65-19.44) #	$H_{2.86}$=14.56; p=0.0007	MPD<CON p=0.00043
Right central cortex	**C_4**	A	3.96(-2.27-13.37)	4.96(-3.74-16.63)	6.18(-4.35-21.05) #	$H_{2.87}$=6.64; p=0.036	MPD<CON p=0.031
Left parietal cortex	**P_3**	A	4.85(-0.32-12.80)	4.53(-2.06-11.96)	5.42(0.16-15.34)	$H_{2.90}$=1.47; p=0.47	-
Right frontal cortex	**P_4**	A	6.48(-1.42-15.00)	8.19(-0.77-19.04)	6.90(0.88-18.29)	$H_{2.85}$=2.62; p=0.26	-
Left occipital cortex	**O_1**	A	6.19(-1.87-13.28)	8,20(-4.63-38-53)	7.38(-0.59-18.55)	$H_{2.90}$=2.89; p=0.23	-
Right occipital cortex	**O_2**	A	4,91(-1.80-46.99)	6.96(-3.72-47.60)	7.86(-5.09-19.24)	$H_{2.94}$=2.37; p=0.305	-

***** *Healthy control (CON) reported increased CTD double cue P300 amplitude compared to Schizophrenia (SCZ) # CON reported increased CTD double cue P300 amplitude compared to Methamphetamine-induced psychotic disorder (MPD). Non-parametric Kruskal Wallis (H-test) and parametric one-way analysis of variance (F-test), Significance P<0.05.*

5.3.9 Cued target detection task double cue P300 latency event-related potential waveform

No significant group differences were found for CTD double cue P300 latency, **Table 5.8**.

Table 5.8 Cued target detection task double cue P300 latency event-related potential waveform

			Healthy control	**Schizophrenia**	**Methamphetamine-induced psychosis**		
			n = 35	n = 38	n = 31		
			15 females/20 males	8 females/30 males	7 females/24 males		
			Median (min-max)	**Median (min-max)**	**Median (min-max)**	**Kruskal-Wallis (H test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	T	513(400-698)	517(400-698)	467(400-698)	$H_{2.80}$=0.44; p=0.79	-
Right prefrontal cortex	**Fp_2**	T	544(408-698)	504(400-698)	512(436-698)	$H_{2.69}$=2.74; p=0.25	-
Left frontal cortex	**F_3**	T	498(420-698)	528(400-698)	519(400-698)	$H_{2.79}$=1.26; p=0.52	-
Right frontal cortex	**F_4**	T	562(418-698)	540(400-698)	540(400-698)	$H_{2.84}$=1.33; p=0.51	-
Left central cortex	**C_3**	T	528(426-698)	493(400-698)	534(400-698)	$H_{2.86}$=2.40; p=0.303	-
Right central cortex	**C_4**	T	530(434-698)	526(402-698)	526(412-698)	$H_{2.87}$=0.066; p=0.96	-
Left parietal cortex	**P_3**	T	612(436-698)	572(400-698)	570(400-698)	$H_{2.90}$=4.00; p=0.13	-
Right frontal cortex	**P_4**	T	522(440-698)	570(400-698)	527(414-698)	$H_{2.85}$=1.76; p=0.41	-
Left occipital cortex	**O_1**	T	526(400-698)	530(400-698)	559(416-692)	$H_{2.90}$=0.11; p=0.94	-
Right occipital cortex	**O_2**	T	519(400-678)	534(400-698)	500(400-696)	$H_{2.90}$=3.66; p=0.16	-

Non-parametric Kruskal Wallis (H-test), Significance P<0.05.

5.3.10 Cued target detection task incongruent P300 amplitude event-related potential waveform

CTD incongruent left prefrontal (Fp_1 ($H_{2.86}$=8.45; p=0.014) reported a group difference where SCZ P300 amplitude was increased compared to CON (Fp_1 p=0.011), **Table 5.9**.

Table 5.9 Cued target detection task incongruent P300 amplitude event-related potential waveform

			Healthy control	**Schizophrenia**	**Methamphetamine -induced psychosis**		
			n = 35	n = 38	n = 31		
			15 females/20 males	8 females/30 males	7 females/24 males		
			Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test/ F test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	A	3.07(-0.53-13.23)	7.52(-1.61-24.80) *	5.43(-9.60-23.48)	$H_{2.86}$=8.45; p=0.014	SCZ>CON p=0.011
Right prefrontal cortex	**Fp_2**	A	5.60(-0.04-28.48)	6.81(-3.30-29.62)	4.61(-0.49-28.61)	$H_{2.62}$=2.78; p=0.24	-
Left frontal cortex	**F_3**	A	3.41(-3.56-9.54)	5.42(-2.75-26.42)	5.76(-3.49-14.01)	$H_{2.75}$=3.74; p=0.15	-
Right frontal cortex	**F_4**	A	4.00(0.02-8.75)	3,57(-2.65-13.75)	3.11(-0.08-10.30)	$H_{2.77}$=1.18; p=0.55	-
Left central cortex	**C_3**	A	3.68(-2.06-16.16)	5,03(-1.28-18.23)	5.07(-1.12-17.25)	$H_{2.86}$=1.14; p=0.48	-
Right central cortex	**C_4**	A	5.33(-5.22-19.89)	6,74(-0.86-20.69)	5.30(0.80-21.57)	$H_{2.87}$=0.58; p=0.74	-
Left parietal cortex	**P_3**	A	3.76(-0.06-18.89)	5.07(-1.84-17.46)	5.02(0.15-19.55)	$H_{2.87}$=2.10; p=0.34	-
Right frontal cortex	**P_4**	A	6.37(-1.37-13.78)	7,64(-1.62-16.71)	6.17(-3.60-18.76)	$F_{2.75}$=1.22; p=0.29	-
Left occipital cortex	**O_1**	A	6.28(-0.34-13.53)	7.18(-1.25-19.78)	5.70(-1.65-15.42)	$H_{2.86}$=2.14; p=0.34	-
Right occipital cortex	**O_2**	A	5.65(-3.52-11.01)	6.57(-2.71-22.00)	4.75(-0.82-18.48)	$H_{2.81}$=3.09; p=0.21	-

***** *Schizophrenia (SCZ) reported greater CTD incongruent P300 amplitude compared to healthy controls (CON). Non-parametric Kruskal Wallis (H-test) and parametric one-way analysis of variance (F-test), Significance P<0.05.*

MPD tobacco lifetime scores positively correlated with the right frontal CTD incongruent P300 amplitude ($F_4R_{Spearman's(n=24)}$=0.96; p=0.000067), **Figure 5.4**.

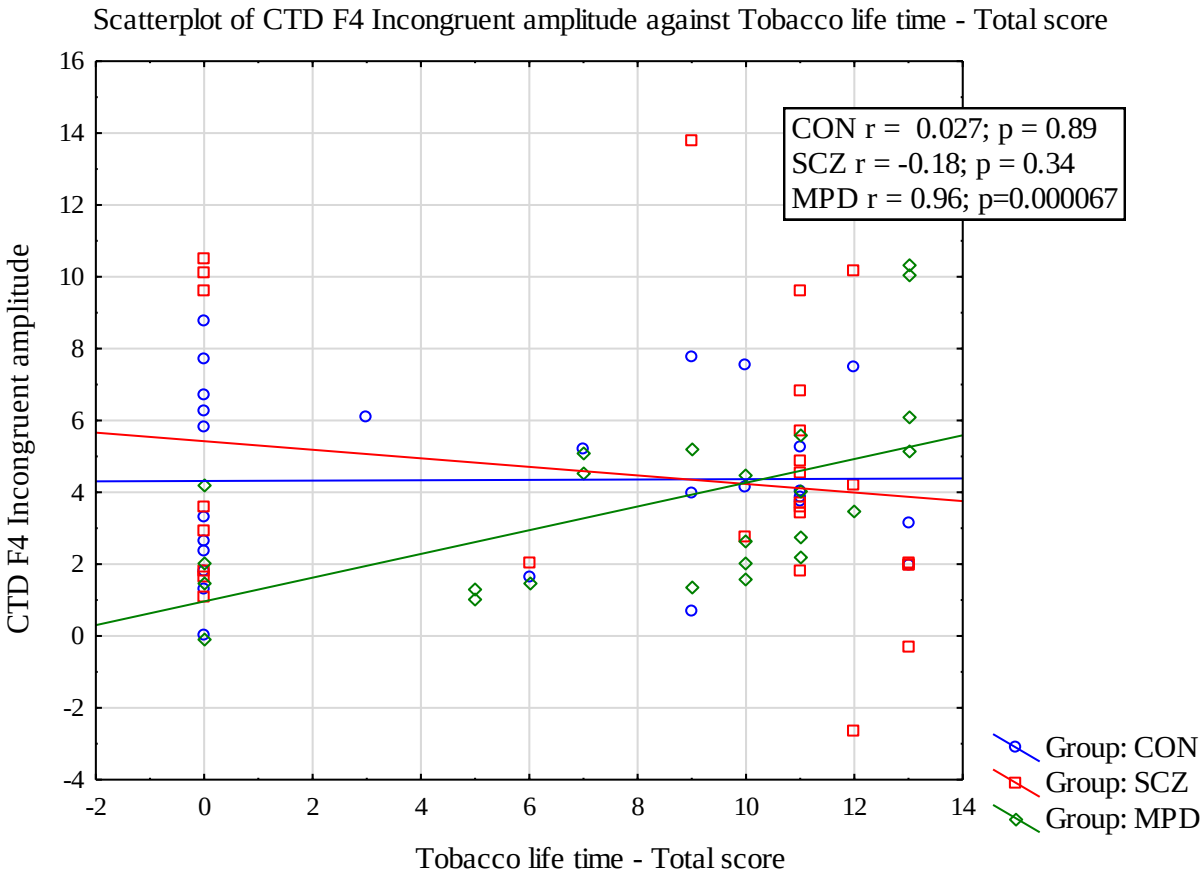


Figure 5.4 Cued target detection task (CTD) relative beta activity for the right frontal (F_4) electrode for MPD positively correlated with the tobacco lifetime score. Healthy controls (CON); Schizophrenia (SCZ); Methamphetamine-induced psychotic disorder (MPD) Significance was reported for p<0.01 and Rho= >±0.60.

5.3.11 Cued target detection task incongruent P300 latency event-related potential waveform

CTD incongruent left parietal (P_3 ($H_{2.87}$=8.065; p=0.017) reported a group difference where SCZ P300 latency was shorter compared to CON (P_3 p=0.022), **Table 5.10**.

Table 5.10 Cued target detection task incongruent P300 latency event-related potential waveform

			Healthy control	**Schizophrenia**	**Methamphetamine-induced psychosis**		
			n = 35	n = 38	n = 31		
			15 females/20 males	8 females/30 males	7 females/24 males		
			Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test/ F test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	T	490(400-684)	498(406-700)	502(402-686)	$H_{2.85}$=0.83; p=0.65	-
Right prefrontal cortex	**Fp_2**	T	476(402-696)	498(400-674)	468(400-632)	$H_{2.62}$=1.73; p=0.42	-
Left frontal cortex	**F_3**	T	536(404-654)	529(410-700)	522(406-678)	$H_{2.75}$=1.18; p=0.55	-
Right frontal cortex	**F_4**	T	592(400-700)	604(426-700)	556(434-700)	$H_{2.77}$=3.11; p=0.21	-
Left central cortex	**C_3**	T	526(408-700)	540(400-700)	485(400-672)	$H_{2.86}$=1.41; p=0.49	-
Right central cortex	**C_4**	T	544(412-700)	502(400-700)	543(444-700)	$H_{2.87}$=5.63; p=0.059	-
Left parietal cortex	**P_3**	T	628(392-700)	573(402-700) *	576(406-696)	$H_{2.87}$=8.065; p=0.017	SCZ<CON p=0.022
Right frontal cortex	**P_4**	T	542(418-700)	543(424-698)	504(400-676)	$H_{2.78}$=3.55; p=0.16	-
Left occipital cortex	**O_1**	T	529(400-700)	542(410--700)	500(402-680)	$H_{2.86}$=1.05; p=0.58	-
Right occipital cortex	**O_2**	T	522(400-700)	524(400-700)	538(422-700)	$F_{2.78}$=0.49; p=0.60	-

***** *Schizophrenia (SCZ) reported a shorter CTD incongruent P300 latency compared to controls (CON). Non-parametric Kruskal Wallis (H-test) and parametric one-way analysis of variance (F-test), Significance P<0.05*.

CON alcohol lifetime scores positively correlated with the right prefrontal CTD incongruent P300 latency ($Fp_2R_{Spearman's(n=21)}$=0.604; p=0.0037), **Figure 5.5**.

SCZ onset of methamphetamine use negatively correlated with the left parietal CTD incongruent P300 latency ($P_3R_{Spearman's(n=8)}$=-0.87; p=0.00084), **Figure 5.6**.

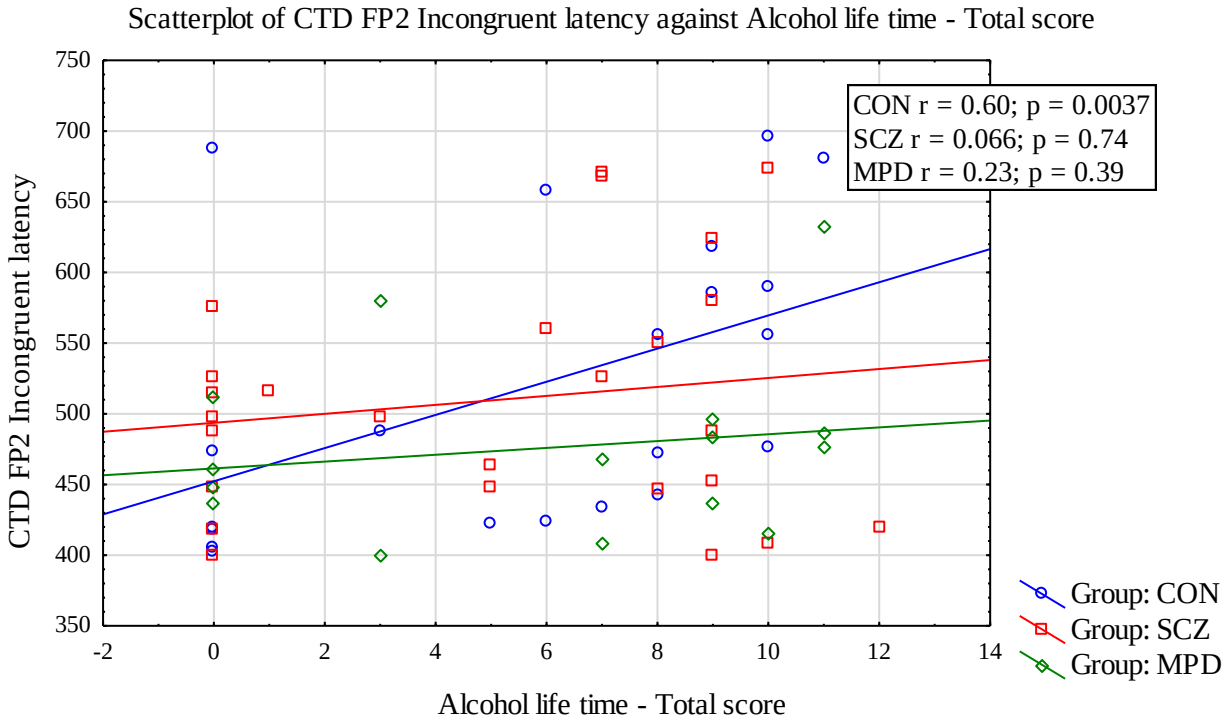


Figure 5.5 Cued target detection task (CTD) incongruent latency for the right prefrontal (Fp_2) electrode for CON positively correlated with the alcohol lifetime score. Healthy controls (CON); Schizophrenia (SCZ); Methamphetamine-induced psychotic disorder (MPD) Significance was reported for $p<0.01$ and Rho= >±0.60.

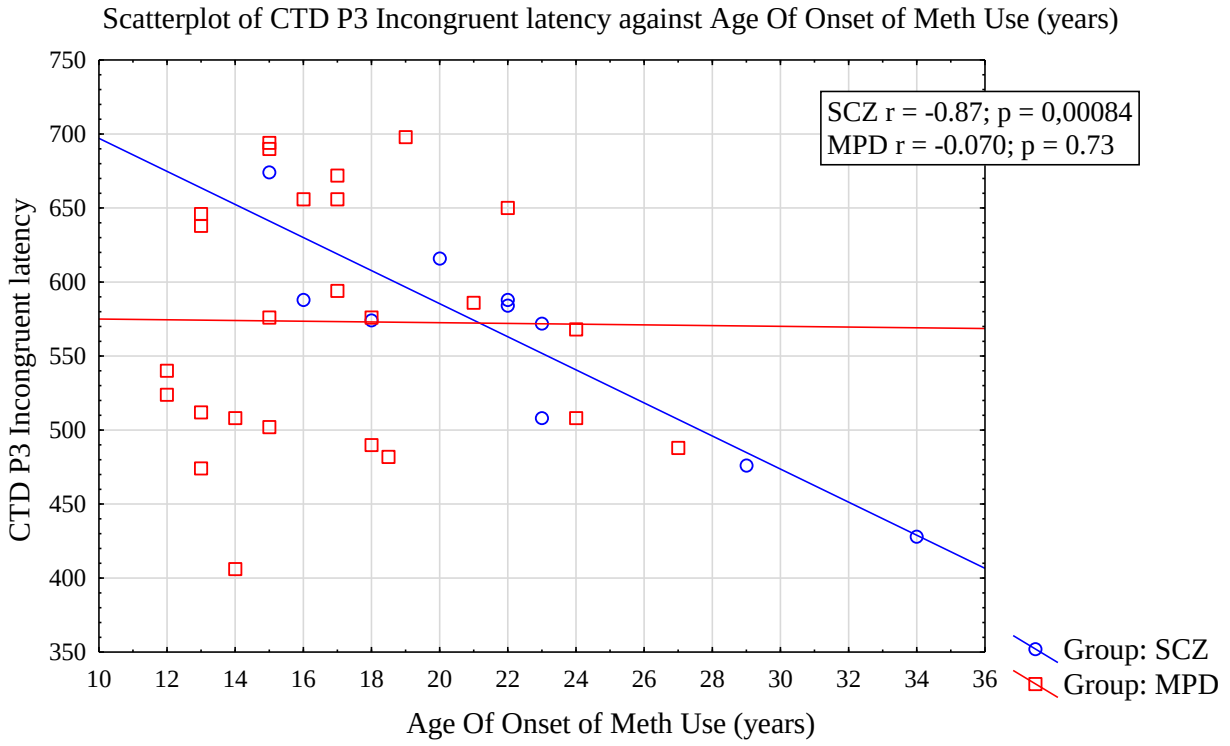


Figure 5.6 Cued target detection task (CTD) incongruent left parietal (P_4) P300 latency negatively correlated with the age of onset of methamphetamine use (years). Schizophrenia (SCZ); Methamphetamine-induced psychotic disorder (MPD). Significance was reported for $p<0.01$ and Rho= >±0.60.

5.3.12 Cued target detection task no cue P300 amplitude event-related potential waveform

No significant group differences were reported for CTD no cue P300 amplitude, **Table 5.11**.

Table 5.11 Cued target detection task no cue P300 amplitude event-related potential waveform

			Healthy control	**Schizophrenia**	**Methamphetamine-induced psychosis**		
			n = 35	n = 38	n = 31		
			15 females/20 males	8 females/30 males	7 females/24 males		
			Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	A	5.59(-4.79-22.45)	7.72(-4.17-42.63)	6.23(-3.44-25.04)	$H_{2.87}$=1.94; p=0.37	-
Right prefrontal cortex	**Fp_2**	A	7.20(-0.92-26.61	7.74(-5.94-33.23)	4.85(-0.90-28.29)	$H_{2.68}$=1.36; p=0.50	-
Left frontal cortex	**F_3**	A	5.19(-2.75-13.14)	4.55(-1.57-25.52)	5.87(-4.83-16.24)	$H_{2.85}$=0.61; p=0.73	-
Right frontal cortex	**F_4**	A	5.31(0.23-22.74)	5.14(-2.26-14.50)	3.28(0.31-41.36)	$H_{2.70}$=1.36; p=0.50	-
Left central cortex	**C_3**	A	3.98(1.25-18.58)	5,49(-0.46-21.39)	6.50(-3.63-15.71)	$H_{2.80}$=4.29; p=0.11	-
Right central cortex	**C_4**	A	7.10(-4.38-16.18)	5.59(-1.88-26.57)	5.33(-0.42-12.01)	$H_{2.87}$=0.66; p=0.71	-
Left parietal cortex	**P_3**	A	5.85((-1.57-18.21)	5.48(-1.66-16.48)	5.56(-1.78-12.69)	$H_{2.85}$=0.47; p=0.78	-
Right frontal cortex	**P_4**	A	7.11(-1.16-19.95)	5.54(-8.42-39.86)	6,20(0.26-17.48)	$H_{2.86}$=0.46; p=0.79	-
Left occipital cortex	**O_1**	A	6.21(0.59-19.60)	6.87(-1.51-41.25)	7.53(-0.36-17.45)	$H_{2.88}$=0.097; p=0.95	-
Right occipital cortex	**O_2**	A	5.86(-0.85-14.61)	7.79(-7.11-50.30)	5.47(-1,80-16.24)	$H_{2.85}$=1.50; p=0.47	-

Non-parametric Kruskal Wallis (H-test), Significance P<0.05.

CON Calgary depression rating scale (CDS) positively correlated with the left central CTD no cue P300 amplitude ($C_3R_{Spearman's(n=24)}$=0.603; p=0.0017), **Figure 5.7**.

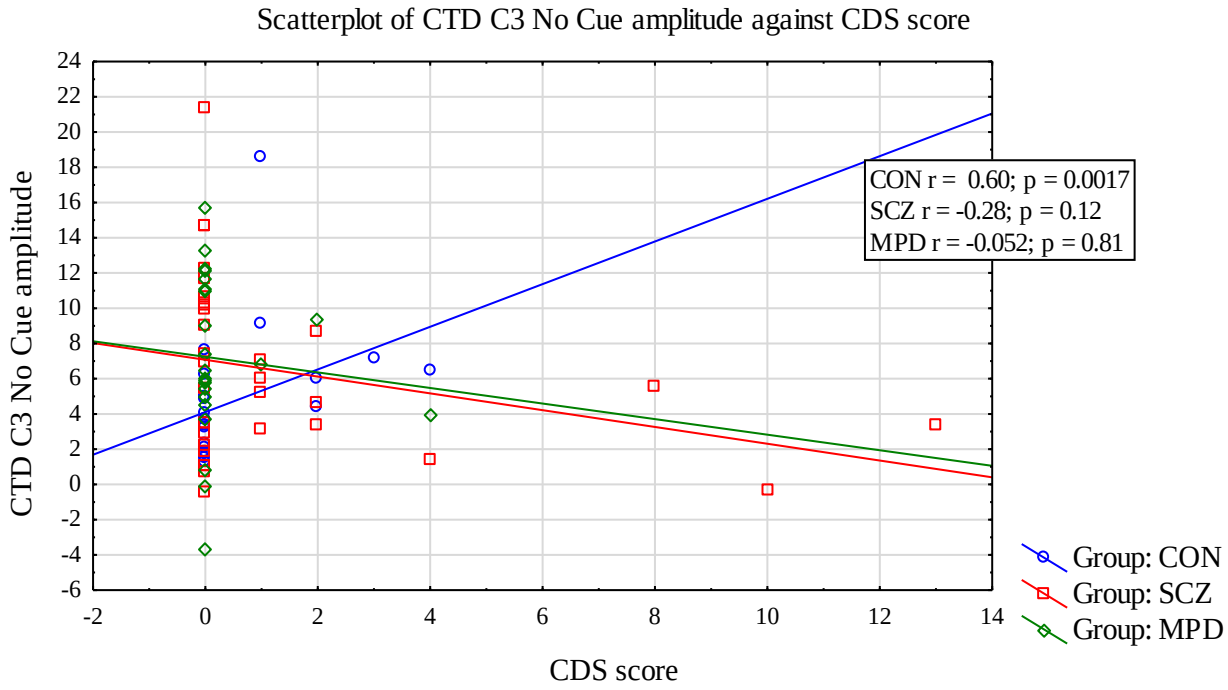


Figure 5.7 Cued target detection task (CTD) no cue P300 amplitude left central (C_3) electrode for CON positively correlated with the Calgary depression rating scale (CDS) score. Healthy controls (CON); Schizophrenia (SCZ); Methamphetamine-induced psychotic disorder (MPD). Significance was reported for $p<0.01$ and Rho= >±0.60.

5.3.13 Cued target detection task no cue P300 latency event-related potential waveform

CTD no cue left prefrontal (Fp_1 ($H_{2.87}$=7.0049; p=0.0301) reported a group difference where MPD P300 latency was delayed compared to CON (Fp_1 p=0.039), **Table 5.12**.

Table 5.12 Cued target detection task no cue P300 latency event-related potential waveform

			Healthy control	**Schizophrenia**	**Methamphetamine-induced psychosis**		
			n = 35	n = 38	n = 31		
			15 females/20 males	8 females/30 males	7 females/24 males		
			Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	T	446(400-700)	491(400-700)	481(400-696) *	$H_{2.87}$=7.0049; p=0.0301	MPD>CON p=0.039
Right prefrontal cortex	**Fp_2**	T	478(414-700)	522(400-700)	489(360-692)	$H_{2.68}$=0.13; p=0.93	-
Left frontal cortex	**F_3**	T	514(426-700)	476(364-700)	506(402-700)	$H_{2.84}$=2.70; p=0.25	-
Right frontal cortex	**F_4**	T	522(428-700)	638(410-700)	532(400-700)	$H_{2.70}$=3.52; p=0.17	-
Left central cortex	**C_3**	T	518(408-700)	506(400-700)	516(406-964)	$H_{2.80}$=1.21; p=0.54	-
Right central cortex	**C_4**	T	544(400-700)	482(400-700)	554(440-700)	$H_{2.87}$=4.82; p=0.089	-
Left parietal cortex	**P_3**	T	622(424-700)	598(422-700)	592(432-700)	$H_{2.85}$=0.50; p=0.77	-
Right frontal cortex	**P_4**	T	526(400-700)	516(404-700)	541(404-700)	$H_{2.86}$=0.79; p=0.67	-
Left occipital cortex	**O_1**	T	536(400-700)	502(406-692)	549(412-700)	$H_{2.88}$=4.72; p=0.094	-
Right occipital cortex	**O_2**	T	544(400-700)	510(402-700)	544(400-700)	$H_{2.85}$=1.54; p=0.46	-

***** *Methamphetamine-induced psychotic disorder (MPD) reported greater CTD no cue P300 latency compared to controls (CON). Non-parametric Kruskal Wallis (H-test), Significance P<0.05.*

MPD tobacco lifetime scores negatively correlated with the right occipital CTD no cue P300 latency ($O_2R_{Spearman's(n=21)}$=-0.61; p=0.0029), **Figure 5.8**.

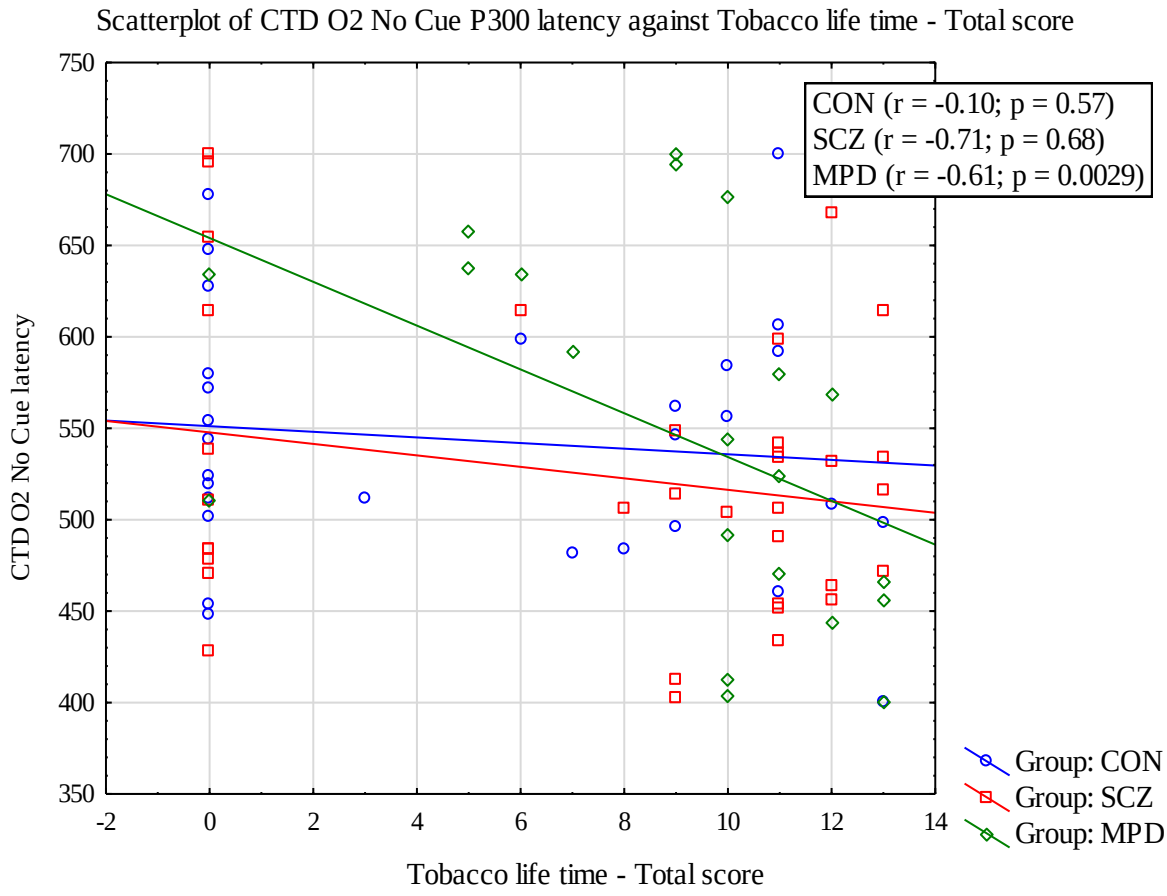


Figure 5.8 Cued target detection task (CTD) no cue P300 latency for the right occipital (O_2) electrode for MPD positively correlated with the tobacco lifetime score. Healthy controls (CON); Schizophrenia (SCZ); Methamphetamine-induced psychotic disorder (MPD). Significance was reported for p<0.01 and Rho= >±0.60.

5.1 Discussion

The main findings of the present study were: group differences where the P300 amplitude was attenuated within the frontal and parietal regions for SCZ, and frontal to central regions for MPD. P300 latency was found to be delayed for the CPT distractor cue in SCZ and CTD with no cue in MPD compared to CON. Correlates found for the CPT target P300 latency indicated methamphetamine use in SCZ negatively correlated with the frontal amplitude but positively correlated with the parietal latency. A negative correlation was found between the parietal region and the age of onset of methamphetamine use in SCZ. Lastly, a positive correlation was found between the prefrontal region and alcohol use in CON. These results indicate impaired cognitive functioning within SCZ and MPD, specifically impaired processing of incoming information and difficulty in concentration.

Continuous performance task

The activation of the prefrontal cortex during methamphetamine use was found to be associated with a reduction in cognitive control (Nestor et al., 2011). As noted in the literature, our study reported that MPD had attenuated amplitude within frontal regions. CPT target reported a group difference for the left prefrontal, central and right frontal electrodes where MPD P300 amplitude was lower compared to CON. This result is in line with frontal lobe atrophy being reported in MPD (Coutinho et al., 2008).

SCZ often reports delays in response to target stimuli (Cerquera et al., 2017). In this study, SCZ duration of methamphetamine use (months) negatively correlated with the CPT target right prefrontal and positively correlated with the right parietal P300 latency. And CPT target anterior P300 latency positively correlated with methamphetamine abstinence in SCZ. Research has shown that reduced dopamine transmission/ activity in the prefrontal cortex has been associated with impaired working memory and negative symptoms in SCZ (Gibert-Rahola & Villena-Rodriguez, 2014; C. A. Riccio et al., 2002). Further, it was found that despite patients abstaining from methamphetamine use, cognitive deficits were shown to persist long after methamphetamine had been stopped (Scott et al., 2007). Therefore, indicating that methamphetamine use potentially has long-term effects on the dopamine system.

Distractor cues are often responded to by individuals who have cognitive impairments such as individuals with damage to the frontal lobe, leading to difficulty in concentration and are therefore easily distracted (Riccio et al., 2002b). In our study, SCZ presented with delayed CPT trick S P300 latency for the right frontal and left parietal electrodes compared to CON. The inclusion of a distractor aids in determining damage to the limbic system. Patients who also presented with an increased number of psychotic episodes and negative symptoms of SCZ have been reported to have attenuated amplitudes (Ethridge et al., 2015).

Cued target detection task

~ Congruent

The CTD task presents four different trials; incongruent, congruent, double cue and no cue. For the congruent trial, which presents a cue with the target presenting within the cue, SCZ left frontal CTD P300 amplitude was increased compared to CON. Medication was found to have adverse effects on cognitive functioning. For MPD, chlorpromazine equivalents negatively correlated with the right frontal CTD congruent P300 amplitude. P300 latency is representative

of response time and attention to a target, Clinical status such as symptom severity can influence response time (D.-W. W. Kim et al., 2013). Substance use was previously found to be associated with delayed latencies and increased amplitudes in individuals (Ceballos et al., 2009; Solowij, Michie, & Fox, 1995).

~ Double cue

The presentation of the double cue provided the participant with information that a target would occur. Literature has presented that a decrease in double cue reaction time is indicative of a decrease in alerting (Witte, Davidson, & Marrocco, 1997). Our study revealed an increase in the anterior CTD double cue P300 amplitude in CON compared to SCZ and MPD. These results indicate an association between alerting and the anterior cortex which is altered with methamphetamine use and education level.

~ Incongruent

CTD incongruent trials test the individuals' ability to CTD incongruent left prefrontal reported a group difference where SCZ P300 amplitude was increased and latency was shorter compared to CON. Substance involvement such as tobacco use, was previously shown to have adverse effects on cognitive functioning (Witte et al., 1997). These effects included the reduction of response time to incongruent trials in substance-using individuals. Our study reported positive correlates between substance use and anterior CTD incongruent P300 amplitude for tobacco lifetime scores in MPD and alcohol lifetime scores in CON. However, a negative correlation was found for the onset of methamphetamine use in SCZ over the parietal region. In literature, negative symptoms were found to have a key role in identifying cuing and cognitive interference during cognitive-related tasks (D.-W. W. Kim et al., 2013). Our results indicate that cognitive function is affected by symptomology and substance use in MPD.

~ No cue

The presence of no cue trials, where a target was presented in either the left or right visual field, resulted in a delayed response to the target for MPD compared to CON. This could be a result of tobacco use where we found a negative correlation for the MPD right occipital CTD no cue P300 latency. As mentioned in the literature, nicotine use affects the cholinergic system which results in altered visuospatial attention (Witte et al., 1997). This is in line with current literature on cognitive impairments and the association with damage to the frontal lobe or altered frontal lobe dopamine transmission (Riccio, Waldrop, Reynolds, & Lowe, 2001; Roberts & Geppert,

2004). Our results indicate that MPD patients suffer from cognitive impairments as a result of MA use damaging neurotransmitter release and brain structure abnormalities.

Limitations of the study are the lack of computer skills from several individuals, as a result of never being given the opportunity to learn or not having access to a computer. A limitation of measuring attention is the increase in mental fatigue which can result in a decrease in attention over time (Reteig et al., 2019). Our study included patients currently on a medication regime and future work should include a control group of patients prescribed medication and those who are unmedicated. Further, studies should include mapping the EEG data to brain structure through structural brain imaging or a combination of fMRI and EEG studies. Further studies on MPD revealed that cognitive deficits were found to persist long after methamphetamine use and were concluded to be caused by frontostriatal and limbic system abnormalities (Petit et al., 2012). As methamphetamine seemed to have a significant effect on cognitive dysfunction in MPD, methamphetamine use in the SCZ patient group could potentially be a confounding factor to the cognitive functioning impairments seen within SCZ.

Conclusion

The P300 amplitude was attenuated within the frontal-parietal regions for SCZ and frontal regions for MPD, indicating impaired cognitive functioning within the psychotic disorders. P300 latency was found to be delayed in SCZ compared to CON, however, no differences were found for P300 latency in MPD. Correlates were found between methamphetamine use for the anterior CPT and CTD P300 latency and amplitude indicating a reduction in attention and cognitive control in SCZ and MPD. Lastly, methamphetamine affected an individual's ability to concentrate (Harmony, 2013). Further studies are needed to understand neurobiological mechanisms that contribute to impaired attention in MPD.

In the current chapter, I addressed attention and cognitive impairments in schizophrenia and methamphetamine-induced psychotic disorder, where I found attenuated P300 event-related potentials indicating impaired cognitive functioning in schizophrenia and methamphetamine-induced psychotic disorder compared to CON. The next chapter will discuss working memory and cognitive control in schizophrenia and methamphetamine-induced psychotic disorder where the frequency activity and N170 and P300 event-related potential waveforms will be investigated.

6 Working memory and cognitive control in schizophrenia and methamphetamine-induced psychotic disorder

Abstract

Introduction: Poor cognitive control and impaired working memory are often seen in schizophrenia (SCZ), however, literature on cognitive impairment measured via electroencephalography in methamphetamine-induced psychotic disorder (MPD) is lacking. In this study, we examined relative frequency activity and the N170 and P300 event-related potentials (ERP) during the STROOP task in SCZ, MPD and healthy controls (CON), and their potential associations with cognitive performance, clinical symptoms, and prescribed medication.

Methodology: EEG was recorded from 104 individuals: SCZ (n=38), MPD (n=31), and controls (n=35), who completed a modified STROOP task containing 20 white squares. Group differences were determined by ANOVA with Bonferroni post-hoc correction or multivariate Kruskal-Wallis test, dependent on data distribution. Associations were determined using Pearson's or Spearman's rank order correlation ($p<0.01$) where appropriate.

Results: SCZ reported poor cognitive performance compared to CON ($p<0.01$) and MPD ($p<0.05$). SCZ reported altered theta cortical activity in the frontal through to the parietal areas compared to MPD (F_3 $p=0.022$) and CON (C_4 $p=0.018$, P_4 $p=0.0070$). SCZ reported delayed P300 latency for the left parietal electrodes compared to MPD (P_3 $p=0.034$). SCZ and MPD participants taking 2nd generation antipsychotics reported increased anterior P300 amplitude compared to those not taking antipsychotics ($p=0.038$) and those taking 1st generation antipsychotics ($p=0.048$). For patients not taking antipsychotic medication behavioural performance negatively correlated with substance involvement, and posterior P300 latency ($p=0.0045$). For patients taking 1st generation antipsychotics, methamphetamine use positively correlated with posterior N170 latency (P_3 $r=0.97$, $p=0.0048$) and N170 amplitude (O_2 $r=0.81$; $p=0.0078$).

Conclusion: SCZ had impaired cognitive processing observed by delayed response times compared to both MPD and CON. This is consistent with previous studies showing poor cognitive processing in SCZ. However, this is the first study to directly compare SCZ and MPD and suggests that although there is an overlap of mechanisms involved in these disorders, there are also differences.

6.1 Introduction

Impaired working memory and cognitive control are common problems in schizophrenia (SCZ) (Mahurin, Velligan, & Miller, 1998). SCZ along with other forms of mental illness such as methamphetamine-induced psychosis, affects approximately 1% of the world's population (James et al., 2018). For years electroencephalography (EEG) has been used to identify cortical arousal signatures within these psychotic disorders. EEG measures real-time electrical brain activity which can provide information about specific frequencies being produced for diagnostic purposes (Ranlund et al., 2014).

The literature presents a large amount of information on EEG frequency activity and event-related potential (ERP) in SCZ (Bunge & Kahn, 2010; Kida et al., 2016). However, EEG frequency activity and ERP waveforms in methamphetamine-induced psychotic disorder (MPD) are lacking due to limited research (Fleur M. Howells et al., 2018). However, despite the limited research in MPD cognitive impairments such as executive functioning, attention and working memory were found to be less severe compared to SCZ (Ezzatpanah et al., 2014). The Stroop task has been used as a research tool to investigate disorders such as SCZ, Alzheimer's disease, memory dysfunction and the effects of ageing on cognitive control (Badzakova-Trajkov, Barnett, Waldie, & Kirk, 2009). The Stroop task (Stroop, 1935) was designed to identify an individual's psychological capacity and executive functioning in frontal lobe dysfunction (Cabeza & Nyberg, 2000).

Brain imaging studies have shown processing of the Stroop task occurs across the frontal cortex, namely the anterior cingulate cortex and the dorsolateral prefrontal cortex (Harrison et al., 2005). Increased activation of the anterior cingulate cortex was found when viewing conflict/ incongruent stimuli (Raz, 2004). Responses to perceptual judgment are drastically slowed when incongruent stimuli are internally maintained in working memory (Kiyonaga & Egner, 2014). The Stroop task also measures the ability to suppress irrelevant information and is one of the most used tests of inhibitory control in neuropsychiatric patients. A study conducted on mind wandering found decreased alpha and theta frequencies across the frontal areas of the brain (Atchley, Klee, & Oken, 2017). However, alpha and theta activity increased when more practice was given for the working memory task irrespective of the stimulus modality. A typical response for the Stroop task is a delayed response time and frequent errors (Tillman & Wiens, 2011). Top-down attentional processes are activated for increased incongruent trials. Alternatively, expected incongruent trials resulted in habitual response processing where the attentional control is less engaged (Tillman & Wiens, 2011). By

increasing the incongruent trial frequency, a decrease in response conflict is noted. This is due to the activation of top-down attentional processing reducing conflict resolution (Tillman & Wiens, 2011).

Decreased executive functioning (such as working memory, memory recall and attention) due to frontal lobe dysfunction is a common problem in SCZ. Studies have found reduced reaction times for the Stroop task in patients with SCZ across all three conditions (Perlstein, Carter, Barch, & Baird, 1998). SCZ also had increased errors made for the Stroop task compared to controls. Chronic methamphetamine use is associated with poorer performance in the Stroop task in adolescents (A. Guerin, 2019). Analysis of Stroop task data revealed greater interference was found in methamphetamine abusers when compared to controls (Thompson et al., 2004). Further investigations on executive functioning in SCZ were conducted using event-related potentials (ERP). ERPs are used to investigate attention and working memory and are extracted from EEG recordings of cognitive tasks.

The N170 ERP waveform was found to appear after the presentation of known words (Dundas, Plaut, & Behrmann, 2014). The N170 ERP waveform is a negative deflection that occurs approximately 170msec after stimulus presentation (Feuerriegel et al., 2015). The N170 amplitude was found bilaterally in relation to executive functioning. However, the amplitude remains slightly attenuated in the left hemisphere compared to the right hemisphere (Tanaka & Curran, 2001). The N170 latency was found to be delayed and the amplitude was increased in healthy individuals with typical development (Hileman et al., 2011). Current literature available on the N170 ERP waveform in SCZ focuses on emotion processing through the presentation of facial cues. Very few studies address attentional processing within SCZ and none to my knowledge in MPD (Okumura, Kasai, & Murohashi, 2015). The N170 amplitude was found to be attenuated in patients with SCZ during the presentation of neutral and emotional facial images (Cao, Ma, & Qi, 2015; Feuerriegel et al., 2015; Onitsuka, Oribe, Nakamura, & Kanba, 2013). In early onset, SCZ, attenuated N170 amplitudes were found in transient visual evoked potential studies (Butler & Javitt, 2005). The N170 latency was found to be delayed in SCZ compared to CON during the processing of words (Jonathan K. Wynn et al., 2015). In another study, the N170 latency was delayed indicating impaired early sensory processing (Garakh et al., 2015). Furthermore, it was found that early visual processing during the presentation of words and/ or letters was consistent with the left lateral N170 amplitude and latency (Okumura et al., 2015) and reduced N170 amplitude was noted during maximum working memory load (Morgan, Klein, Boehm, Shapiro, & Linden, 2008). However, despite

the limited resources found for MPD, working memory, and maintaining attention during a task appeared to be worse in SCZ when compared to MPD.

The P300 ERP waveform has been widely studied in SCZ (Oribe et al., 2015; Roth et al., 2007). The P300 ERP waveform is a positive deflection that occurs approximately 300msec post-stimulus presentation and is thought to be indicative of cortical processing (Sur & Sinha, 2009). The P300 waveform has been vastly studied within a variety of visual and auditory tasks in healthy controls and individuals with various mental disorders. Current literature has shown that the P300 amplitude is attenuated and latency is delayed in response to target stimuli (Van Tricht et al., 2010; VanMeerten, Dubke, Stanwyck, Kang, & Sponheim, 2016). The attenuated P300 amplitude and delayed latency were suggested to provide insight into the mechanisms that are involved in attentional processing in SCZ (VanMeerten et al., 2016). Further, a global reduction in P300 waveform amplitude literature revealed that impaired attentional processing in SCZ is noted through a global reduction of the P300 amplitude (Kuperberg, 2004; Tekok-Kilic, Shucard, & Shucard, 2001). Reduced P300 amplitudes over the frontal and parietal regions suggest a reflection of primary cognitive impairments within SCZ (Roth et al., 2007; Turetsky et al., 2007; T. Y. Wang et al., 2017). Although MPD presents with similar symptoms as SCZ, to my knowledge limited information is available on cognitive deficits and the relation to the P300 ERP waveform is available.

Cognitive impairments such as attention are known in SCZ, however, limited information is known about the ability of individuals diagnosed with MPD being able to maintain attention during a cognitive task. The STROOP task was used to investigate working memory and executive control in this study. We aimed to determine whether there were relative frequency activity and (N170, P300) ERP waveform differences for the STROOP task between groups for (a) SCZ, MPD and CON, and (b) psychotic groups only separated by 1st generation antipsychotics (1st), 2nd generation antipsychotics (2nd), and not taking any antipsychotic medication (NONE). Then relationships were determined between population characteristics and relative frequency activity and, N170 and P300 ERP waveform differences for the STROOP task. This will enhance our neurobiological understanding of these disorders, and potentially distinguish neural circuitry activation signatures which are unique to psychotic disorders. The Stroop effect presents fundamental cognitive processes which take place. We expect to see delayed response times and increased errors in SCZ after conducting behavioural analysis. For MPD we expect to see increased errors when completing the task. ERP waveform differences expected are attenuated amplitudes for the N170 ERP waveform and delayed P300

latency. Further, we expect to see variations in ERP waveforms for the frontal-central areas in SCZ and MPD due to the activation of the anterior cingulate cortex and executive functioning while completing the task. For our patients, we expect to see reduced working memory due to impaired cognitive functioning as seen in various studies conducted in SCZ. This study will further delineate ERP differences found in the Stroop task within CON, SCZ and MPD.

6.2 Method

6.2.1 *Research participants*

104 South African individuals, between the ages of 20 and 45 years, participated in this study: 38 with SCZ (8 females/30 males), 31 with MPD (7 females/24 males), and 35 healthy controls (CON: 15 females/20 males). The study was approved by the Health Sciences Research Ethics Committee, at the University of Cape Town (HREC Ref. No.: 479/2019). Western Cape Provincial and Hospital approval was also obtained. All research activities were conducted in accordance with the Declaration of Helsinki. All research participants provided voluntary informed consent.

Participants visited the laboratory twice. The first visit included the provision of informed consent and an assessment clinical interview. All participants underwent a Structured Clinical Interview for Diagnostic Systematic Manual- IV (SCID-DSM-IV), with modifications to include changes made in DSM-5. Control participants were excluded if there was a history of psychotic symptoms or a family history of psychotic disorder. Participants with a psychotic disorder were excluded if they did not meet the diagnostic criteria for the study conditions: for example, participants with schizoaffective disorder were excluded. Participants were also excluded if they were younger than 19 years or older than 40 years, had general medical conditions that required prescription medications, had an apparent learning disability, had major brain trauma/surgery, had any history of cardiovascular insult, individual or family history of epilepsy, medical implants or any metal within their person, for example, shrapnel.

Female participants were excluded if they were pregnant or lactating. Patients with SCZ were excluded if any of their episodes were considered to be related to the use of a substance. MPD included psychotic symptoms with onset during methamphetamine intoxication or withdrawal and did not persist beyond 1 month since the last use of methamphetamine, or evidence of an underlying ‘primary’ psychotic disorder not related to the use of methamphetamine. Evidence that the symptoms are better accounted for by a psychotic disorder that is not methamphetamine-induced included the following: the symptoms precede the onset of the

methamphetamine use; the symptoms persist for a substantial period of time after the cessation of acute withdrawal or severe intoxication, or are substantially in excess of what would be expected given the amount of methamphetamine used or the duration of use; or there is other evidence that suggests the existence of an independent non-MPD (e.g. a history of recurrent non-methamphetamine- related episodes). Patients with MPD were excluded if it was unclear if methamphetamine was causal to their symptoms or diagnosis, and if any of their psychotic episodes may have been related to another substance of abuse.

6.2.2 *Study design*

The second visit included a full morning of brain imaging. All EEGs were performed between 09h00-11h00, on a weekday. All clinical scales were performed on the same day and after the morning of brain imaging by trained clinical personnel.

Clinical rating scales included the Positive and Negative Syndrome Scale (PANSS); Calgary Depression Scale for Schizophrenia; Hamilton Rating Scale for Depression. Chlorpromazine equivalents were calculated from current medication regimes. Drug use history, nicotine, alcohol and methamphetamine were recorded using the Kreek-McHugh-Schluger-Kellogg scale (KMSK).

6.2.3 *Electroencephalography*

Stroop task

The Stroop task assesses selective attention, cognitive flexibility, processing speed and executive functioning directed to frontal lobe dysfunction (Naylor, Stanley, & Wicha, 2012). The Stroop effect, named after John Ridley Stroop, is based on the phenomenon that the brain's reaction time slows down when processing conflicting information. In terms of the Stroop task conditions, the Stroop effect is a phenomenon where the reaction time of an incongruent condition is compared to the congruent condition (Coderre, Conklin, & Van Heuven, 2011). The Stroop paradigms can be divided into three groups: neutral, congruent, and incongruent. Congruent trials present a colour word being presented in the same colour (i.e., the word red being shown in the colour red). For this study, incongruent are presented. The incongruent trials present a colour word being presented in a different colour (i.e., the word red being presented in the colour green). Neutral trials present a colour word being shown in grey (i.e., red being shown in the colour grey) or a word not referring to a colour being presented in the specified colours being used within the task. Incongruent stimuli introduce competing information that taxes top-down attention control by increased demands on selective attention

and working memory due to interference between competing task-relevant and task irrelevant information (i.e., word reading versus colour naming) and by activating two competing motor responses and generating response conflict (response to the word meaning versus the colour ink). The Stroop conflict hypothesis is based on the interference created between the word response and colour response (Zurrón, Pouso, Lindín, Galdo, & Díaz, 2009). More specifically, the Stroop task has been used to study the executive functioning required to suppress task-irrelevant information (Saban, Gabay, & Kalanthroff, 2016). However, a problem with the Stroop task questions whether interference is caused during the stimulant encoding stage or the response production (Sahinoglu & Dogan, 2016). Interference is defined as the slow response to an incongruent stimulus compared to a neutral or congruent stimulus (Harrison et al., 2005). It was shown that words are processed faster compared to pictures. For example, responding "red" to the word blue written in red font (incongruent stimulus) will result in a slower reaction time compared to responding to the word blue written in blue font. Reading pathways were found to interfere with incongruent stimuli but aid in responding to congruent stimuli (Harrison et al., 2005).

EEG recording of REO and REC was undertaken using a simple EEG montage that included prefrontal (Fp1 and Fp2), frontal (F3 and F4), central (C3 and C4), parietal (P3 and P4) and occipital (O1 and O2) electrodes. Standard 10/20 caps (Electro-Cap International, Inc.) were used, of either medium or large size depending on the head circumference of the participant. Participants were grounded peripherally, linked earlobe reference was applied, and electrooculography (EOG) was recorded. The EEG system used was the Biopac MP150 system with 100 C EEG amplifiers and an EOG amplifier (Biopac Systems, Inc.). Digital EEG data and analogue data, from E-prime, were collected via the MP150 system, with a sampling rate of 500Hz, and were visualised in real-time using Acq-Knowledge 4.1 (Biopac Systems, Inc.).

For EEG data processing, data were first eye blink corrected and movement corrected (EOG), using automated ICA EOG correction in Acqknowledge 4.1 (Biopac Systems, Inc.), and then bandpass filtered 0.1–30Hz and Fourier transformed, using an in-house Matlab GUI, to accommodate differences in participant electrical brain activity conduction. Relative (%) frequency bands power activity was extracted: delta (0.1–4.0Hz), theta (4–7Hz), alpha (7–14Hz) and beta (15–30Hz).

Stroop colour word conflict task

The Stroop task was designed to identify executive functioning associated with frontal lobe dysfunction. The task consists of the individual appearance of four colour words (red, blue, yellow and green), displayed in five different colours (red, blue, yellow, green, and grey) in the centre of a computer monitor on a black background. Each cue is displayed in either coloured (red, blue, yellow or green) or grey ink (distractor cues) but never displayed congruently in the same colour as the written word (e.g. never the written word "blue" in blue font). In total, 108 cues are randomly presented, 18 incongruent colour words in each of the 4 colours red, blue, green and yellow (72 incongruent words in total); and 18 grey words. Participants respond as quickly and accurately as possible by pressing single keys on a standard computer keyboard which correspond with the various word/colour arrangements. The participants respond to the colour of the word and not the written word, except if the word is written in grey ink where a response to the written word itself is required. Incorporating grey words it ensures that participants have to read and recognize the word prompts rather than just notice the colours, thereby invoking the Stroop effect i.e. dissonance (Stroop, 1935). Behaviourally, the reaction time, correct detection, omission errors and commission errors will be extracted and analysed.

6.2.4 *Statistical analysis*

Statistical analysis was conducted using Statistica (Dell Inc, 2015). To determine group differences in relative frequency, N170 and P300 ERP waveforms for the Stroop task, and cognitive performance, an analysis was conducted for (a) three groups (CON, SCZ and MPD) and (b) psychotic groups (SCZ, MPD) according to antipsychotic medication (Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). For correlation analysis, the demographics (age on the day of testing, duration at school, tertiary education, and total years of education), 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, duration of illness, drug use (methamphetamine, alcohol, tobacco, cannabis), and medication use (chlorpromazine equivalent dose) were included.

First, an analysis of the distribution for each variable, using the Shapiro-Wilks test was conducted. 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 ($p < 0.05$). Where appropriate, according to the data distribution, correlation analysis was performed using Pearson's or Spearman's rank order (Rho $>\pm 0.6$ and p-value <0.01).

6.3 Results

6.3.1 Participant demographics

A total of one hundred and four individuals, between the ages of 20 and 45 years, participated in this study: thirty-eight participants with a diagnosis of schizophrenia (SCZ n=38; 8 females/30 males), thirty-one participants with a diagnosis of methamphetamine-induced psychotic disorder (MPD n=31; 7 females/24 males), as well as thirty-five socio-demographically matched control participants (CON n=35; 15 females/20 males).

STROOP task cognitive performance differences were found for correct responses ($H_{2,100}$=16.88; p=0.00020) where fewer correct responses were reported in SCZ compared to CON (p=0.00031); the number of omissions ($H_{2,100}$=23.68; p<0.0001) where CON reported fewer omissions compared to SCZ (p=0.000008) and MPD (p=0.0060); the number of commissions ($H_{2,100}$=23.68; p<0.0001) where CON reported fewer commissions compared to SCZ (p=0.010); square count ($H_{2,104}$=10.33; p=0.0057) where square counts were more in CON compared to SCZ (p=0.0093) and MPD (p=0.040), **Table 6.1**.

Table 6.1 STROOP task cognitive performance

	Healthy control	**Schizophrenia**	**Methamphetamine-induced psychosis**		
	n = 35	n = 38	n = 31		
	15 females/20 males	8 females/30 males	7 females/24 males		
STROOP task	**Median (min-max)**	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test)**	**Post-Hoc**
Square count	19(0-23)	11(0-30)	8(0-35)	$H_{2,104}$=10.33; p=0.0057	SCZ<CON p=0.0093 MPD<CON p=0.040
Correct responses	56(1-60)	30(0-58)	2(0-60)	$H_{2,100}$=16.88; p=0.00020	SCZ<CON p=0.00031
Average reaction time	943(432.65-1565.73)	1045.20(0-2165)	912.37(0-1569.15)	$H_{2,100}$=0.30; p=0.85	-
Errors of commission	2(0-58)	18(0-58)	6.5(0-55)	$H_{2,100}$=23.68; p<0.0001	SCZ>CON p=0.010
Errors of omission	1(0-7)	5(0-60)	2(0-24)	$H_{2,100}$=23.68; p<0.0001	SCZ>CON p=0.000008 MPD>CON p=0.0060

Non-parametric Kruskal Wallis (H-test), Significance P<0, 05.

For patients not taking antipsychotics (n=20 where, SCZn= 7; MPDn=13), the STROOP square count negatively correlated with the PANSS negative subscale ($R_{Spearman's(n=20)}$=-0.66; p=0.0014) and positively correlated with tobacco use ($R_{Spearman's(n=20)}$= 0.67; p=0.0012), **Figure 6.1**. STROOP correct responses negatively correlated with PANSS negative subscale

($R_{Spearman's(n=20)}$=-0.66; p=0.0014) and positively correlated with alcohol use ($R_{Spearman's(n=20)}$=0.66; p=0.0026), **Figure 6.2**.

For patients taking 1st generation antipsychotics (n=12 where SCZn= 5; MPDn=7), the STROOP square count negatively correlated with PANSS general subscale ($R_{Spearman's(n=12)}$=0.66; p=0.0026), **Figure 6.3**. and tobacco use ($R_{Spearman's(n=12)}$=-0.72; p=0.0076), **Figure 6.1**.

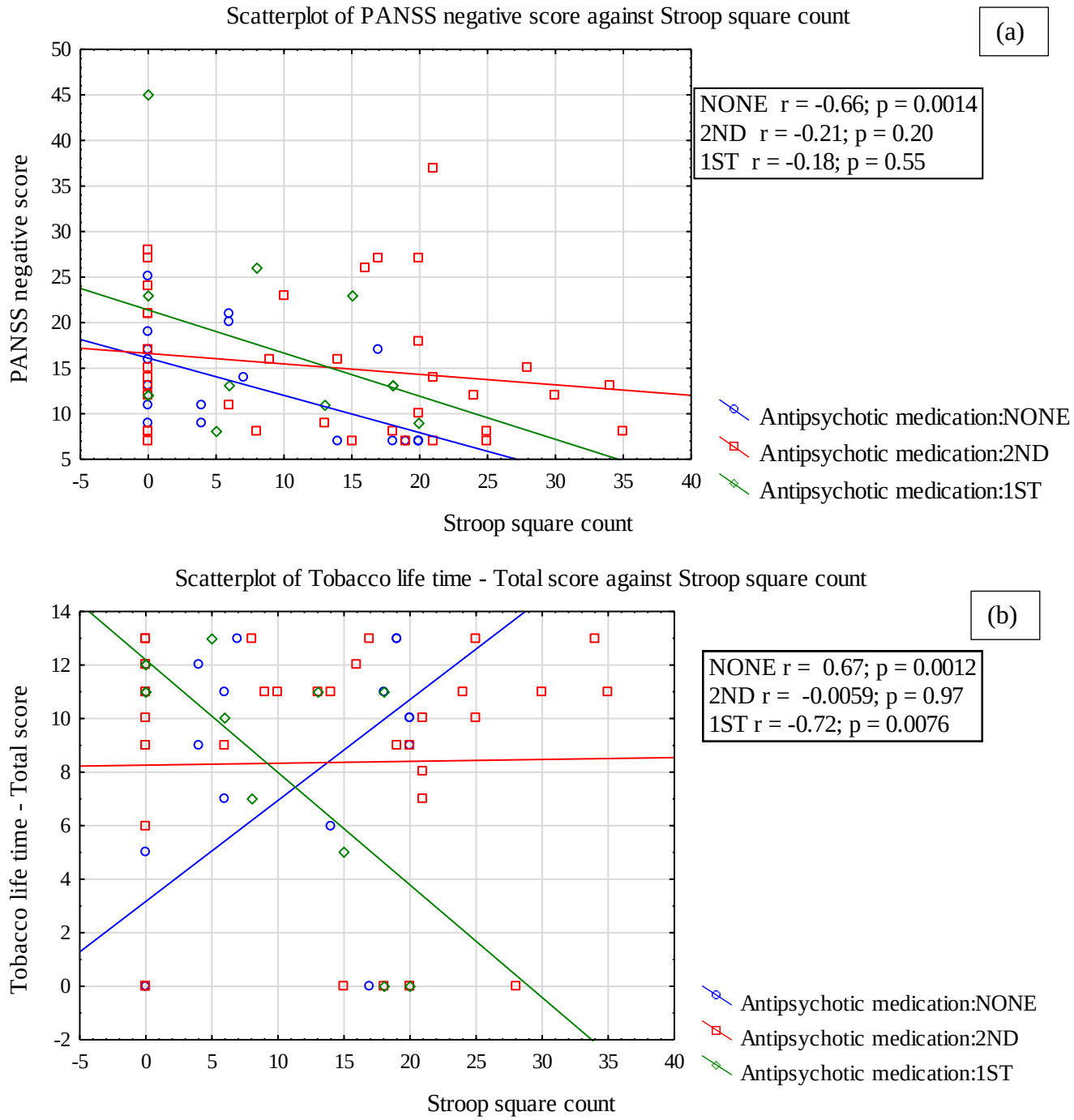


Figure 6.1 **(a)** Patients not taking antipsychotic medication STROOP square count negatively correlated with the PANSS negative subscale and **(b)** patients prescribed 1st generation antipsychotics positively correlated with the tobacco lifetime scores. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= >±0.60.

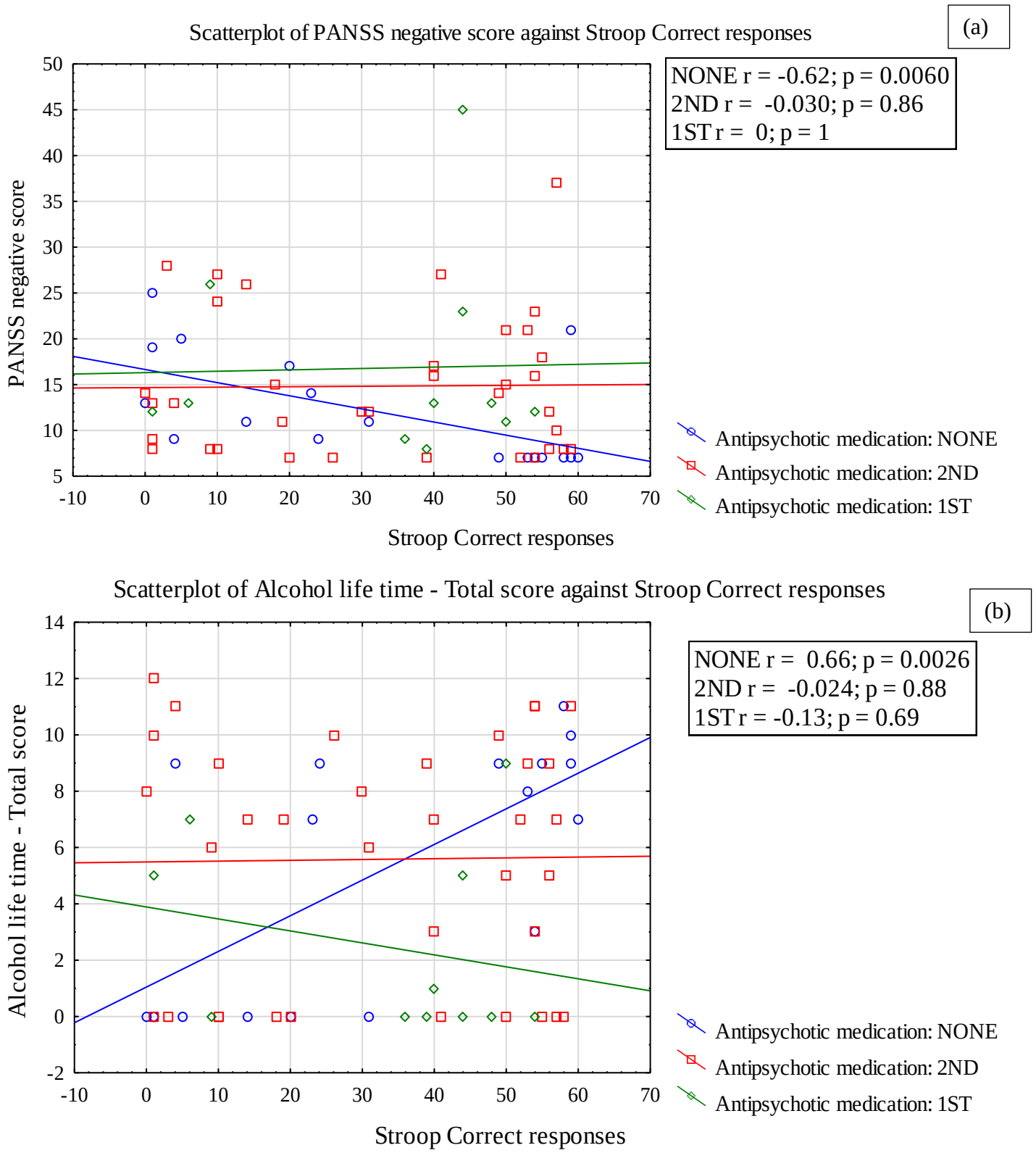


Figure 6.2 Patients not taking antipsychotic medication STROOP correct responses **(a)** negatively correlated with the PANSS negative subscale and **(b)** positively correlated with the alcohol lifetime scores. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm 0.60$.

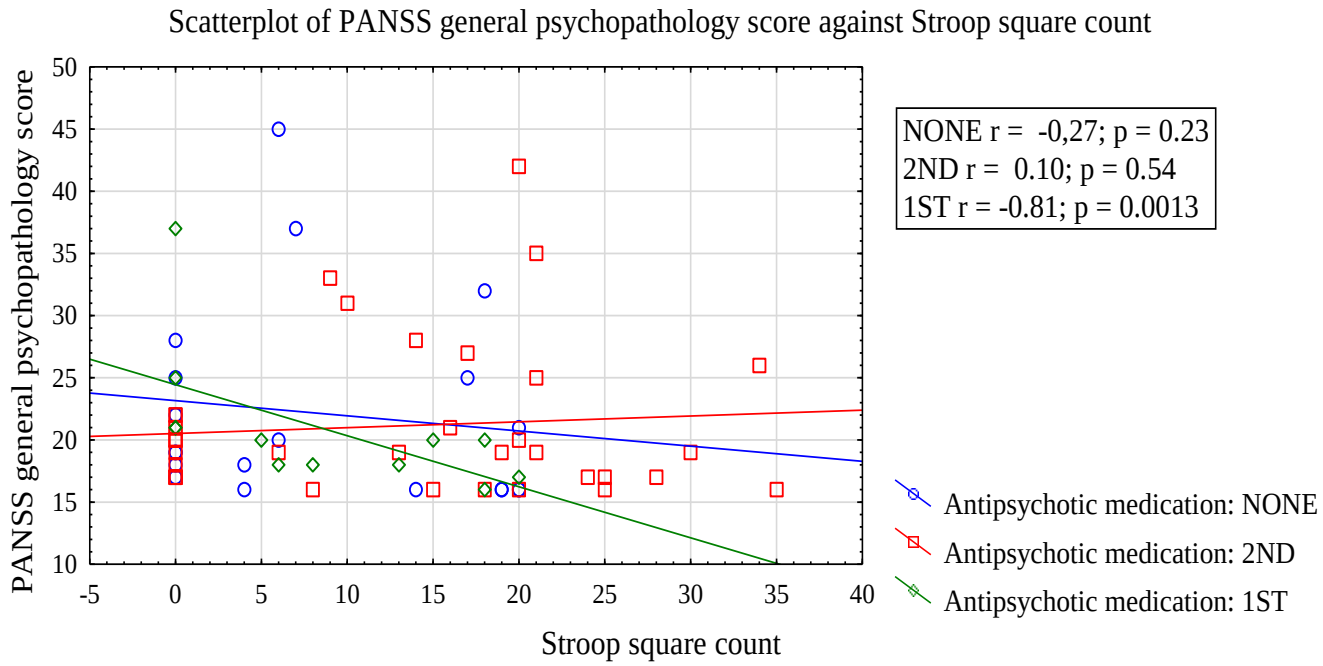


Figure 6.3 Patients taking 1st generation antipsychotic medication STROOP correct responses negatively correlated with the PANSS general subscale. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for p<0.01 and Rho= >±0.60.

6.3.2 STROOP task relative delta activity

No significant group differences were found for STROOP relative delta activity, **Table 6.2**.

Table 6.2 STROOP task relative delta frequency activity

		Healthy control	**Schizophrenia**	**Methamphetamine-induced psychosis**		
		n = 35	n = 38	n = 31		
		15 females/20 males	8 females/30 males	7 females/24 males		
		Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	44.67(31.20-81.54)	44.46(27.51-74.73)	49.34(25.51-67.60)	$H_{2,100}$=0.75; p=0.68	-
Right prefrontal cortex	**Fp_2**	39.58(26.58-75.54)	41.71(25.37-56.54)	40.31(27.04-67.84)	$H_{2,100}$=0.30; p=0.85	-
Left frontal cortex	**F_3**	41.90(18.05-82.38)	41.90(24.93-74.04)	47.51(24.52-74.35)	$H_{2,100}$=1.82; p=0.40	-
Right frontal cortex	**F_4**	34.47(20.49-77.75)	37.32(18.25-56.22)	38.05(24.53-69.54)	$H_{2,100}$=0.52; p=0.76	-
Left central cortex	**C_3**	34.82(21.55-68.66)	41.55(23.83-74.47)	42.12(24.40-74.17)	$H_{2,100}$=3.02; p=0.22	-
Right central cortex	**C_4**	35.89(21.09-81.97)	42.87(24.80-75.32)	46.49(24.66-73.12)	$H_{2,100}$=3.12; p=0.20	-
Left parietal cortex	**P_3**	36.81(18.38-68.70)	38.59(19.53-70.60)	36.70(18-.62-75.53)	$H_{2,100}$=1.23; p=0.54	-
Right frontal cortex	**P_4**	36.51(18.99-81.84)	38.87(18.36-74.20)	40.54(24.54-76.28)	$H_{2,100}$=3.16; p=0.20	-
Left occipital cortex	**O_1**	36.78(23.20-68.99)	41.27(24.81-69.36)	45.29(22.84-68.69)	$H_{2,100}$=2.66; p=0.26	-
Right occipital cortex	**O_2**	40.15(23.14-80.52)	40.80(20.15-72.17)	41.78(24.92-74.07)	$H_{2,100}$=1.49; p=0.47	-

Non-parametric Kruskal Wallis (H-test), Significance P<0, 05.

In patients taking 2nd generation antipsychotics (n = 37 where SCZn= 26; MPDn=11), STROOP left central delta activity negatively correlated with the number of psychotic episodes ($C_3R_{spearman's(n=36)}$=-0.60; p=0.000082), **Figure 6.4**.

For patients taking 1st generation antipsychotics (n = 12 where, SCZn= 5; MPDn=7), STROOP right prefrontal delta activity positively correlated with average reaction time ($Fp_2R_{spearman's(n=10)}$=0.84; p=0.0022), **Figure 6.5**.

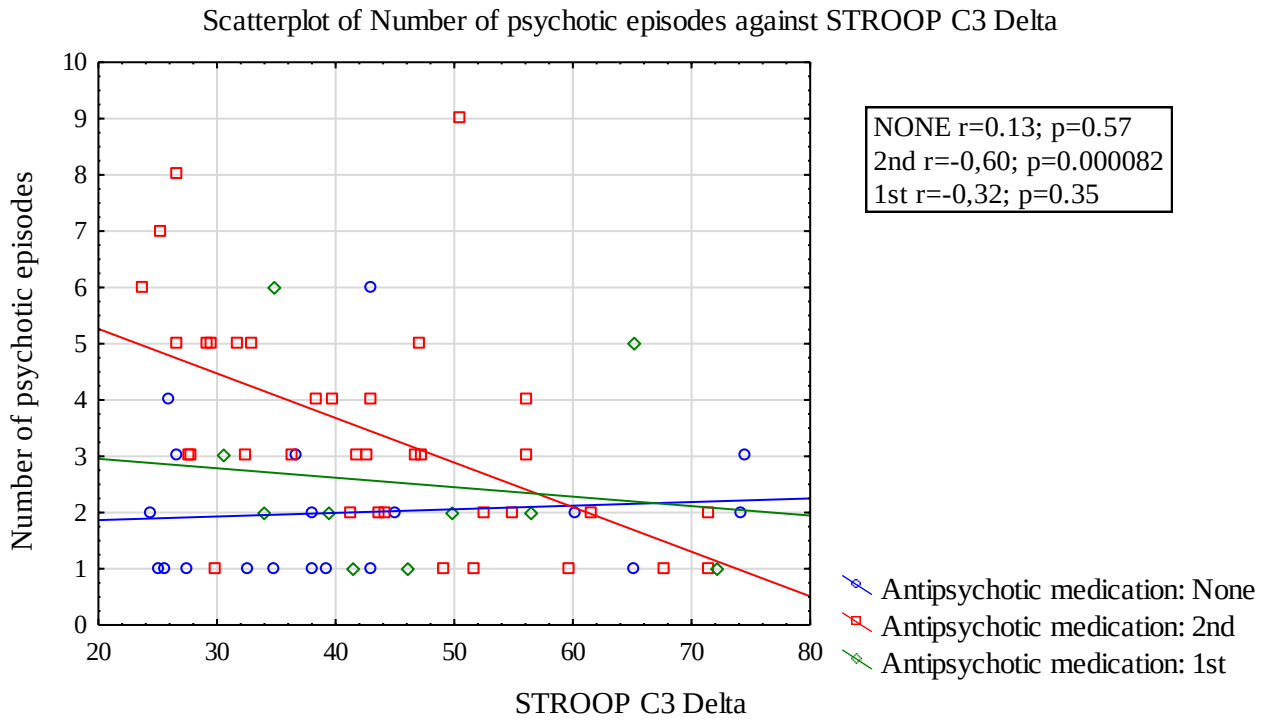


Figure 6.4 Patients prescribed 2nd generation antipsychotic medication left central (C_3) electrode relative delta activity during STROOP positively correlated with the number of psychotic episodes. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= >±0.60.

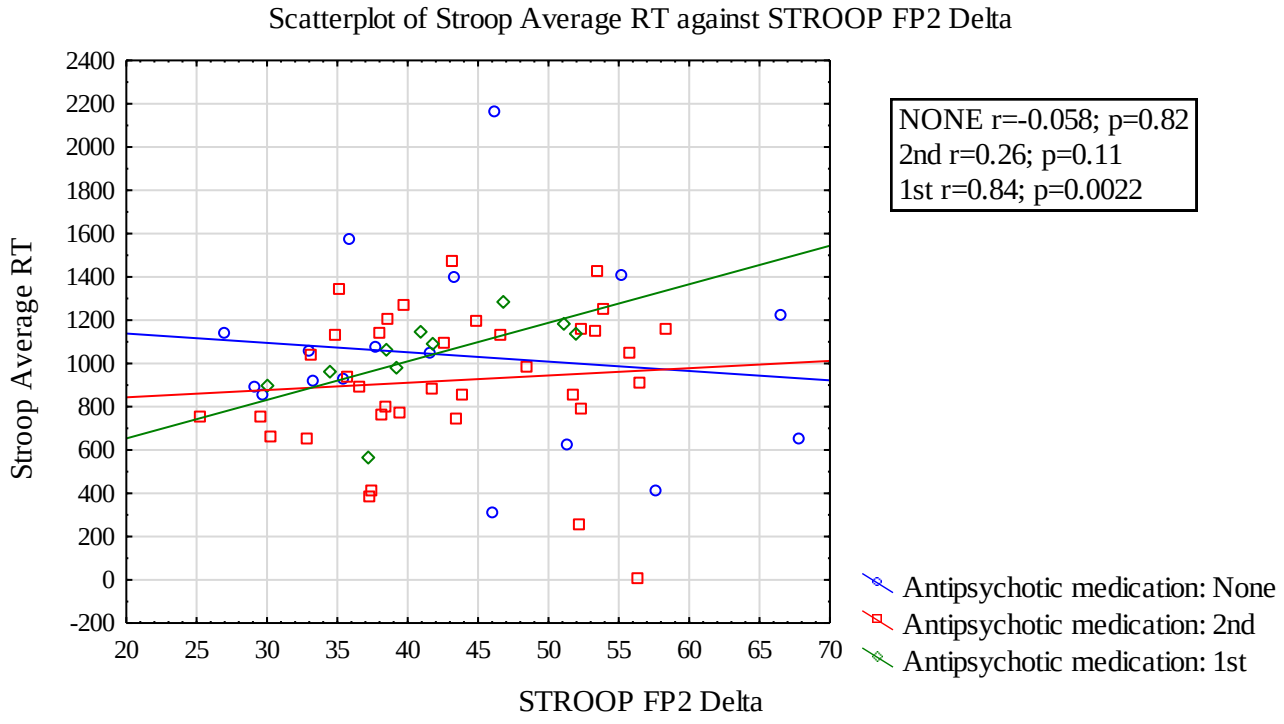


Figure 6.5 Patients prescribed 1st generation antipsychotic medication right prefrontal (Fp_2) electrode relative delta activity during STROOP negatively correlated with average reaction time (RT). Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= >±0.60.

6.3.3 STROOP task relative theta activity

STROOP theta reported a group difference for the left frontal, right central and right parietal electrodes (F_4 ($F_{2.97}$=4.29; p=0.016), C_4 ($H_{2.100}$=8.04; p=0.017), P_4 ($H_{2.100}$=10.11; p=0.0064)) where SCZ theta activity was lower compared to MPD (F_3 p=0.022) and increased compared to CON (C_4 p=0.018, P_4 p=0.0070), **Table 6.3**.

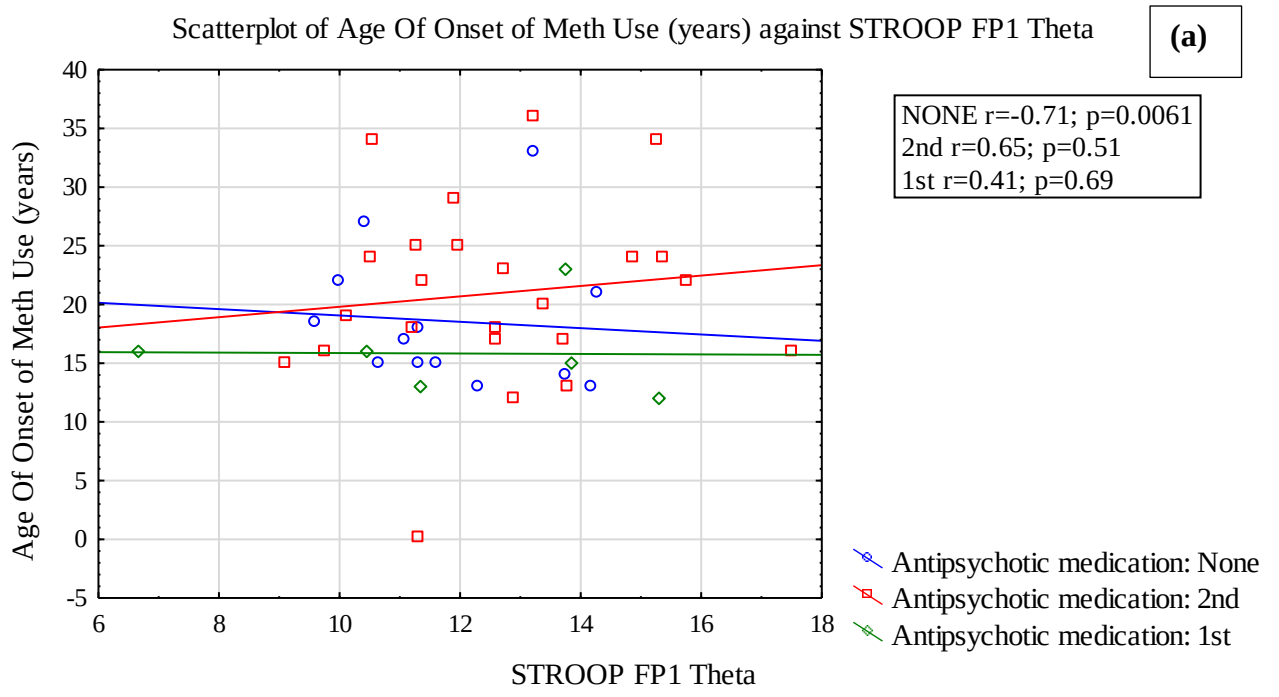
Table 6.3 STROOP task relative to theta frequency activity

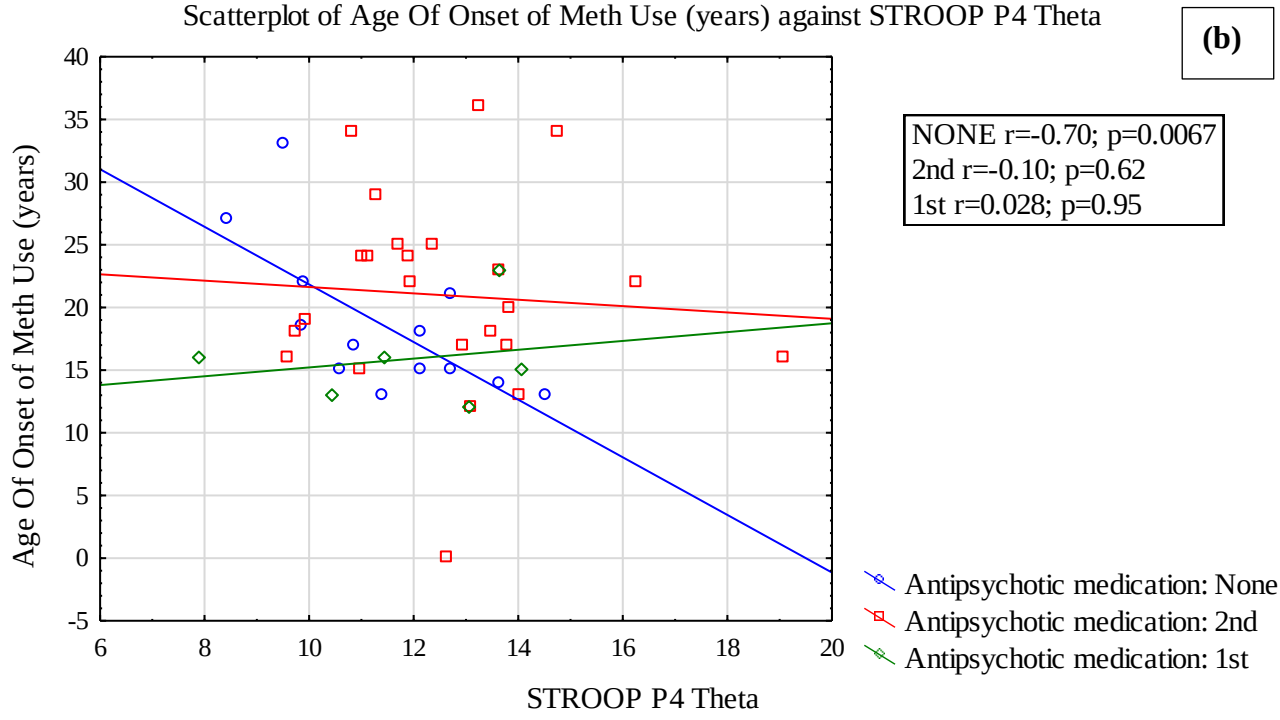
		Healthy control	**Schizophrenia**	**Methamphetamine-induced psychosis**		
		n = 35	n = 38	n = 31		
		15 females/20 males	8 females/30 males	7 females/24 males		
		Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test/ F test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	11.82(7.82-16.58)	12.80(8.93-15.75)	11.32(6.67-17.51)	$F_{2.97}$=1.98; p=0.14	-
Right prefrontal cortex	**Fp_2**	11.92(9.18-16.58)	12.85(9.36-15.51)	12.17(9.82-16.35)	$F_{2.97}$=0.84; p=0.43	-
Left frontal cortex	**F_3**	11.33(7.96-16.63)	12.66(9.07-17.11)	11.22(7.26-14.46) *	$F_{2.97}$=4.29; p=0.016	SCZ<MPD p=0.022
Right frontal cortex	**F_4**	11.52(7.11-17.15)	12.22(8.39-25.44)	12.37(7.42-18.27)	$H_{2.100}$=4.85; p=0.088	-
Left central cortex	**C_3**	11.50(9.71-16.66)	12.42(8.79-16.98)	11.73(7.68-19.00)	$F_{2.97}$=0.90; p=0.40	-
Right central cortex	**C_4**	11.04(8.30-17.38)	12.64(8.94-17.04) #	11.29(7.96-19.10)	$H_{2.100}$=8.04; p=0.017	SCZ>CON p=0.018
Left parietal cortex	**P_3**	11.32(8.35-16.83)	11.99(8.24-17.17)	11.61(7.61-19.14)	$H_{2,100}$=0.72; p=0.69	-
Right frontal cortex	**P_4**	11.52(7.94-16.99)	12.71(8.15-16.82) #	11.40(7.89-19.06)	$H_{2.100}$=10.11; p=0.0064	SCZ>CON p=0.0070
Left occipital cortex	**O_1**	11.42(8.52-16.87)	12.80(9.31-16.06)	11.70(8.41-19.10)	$H_{2,100}$=5.83; p=0.054	-
Right occipital cortex	**O_2**	11.37(8.19-16.83)	12.74(8.65-16.70)	11.29(7.59-19.17)	$F_{2.97}$=3.06; p=0.051	-

****** Methamphetamine-induced psychotic disorder (MPD) reported greater relative theta activity during STROOP compared to Schizophrenia (SCZ) # SCZ reported greater relative theta activity during STROOP compared to controls (CON). Non-parametric Kruskal Wallis (H-test) and parametric one-way analysis of variance (F-test), Significance P<0.05.*

For patients not taking antipsychotics (n=20 where, SCZn= 7; MPDn=13), age of onset of methamphetamine use negatively correlated with the STROOP left prefrontal theta ($Fp_1R_{spearman's(n=13)}$=-0.71; p=0.0061), right central theta ($C_4R_{spearman's(n=13)}$=-0.70; p=0.0067), right parietal theta ($P_4R_{spearman's(n=13)}$=-0.70; p=0.0067) and right occipital theta ($O_2R_{spearman's(n=13)}$=-0.72; p=0.0050) cortical electrodes, **Figure 6.6**.

Patients taking 1st generation antipsychotics (n=12 where SCZn= 5; MPDn=7), STROOP left occipital theta negatively correlated with PANSS total scores ($O_1R_{spearman's(n=10)}$=-0.80; p=0.0052), **Figure 6.7.**


Scatterplot of Age Of Onset of Meth Use (years) against STROOP FP1 Theta
(a)
NONE r=-0.71; p=0.0061
2nd r=0.65; p=0.51
1st r=0.41; p=0.69
Age Of Onset of Meth Use (years)
STROOP FP1 Theta
Antipsychotic medication: None
Antipsychotic medication: 2nd
Antipsychotic medication: 1st


Scatterplot of Age Of Onset of Meth Use (years) against STROOP P4 Theta
(b)
NONE r=-0.70; p=0.0067
2nd r=-0.10; p=0.62
1st r=0.028; p=0.95
Age Of Onset of Meth Use (years)
STROOP P4 Theta
Antipsychotic medication: None
Antipsychotic medication: 2nd
Antipsychotic medication: 1st

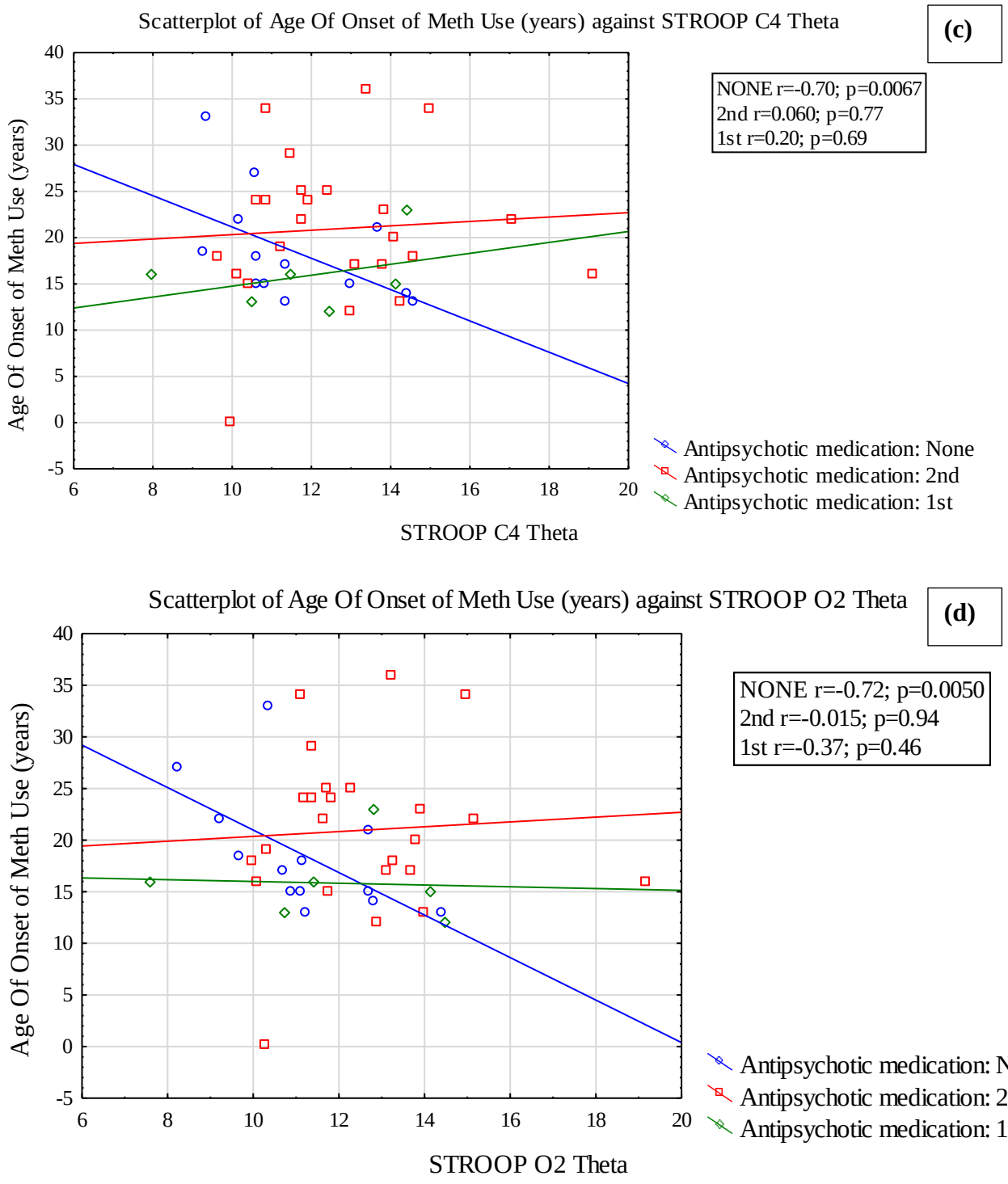


Figure 6.6 STROOP onset of methamphetamine for MPD negatively correlated with use relative theta activity for the **(a)** left frontal (Fp_1), **(b)** right central (C_4), **(c)** right parietal (P_4) and **(d)** right occipital (O_2) cortical electrodes. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm0.60$.

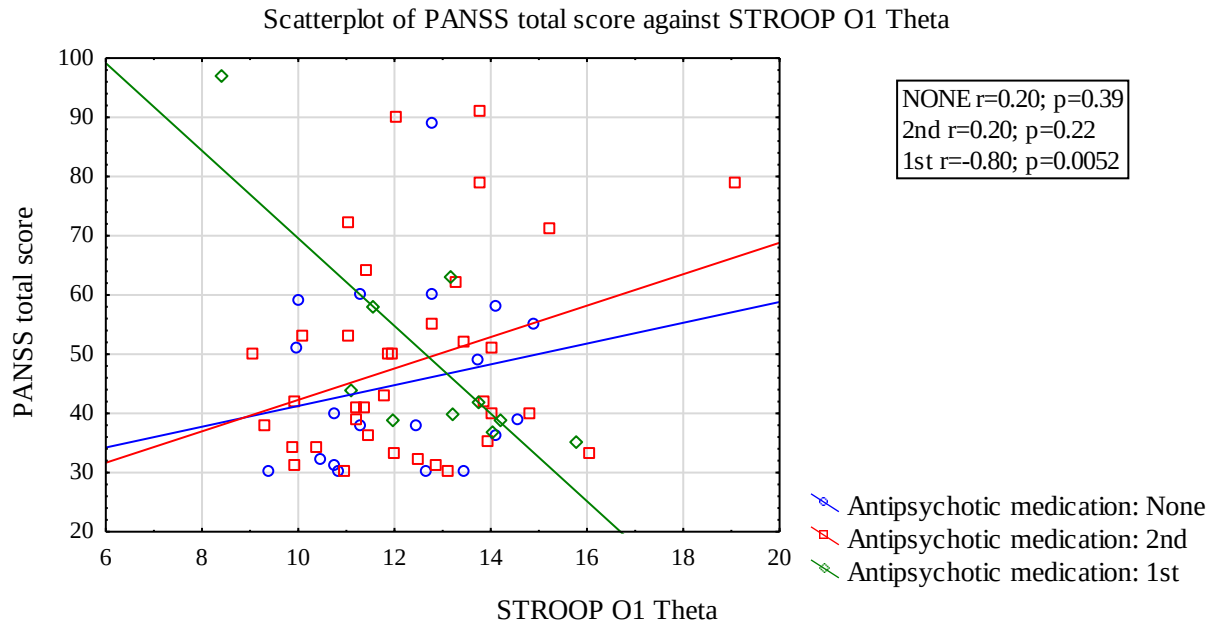


Figure 6.7 STROOP relative theta activity for the left occipital (O_1) electrode for patients prescribed 1st generation antipsychotic medication negatively correlated with PANSS total scores. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance reported for p<0.01 and Rho= >±0.60.

6.3.4 STROOP task relative alpha activity

No significant group differences were found for STROOP relative alpha activity, **Table 6.4**.

Table 6.4 STROOP task relative alpha frequency activity

		Healthy control	**Schizophrenia**	**Methamphetamine-induced psychosis**		
		n = 35	n = 38	n = 31		
		15 females/20 males	8 females/30 males	7 females/24 males		
		Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test/ F test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	16.71(5.98-22.84)	17.21(8.15-23.52)	16.40(7.22-23.42)	$H_{2.100}$=0.44; p=0.80	-
Right prefrontal cortex	**Fp_2**	19.84(8.27-26.59)	18.28(13.77-23.74)	19.27(9.39-24.61)	$F_{2.97}$=0.35; p=0.70	-
Left frontal cortex	**F_3**	17.90(5.67-26.85)	18.78(8.07-27.00)	17.51(8.24-23.14)	$F_{2.97}$=1.26; p=0.28	-
Right frontal cortex	**F_4**	21.03(6.90-26.34)	19.17(14.49-27.17)	19.87(11.21-23.94)	$H_{2.100}$=4.08; p=0.13	-
Left central cortex	**C_3**	21.34(9.67-27.19)	19.56(8.03-26.80)	19.21(8.76-23.65)	$H_{2.100}$=5.63; p=0.059	-
Right central cortex	**C_4**	21.04(6.04-27.89)	18.76(7.94-26.80)	18.31(9.14-23.20)	$H_{2.100}$=3.96; p=0.13	-
Left parietal cortex	**P_3**	21.45(10.04-27.81)	20.10(10.76-25.72)	20.29(8.66-25.32)	$H_{2.100}$=2.5; p=0.28	-
Right frontal cortex	**P_4**	21.49(5.92-28.57)	19.60(9.10-26.82)	19.63(8.00-24.92)	$H_{2.100}$=2.61; p=0.27	-
Left occipital cortex	**O_1**	21.23(9.58-27.07)	19.47(11.01-28.16)	18.49(12.05-25.82)	$F_{2.97}$=1.70 p=0.18	-
Right occipital cortex	**O_2**	20.66(6.42-27.76)	19.70(9.75-28.22)	18.82(8.69-26.04)	$H_{2.100}$=1.96; p=0.37	-

Non-parametric Kruskal Wallis (H-test) and parametric one-way analysis of variance (F-test), Significance P<0.05.

For patients prescribed 1st generation antipsychotic medications (n=12 where, SCZn= 5; MPDn=7), cannabis use positively correlated with STROOP relative alpha activity for the right frontal cortical electrode ($F_4R_{Spearman's(n=10)}$=0.76, p=0.0095), **Figure 6.8**.

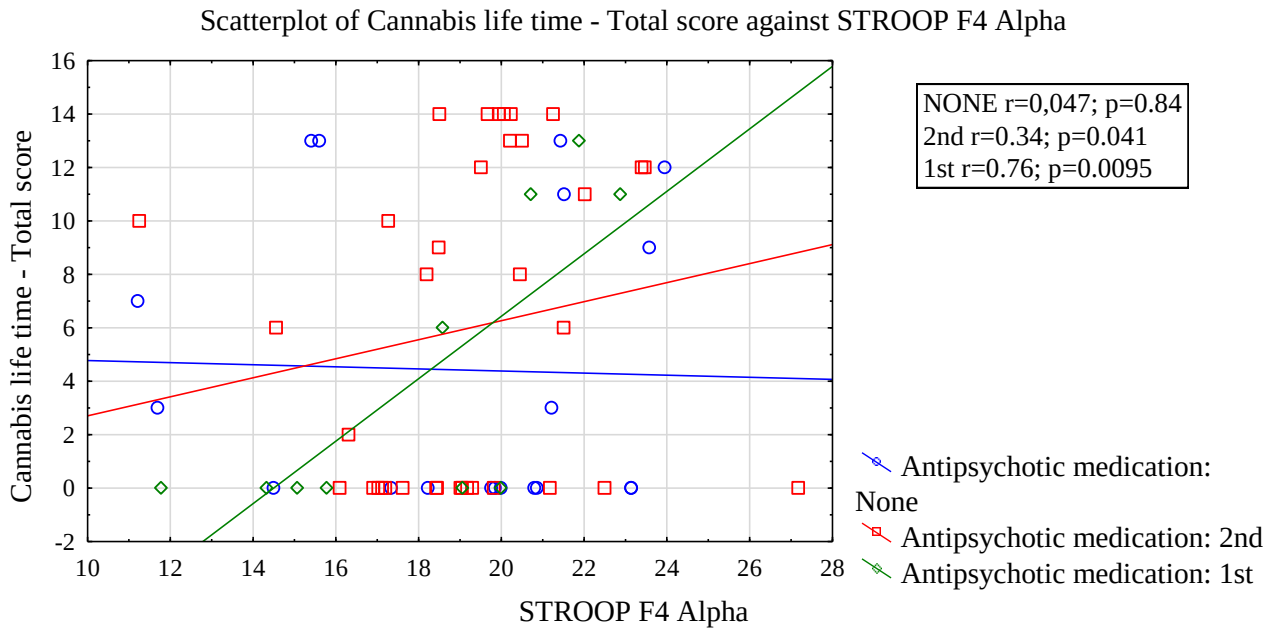


Figure 6.8 STROOP relative alpha activity for the right frontal (F_4) electrode for patients prescribed 1st generation antipsychotic medication positively correlated with cannabis use. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance reported for p<0.01 and Rho= >±0.60.

6.3.5 STROOP task relative beta activity

No significant group differences were found for STROOP relative beta activity, **Table 6.5.**

Table 6.5 STROOP task relative beta frequency activity

		Healthy control	**Schizophrenia**	**Methamphetamine-induced psychosis**		
		n = 35	n = 38	n = 31		
		15 females/20 males	8 females/30 males	7 females/24 males		
		Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test/ F test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	25.83(4.64-35.98)	23.42(8.16-36.99)	22.69(7.98-39.41)	$H_{2.100}$=0.35; p=0.830	-
Right prefrontal cortex	**Fp_2**	27.08(6.98-36.98)	26.95(14.88-39.94)	27.05(10.82-39.93)	$F_{2.97}$=0.70; p=0.93	-
Left frontal cortex	**F_3**	28.87(3.97-42.83)	26.03(8.80-45.09)	24.79(7.88-39.59)	$F_{2.97}$=0.43; p=0.65	-
Right frontal cortex	**F_4**	30.96(7.55-48.74)	30.59(13.82-54.04)	28.74(7.75-45.02)	$F_{2.97}$=0.83; p=0.43	-
Left central cortex	**C_3**	31.04(10.09-43.96)	26.11(8.25-47.59)	25.04(8.26-42.95)	$H_{2.100}$=3.31; p=0.19	-
Right central cortex	**C_4**	30.76(3.67-44.86)	25.04(7.78-46.70)	24.83(6.99-39.22)	$H_{2.100}$=3.25; p=0.19	-
Left parietal cortex	**P_3**	30.47(9.36-49.27)	26.63(8.71-53.42)	27.25(7.53-51.10)	$H_{2.100}$=1.82; p=0.40	-
Right frontal cortex	**P_4**	30.59(4.28-51.48)	28.90(7.77-54.27)	26.09(7.29-39.46)	$F_{2.97}$=1.77; p=0.17	-
Left occipital cortex	**O_1**	30.34(10.27-41.92)	25.88(9.59-46.13)	25.75(8.81-39.01)	$H_{2.100}$=2.20; p=0.33	-
Right occipital cortex	**O_2**	28.43(4.81-42.01)	26.20(9.14-47.60)	27.31(8.90-39.29)	$F_{2.97}$=1.21; p=0.30	-

Non-parametric Kruskal Wallis (H-test) and parametric one-way analysis of variance (F-test), Significance P<0.05.

For patients 2nd generation antipsychotic medication (n=37 where, SCZn=26; MPDn=11), the number of psychotic episodes positively correlated with STROOP relative beta activity for the left central beta cortical electrode ($C_3R_{Spearman's(n=36)}$=0.60, p=0.000095), **Figure 6.9**.

For patients prescribed 1st generation antipsychotic medications (n=12 where, SCZn= 5; MPDn=7), average reaction time negatively correlated with STROOP relative beta activity for the right prefrontal cortical electrode ($Fp_2R_{Spearman's(n=10)}$=-0.84, p=0.0022), **Figure 6.10**; Cannabis use positively correlated with the left parietal beta cortical electrode ($P_3R_{Spearman's(n=10)}$=0.77, p=0.0085), **Figure 6.11.**

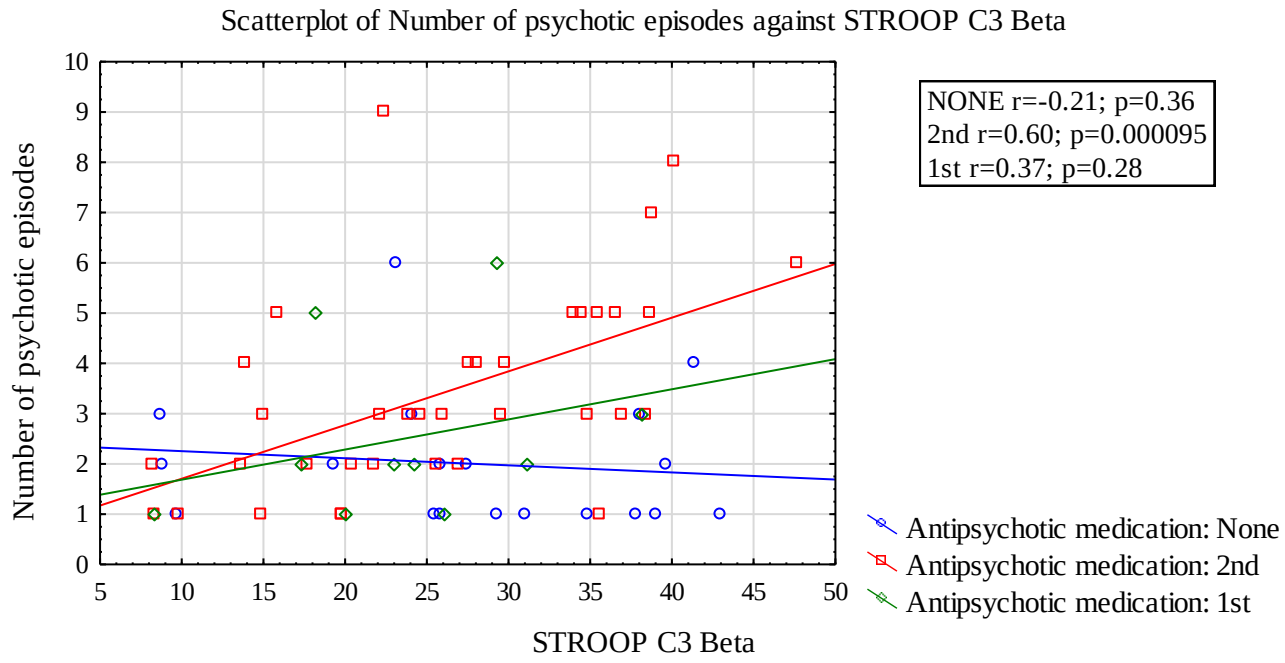


Figure 6.9 STROOP relative beta activity left central (C_3) electrode for patients prescribed 2nd generation antipsychotic medication positively correlated with the number of psychotic episodes. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for p<0.01 and Rho= >±0.60.

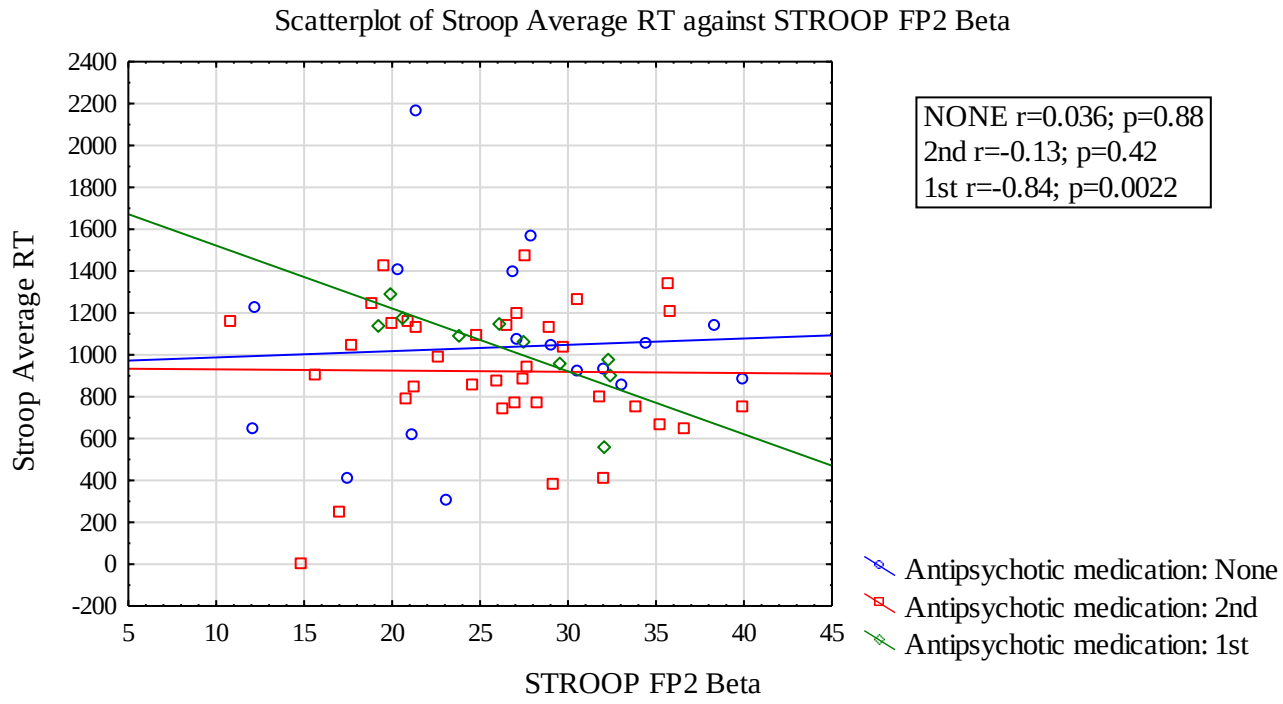


Figure 6.10 STROOP relative beta activity right prefrontal (Fp_2) electrode for patients prescribed 1st generation antipsychotic medication negatively correlated with average reaction time. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= >±0.60.

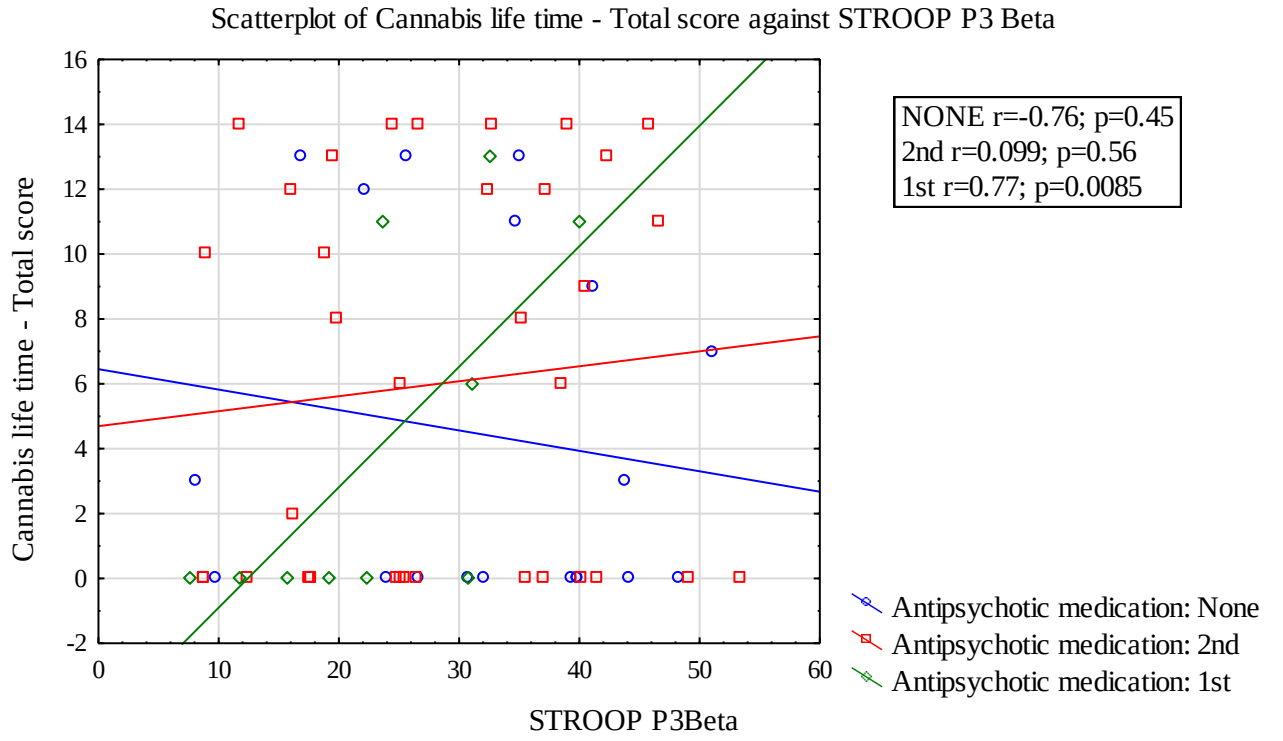


Figure 6.11 STROOP relative beta activity left parietal (P_3) electrode for patients prescribed 1st generation antipsychotic medication positively correlated with the cannabis total score. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= >±0.60.

6.3.6 STROOP task P300 event-related potential waveform

STROOP P300 latency reported a group difference for the left parietal electrodes (P_3 $H_{2.95}$=7.54; p=0.023) where SCZ latency was delayed compared to MPD (P_3 p=0.034). Then the right frontal P300 amplitude (F_4 $H_{2.69}$=6.92; p=0.038) was lower in patients not taking antipsychotics compared to those taking 2nd generation antipsychotics (p=0.038). The left central P300 amplitude (C_3 $H_{2.60}$=13.96; p=0.0009) was increased in patients prescribed 2nd generation antipsychotics compared to those not taking antipsychotics (p=0.0022) and those taking 1st generation antipsychotics (p=0.048), **Table 6.6**.

Table 6.6 STROOP task P300 event-related potential waveform

			Healthy control	**Schizophrenia**	**Methamphetamine-induced psychosis**		
			n = 35	n = 38	n = 31		
			15 females/20 males	8 females/30 males	7 females/24 males		
			Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test/ F test)**	**Post-Hoc**
Left prefrontal cortex	**Fp_1**	A	8,03(-11,87-62,25)	10,15(-9,33-32,11)	9,28(-5,48-48,99)	$H_{2.92}$=0.23; p=0.89	-
		T	352(250-450)	368(250-450)	384(250-450)	$H_{2.92}$=1.11; p=0.57	-
Right prefrontal cortex	**Fp_2**	A	4,39(-13,05-21,64)	5,51(-56,29-26,46)	4,49(-13,12-84,1)	$H_{2.81}$=0.93; p=0.62	-
		T	348(250-450)	340(250-450)	354(250-448)	$H_{2.81}$=0.28; p=0.86	-
Left frontal cortex	**F_3**	A	4,77(-10,32-42,14)	8,21(-6,98-29,11)	6,12(-5,65-34,52)	$H_{2.95}$=2.23; p=0.32	-
		T	374(250-450)	380(250-450)	384(250-450)	$H_{2.95}$=0.03; p=0.98	-
Right frontal cortex	**F_4**	A	1,64(-10,67-10,86)	3,52(-5,97-22,39)	1,8(-10,61-15,81)	$H_{2.94}$=5.39; p=0.067	-
		T	332(250-450)	369(250-450)	368(250-450)	$H_{2.94}$=3.83; p=0.14	-
Left central cortex	**C_3**	A	3,51(-7,39-21,72)	5,38(-6-39,45)	3,3(-17,3-19,13)	$H_{2.95}$=4.20; p=0.12	-
		T	334(250-450)	356(250-450)	380(250-450)	$H_{2.95}$=5.25; p=0.072	-
Right central cortex	**C_4**	A	4,35(-16,79-34,97)	6,55(-9,79-23,74)	4,51(-1,13-22,52)	$H_{2.95}$=4.56; p=0.10	-
		T	320(250-450)	354(250-450)	366(250-450)	$H_{2.95}$=2.77; p=0.24	-
Left parietal cortex	**P_3**	A	2,52(-2,9-11,25)	3,33(-6,65-36,11)	2,05(-1,39-22,75)	$H_{2.95}$=1.13; p=0.56	-
		T	320(200-400)	332(200-400) *	266(200-386)	$H_{2.95}$=7.54; p=0.023	SCZ>MPD p=0.034
Right frontal cortex	**P_4**	A	4,69(-3,97-27,9)	7,07(-3,22-24,89)	6,22(-2,8-16,71)	$H_{2.95}$=3.19; p=0.20	-
		T	310(200-400)	326(202-3236)	344(200-400)	$H_{2.95}$=1.42; p=0.49	-
Left occipital cortex	**O_1**	A	5,88(-0,73-21,84)	8,3(-4,68-25,58)	10,06(1,37-26,51)	$F_{2.92}$=2.36; p=0.099	-
		T	294(200-400)	296(212-400)	274(210-398)	$H_{2.95}$=0.74; p=0.68	-
Right occipital cortex	**O_2**	A	4,38(-0,33-20,51)	8,61(-5,09-23,05)	7,06(-1,85-29,31)	$H_{2.95}$=1.82; p=0.40	-
		T	298(200-400)	282(212-400)	284(200-400)	$H_{2.95}$=0.88; p=0.64	-

****** Schizophrenia (SCZ) reported delayed STROOP P300 latency compared to Methamphetamine-induced psychotic disorder (MPD) % No significance between groups after post-hoc testing. Non-parametric Kruskal Wallis (H-test) and parametric one-way analysis of variance (F-test), Significance P<0.05.*

In SCZ (n=10), the duration of methamphetamine abstinence positively correlated with STROOP right frontal P300 amplitude ($F_4R_{spearman's(n=10)}$=0.87; p=0.00090), **Figure 6.12**.

In patients not taking antipsychotics (n=20 where, SCZn= 7; MPDn=13), behaviourally correct responses negatively correlated with the left parietal P300 latency ($P_3R_{Spearman's(n=15)}$=-0.64, p=0.0087), **Figure 6.13**. Cannabis use negatively correlated with the STROOP right occipital P300 latency ($O_2R_{Spearman's(n=16)}$= -0.66; p=0.0045), **Figure 6.14**.

In patients taking 1st generation antipsychotics (n=12 where, SCZn= 5; MPDn=7), duration of methamphetamine use negatively correlated with the STROOP left prefrontal ($Fp_1R_{Spearman's(n=5)}$= -0.97; p=0.0048), right central ($C_4R_{Spearman's(n=5)}$= -0.97; p=0.0048) and

right parietal ($P_4R_{Spearman's(n=5)}$= -0.97; p=0.0048) P300 amplitude, **Figure 6.15**. The number of psychotic episodes positively correlated with the STROOP left ($O_1R_{Spearman's(n=9)}$=0.79; p=0.0099) and right ($O_2R_{Spearman's(n=9)}$=0.89; p=0.00098) occipital P300 latency, **Figure 6.16**. Lastly, PANSS negative subscale scores positively correlated with the STROOP right occipital P300 latency ($O_2R_{Spearman's(n=9)}$=0.91; p=0.00055), **Figure 6.17**.

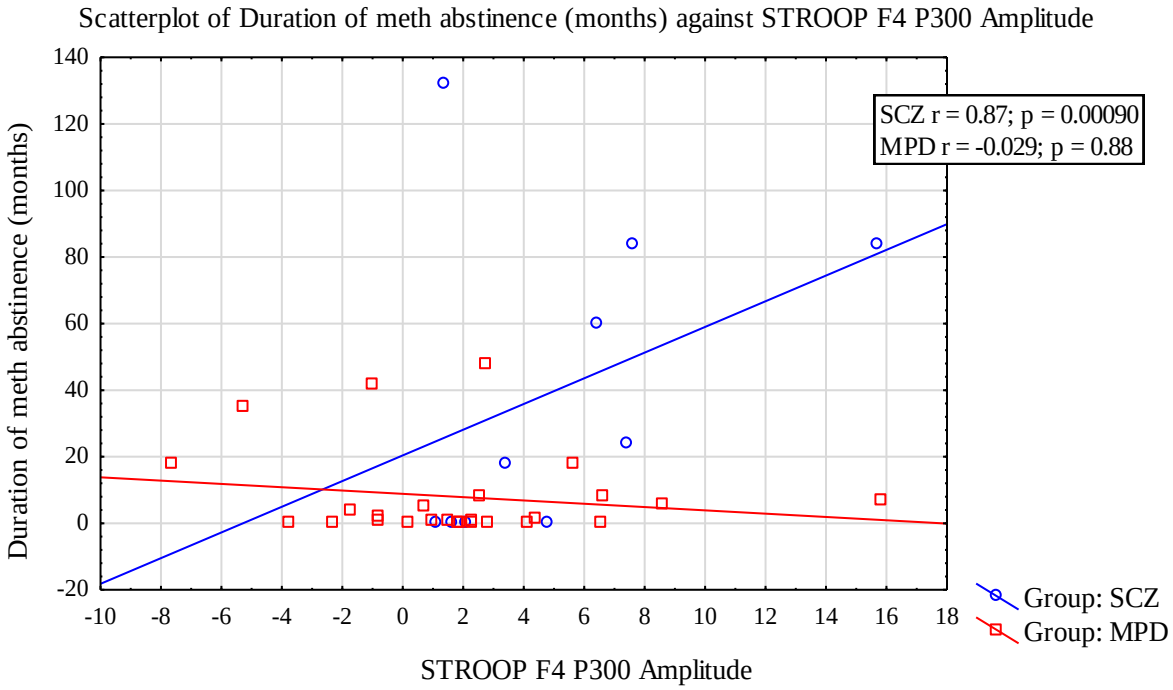


Figure 6.12 STROOP P300 amplitude for the duration of methamphetamine abstinence in months for Schizophrenia positively correlated with the right frontal (F_4) electrode. Schizophrenia (SCZ); Methamphetamine-induced psychotic disorder (MPD). Significance was reported for p<0.01 and Rho= >±0.60.

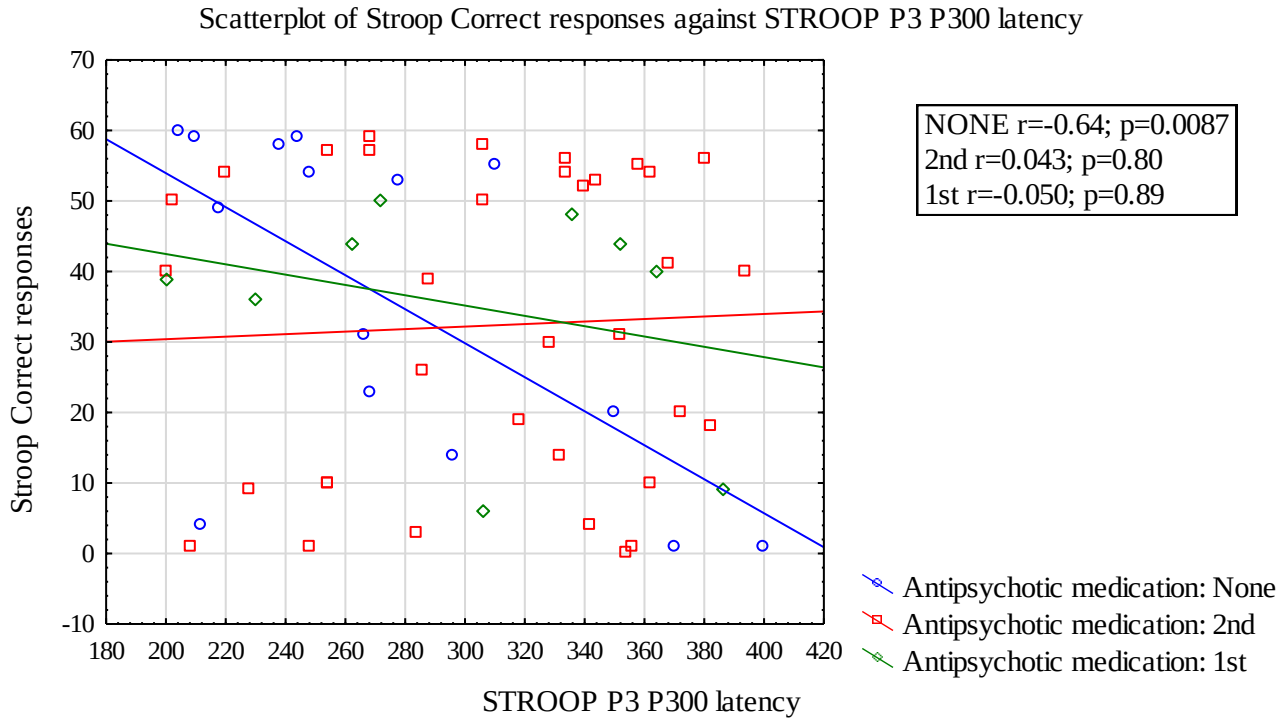


Figure 6.13 STROOP for patients not taking antipsychotic medication negatively correlated with the number of correct responses for the left parietal P300 latency (P_3). Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for p<0.01 and Rho= >±0.60.

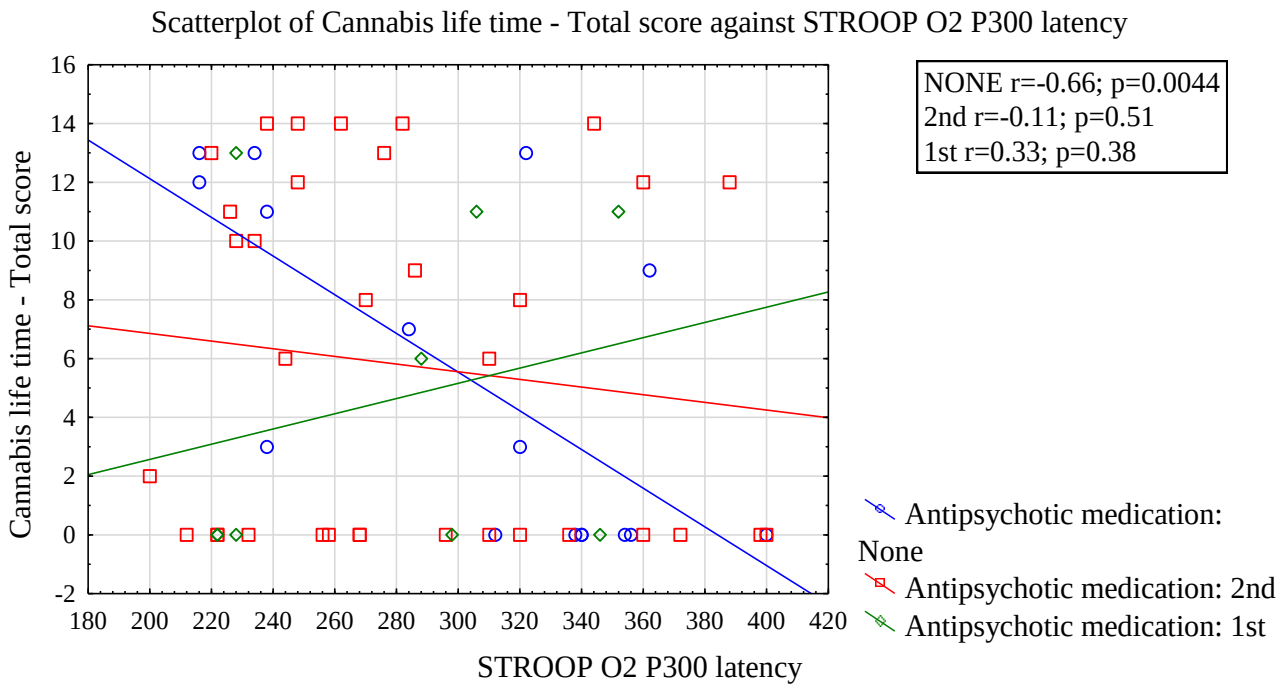
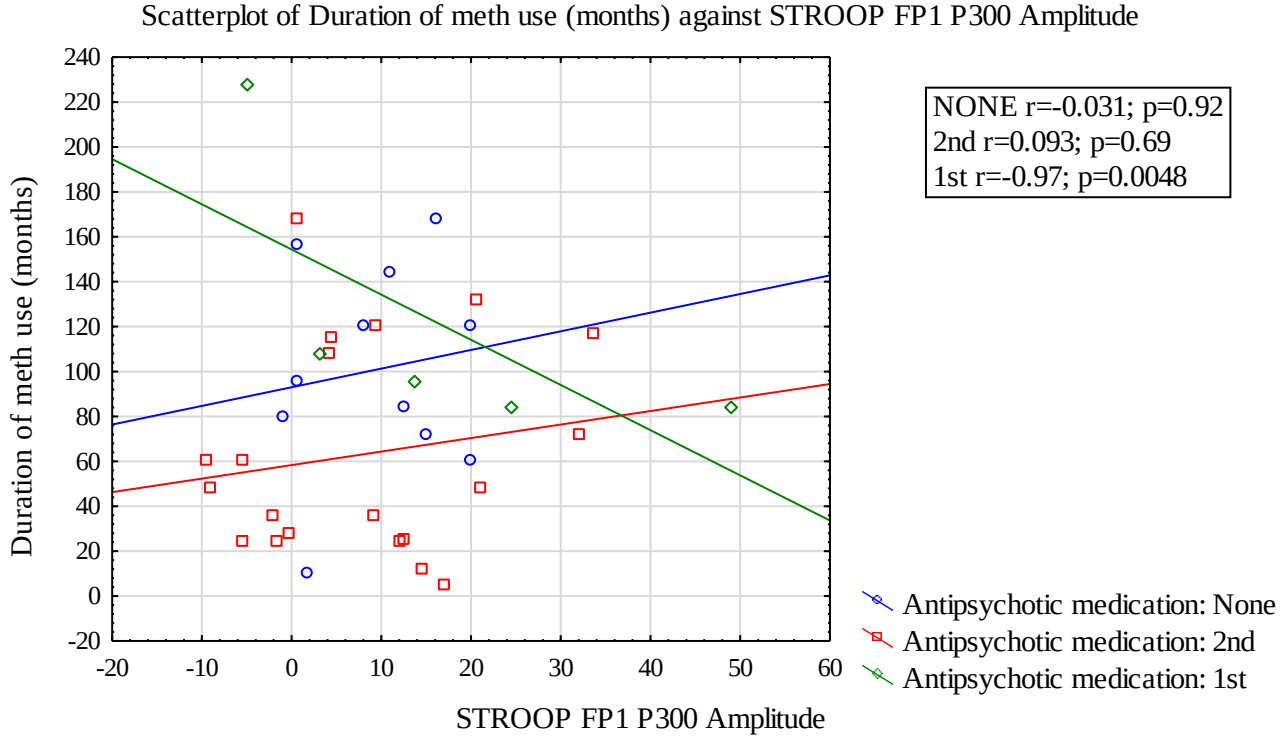


Figure 6.14 STROOP for patients not taking antipsychotic medication negatively correlated with cannabis for the right occipital P300 latency (O_2). Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance reported for $p<0.01$ and Rho= $>\pm 0.60$



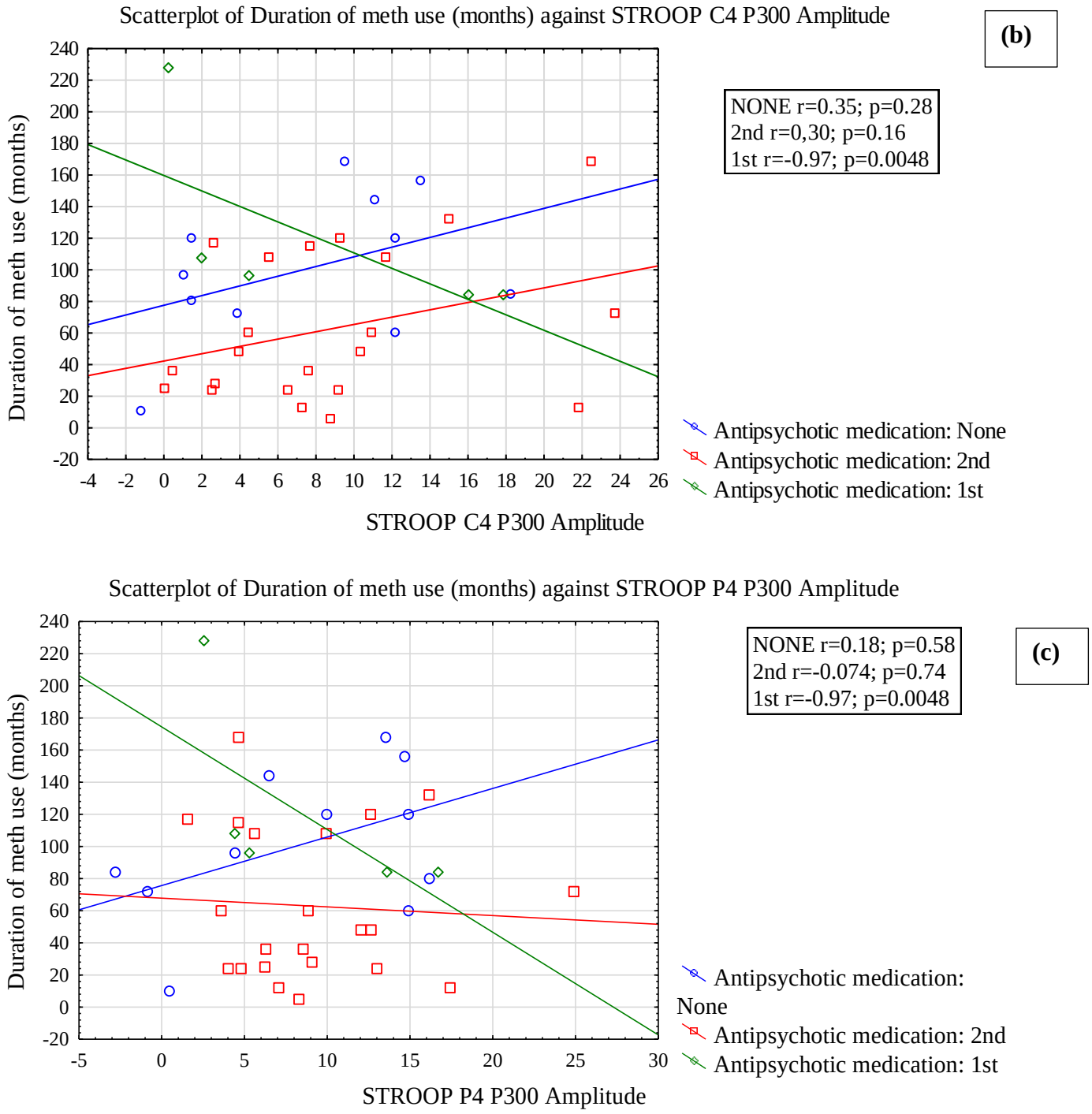


Figure 6.15 STROOP for patients prescribed 1st generation antipsychotic medication negatively correlated with the duration of methamphetamine use for the P300 amplitude **(a)** left prefrontal (Fp_1), **(b)** right central (C_4) and **(c)** right parietal (P_4). Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance reported for $p<0.01$ and Rho= $>\pm 0.60$

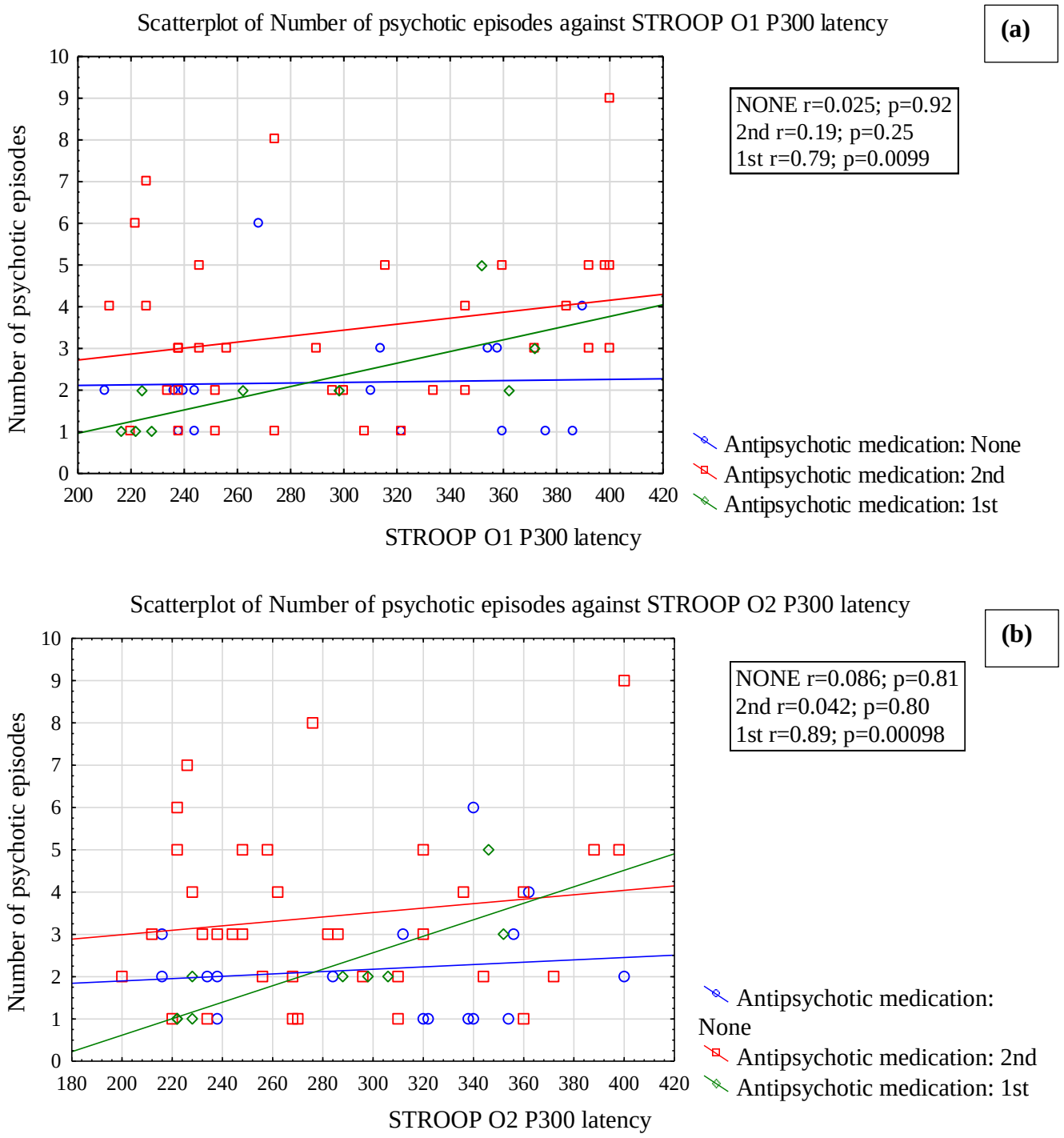


Figure 6.16 STROOP for patients prescribed 1st generation antipsychotic medication number of psychotic episodes positively correlated with the P300 **(a)** left occipital (O_1) and **(b)** right occipital (O_2) latency. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance reported for $p<0.01$ and Rho= >±0.60

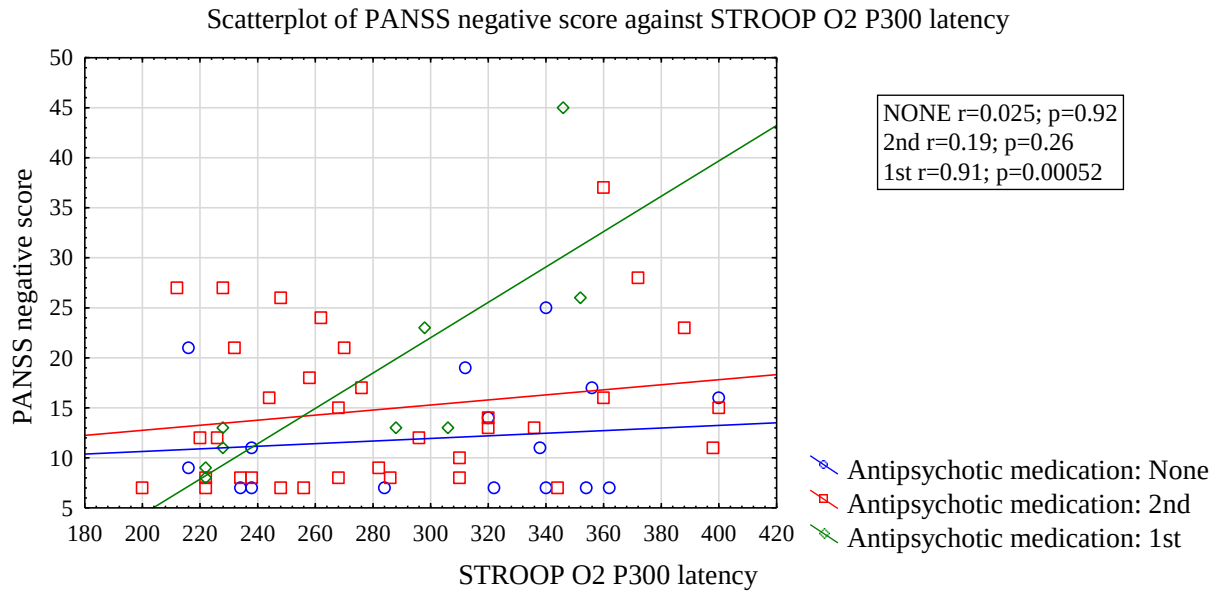


Figure 6.17 STROOP for patients prescribed 1st generation antipsychotic medication the PANSS negative subscale positively correlated with the P300 right occipital (O_2) latency. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance reported for p<0.01 and Rho= >±0.60

6.3.7 STROOP task N170 event-related potential waveform

STROOP N170 latency reported a group difference for the left parietal ($H_{2.95}$=9.86; p=0.0072), right parietal ($H_{2.95}$=6.07; p=0.047) and left occipital ($H_{2.95}$=18.45; p=0.0001) electrodes where MPD latency was delayed compared to CON (P_3 p=0.0069; P_4 p=0.046; O_1 p=0.000074) and SCZ (O_1 p=0.0077), **Table 6.7**.

Table 6.7 STROOP task N170 event-related potential

			Healthy control	**Schizophrenia**	**Methamphetamine-induced psychosis**		
			n = 35	n = 38	n = 31		
			15 females/20 males	8 females/30 males	7 females/24 males		
			Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test/ F test)**	**Post-Hoc**
Left parietal cortex	**P_3**	A	-1,88(-9,61-1,45)	-1,77(-38,39-3,66)	-0,93(-4,26-8,84) *	$H_{2.95}$=1.11; p=0.57	-
		T	172,00(15-198)	142(100-198)	136(100-198)	$H_{2.95}$=9.86; p=0.0072	CON>MPD p=0.0069
Right frontal cortex	**P_4**	A	-2,11(-12,07-18,14)	-2,24(-17,55-16,11)	-2,21(-10,94-7,2)	$H_{2.95}$=1.11; p=0.57	-
		T	170,00(100-198)	142(100-198)	134(100-198)	$H_{2.95}$=6.07; p=0.047	CON>MPD p=0.046
Left occipital cortex	**O_1**	A	-6,11(-22,44-13,55)	-5,81(-21,07-5,48)	-2,87(-15,81-4,71)	$F_{2.92}$=2.36; p=0.099	CON>MPD p=0.000074
		T	174,00(110-198)	162(106-198)	136(100-190)	$H_{2.95}$=18.45; p=0.0001	SCZ>MPD p=0.0077
Right occipital cortex	**O_2**	A	-5,87(-24,11-2,99)	-6,79(-17,02-10,06)	-4,28(-15,32-3,61)	$H_{2.95}$=3.93; p=0.14	-
		T	164,00(100-198)	156(100-198)	142(100-198)	$H_{2.95}$=3.79; p=0.14	-

Non-parametric Kruskal Wallis (H-test) and parametric one-way analysis of variance (F-test), Significance P<0.05.

In patients taking 1st generation antipsychotics (n=12 where SCZn= 5; MPDn=7), duration of methamphetamine use positively correlated with the STROOP left parietal N170 latency ($P_3R_{Spearman's(n=3)}$=0.97, p=0.0048), **Figure 6.18**. The methamphetamine total scores positively correlated with the STROOP right occipital N170 amplitude ($O_2R_{Spearman's(n=9)}$=0.81; p=0.0078), **Figure 6.19**.

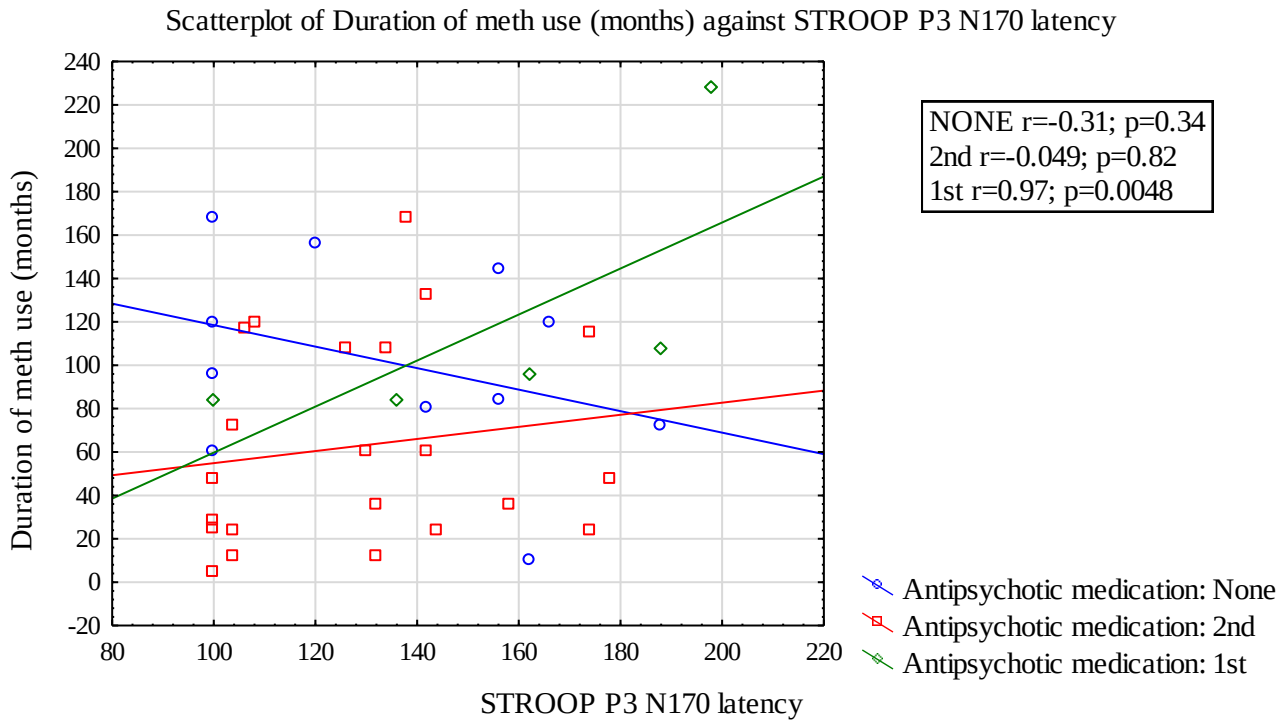


Figure 6.18 STROOP patients prescribed 1st generation antipsychotic medication for the duration of methamphetamine use positively correlated with the left parietal (P_3) N170 latency. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance was reported for $p<0.01$ and Rho= $>\pm0.60$.

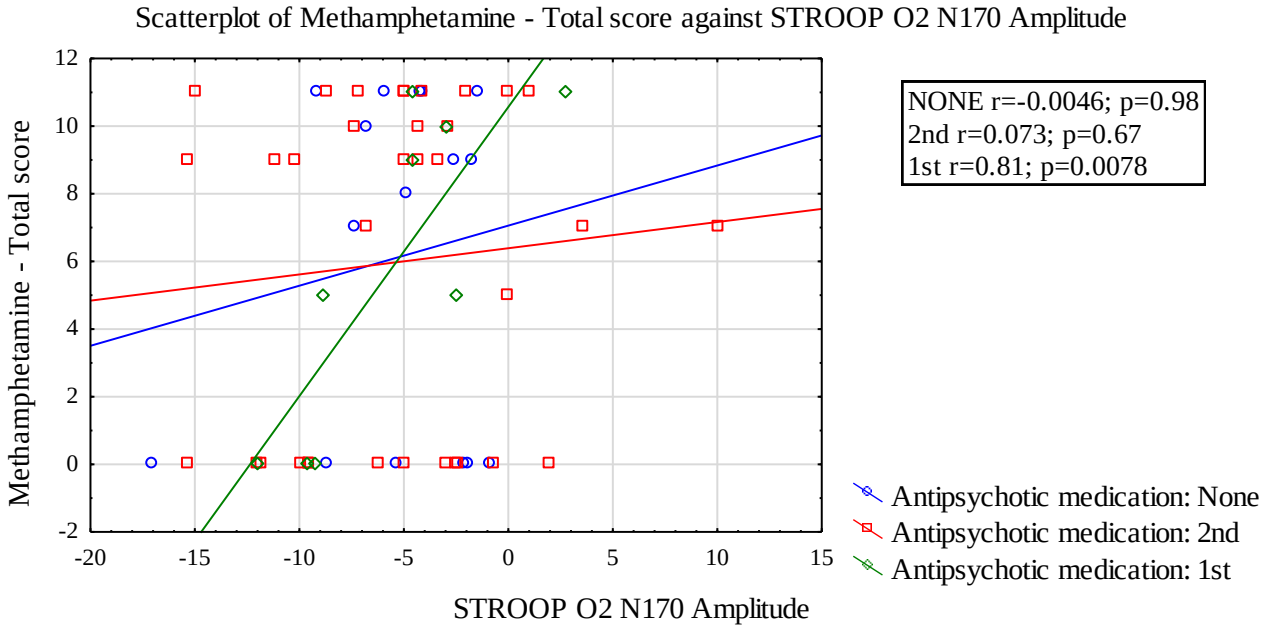


Figure 6.19 STROOP for patients prescribed 1st generation antipsychotic medication the methamphetamine total scores positively correlated with the right occipital (O_2) N170 amplitude. Not taking antipsychotic medication (NONE); prescribed 1st generation antipsychotic medication (1st); prescribed 2nd generation antipsychotic (2nd). Significance reported for $p<0.01$ and Rho= $>\pm0.60$

6.4 Discussion

The present study examined relative frequency activity and the N170 and P300 event-related potentials during the STROOP task in SCZ, MPD and CON, and their potential associations with behavioural performance, clinical symptoms, and prescribed medication. Our main findings suggest that: (1) SCZ and MPD have impaired working memory and cognitive control compared to CON. This was seen by decreased theta cortical activity noted in the frontal through to the parietal area in SCZ and increased errors of commission and reduced working memory reported by square count recall. Further, patients prescribed 2nd generation antipsychotics had improved cognitive processing compared to patients not taking antipsychotics and those prescribed 1st generation antipsychotics. (2) Correlates found within behavioural, clinical and substance involvement which findings further suggest impaired working memory and slowed processing of the information given to respond to in patients compared to controls.

Group differences

The analysis of the cognitive performance assessed via the STROOP task behavioural data revealed SCZ performed poorer than MPD and CON. This included the reporting of fewer correct responses and more commissions compared to CON, and in both SCZ and MPD, more omissions and fewer square counts were reported in comparison to CON. The reduction in square count recall and increased omissions could be a result of negative symptoms and substance use, as seen by negative associations in patients not taking antipsychotics and those taking 1st generation antipsychotics. These results are comparable with our previous study, showing poor performance in SCZ during cognitive tasks (Williams, 2019). Current literature on impaired cognitive function in SCZ revealed theta activity is increased (Wichniak et al., 2015). Our study presents theta activity in SCZ decreases for the left frontal, right central and right parietal electrodes compared to MPD and CON. These results indicate that the attention network within SCZ is impaired (Posner & Petersen, 1990). The use of tobacco was shown to enhance the ability to ignore irrelevant stimuli (Veltri, Taroyan, & Overton, 2017).

Attention-based tasks have been used to identify cognitive deficits where a focus on the P300 ERP waveform is of interest within psychotic disorders. In our study, SCZ reported delayed P300 latency compared to MPD. As seen in the literature, SCZ was shown to present with

increased P300 amplitudes and lengthened latencies (Onitsuka et al., 2013). However, as previously mentioned, medication can affect EEG activity (Babin et al., 2011). We found that patients prescribed 2nd generation antipsychotics presented with increased right frontal and left central P300 amplitudes, which is associated with the anterior cingulate cortex, a brain region responsible for cognitive functioning, attention and error detection (Raz, 2004). Further, a negative association was reported between square count and the number of correct responses with the PANSS negative subscale and substance involvement in patients not taking antipsychotics. And, for patients taking 1st generation antipsychotics, the square count negatively correlated with PANSS general psychopathy subscale and tobacco use. The use of tobacco was shown to enhance the ability to ignore irrelevant stimuli (Veltri et al., 2017). These findings suggest that despite the use of medication cognitive deficits in MPD and SCZ. The literature presents cognitive deficits are more severe among substance abusers, however, these results indicate that the deficits in SCZ are more severe compared to MPD and CON. As the neurophysiological mechanisms to understanding MPD are limited, a secondary investigation into the association cognitive performance has on the frequency and the P300 ERP waveform was conducted.

Cognitive performance, frequency and P300 event-related potential waveform correlates

In this study, methamphetamine abstinence was found to positively correlate with the P300 amplitude in the right frontal region in SCZ. The P300 amplitude was found to be increased over anterior regions in individuals who abstained from methamphetamine use (Haifeng et al., 2015). These results follow current literature showing increased P300 amplitude during the STROOP task. However, in patients taking 1st generation antipsychotics, the duration of methamphetamine use negatively correlated with the left prefrontal, right central and right parietal P300 amplitude. This is consistent with current literature showing decreased cognitive functioning in long-term methamphetamine users as a result of brain structural abnormalities (Berman, O'Neill, Fears, Bartzokis, & London, 2008). In patients taking 1st generation antipsychotics, the square count positively correlated with tobacco use, and correct responses positively correlated with alcohol use. Cannabis use negatively correlated with the right occipital P300 latency in patients not taking antipsychotics, but positively correlated with the right frontal alpha and left parietal beta cortical electrode in patients prescribed 1st generation antipsychotics. Cannabis use was found to reduce cortical function in high-risk psychosis patients (Winton-Brown et al., 2015). In literature, left hemispheric activation was shown to result from task repetition (Nemrodov, Harpaz, Javitt, & Lavidor, 2011), which is noted during

the STROOP task due to the repetitive flashing of colour-named words in the incorrect colour creating conflict. In patients taking 1st generation antipsychotics, posterior P300 latency positively correlated with the number of psychotic episodes, and negatively correlated with the number of correct responses. Cognitive deficits in SCZ are noted in the literature to present with increased P300 amplitudes and lengthened latencies (Onitsuka et al., 2013). These results add to the current literature showing delayed P300 latency in SCZ compared to MPD. Longer latencies were found to be associated with the severity of symptoms within psychotic groups (Clayson, Baldwin, & Larson, 2013; Polich, 1992). In another study, increased N170 amplitude and delayed latency across the frontal parietal region, were found to be a characteristic of impaired cognitive control and attention-based dysconnectivity in unmedicated SCZ patients (Kraguljac et al., 2016). In our study, a positive correlation was found for the posterior N170 amplitude and latency in methamphetamine users. The duration of methamphetamine use correlated with the N170, indicating that longer use of methamphetamine can have detrimental effects on the processing of information and cognitive control despite being prescribed antipsychotic medication.

This study included 104 individuals recruited from hospitals within South Africa. As not every individual has had access to a computer, the limitations of the study are the lack of computer skills from several individuals. In this study patients who were on a medication regime were included; however future work should include a control group of unmedicated patients. Further, studies should include mapping the EEG data to brain structure through structural brain imaging or a combination of fMRI and EEG studies.

In this chapter, I aimed to identify cognitive impairments in SCZ, MPD and CON by investigating relative frequency activity and the N170 and P300 event-related potentials during the STROOP task, and their potential associations with behavioural performance, clinical symptoms, and prescribed medication. As expected, we found SCZ had impaired cognitive processing seen by delayed response times. Further indications of cognitive impairments were seen through delayed N170 and P300 ERP waveform latencies in SCZ compared to MPD and CON. Working memory and cognitive control are impaired in both SCZ and MPD, more so in SCZ.

In the current and previous chapters, I investigated cortical processing, cognitive functioning, attention, working memory, cognitive control and executive functioning in schizophrenia and methamphetamine-induced psychotic disorder. Both these psychotic disorders have impaired

cognitive functioning. In the next chapter, I explored the relationships between (neuro) immune markers, relative frequency and P300 event-related potential waveforms in schizophrenia and methamphetamine-induced psychotic disorder to delineate neuroinflammatory mechanisms that are involved in the electrophysiological functions.

7 An explorative study on neuroimmune markers, electroencephalography frequency and the cognitive P300 in psychotic disorders

Abstract

Introduction: An abnormal immune status, characterized by increased pro-inflammatory cytokines across psychotic disorders, has gained increasing interest in recent years. However, research on the association (neuro) inflammation has on cortical arousal and neural circuitry is lacking in schizophrenia (SCZ), and more so in methamphetamine-induced psychotic disorder (MPD). In this exploratory study, we aimed to investigate associations in peripheral immune markers with electroencephalography (EEG) relative frequency (alpha, theta, beta, and delta) during resting state and cognitive tasks, including the P300 event-related potential waveform between healthy controls, SCZ, and MPD.

Methods: EEG was recorded from 104 individuals: SCZ (n=38), MPD (n=31), and controls (n=35), who completed resting state, and three cognitive tasks which addresses cognitive function (STROOP, continuous performance task (CPT) and cued target detection task (CTD)). IL-8, IL-10, IL-12p70, IL-1β, TNF-α and IFN-γ concentrations were measured in serum samples with a multiplex bead array (Merck). Group differences were determined by ANOVA with Bonferroni post-hoc correction or multivariate Kruskal-Wallis test, dependent on data distribution. Associations were determined using Pearson's or Spearman's rank order correlation ($p<0.01$) where appropriate.

Results: No significant group differences were found between groups, however, significant correlations were found where; IFN-γ negatively correlated with the left parietal CTD no cue P300 latency in SCZ ($r=-0.60;p=0.00035$), and positively correlated with the right frontal CTD no cue P300 latency in MPD ($r=0.64;p=0.0031$). Lastly, IL-12p70 positively correlated with the right occipital CTD incongruent P300 amplitude in MPD ($r=0.61;p=0.0032$).

Conclusion: Our study found that associations between (neuro) inflammation, and cognition is apparent in SCZ and MPD. These associations further suggest links between altered (neuro) inflammation with the anterior cingulate cortex, involved in fundamental cognitive functioning processes, and visual information processing. This study indicates that more research is needed on the role of neuroinflammatory pathways in the disease mechanisms of SCZ and MPD.

7.1 Introduction

An abnormal immune status, characterized by increased pro-inflammatory cytokines, has been reported in psychotic disorders (Dimitrov, Lee, Yantis, Honaker, & Braida, 2014; Vezzani, 2020). However, the link between (neuro) inflammation, electroencephalography (EEG) frequency and event-related potential (ERP) in psychotic disorders is not yet known. EEG is defined as a measure of real-time electrical brain activity which can provide information about specific frequencies being produced for diagnostic purposes (Ranlund et al., 2014). Increased (neuro) immune marker levels in blood were found to associate with cognitive decline in individuals with neurodegenerative disorders (Sankowski et al, 2015; Kempuraj et al, 2016), Alzheimer's (Moynagh, 2005); Al-Qazzaz et al, 2014), and some research on inflammation and its associations with epilepsy (Vezzani, 2020). (Neuro) inflammation is defined as a specialized inflammatory response in the brain and is involved in the pathophysiology of many brain disorders. Neuroinflammatory processes affect the nervous system, causing alterations in neurotransmitter metabolism, dysregulation of the hypothalamus-pituitary-adrenal axis, pathologic microglial cell activation, impaired neuroplasticity, and structural and functional brain changes that consequently affect cognition and emotional behaviour (Rhie et al, 2020).

The relationship between cytokine profiles and EEG, relative frequency (alpha, beta, delta, and theta) band activity and ERP activity, is largely absent in SCZ and completely absent in MPD. Altered levels of cytokines were found in patients diagnosed with SCZ. IL-6 was found to be increased in individuals who are at risk of developing psychosis (Dimitrov et al., 2014). Increased inflammatory markers IL-5, IL-10, and TNF-α in individuals with SCZ (Upthegrove, Manzanares-Teson, & Barnes, 2014) and increases in IL-6, IL-1β, and TNF-α were reported in individuals using MA (X. Li et al., 2018). Moreover, levels of pro-inflammatory cytokines (IL-1β, IL-6, IL-8, IFN-γ) were decreased among amphetamine-using individuals with psychosis compared to those using amphetamine without psychosis (Chang Kuo et al., 2018). The current literature in SCZ suggests IL-1β, IL-6, and TNF-β serve as state markers in SCZ and the presence of IL-12, IFN-γ and TNF-α are possible trait markers for SCZ (Momtazmanesh et al., 2019). Trait markers refer to the behavioural properties and biological processes that play an important role in the predisposition of SCZ whereas state markers refer to the status of clinical manifestations in the patient. Additionally, signs of inflammation in SCZ brains have been found, indicating that processes involving microglia activation in the central nervous system could be the cause of sickness behaviour i.e. depression, anxiety, loss of concentration and reduction in grooming (Müller, Weidinger, Leitner, & Schwarz, 2015).

Studies with a focus on neuroinflammatory markers in MPD are lacking, especially on the differential neuroinflammatory profiles which underlie SCZ and MPD. However, the use and abuse of substances were found to associate with immune function alterations, causing an increased susceptibility to infection and diseases (Loftis & Janowsky, 2014; Mahadevan et al., 2017). The subsequent involvement and activation of cytokines and their' release were found to be associated with methamphetamine abuse (Guerri & Pascual, 2018). Induced hypothermia as a result of methamphetamine use, increased IL-1β levels in the brain (Numachi et al., 2007). Furthermore, the neurotoxicity from methamphetamine results in neuroinflammation and necrosis of neurons (Adhikary, 2014), which indirectly can activate neuroinflammatory pathways. Another EEG study assessed the effects of (neuro) inflammation on attention specifically alerting, orienting and executive control. They found that in alerting attention, inflammation was associated with an increase in cue-induced suppression of the alpha power. It was also noted that no association was found between inflammation and the orienting or executive control attentional process (Balter et al., 2019). However, in SCZ most research on the topic of (neuro) inflammation need to account for medication, as the medication prescribed to SCZ may contain anti-inflammatory properties (Pasternak et al., 2016). The effects of antipsychotic medication on inflammation are dependent on whether the antipsychotic is an atypical or typical antipsychotic (Radtke et al., 2017). Typical antipsychotics decrease the levels of IL-1β, IL-6 and TNF-α in SCZ, whereas atypical antipsychotics increase inflammatory responses (Na et al., 2014). It is important to understand the role of neuroinflammatory processes in the pathogenesis of cognitive decline in SCZ and MPD due to the impact it has on an individual's recovery before, during and after a psychotic episode.

As the literature on the association of neuroinflammation on EEG data is limited, for this study we will explore the relationships between peripheral cytokine expression (IL-1β, IL-8, IFN-γ, TNF-α, IL-12 and IL-10) and EEG tonic and phasic activity along with resting state EEG (alpha, theta, beta, and delta) and the P300 ERP waveform of three cognitive tasks. To my knowledge, there are no studies which have focused on the effects of inflammation on cortical arousal and cognition in SCZ and MPD. This will be the first study to investigate neuroinflammation and its association with electrophysiology in MPD. By determining the associations that (neuro) inflammation has on cortical arousal and cognition, these associations can aid in understanding the neural networks involved in SCZ and MPD and how neuroinflammatory processes play a role in the disorders. This exploratory study aimed to investigate whether there are relationships between peripheral blood cytokine levels (IL-1β,

IFN-γ, IL-12p70, IL-8, IL-10 and TNF-α) and EEG tonic and phasic activity between SCZ, MPD and healthy controls (CON). Then relationships were determined between cytokine levels and the population characteristics, relative frequency (resting states, continuous performance (CPT) task, cued target detection (CTD) task and STROOP task) and P300 ERP waveform (CPT, CTD and STROOP task). We expect to find increased inflammatory markers in individuals with SCZ. In the literature, increased levels of immune markers IL-10, and TNF-α were noted and showed significant differences in MPD compared to CON (Burns & Ciborowski, 2016). Moreover, levels of pro-inflammatory cytokines (IL-1β, IL-8, IFN-γ) were decreased within MPD (X. Li et al., 2018). This study will further support markers of (neuro) inflammation within SCZ and MPD. This will be the first study to investigate (neuro) inflammation and its association with electrophysiology in MPD.

7.2 Methods

7.2.1 Research participants

104 South African individuals, between the ages of 20 and 45 years, participated in this study: 38 with SCZ (8 females/30 males), 31 with MPD (7 females/24 males), and 35 healthy controls (CON: 15 females/20 males). The study was approved by the Health Sciences Research Ethics Committee, at the University of Cape Town (HREC Ref. No.: 479/2019). Western Cape Provincial and Hospital approval was also obtained. All research activities were conducted in accordance with the Declaration of Helsinki. All research participants provided voluntary informed consent.

Participants visited the laboratory twice. The first visit included the provision of informed consent and an assessment clinical interview. All participants underwent a Structured Clinical Interview for Diagnostic Systematic Manual- IV (SCID-DSM-IV), with modifications to include changes made in DSM-5. Control participants were excluded if there was a history of psychotic symptoms or a family history of psychotic disorder. Participants with a psychotic disorder were excluded if they did not meet the diagnostic criteria for the study conditions: for example, participants with schizoaffective disorder were excluded. Participants were also excluded if they were younger than 19 years or older than 40 years, had general medical conditions that required prescription medications, had an apparent learning disability, had major brain trauma/surgery, had any history of cardiovascular insult, individual or family history of epilepsy, medical implants or any metal within their person, for example, shrapnel.

Female participants were excluded if they were pregnant or lactating. Patients with SCZ were excluded if any of their episodes were considered to be related to the use of a substance. MPD included psychotic symptoms with onset during methamphetamine intoxication or withdrawal and did not persist beyond 1 month since the last use of methamphetamine, or evidence of an underlying 'primary' psychotic disorder not related to the use of methamphetamine. Evidence that the symptoms are better accounted for by a psychotic disorder that is not methamphetamine-induced included the following: the symptoms precede the onset of the methamphetamine use; the symptoms persist for a substantial period of time after the cessation of acute withdrawal or severe intoxication, or are substantially in excess of what would be expected given the amount of methamphetamine used or the duration of use; or there is other evidence that suggests the existence of an independent non-MPD (e.g. a history of recurrent non methamphetamine-related episodes). Patients with MPD were excluded if it was unclear if methamphetamine was causal to their symptoms or diagnosis, and if any of their psychotic episodes may have been related to another substance of abuse.

7.2.2 Study design

The second visit included a full morning of brain imaging. All EEGs were performed between 09h00-11h00, on a weekday. All clinical scales were performed on the same day and after the morning of brain imaging by trained clinical personnel.

Clinical rating scales included the Positive and Negative Syndrome Scale (PANSS); Calgary Depression Scale for Schizophrenia; Hamilton Rating Scale for Depression. Chlorpromazine equivalents were calculated from current medication regimes. Drug use history, nicotine, alcohol and methamphetamine were recorded using the Kreek-McHugh-Schluger-Kellogg scale (KMSK).

7.2.3 Peripheral immune marker analysis

Blood was collected via venepuncture into serum tubes that were kept a room temperature for 30 minutes to allow for clotting. The tubes were centrifuged, and serum samples were collected into cryovials and immediately stored at -80°C.

The immune markers; IL-1β IL-8, IL-10, IL-12p70 TNF-α and IFN-γ, were analysed with a Milliplex® Luminex human cytokine magnetic bead panel (HSTCMAG28SK07; Merck) according to the manufacturer's instructions. Plates were assayed on a Luminex system (Bio-Plex 200 System; Bio-Rad). All samples were blinded and assayed in duplicate. The plates were then incubated overnight at 4°C. The plates were washed three times and detection

antibodies were added to each well and incubated for 2 hours at room temperature. The plates were washed and Streptavidin-Phycoerythrin was added to each well and incubated for 30min at room temperature. All incubations were performed on an orbital shaker at 800rpm. The plates were washed and read on a Luminex system (Bio-Plex 200 System; Bio-Rad). The ranges of the R^2 values for the standard curves were between 0.996–1. All the controls were within the range supplied by the manufacturer. All plates were analysed simultaneously on the same day. The intra-assay coefficients of variation for each cytokine marker were <14%.

7.2.4 Electroencephalography

EEG recording of REO and REC was undertaken using a simple EEG montage that included prefrontal (Fp1 and Fp2), frontal (F3 and F4), central (C3 and C4), parietal (P3 and P4) and occipital (O1 and O2) electrodes. Standard 10/20 caps (Electro-Cap International, Inc.) were used, of either medium or large size depending on the head circumference of the participant. Participants were grounded peripherally, linked earlobe reference was applied, and electrooculography (EOG) was recorded. The EEG system used was the Biopac MP150 system with 100 C EEG amplifiers and an EOG amplifier (Biopac Systems, Inc.). Digital EEG data and analogue data, from E-prime, were collected via the MP150 system, with a sampling rate of 500Hz, and were visualised in real-time using Acq-Knowledge 4.1 (Biopac Systems, Inc.).

For EEG data processing, data were first eye blink corrected and movement corrected (EOG), using automated ICA EOG correction in Acqknowledge 4.1 (Biopac Systems, Inc.), and then bandpass filtered 0.1–30Hz and Fourier transformed, using an in-house Matlab GUI, to accommodate differences in participant electrical brain activity conduction. Relative (%) frequency bands power activity was extracted: delta (0.1–4.0Hz), theta (4–7Hz), alpha (7–14Hz) and beta (15–30Hz).

Resting states

Prior to obtaining EEG records, participants were familiarised with the different conditions: REO, and REC. For REO, using E-prime, a cross-hair, +, was presented on the screen and participants were asked to relax and look at the cross-hair. For REC ‘CLOSE EYES’ was presented on the screen in front of them. Records of 3 min EEG were obtained for each of the resting-state conditions.

Continuous performance task

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 are presented with 60 trials with three consecutive S's, the presentation of the third S requires a behavioural response. In addition, 40 single S's or trick S's are embedded in the task with 300 inter-stimuli letters. The trick stimulus was presented to distract the participant from the presentation of the three consecutive S's. The task contains 20 letters of the alphabet and excluded the vowels, A, E, I, O, and U as well as the letter X. Each letter was presented for 500msec with a 100 msec inter-stimulus interval before the next stimulus. However, the participant can shorten the presentation of the third S if a response is given before the 500msec time limit. Once the task was complete, the participant was asked to relax. The mental effort scale was handed to the participant for them to mark how much effort was applied to conduct the task. The behavioural data collected, were extracted using E-prime and were cross-checked with the digital inputs to an EEG data file Acknowledge 4.1 (Biopac Systems, Inc.). The behavioural data extracted included the number of correct responses, response time duration, errors of omission and commission.

Cued-target detection task

The cued target detection task (CTD) focuses on assessing attention, more specifically divergent attention. The CTD requires participants to focus on a solid grey circle in the centre of the computer screen. An outline of a grey rectangle was positioned on either side of the central cue, which remains throughout the cognitive task. The participant is required to respond to the presentation of a square within either of the rectangles. For this task, there are four conditions: (1) congruent cue and stimulus presentation; (2) incongruent cue and stimulus presentation; (3) double cue and stimulus presentation; and (4) no cue and stimulus presentation. The cues are presented for 500 msec and the stimulus is presented for 500 msec. The inter-stimulus interval is variable throughout the task, with durations of 500, 1000, or 1500 msec. The CTD has 64 congruent stimuli; 16 incongruent stimuli; 16 double-cueing stimuli; and 16 no-cue stimuli. The ERP waveform windows we are expecting to see due to their link with attention are the P100, P150, N170 and P300. Behaviourally, the reaction time, correct detection, omission errors and commission errors will be extracted and analysed.

Stroop colour word conflict task

The Stroop task was designed to identify executive functioning associated with frontal lobe dysfunction. The task consists of the individual appearance of four colour words (red, blue, yellow and green), displayed in five different colours (red, blue, yellow, green, and grey) in the centre of a computer monitor on a black background. Each cue is displayed in either coloured (red, blue, yellow or green) or grey ink (distractor cues) but never displayed congruently in the same colour as the written word (e.g. never the written word "blue" in blue font). In total, 108 cues are randomly presented, 18 incongruent colour words in each of the 4 colours red, blue, green and yellow (72 incongruent words in total); and 18 grey words. Participants respond as quickly and accurately as possible by pressing single keys on a standard computer keyboard which correspond with the various word/colour arrangements. The participants respond to the colour of the word and not the written word, except if the word is written in grey ink where a response to the written word itself is required. Incorporating grey words ensures that participants have to read and recognize the word prompts rather than just notice the colours, thereby invoking the Stroop effect i.e. dissonance (Stroop, 1935). Behaviourally, the reaction time, correct detection, omission errors and commission errors will be extracted and analysed.

7.2.5 Statistical analysis

Statistical analysis was conducted using Statistica (Dell Inc, 2015). To identify group differences in cytokine levels (IFN-γ, IL-8, IL-12p70, TNF-α, IL-1β and IL-10), an analysis was conducted for (a) three groups (CON, SCZ and MPD). For correlation analysis, the demographics (age on the day of testing, duration at school, tertiary education, and total years of education), 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, duration of illness, drug use (methamphetamine, alcohol, tobacco, cannabis), and medication use (chlorpromazine equivalent dose), then EEG relative frequency activity (resting states, STROOP, CPT and CTD) and P300 ERP waveform in the cognitive tasks (STROOP, CPT and CTD) were included.

First, an analysis of distribution for each cytokine, using skewness and kurtosis 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 between-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 ($p < 0.05$).

Where appropriate, according to the data distribution, correlation analysis was performed using Pearson's or Spearman's rank order (Rho >±0.6 and p-value <0.01). Cytokine levels that were below the lower limit of detection (IFN-γ (n=0), IL-1β (n=2), IL-8 (n=0), IL-12p70 (n=0), TNF-α (n=1), IL-10 (n=35)) were replaced by values representing the lowest value of on the standard curve to avoid statistical bias.

7.3 Results

7.3.1 Differences in cytokine concentrations between groups

A total of one hundred and four South African individuals, between the ages of 20 and 45 years, participated in this study: thirty-eight participants with a diagnosis of schizophrenia (SCZ n=38; 8 females/30 males), thirty-one participants with a diagnosis of methamphetamine-induced psychotic disorder (MPD n=31; 7 females/24 males), as well as thirty-five socio-demographically matched control participants (CON n=35; 15 females/20 males).

No significant group differences were found for IFN-γ, IL-8, IL-12p70, TNF-α, IL-1β and IL-10, **Table 7.1**.

Table 7.1 Cytokine concentrations

	Healthy control	**Schizophrenia**	**Methamphetamine-induced psychosis**		
	n = 35	n = 38	n = 31		
	15 females/20 males	8 females/30 males	7 females/24 males		
	Median (min-max)	**Median (min-max)**	**Median (min-max)**	**ANOVA (H test/ F test)**	**Post-Hoc**
IFN-γ	2.20(0.70-3.90)	1.71(0.76-4.16)	1.46(0.63-3.98)	$H_{2.104}$=2.81; p=0.2447	--
IL-10	0.88(-3.50-3.68)	0.88(-3.50-3.61)	0.92(-3.50-3.46)	$H_{2.104}$=1.24; p=0.5361	--
IL-12p70	2.02(0.75-3.63)	1.89(0.13-3.70)	1.56(-0.40-3.17)	$F_{2.101}$=2.68; p=0.0730	--
IL-1βb	0.49(-0.46-2.61)	0.33(-0.09-2.71)	0.25(-0.34-1.81)	$H_{2.104}$=1.18; p=0.5523	--
IL-8	2.01(0.98-4.38)	1.90(0.81-3.61)	1.96(0.44-3.06)	$F_{2.101}$=0.060; p=0.9417	--
TNF-α	1.28(0.57-3.044)	1.22(0.48-3.17)	1.24(0.04-3.02)	$H_{2.104}$=0.57; p=0.7504	--

Non-parametric Kruskal Wallis (H-test) and parametric one-way analysis of variance (F-test), Significance P<0.05.

7.3.2 IFN-γ correlates

In SCZ, IFN-γ negatively correlated with the left parietal CTD no cue P300 latency ($P_3R_{spearman's(n=30)}$=-0.60; p=0.00035), **Figure 7.1**.

In MPD, IFN-γ positively correlated with the right frontal CTD no cue P300 latency ($F_4R_{spearman's(n=19)}$=0.64; p=0.0031), **Figure 7.2**.

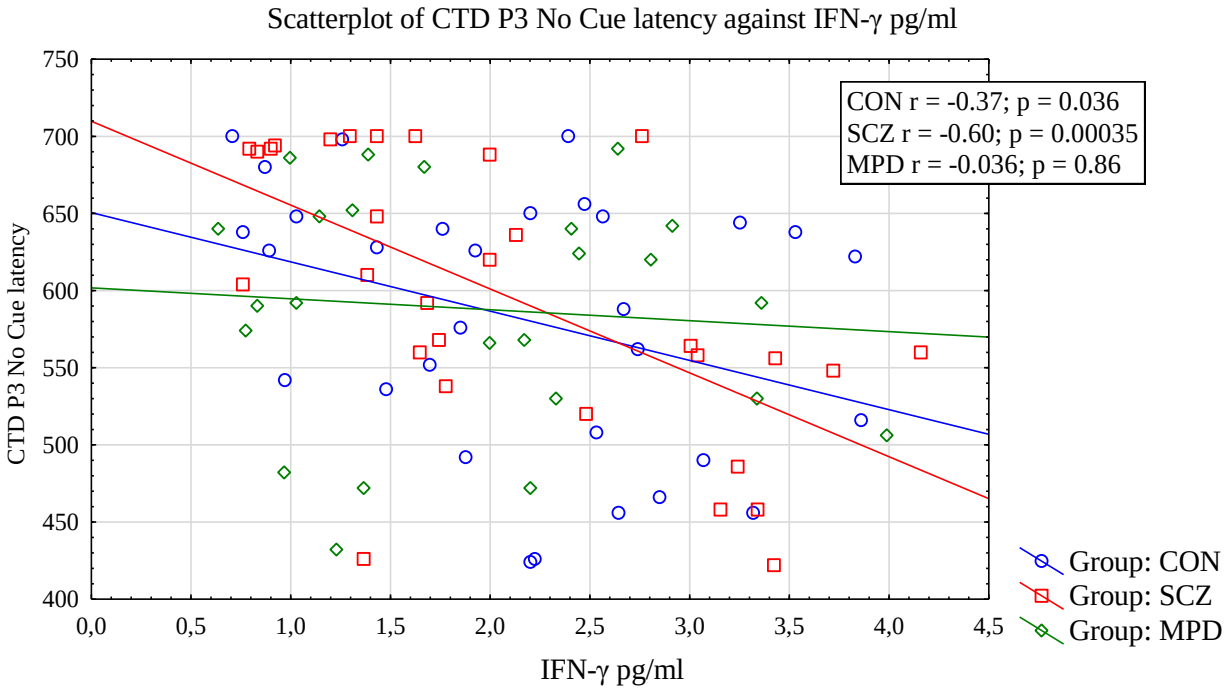


Figure 7.1 Cued target detection task (CTD) no cue P300 latency for the left parietal (P_3) electrode for SCZ negatively correlated with IFN-y. Healthy controls (CON); Schizophrenia (SCZ); Methamphetamine-induced psychotic disorder (MPD). Significance was reported for p<0.01 and Rho= >±0.60.

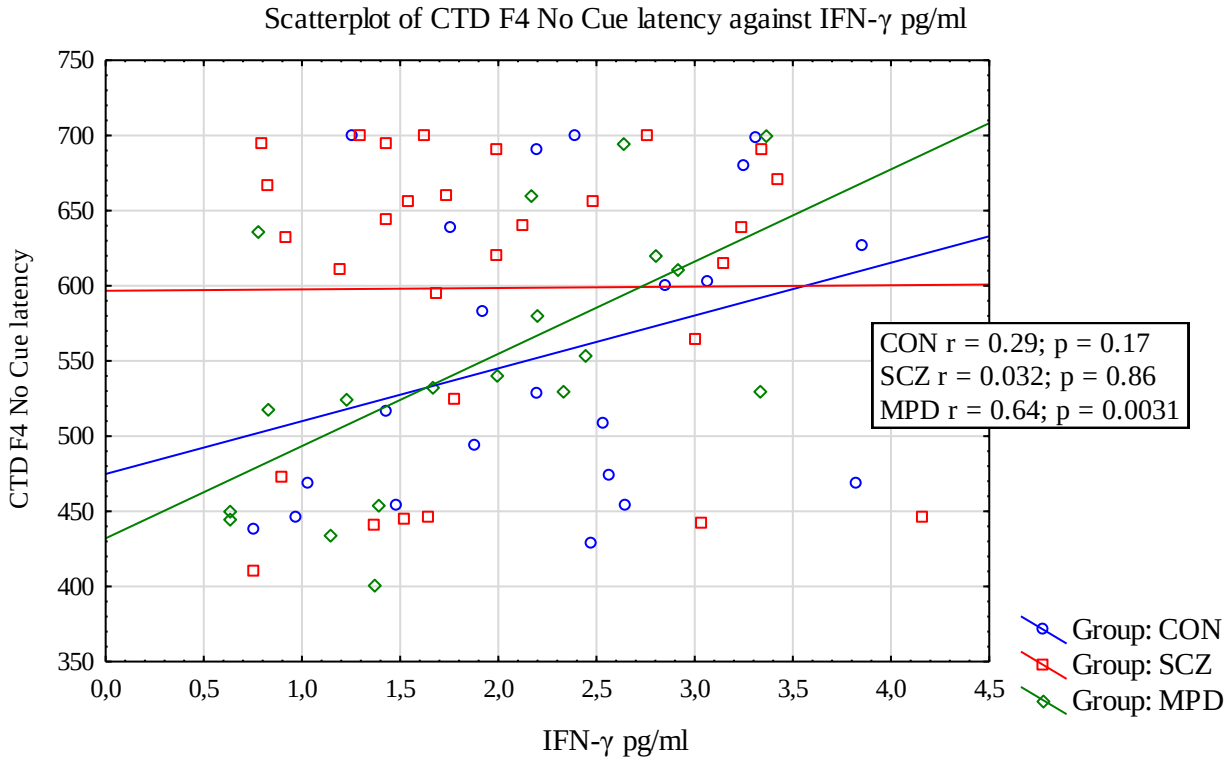


Figure 7.2 Cued target detection task (CTD) no cue P300 latency for the right frontal (F_4) electrode for MPD positively correlated with IFN-γ. Healthy controls (CON); Schizophrenia (SCZ); Methamphetamine-induced psychotic disorder (MPD). Significance was reported for p<0.01 and Rho= >±0.60.

7.3.3 IL-12p70 correlates

MPD IL-12p70 positively correlated with the right occipital CTD incongruent amplitude ($O_2R_{Spearman's(n=21)}$=0.61, p=0.0032), **Figure 7.3**.

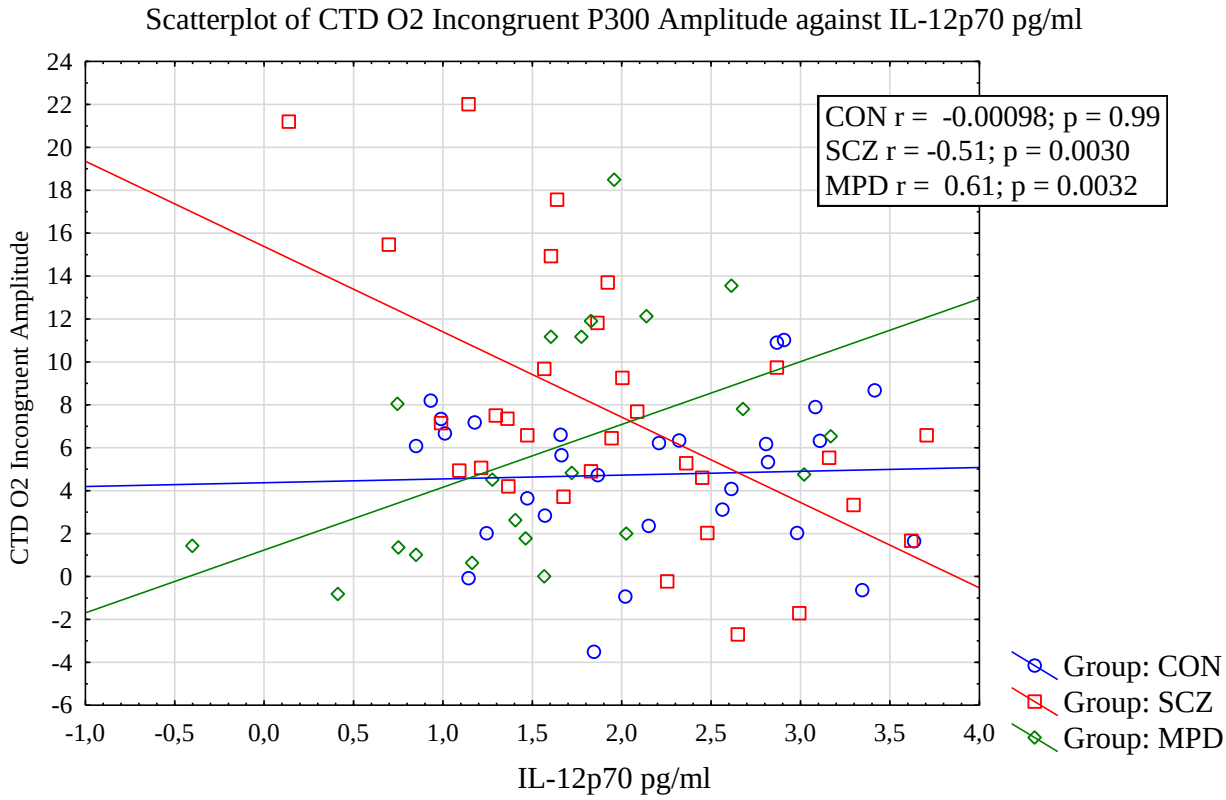


Figure 7.3 Cued target detection task (CTD) incongruent P300 amplitude for the right occipital (O_2) electrode for MPD positively correlated with IL-12p70. Healthy controls (CON); Schizophrenia (SCZ); Methamphetamine-induced psychotic disorder (MPD). Significance was reported for p<0.01 and Rho= >±0.60.

7.4 Discussion

This exploratory analysis showed that no significant group differences were found, however significant correlations were found between cytokines and the P300 ERP waveform of the CTD task within SCZ and MPD. The main findings of this study are IFN-γ negatively correlated with the left parietal CTD no cue P300 latency in SCZ, and positively correlated with the right frontal CTD no cue P300 latency in MPD. Lastly, IL-12p70 positively correlated with the right occipital CTD incongruent P300 amplitude in MPD. These results indicate associations between (neuro) immune markers, and cognition is apparent in SCZ and MPD.

Evidence from the literature suggests that IL-6, TNF-α and IL-1β are associated with cognitive decline in SCZ, however, this evidence is based on correlational analysis within group

population characteristics and cognitive task performance via the attention network test (a task involving a cueing paradigm) (Balter et al., 2019; Romeo, Brunet-Lecomte, Martelli, & Benyamina, 2018). Our study included cognitive tasks to assess whether associations were present between neuroimmune markers, and cortical arousal measured via EEG frequency and the P300 in SCZ and MPD. Our study reported a negative correlation between IFN-γ and the left parietal CTD no cue P300 latency in SCZ and positively correlated with the right frontal CTD no cue P300 latency in MPD. Our results suggest impaired cognitive functioning and visuospatial attention in both SCZ and MPD are associated with decreased IFN-γ in the frontal and parietal regions of the brain (Momtazmanesh et al., 2019; Reale et al., 2021). Literature indicated that SCZ and MPD were reported to have delayed latencies when responding to the target stimulus in the cued target detection task. Further research suggested the subsequent involvement and activation of cytokines and their' release were associated with methamphetamine abuse (Guerri & Pascual, 2018). Literature also reported a reduction in IFN-γ in methamphetamine-using individuals (Chang Kuo et al., 2018). In our study, MPD IL-12p70 positively correlated with the right occipital CTD incongruent amplitude. IL-12p70 was found to be elevated in patients with first-episode psychosis (Momtazmanesh et al., 2019). However, in this study, IL-12p70 was found to be reduced in MPD compared to SCZ and CON. This result is in line with Oribe and colleagues (2015) and Momtazmanesh and colleagues (2019), where reduced P300 amplitude and lower IL-12p70 concentrations indicate cognitive impairment as a result of symptomology (Oribe et al., 2015).

The current study presents with several limitations; first IL-10 levels were below the detectable range in a third of the study participants. Second, the cognitive tasks required the participants to work on a computer and a handful of the participants did not know how to use the computer and had to be given a tutorial. Future work should first include unmedicated patients. Third, diminishing statistical power due to the relatively limited number of study participants.

The discovery of specific (neuro) immune markers along with the electrophysiological markers may potentially be useful for diagnostic and treatment purposes of specific psychotic disorders. In this study associations found between (neuro) inflammation, and cognition is apparent in SCZ and MPD. The results from this study suggest that further research is needed to delineate the neuroinflammatory mechanisms that are involved in the electrophysiological functions between SCZ and MPD.

8 Discussion and Conclusion

Both schizophrenia (SCZ) and methamphetamine-induced psychotic disorder (MPD) present with general positive and negative symptoms of SCZ (hallucinations, disorganized speech, delusions, and confusion), along with cognitive impairments including, executive functioning, attention and working memory (Wearne & Cornish, 2018a). The purpose of this study was to investigate differences in brain electrical activity between SCZ and MPD to determine whether there are overlapping or distinct mechanisms in these conditions. This work follows a long tradition of comparing the phenomenology and psychobiology of SCZ and MPD and yet is the first to directly compare electroencephalography (EEG) findings in SCZ and MPD.

The five aims of the study were to investigate key differences in brain electrical activity on EEG between SCZ and MPD by investigating; (1) relative frequency (alpha, theta, beta and delta) at rest; (2) cognitive performance and relative frequency activity during the continuous performance task (CPT) and cued target detection task (CTD); (3) differences in the P300 event-related potential waveform, a measure of attention, during the CPT and CTD; (4) cognitive performance and relative frequency and event-related potentials (ERP) (N170, P300) during the STROOP task, a measure of working memory and executive function; (5) the associations of (neuro) inflammatory markers with relative frequency and the P300 ERP waveform.

The study recruited a total of one hundred and four individuals from a South African population, who were between the ages of 20 and 45 years: thirty-eight participants with a diagnosis of SCZ (n=38; 8 females/30 males), thirty-one participants with a diagnosis of MPD (n=31; 7 females/24 males), as well as thirty-five socio-demographically matched healthy control (CON) participants (n=35; 15 females/20 males). Although an attempt was made to match healthy controls to the patient groups, several significant differences were found. Years of education were found to differ, with SCZ and MPD completing fewer years of education than CON, and individuals with SCZ completing fewer years of tertiary education compared to healthy controls. These results are in line with previous work showing fewer years of education in both SCZ and methamphetamine users, consistent with cognitive impairment and in these conditions (M. Paulus, 2017).

SCZ and MPD had similar levels of positive and negative symptom scale scores, consistent with previous work that has indicated substantial overlap in the phenomenology of these two conditions. Lifetime abuse of methamphetamine was higher in MPD than in SCZ or CON, consistent with the clinical diagnosis. Individuals with SCZ had a longer duration of illness, more psychotic episodes, and used higher chlorpromazine equivalent doses than MPD, consistent with work showing that SCZ is a chronic psychotic disorder, while MPD has acute onset due to ingestion of a substance and in some individuals may eventually resolve. The age of initial methamphetamine use was earlier in MPD, consistent with previous work showing relatively early onset of substance use in the South African setting.

Main Findings

In Chapter 3, I reported on differences in resting state cortical arousal on EEG in SCZ and MPD. Relative frequency (alpha, theta, beta, and delta) was extracted from resting states in both open-eye and closed-eye conditions. Compared to CON, at rest with eyes closed, decreased relative alpha, and increased relative theta and beta frequencies were found in SCZ, while reduced relative delta activity was found in MPD. These findings are consistent with prior work but are the first report from a direct comparison of the two disorders. Thus prior work reported decreased alpha and increased theta frequency activity in SCZ (Andreou et al., 2015; Garakh et al., 2015), and decreased delta activity was reported after dexamphetamine administration (Albrecht et al., 2016). Further work is needed to determine whether these differences could be useful in differentiating SCZ and MPD in the clinical setting.

In Chapter 4, I investigated the differences between SCZ and MPD in cognitive performance and the relative frequency of the CPT and CTD. During the CPT, cognitive performance was poorer in SCZ and MPD compared to CON, with increased left central and parietal theta activity in MPD. These data are again consistent with previous reports of cognitive deficits in SCZ and MPD, but this is the first to directly compare cognitive performance in the two disorders. Notably, however, individuals with SCZ had altered P300 ERP waveforms which is consistent with severe visual processing deficits as seen by the response to stimuli, which activate the magnocellular/dorsal pathway (A. Martinez et al., 2015), findings that may be consistent with work on altered dopamine transmission in the thalamus and striatum (Brisch, 2014). While MPD also involves disruption to the dopaminergic system, there may therefore be differences between the two conditions in the mechanisms of altered dopaminergic function.

In Chapter 5, I investigated group differences in the P300 ERP waveform during the CPT and CTD. Compared to CON, P300 amplitude was attenuated in frontal-parietal regions in SCZ and frontal regions in MPD. These findings are consistent with previous work reporting reduced P300 ERP waveforms indicating increased severity of positive symptoms (Oribe et al., 2015). Further analysis found that an association was present in individuals with SCZ for methamphetamine use with increased P300 amplitude and latency during the CPT and CTD tasks. This finding is consistent with the conclusion that methamphetamine use negatively impacts cognitive performance (A. Guerin, 2019).

In Chapter 6, I investigated working memory and executive functioning and extracted relative frequency activity and the N170 and P300 ERP waveforms during the STROOP task in SCZ and MPD. This chapter presents information on relative frequency activity and the P300 and N170 ERP waveforms within resting states and cognitive tasks which has not been conducted in MPD. During the STROOP task, in individuals with SCZ, compared to CON, there were increased errors of commission and reduced working memory, as well as decreased theta activity in frontal through to parietal regions; while compared to MPD and CON there were delayed N170 and P300 ERP waveform latencies. The delayed N170 and P300 ERP waveform found in SCZ compared to MPD and CON indicates particularly impaired cognitive processing in this condition. Further analysis found that irrespective of diagnosis, individuals prescribed 2nd generation antipsychotics had improved cognitive processing compared to those not taking antipsychotics and those prescribed 1st generation antipsychotics. This is consistent with previous work suggesting that 2nd generation antipsychotics are associated with less impaired cognition than other antipsychotic agents (Rehse et al., 2016).

In Chapter 7, in an exploratory analysis of the associations of (neuro) inflammatory markers with relative frequency activity and the P300 ERP waveform in SCZ and MPD, I found no significant group differences. However, significant correlations were found, with IFN-γ negatively correlated with the left parietal CTD no cue P300 latency in SCZ, and positively correlated with the right frontal CTD no cue P300 latency in MPD. The correlation of IFN-γ with the parietal region suggests that (neuro) immune mechanisms may be involved in the altered processing of somatosensory information in SCZ, while the correlation of IL-12p70 right occipital CTD incongruent P300 amplitude suggests that (neuro) immune mechanisms may be in involved in visual perception or processing in MPD (Taylor, Scheffer, & Berkovic,

2003), although further work is needed before claims of causality can be made. Taken together, these results indicate differences in (neuro) immune function between SCZ and MPD.

Strengths of the study

One of the strengths is this study is the first study of its kind to include clinical and cognitive assessment in combination with EEG and cytokine measures, age and sex-matched study groups in a South African population. Second, South Africa contains a diverse population and an increased number of methamphetamine drug dealers and methamphetamine users.

Limitations

Several limitations of this study deserve emphasis. First, in chapter three, we noted that healthy controls completed more years of education compared to SCZ and MPD. This is consistent with prior work showing fewer years of education in SCZ (Salo, Ravizza, & Fassbender, 2011), and in methamphetamine users (M. Paulus, 2017). We did not control for years of education in our population demographic analysis, however, covariate analysis was conducted for education during the analysis of the resting states frequency analysis but, no significant differences were found.

Second, this study recruited patients who were on an antipsychotic medication regimen, with a chlorpromazine equivalent dose higher in SCZ compared to MPD. This is a limitation because our findings may reflect differences in medication rather than differences in pathophysiology across the groups. We addressed these issues to some extent by studying the relationships between medication and EEG data, as noted above. However, our findings on the lower rate of cognitive impairment seen with 2nd generation antipsychotics do not remove this limitation.

Third, this study is part of a larger study where magnetic resonance imaging was conducted prior to recording the EEG. The participant sat for an hour-long testing schedule of two resting state tasks and three cognitive tasks. An increase in mental fatigue could affect the results obtained during the completion of the cognitive tasks (Reteig et al., 2019). Further, if an individual feels stressed being in a confined space, elevated cortisol levels can affect the EEG (Fleur Margaret Howells, Stein, & Russell, 2012).

Fourth, approximately 30% of the IL-10 measures were below the detectable limit, which may bias findings. Cytokine findings below the detectable limit were also noted in a study investigating serum levels in relation to the symptomology in SCZ (Erbagci, Herken,

Köylüoglu, Yilmaz, & Tarakçioglu, 2001). Erbagci and colleagues suggested that differences might still be present however the differences might be below the detectable limit, and more sensitive assays are needed in this case.

Lastly, in this study, SCZ had a handful of individuals using methamphetamine. To account for this limitation, we compared findings in SCZ individuals with and without methamphetamine use. This sensitivity analysis found differences between those individuals with and without comorbid methamphetamine, so reinforcing that this limitation may be an important one.

Future Research Directions

Several future research directions are suggested by this study. First, future work could assess genetic overlaps and differences between SCZ and MPD, including the overlap of genetic architecture with both cognitive alterations and EEG alterations seen in these disorders. Research conducted on the genetic architecture of altered frequency in SCZ suggests that altered theta activity in SCZ is mediated by gene clusters involved in glutamatergic pathways (B Narayanan et al., 2015).

Second, further work on associations of endocrine markers could be conducted on SCZ and MPD as recent work has shown the gut microbiome plays a big role in metabolic imbalances and its association with inflammation (Severance, Dickerson, & Yolken, 2020).

Third, more sophisticated work on immune markers could be conducted. In an updated review, increased levels of IL-1β, IL-6, and TNF-α were found in first-episode psychotic patients, however, additional information was found regarding other influences such as cortisol levels, a measure of stress, and hormone levels (Galińska-Skok & Waszkiewicz, 2022),

Fourth, these studies indicate that despite the growing research in discovering potential biomarkers for SCZ, there is still a large gap in the understanding of the mechanisms involved in these psychotic disorders. This data along with additional information such as salivary assays for cortisol and α-amylase (Carol, Spencer, & Mittal, 2021) should be added to a database for epigenetic studies to be conducted to strengthen determining the risk of an individual developing a psychotic illness for future clinical purposes. A review conducted on the epigenetics of SCZ found that most epigenetic studies are conducted on post-mortem tissue samples (Richetto & Meyer, 2021). Richetto and Meyer suggested that longitudinal studies are

needed with the inclusion of peripheral blood and saliva which will further aid in understanding the disease course.

Fifth, future studies should include an investigation of associations of EEG with brain anatomy and physiology, using measures obtained from structural and functional brain imaging. Such work has not been done in SCZ (Manyukhina, Tomyshev, Kaleda, & Lebedeva, 2020), and MPD, and yet may be useful for understanding the overlap and distinctions between these two conditions.

Conclusion

To conclude, the main aim of this study was to identify differences in cognitive performance and EEG in SCZ and MPD. Impairments in cognitive function, including reduced attention and cognitive control in both SCZ and MPD are consistent with prior work, although this is one of the first studies to have directly compared the two disorders. Different resting state functional networks are altered in SCZ and MPD, suggesting that they are underpinned by different neurobiological mechanisms. The delayed N170 and P300 ERP waveform found in SCZ compared to MPD and healthy controls indicates particularly impaired cognitive processing in this condition. There was preliminary evidence of an association between alterations in the P300 ERP waveform and some cytokines, but with different findings in SCZ and MPD, suggestive of differences in underlying neuro-immune mechanisms. Taken together, these findings point to both overlap in and differences between SCZ and MPD, a conclusion consistent with other work.

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Appendix A. Research study consent, questionnaires, and protocols

A.1 Informed consent

UNIVERISITY OF CAPE TOWN

Modelling neuro-inflammation in schizophrenia: A magnetic resonance imaging, electroencephalography, and cytokine study

RESEARCH STUDY

UCT FHS HREC Ref no. 413/2016

Participant information sheet

Your body protects itself from harm through activation of your immune system, e.g., when you have a cold/flu your body's immune system works really hard to kill off the germs that make the cold/flu.

How the immune system works has been shown to change when you have a mental illness. We don't understand how it works in these illnesses. This research study will look at your immune system, by drawing blood and analyzing your immune system. Then we will scan your brain and record from your brain to see if what is in your blood is related to what is in your brain to understand mental illness better. This information may help researchers to develop better medication for people with mental illness.

We are recruiting 105 people, 70 of which have a diagnosis of either schizophrenia or methamphetamine-induced psychotic disorder. Then we are recruiting 35 people from similar backgrounds. All people who participate need to be within the ages of 20 and 50 years old.

***

You cannot participate if you have any of the following: *chronic medical illness that is known to interfere with metabolic processes (e.g. hyper/hypo-thyroidism, diabetes type I or II, etc.) or immune dysfunction or immune system is compromised (e.g. HIV, TB, lupus, etc.); major brain trauma, brain injury, or brain surgery which resulted in hospitalization or clinical examination; clinical appearance of mental retardation; female participants will be excluded if there is current or recent pregnancy, or if they are breastfeeding.*

Additional criteria for participants with a diagnosis of schizophrenia: Participants will be excluded from the study if they present with psychosis due to a medical condition or substance abuse/use.

Additional criteria for participants with a diagnosis of methamphetamine-induced psychotic disorder if applicable: *Participants will be included if they have a history of MA dependence and MA-induced psychotic disorder; participants will be excluded from the study if they present with a current or past substance dependence or excessive abuse other than MA or nicotine or alcohol (e.g., cannabis, methaqualone, MDMA (ecstasy) or cathinone).*

Additional criteria for the control group if applicable: *Control participants should have no known family history of psychotic illness; participants should not meet the criteria for an axis 1 disorder as per SCID tool.*

***

1st Research morning

08h30-13h30, may finish earlier @ Department of Psychiatry, UCT, Groote Schuur Hospital

The first morning, starting @ 8h30, we will take you through this form and will ask you to sign the end of this document if you would like to be part of this research study. Then we will draw blood from your arm, we will draw less than 50ml of blood – which is a similar amount that you find in a deodorant bottle (Figure 1). **It is very important that you don't have breakfast that morning.** Bruising may occur around the needle site, a day or two after, so please do not be alarmed by this if it occurs. After we have drawn your blood we will give you snacks and a cool drink for breakfast.

Figure 1 How much blood is drawn

Then you are interviewed, we ask you lots of questions, about your life and how you feel. This is a lot of talking but if you need a short break at any time you can do this. After this, no later than 13h30, we will give you a R100 grocery voucher for Pick 'n Pay and R50 cash which is towards you traveling to us and back home.

***

2nd Research morning

08h30-12h30, may finish earlier @ Department of Psychiatry, UCT, Groote Schuur Hospital

The second morning, which has to happen within the next 10 days, includes the brain scan, the brain recordings, and a few more questions. Again we will start @ 8h30, but will be finished sooner before 12h30. When you come in we will ask for a saliva (spit) sample (Research to show them the device and how it works). Afterwards we will give you snacks and cool drink, you can have breakfast before you come to us. We will also give you a R200 grocery voucher for Pick 'n Pay and R50 cash which is towards your traveling to us and back home.

How do we scan your brain?

The brain scan that we will perform is called a magnetic resonance imaging or MRI scan. You lie on a bed and are put into the scanner for less than 1 hour.

1. You are checked to see whether you are will be okay in the scanner by a radiographer. He/she will check whether you have any kind of metal in your body and ask general health questions.

2. You are put on a hospital gown in a change room.

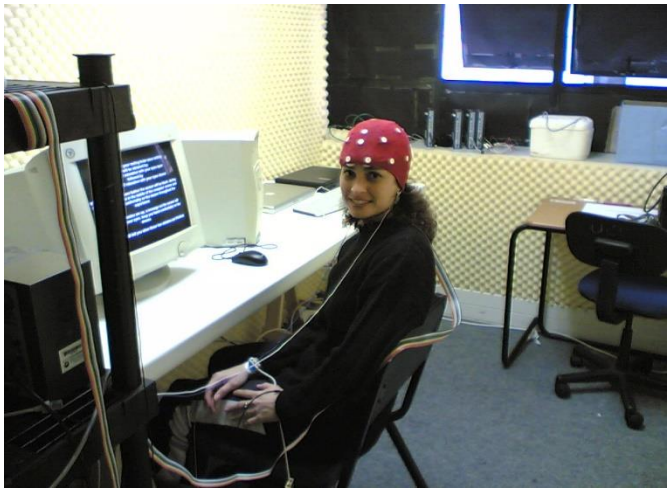
3. You lie down on the scanner bed once you are comfortable. Then a mask is clicked in over your face. Then the scanner bed moves into the tunnel.

It is so important that you lie still in the scanner, else we don't get a good scan of your brain and can't use it – so make sure you are really comfortable before you move into the tunnel.

****The MRI scanner makes a lot of noise so you will be given ear protection. You will still hear the scanner and all the weird noises it makes but your ears will be protected from the noise the scanner makes.****

How do we record from your brain?

The brain recording that we will do is called an electroencephalography or EEG. You sit in front of a screen and you have a cap, like a swimming cap, put on your head. This cap records from you and nothing goes into you from the equipment we use. This record takes less than 1 hour.



1. You are checked to find out whether you have had or have a family member with epilepsy – this is when the brain has a storm of activity.

2. You sit down in front of the screen

3. You have a cap put on you and other wires are attached, we only record from you – nothing goes into you.

4. Then you relax and complete some tests which you do your best at completing.

The EEG record does not make any noise, but you do need to sit and be relaxed during the record

After the MRI and EEG we will work with you and complete some additional questions, that are related to your drug use, experiences during childhood, and some other questions about who you are and whether you worry about different things.

It is important to note that all necessary regulations are and will be followed, including adherence to human research guidelines as stipulated in the Declaration of Helsinki (World Medical Association, 2001). The protocol has been approved by the University of Cape Town's Human Research Ethics Committee (UCT HSF HREC). All necessary research clearances are kept up to date by the research team.

If you want to stop being in the research project at any time, you can. This will not affect your current or future medical care. This study is for research purposes only, and not funded by a drug company. Your personal details will be held confidentially, you name will not be attached to the information we collect from you. All the data, interview, questions, blood, scan, and EEG information collected will only be used for research purposes.

If you have any questions with respect to the present study do not hesitate to contact the principal investigator howellsfleur@gmail.com else 021 404 5480

If you would like to participate or would like to refer a potential research participant please mail participantstar@gmail.com to be in contact with research team.

If you would like to contact the Research Ethics Committee: The UCT's Faculty of Health Sciences Human Research Ethics Committee can be contacted on 021 406 6338 in case you have any ethical concerns or questions about your rights or welfare as a participant on this research study.

Participant Name _____ Participant Number _____

Modelling neuroinflammation in schizophrenia:

A magnetic resonance imaging, electroencephalography, and cytokine study

RESEARCH STUDY

UCT FHS HREC Ref no. 413/2016

CONSENT FORM

I voluntarily agree to participate in the present study: modelling neuroinflammation in schizophrenia: a magnetic resonance imaging, electroencephalography, and cytokine study

YES NO

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

YES NO

I consent (willing to complete) all of the procedures that are needed for this research project, checklist of procedures:

1. Psychiatrist interview with clinical scales YES NO
2. Blood draw YES NO
3. Saliva sample YES NO
4. Magnetic resonance imaging (MRI) brain scan YES NO
5. Electroencephalography (EEG) brain scan YES NO
6. More questionnaires with a researcher YES NO

If there are any procedures that the participant is not willing to undergo note here:

_____

I understand that all information and data collected will be used for research purposes only, and will not affect my current or future medical treatment.

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 from the researcher before you sign this consent form). I am allowed to ask questions from any of the researchers that are involved in the research study that I interact with.

YES NO

What if Something Goes Wrong?

The University of Cape Town (UCT) has insurance cover for the event that research-related injury or harm results from your participation in the trial. The insurer will pay all reasonable medical expenses in accordance with the South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI) in the event of an injury or side effect resulting directly from your participation in the trial. You will not be required to prove fault on the part of the University.

The University **will not be liable** for any loss, injuries and/or harm that you may sustain where the loss is caused by

- The use of unauthorised medicine or substances during the study
- Any injury that results from you not following the protocol requirements or the instructions that the study doctor may give you
- Any injury that arises from inadequate action or lack of action to deal adequately with a side effect or reaction to the study medication✸
- An injury that results from negligence on your part✸

[✸Researchers must bear in mind that it is unacceptable to impose a burden on participants who may not recognize symptoms or have the ready means to take action.]

"By agreeing to participate in this study, you do not give up your right to claim compensation for injury where you can prove negligence, in separate litigation. In particular, your right to pursue such a claim in a South African court in terms of South African law must be ensured. Note, however, that you will usually be requested to accept that payment made by the University under the SA GCP guideline 4.11 is in full settlement of the claim relating to the medical expenses. "

An injury is considered trial-related if, and to the extent that, it is caused by study activities. You must notify the study doctor immediately of any side effects and/or injuries during the trial, whether they are research-related or other related complications.

UCT reserves the right not to provide compensation if, and to the extent that, your injury came about because you chose not to follow the instructions that you were given while you were taking part in the study. Your right in law to claim compensation for injury where you prove negligence is not affected. Copies of these guidelines are available on request.

I ……..…….. (participant 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 (affect) on my current or future medical treatment.

Participant signature ……..…… date: DAY / MONTH / YEAR

Participant email and/or contact number:
…….

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

Researcher signature …… date: DAY / MONTH / YEAR

A.2 Ethical clearance

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-48 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

21 September 2016

HREC REF: 413/2016

Dr F Howells
Psychiatry and Mental Health
J-Block, Office 105
GSH

Dear Dr Howells

PROJECT TITLE: MODELING NEUROINFLAMMATION IN SCHIZOPHRENIA: A MAGNETIC RESONANCE IMAGING, ELECTROENCEPHALOGRAPHY AND CYTOKINE STUDY (Doctoral candidate-A Burger & MSc-candidate K Williams) Sub-study linked to 719/2015

Thank you for your response to the Faculty of Health Sciences Human Research Ethics Committee dated 19 September 2016.

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

Approval is granted for one year until the 30th September 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

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

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

The HREC acknowledge that the students, Antoinette Burger and Kimberley Williams will also be involved in this study.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

A.3 Clinical scales and subjective/non-clinical questionnaires

A.3.1 Positive and negative syndrome scale

Positive and negative syndrome scale (PANSS) – an operationalised and drug-sensitive instrument that provides a balanced representation of positive and negative symptoms in schizophrenia, as well as the relationship between the symptoms and its relation to global psychopathology (Kay & Fiszbein, 1987).

Participant Number_____ Clinician _____ Date / /

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

		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 conversaiton	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

	Total
Positive scale	
Negative scale	
General psychopathology	
Total score	

A.3.2 Calgary depression scale

Calgary depression scale – a measurement of depression in schizophrenia (Addington et al., 1990).

A.3.3 Hamilton Depression rating scale

Hamilton Depression rating scale - the most widely used clinician-administered depression assessment scale, pertaining to symptoms of depression experienced for a period of a week (Hamilton, 1960).

Participant Number_____ Clinician _____ Date / /

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 persisting 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 accused.
3	Severe	Persistent 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	Occasionally 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 occasional 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

HAMILTON DEPRESSION RATING SCALE (HAM-D)

Participant Number _____ Clinician _____ Date / /

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 in 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 or 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 doubtful 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 3-4 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 experience 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 report 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 the 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 without 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 from 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) which 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 to 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 not 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; insects 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), but 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.	☐

A.3.4 Kreek-McHugh-Schluger-Kellogg scale

Kreek-McHugh-Schluger-Kellogg scale (KMSK scale) - assesses the frequency, amount, and duration of use of a particular substance during the participant's period of greatest consumption, as well as the mode of use, whether the substance use is current or past, and whether each substance is the substance of choice (Kellogg et al., 2003).

Participant Number_____ Clinician _____ Date / /

KMSK Scale

Have you ever used any of the following substances?

	YES	NO
Alcohol		
Tobacco		
Cocaine		
Heroin		
Opiates		
Cannabis		
Methamphetamine / Amphetamine		

ALCOHOL (1 drink = 1 beer / 1 glass of wine)

At the time when you were drinking the most alcohol, were you drinking it:	Every day/nearly every day (5 points)	Three or more days per week (4 points)	Every weekend, most weekends and holidays (3 points)	Once a week or less (2 points)	A few times a year/ special occasions (1 point)	Never (0 points)
When was this?						
How long did this pattern of drinking last?	12+ months (3 points)	6-12 months (2 points)	Less than 6 months (1 point)			
During the last 30 days, how many days did you drink alcohol?	15-30 days (5 points)	6-14 days (4 points)	4-5 days (3 points)	2-3 days (2 points)	1 day (1 point)	None (0 points)
How long has this current pattern of drinking been going on?	12+ months (3 points)	6-12 months (2 points)	Less than 6 months (1 point)	No use (0 points)		
During the 30 days, when you were drinking the most, how many drinks at a time or in a day would you typically drink?	10+ (5 points)	5-10 (4 points)	4-5 (3 points)	2-3 (2 points)	1-2 (1 point)	None (0 points)
Is alcohol your drug of choice?	YES	NO				

TOBACCO (cigarettes / cigars)

At the time of your life when you were smoking the most, were you smoking:	At regular intervals every day/ most days (5 points)	In clusters, at specific times of day (lunch, breaks) every day / most days (4 points)	Once a day - every day or most days (3 points)	20-100 times in lifetime (2 points)	Fewer than 20 times in lifetime (1 point)	Never smoked (0 points)
When was this?						
Are you smoking currently?	YES	NO				
How long did this pattern of smoking last?			12+ months (3 points)	6-12 months (2 points)	Less than 6 months (1 point)	
During the last 30 days, how many packs of cigarettes would you typically smoke at your heaviest use?	2+ packs (5 points)	1-2 packs (4 points)	1 pack (3 points)	½ pack (2 points)	Less than ½ pack (1 point)	None (0 points)
Is tobacco your drug of choice?	YES	NO				

COCAINE

At the time in your life when you were using the most cocaine, were you using it:	Several times a day/most days or use as long as drug is available (7 points)	3+ more times a day, three to five days a week (6 points)	3+ more times a day, one to three days a week (5 points)	Once a day, every day or most days (4 points)	100+ times in lifetime (3 points)	20-100 times in lifetime (2 points)	Fewer than 20 times in lifetime (1 point)
How did you use it?		smoking	snorting	freebasing	skin popping	IV injection	
When was this?							
Are you currently using?	YES	NO					
How long did this pattern of cocaine use last?		12+ months (3 points)	6-12 months (2 points)	Less than 6 months (1 point)			
During the last 30 days, how many days did you use cocaine?		19-30 days (4 points)	8-18 days (3 points)	3-7 days (2 points)	1-2 days (1 point)	None (0 points)	
During the time when you were using the most cocaine, how much would you use / spend at a time?		_____ grams		R_____			
Is cocaine your drug of choice?	YES	NO					

HEROIN

At the time in your life when you were using the most heroin, were you using it:		Several times a day, every day / most days (4 points)	Once a day, every day / most days (3 points)	20-100 times in lifetime (2 points)	Less than 20 times in lifetime (1 point)	Never used (0 points)	
How did you use it?		smoking	snorting	freebasing	skin popping	IV injection	
When was this?							
Are you currently using?	YES	NO					
How long did this pattern of heroin use last?		12+ months (3 points)	6-12 months (2 points)	Less than 6 months (1 point)			
During the last 30 days, how much heroin would you use at a time? (1 bag = 1 dose)	10+ doses (6 points)	8-9 doses (5 points)	6-7 doses (4 points)	4-5 doses (3 points)	2-3 doses (2 points)	<1 - 1 dose (1 point)	0 doses (0 points)
During the time you were using the most heroin, how much would you spend at a time?		R_____					
Is heroin your drug of choice?	YES	NO					

CANNABIS

At the time in your life when you were using the most cannabis, were you using it:	Several times a day, every day (6 points)	Every day / nearly every day (5 points)	3+ days per week (4 points)	Every weekend / most weekends and holidays (3 points)	1x per week or less (2 points)	Few times a year, on special occasions (1 point)	Never used (0 points)
What form did you use?		plant	oil	hash	_____	_____	
When was this?							
Are you currently using?	YES	NO					
How long did this pattern of cannabis use last?		12+ months (3 points)	6-12 months (2 points)	Less than 6 months (1 point)			
During the last 30 days, how much cannabis did you use at a time?		5+ joints (5 points)	4-5 joints (4 points)	2-3 joints (3 points)	1-2 joints (2 points)	< 1 joint (1 point)	None (0 points)
Is cannabis your drug of choice?	YES	NO					

METHAMPHETAMINE / AMPHETAMINE

At the time in your life when you were using the most methamphetamine / amphetamine, which drug did you use primarily?		Methamphetamine			Amphetamine		
Were you using it:		Every day/nearly every day (5 points)	Three or more days per week (4 points)	Every weekend, most weekends and holidays (3 points)	Once a week or less (2 points)	A few times a year/ special occasions (1 point)	Never (0 points)
When was this?							
Are you currently using?	YES	NO					
How long did this pattern of methamphetamine / amphetamine use last?		12+ months (3 points)	6-12 months (2 points)	Less than 6 months (1 point)			
During the last 30 days, how many days did you use methamphetamine / amphetamine?		21-30 days (4 points)	11-20 days (3 points)	3-10 days (2 points)	1-2 days (1 point)	None (0 points)	
When you were using methamphetamine / amphetamine, how did you use it?		Intravenous (4 points)	Smoking (3 points)	Intranasal "snorting" (2 points)	Oral - pills, licking (1 point)		
Is methamphetamine / amphetamine your drug of choice?		YES	NO				

Edinburgh's handedness questionnaire – standardly reported (R. C. Oldfield, 1971)

Participant Number_____ Research details _____ 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 the 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?

A.5 Study operation protocols

A.5.1 Imaging day protocol

Data collection protocol ***Day 1: (Valkenberg Hospital OR Groote Schuur Hospital – Department of Psychiatry and Mental Health)***

08h30-09h00 Information sheet and informed consent (Appendix A) obtained prior to proceeding
09h00-09h30 Blood draw (fasting bloods – participant to be asked to not eat in the morning – we will provide them with breakfast bar and other snacks once blood draw is completed
09h30-11h30 Structured clinical interview (SCID-DSM-IV)
(Break between as is needed by the participant)
11h30-13h00 Clinical scales (Appendix B)

1. Positive and negative syndrome scale (PANSS)
2. Calgary depression scale
3. Hamilton Depression rating scale (HAM-D)
4. Generalized Anxiety Disorder 7-item (GAD-7) scale
5. Global assessment of functioning (GAF)
6. Global impression severity scale (CGI-S)
7. Simpson-Angus extrapyramidal side-effects
8. Barnes Akathisia Rating Scale (BARS)
9. Abnormal Involuntary Movement Scale

13h00-13h10 Snacks and cool drink, hand-over voucher (R100), travel reimbursement (R50) and researcher to make Imaging appointment with participant (confirm contact information as is needed)

Day 2: (Groote Schuur Hospital – Department of Psychiatry and Mental Health)
Within 10 days of Day 1, the MRI scan and EEG record may be swopped around in order as is needed
.
08h30-09h00 Participant is refreshed to the proceedings of the morning, and screen by radiographer
Obtain passive drool saliva sample
09h00-10h20 MRI scan

MRI scan sequence with time allocation	
6.39 min	MPRAGE structural scan
9:36 min	MRS 2D-CSI slice 1
10:52 min	MRS 2D-CSI slice 2
4:36 min	MRS Single voxel with water reference (normal) with water reference
12:02 min	MRS Single voxel with water reference (glu)
4:36 min	MRS Single voxel with water reference (normal)
12.02 min	MRS Single voxel with water reference (glu)
59.03 min	**Total scan time**

10h20-10h30 *Break and move to EEG suite*
10h30-11h00 EEG testing

EEG record sequence with time allocation	
3:00 min	Resting eyes open condition
3:00 min	Resting eyes closed condition
10:00 min	Continuous performance task (1st control task)
6:20 min	Cued Target Detection task (2nd control task)
6:30 min	Stroop colour word conflict task to address error-related negativity
12:00 min	Go/no-go task to address error-related negativity
58:50 min	**Total recording time**

11h00-12h00 Non-clinical/subjective questionnaires (Appendix C)

1. Mental effort scale will be performed intermittently during the EEG testing session only
2. Kreek-McHugh-Schluger-Kellogg scale (KMSK scale)
3. Penn-State Worry Questionnaire
4. Bernstein's Childhood Trauma Questionnaire (CTQ)
5. Cloninger's Tridimensional personality questionnaire subscale of harm avoidance
6. Edinburgh's handedness questionnaire

12h00-12h10 Snacks and cool drink, hand-over voucher (R200), and travel reimbursement (R50) and researcher will thank the participant for their participation in the research project.

A.5.2 Standard operating protocol – Blood draw - researcher

DO BEFORE PARTICIPANT ARRIVES

1. Make sure you have a cooler bag (with ice brick and tissue) for EDTA filled vials and the ability to stand SERUM tubes after inverting.
2. Make sure you have the biohazard sharps container and biohazard bin nearby (if biohazard bin not nearby use red bag in the blood draw kit).
3. Vacutainers (Blood collection devices), need to collect 2 SERUM (red) tubes and 3 EDTA (purple) tubes.
   ENSURE THESE ARE CLEARLY LABELLED WITH PARTICIPANT NUMBER (with a permanent marker)
4. Have at least one extra of each vacutainer tubes on hand if needed, e.g. vacuum lost or a tube not filled.
5. Unpack blood draw kit: Unfold napkin and place alcohol swabs, needle (still sealed and capped), vacutainer tubes, and tourniquet on napkin.
6. Have two pairs of gloves ready – in both size medium and large – one pair for clinician and one pair for researcher working with clinician.

WHEN PARTICIPANT ARRIVES

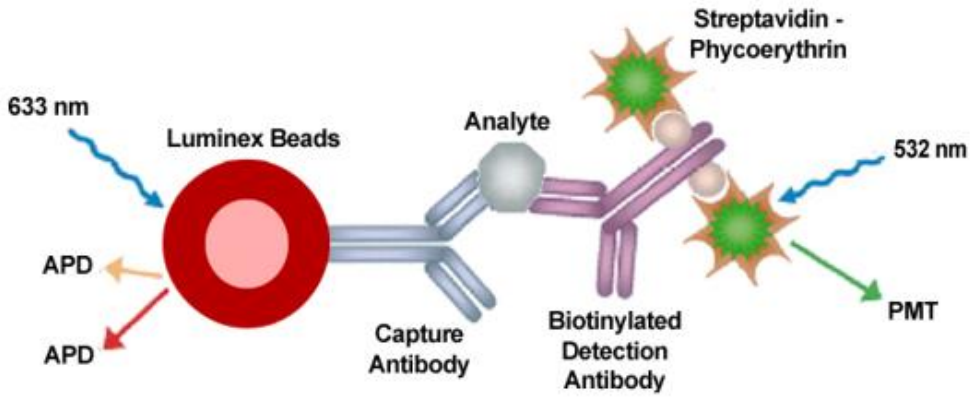
1. Explain to the participant that blood is going to be drawn from them – it will already have been covered in the consent but recap the blood draw step indicating that 48ml of blood will be collected an equivalence to four tablespoons of blood.
2. Clinician and researcher to both wear gloves.
3. Clinician to clean site of potential venepuncture with alcohol swab(s).
4. Open needle packet, attach vacutainer holder (clear plastic tube), and hand sheathed needle to the clinician – do not put it back on the towel. Discard in Biohazard sharps bin.
5. When needle inserted clinician to indicate ready for blood draw from site punctured.
6. Insert/plug vacutainer into collection device to collect blood (the tube creates a vacuum, if the clinician is in a vein blood will enter the vacutainer, reasons for lack of blood draw, incorrect needle placement else damage to vacutainer vacuum).
7. Ensure clinician has sight to the needle puncture as they are holding the needle in place, and work carefully with them.
8. Fill one EDTA (purple) and one SERUM (red) tube first, then follow with the rest of the tubes.
9. When 1st EDTA tube is filled, swop out with 1st SERUM tube, while SERUM tube is filling invert the filled EDTA tube, and continue this process until all 5 vacutainer tubes are filled.
10. If a tube is not properly filled (view marker on tube to see fill line – vacuum will also stop), hand another tube of the same kind to the clinician to fill.
11. SERUM tubes must be inverted eight times, then left standing upright in room temperature for 30 minutes before transportation.
12. EDTA tubes must be inverted eight times, and put into cooler box – do not put directly onto ice bricks. Use paper towel as buffer if needed.
13. When drawing of blood is completed, hand cotton wool to clinician so they can replace the needle site with cotton wool swab and apply pressure. The Dr/Sr is to place the needle directly into the sharps container so make sure very close by *(they are not to pass the needle to you and you are not to take the needle as this can create a window of needle stick)*.
14. Cover puncture site with a plaster / cotton wool with medical tape.
15. Full clean-up: Ensure all sharps have been put into sharps container, and all other material in a biohazard container.
16. Upon completion of the blood draw, issue participant with a snack pack and water.

A.5.3 Cytokine preparation

Information for the Multiplex system

The Multiplex system is based on a Luminex xMap technology which comprises of beads with a unique red blend of red dye and UV dye. This blend gives each bead a signature which can be identified by the instrument when the bead is excited by the red laser (632 nm).

Each analyte is bound to a detection antibody that is conjugated to Phycoerythrin (PE). Pe is excited by the 532 nm green laser and the detection is around 677nm. The instrument first identifies the bead and then detects the PE emission from that bead region. The diagram below is what happens for each bead detected



Preparation of samples for multiplex:

1. Prepare lab space

- ensure 1ml and 200ul pipette tip boxes are loaded

- ensure paper towel down where you will be aliquoting to absorb condensation.

- prepare eppies (labeling and order in line with samples) for aliquoting your samples

2. Fill the Styrofoam container with ice chips.
3. Remove 10 cyrovials at a time - as have been entered, each having 38 samples, starting with CON, second SCZ, third group MPD.
4. Extract 500µl from the thawed serum cryovial.
5. Spin down the 500ul aliquot serum samples for 10 minutes at 2000rpm.
6. While spinning down - return your cyrovials and take the next ten samples to be thawed on ice

7. From the spun down 500ul aliquot - aliquot 100ul of the supernatant into clearly marked Eppendorf tubes (these will be used for the cytokine assays) and store into your cryovial box (labelled A1) in the identical order as the cyrovials.

9. Discard the remaining spun down sample from the 500ul aliquot.

Repeat 4-9 until all of your 38 samples are processed. Replace ice if needed

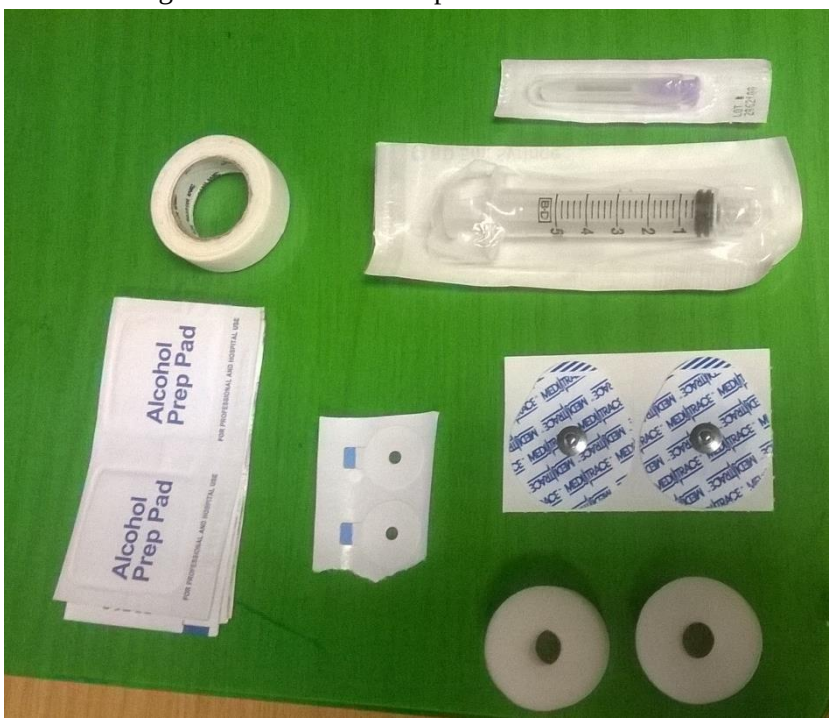
A.5.4 Standard operating protocol – EEG - researcher

TO HAVE ON HAND WHEN PARTICIPANT ARRIVES

1. Collect the participant file with questionnaires from the MRI researcher
2. Saliva collection aid and cryovial (icepack with cooler bag) with their unique participant number written on
3. Tablet (if not already completed)
4. Electroencephalography setup

PRIOR TO PARTICIPANT ARRIVAL:

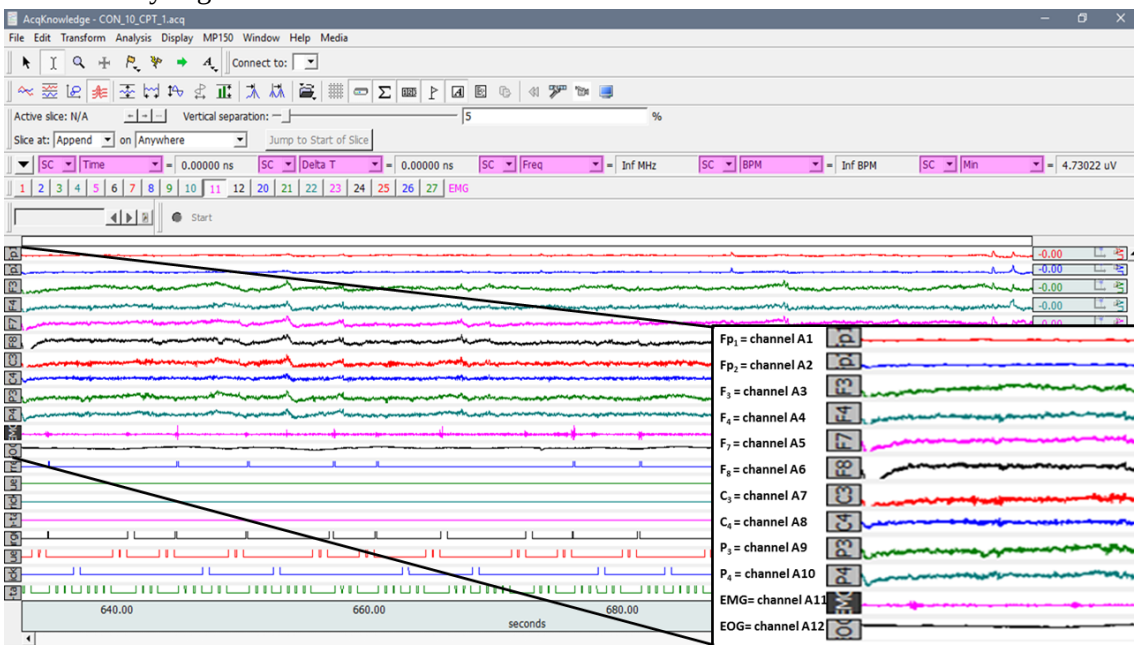
5. Setup the EEG station with;
   - 2x Sponge disks
   - 2x Foam ECG electrodes
   - 2x EOG 4mm adhesive disks
   - 1x 5ml luer adapter syringe
   - 1x Blunt needles
   - 4x Alcohol swabs
   - 2x EEG cap (large blue and medium red cap)
   - 1x Biopac amplifier with; EOG module and 4mm shielded electrodes, ECG module with 2 ECG clamps and RSP module with a respiratory Velcro strap belt
   - 1x Soft black rope for securing the EEG cap
   - 1x Electro gel
   - 1x Isotonic EOG gel
   - 1x Orange stick
   - 1x paper towel roll
   - 1x towel for drying of the EEG cap
   - 1x Ivory gel wash for washing of the EEG cap after use
   - 1x Ishihara colour plates- 38 set book for colour blindness test using plates 1, 13 and 25.
   - 2x STROOP task example pages
   - 1x Continuous performance task example
   - 1x Cued target detection task example



6. Open folders on both computers labelled with the participant number. On the Biopac computer copy the Acqknowledge templates into the participant folder.

WHEN THE PARTICIPANT ARRIVES:

7. Explain to the participant what the EEG will consist of and let them know that they will not be hurt. Also, that a blunt needle will be used to put electro gel into the EEG cap. **Show them that the needle is blunt.** This will be covered during the consent on day one but will be repeated on scan day.
8. Ask the participant to sit down at the computer, and to make sure their cell phone is off to ensure that there is no other electronic interference.
9. Explain to the participant that you will be using an alcohol swab to clean the participants forehead, collar bones and the side and bottom of the right eye – which is where the adhesive discs will be placed.
10. While the alcohol evaporates ask the participant to raise their arms for the placement of the respiratory belt. Place the belt around the participants' chest inserting the Velcro strap through the loop of the respiratory monitor asking the participant to inhale and exhale while you are tightening the belt around their chest. Ask the participant if they are comfortable and if they say yes, continue placing the rest of the electrodes.
11. Place the ECG electro tabs on the collar bone tab down. Attach the red and white ECG electrodes on the ECG adhesive tabs.
12. Place the ear linked reference electrodes on the earlobes of the left and right ear.
13. Then place the sponge discs on the forehead in line with the pupils of the eye, 3cm away from the bridge of the nose (this will mark the pre-frontal electrodes on the EEG cap). Place the EOG electrodes 1cm to the right of the right eye and 1cm below the right eye (ensure that the electrodes are placed on the muscles surrounding the eye- ask the participant). Prior to placing the EEG cap on the participant ensure that the seams of the cap are vertical with the label pointing down. The first two electrodes at the front of the cap need to be placed in the sponge discs on the forehead. Ask the participant to help you by holding the cap on the forehead while you pull the cap to the back of the head and down towards the ears. **NOTE: ASK THE PARTICIPANT IF THE CAP FEELS TOO TIGHT, if you are using the red cap and the cap is too tight switch to the blue cap and ask the participant again if the newer cap feels better (if the cap is too tight it will cause the participant to get a headache).** Once the EEG cap is in place, fill the 5ml syringe with electro gel and screw on the blunt needle. Remove the cap of the blunt needle and fill each electrode along the seam of the EEG cap ensuring that there are no bubbles and that the participant feels the cold gel touching their scalp.
14. Ask the participant to relax. Open the Acqknowledge template for resting eyes open task and ask the participant to inhale and exhale three times to ensure that the respiratory belt is measuring each breathe. Ask the participant to blink three times at the count of 1 – 2 – 3. Check to see that the participants heartrate is registering. And check that all 10 electrodes from the EEG cap is registering as well. If any of the electrodes of the EEG cap shows as a thick solid line or is not conforming to a similar waveform as the other electrodes, check to see if there is enough gel in the electrode or if there is a bubble in the gel of that electrode. If there is a bubble in the gel of that electrode hold the electrode down onto the scalp and add more gel using the blunt needle and syringe.



15. Once all the electrodes are registering, inform the participant that they need to keep their feet still throughout testing. **NOTE: inform the participant that both you and them are not allowed to speak during testing at all. Make it clear that you are only allowed to speak to them before and after tasks.**

EEG TASKS

1. Explain to the participant that they will be doing 5 different tasks which will involve 2 baseline tasks, where they will be looking at a white cross on a black screen for 3 minutes (a) and then closing their eyes (b) and relaxing for a further 3 minutes. Using the Continuous performance task (c) example page and Cued target detection task (d) example page and STROOP task (e) example pages explain each task to them.

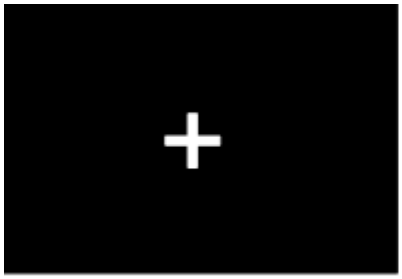


Figure 1: (a) Resting eyes open (REO) and (b) resting eyes closed (REC) baseline task: The REO task is conducted in 3 minutes by asking the participant to look at a white cross situated on a white screen. During the REC baseline task, the participant is asked to keep their eyes closed to breathe as per normal. For both tasks the participant is asked to remain as still as possible.

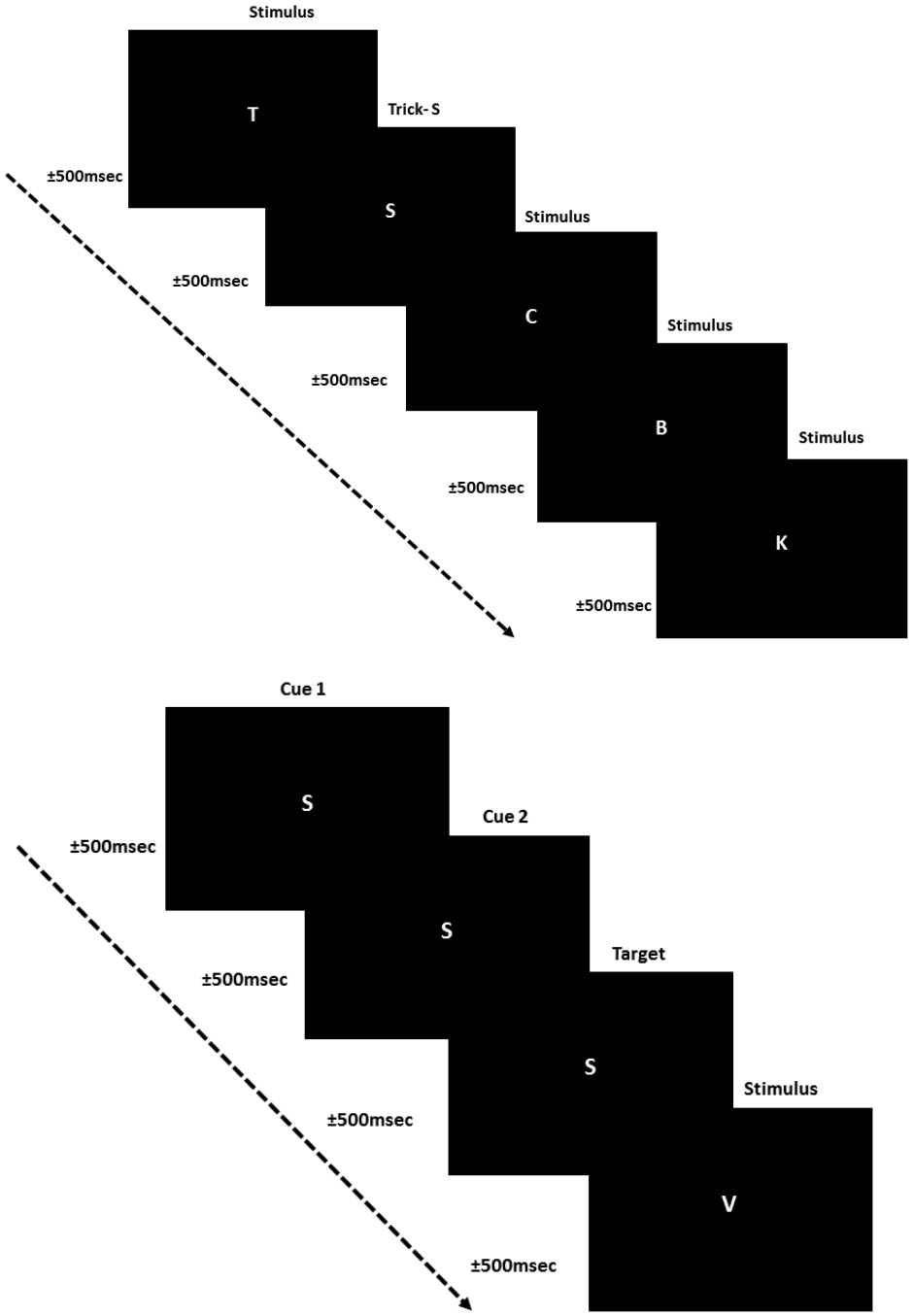


Figure 2 Representation of the visual Continuous Performance task. The continuous performance task was designed as a time-locked response task, where the letters appeared in a randomized order. Each letter was presented individually, appearing for 500 msec and disappearing for 100 msec before the next 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.

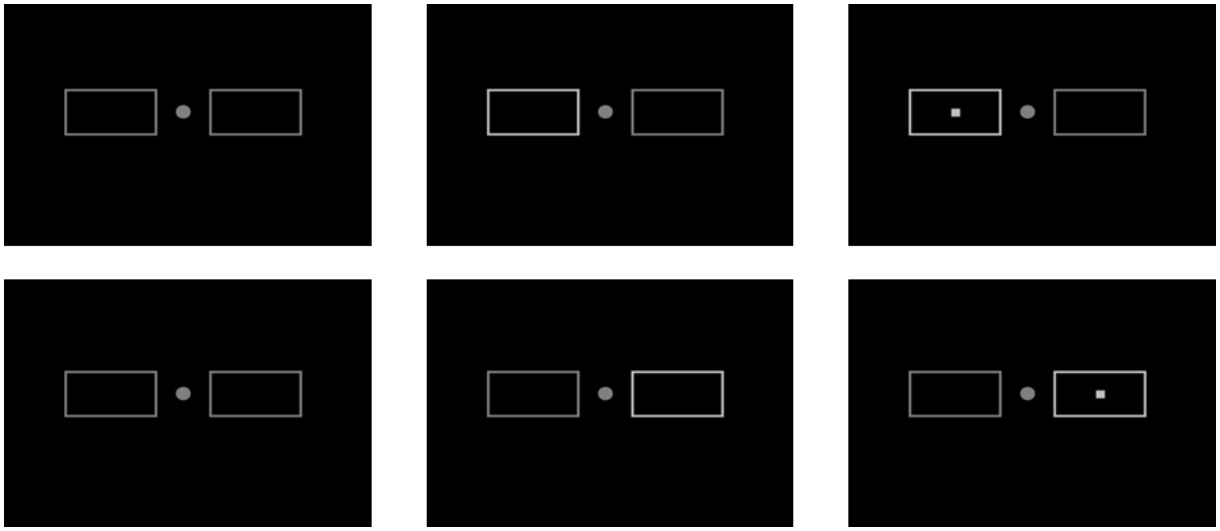


Figure 3: (d) Cued target detection task.

Figure 4: (e) Representation of the Stroop task. The words occur in a randomized order containing white squares which pop up in between the various colour/ word cues.

2. Let the participant know that they will need to complete a mental effort scale indicating that they need to make a mark on the line indicating what their mental effort was for that task (a rating from 0- 10).
3. **DO NOT TALK TO THE PARTICIPANT DURING EEG TESTING** unless you see that they are moving a lot or if they are not responding to the task. The participant **should not** scratch their head while the EEG cap is on. This should all be explained to them before conducting the EEG.
4. Should the participant do the EEG first do the first saliva sample before the MRI scan and the second sample after the MRI. **Make sure the tube is labelled with the participant code, date, and PRE/POST**. Note down the time of the saliva sample next to saliva sample 1/2 on the bench sheet. Ask the participant to use their tongue to tickle their palette (as you explain to them show them what you mean). Alternatively complete the tablet/questionnaires with the participant while they do the saliva sample to focus their attention on something else.
5. Complete any outstanding questionnaires.
6. Should the participant have completed the MRI first, hand them the treat bag and vouchers and sign the receipt. In the event the participant is completing the EEG first, guild them to the researcher who is completing the MRI. And hand the researcher the participants' file and inform them of any incomplete questionnaires.