University of Oxford

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No man is an island:

The role of social defeat and cognition in excitation/inhibition balance in first episode psychosis

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Thesis submitted for the degree of Doctor of Philosophy

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Acknowledgements

As this thesis will attest, in more ways than one,

"no man is an island, entire of itself" (John Donne)

Words cannot do justice to the support, affection and tethering that my favourite people and invaluable colleagues have provided throughout this DPhil process.

I would like to firstly thank my three incredibly generous, patient and knowledgeable supervisors: Prof. Dr. Belinda Lennox, Dr. Beata Godlewska and Dr. Lilian Weber. Without whose experience and guidance this thesis would have either never happen or taken a little less than an eon to complete.

This thesis was made possible by the assistance of my colleagues: Shah Tarfarosh, Judith Nottage, Anna Camera, Mark Roberts, Maja Friedman, Amy Li, Amy Sylvester, Sylvana Vilca-Melendez, Harriet Feldman, Jack Faneshaw, Amedeo Minichino, Ksenija Yeeles, and Jane Hainsworth. I would also like to thank the team at FMRIB, especially Jon Campbell, Michael Sanders, Juliet Semple, David Parker and Nicky Aikin.

To my loved ones, near and far, from Cowley to Kathmandu, thank you for being my pillars. To Joe, Dunja, Vaish, Rose, Nina, Rashi, Alice, Xenia, Myriam, Alan, Bobby, Emma, Seb, Wombell, Jean, Niamh, Maddy, Vladi, Tingyee: thank you for listening to me stress cry over things that definitely did not really matter, for pestering your social circles for study participants, for your endless patience for my rain checks and scattered interactions, and for getting over-priced wine to celebrate any small win. Your friendships nurtured my mind and heart, and have allowed me to grow in ways that were always exciting and novel. To these life companions, who will forever be the highlight of these last few years, I am endlessly grateful.

To my mum, Milica, whose brain functions very well according to her EEG, thank you for all you have done. Thank you for putting up with me when I was not the most fun to be

around and for always pushing and helping me no matter what.

Lastly, and perhaps most importantly, I would like to thank all of those who volunteered to take part in the studies included in this thesis. In particular, thank you to the thirty-two participants with lived-experience of psychosis, who gave me their time, energy and enthusiasm. Our conversations and time together taught me more than any paper or scan ever could, and provided a grounding reminder of what this DPhil was all for.

The words in this thesis may be my own, but it would have not been possible without the support and love from all those I was, and hope to continue to be, surrounded by.

Declaration

The work described in this thesis was carried out between October 2020 and July 2023 under the supervision of Prof. Dr. Belinda Lennox, Dr. Beata Godlewska and Dr. Lilian Weber. The work in this thesis is my own, with only the exceptions listed below:

- The pre-processing script for EEG data in Chapter 4 and Chapter 5 was carried out in collaboration with Lilian A. Weber
- The data analysis script for spectral EEG data in Chapter 5 was carried out in collaboration with Joseph Hickie
- The pre-processing script for MRS data in Chapter 6 was done by Dr Uzay E. Emir

I declare that the work presented in this thesis has not been submitted for any other degree, in this or in any other university.

Abstract

Rationale

Social defeat (SD) and cognition have been positioned as features of those at high-risk of developing psychosis (McCleery and Nuechterlein, 2019; Selten and Cantor-Graae, 2005). SD, in particular, has been hypothesised to be a mediating factor between demographic factors and increased risk of psychosis (Schalbroeck, 2023; Van Nierop et al., 2014). Moreover, the balance between excitatory and inhibitory (E/I) activity has been shown to be vital in the functioning of the brain and how information gets transferred (Gao and Penzes, 2015). The balance between E/I is largely maintained through glutamatergic and GABAergic activity, and has been hypothesised to be an intermediate phenotype for psychosis (Grent-'t Jong et al., 2018). Social defeat, cognition and E/I balance have all been understood as mechanisms in psychosis, and could provide significant insight into potential risk factors, E/I markers and novel targets for interventions (Lee et al., 2022).

Objectives

This thesis aims to investigate the relationship between social defeat, cognition, and potential E/I markers in first-episode psychosis. Additionally, this thesis anticipates to explore the interaction between the three different potential E/I markers: mismatch negativity, relative spectral band power and E/I related metabolite levels.

Methods

The data for this thesis was collected during two separate experimental study session: electroencephalography (EEG) and magnetic resonance spectroscopy (MRS). The EEG study included the use of mismatch negativity (MMN) and relative spectral band power for delta, theta, alpha, beta and gamma bands. Both the MMN and spectral band power were assessed for the FCz (fronto-central) electrode, with the MMN being measured during a visual task and the spectral band power measured during resting state. The EEG

session included a SD manipulation with false feedback to induce feelings of social defeat in participants. Spectral band power was compared before and after the SD manipulation to assess the potential role of SD on frontal neural activity. A total of 21 healthy controls (HC) and 22 patients with first-episode psychosis (FEP) were recruited for the EEG sessions. Proton MRS data was acquired from the anterior cingulate cortex (ACC) and dorso-lateral prefrontal cortex (DLPFC) using a 7-tesla Siemens scanner with 32 channel head coils. A total of 20 healthy controls and 20 patients with FEP were recruited for the MRS study.

Social defeat was measured using the social defeat scale (SDS) and the social comparison rating scale (SCRS). In the EEG study session cognitive performance was measured using an adapted continuous random dot motion visual task. In the MRS study session cognitive performance was measured using the Brief Assessment of Cognition in Schizophrenia (BACS), N-Back and Stroop Colour test. There were several clinical questionnaires to assess symptoms of psychosis and other categories including: the Positive and Negative Symptom Scale, Hamilton Depression Rating Scale and Young Mania Rating Scale.

Results

In this thesis SD was seen to be consistently significantly increased in the FEP group compared to HC ($p = 0.038$). Moreover, SD was seen to be correlated with both positive ($p = 0.036$) and general ($p < 0.001$) symptoms of psychosis but not negative symptoms. There were several significant correlations between SD and performance across several cognitive tasks for the FEP group, but none for the HC group.

SD was associated with MMN amplitudes in the HC group ($p = 0.045$) but not in the FEP group. SD was not correlated with any relative frontal spectral band power in either group. Further, SD was not correlated with neither ACC nor DLPFC E/I metabolite levels in the FEP nor HC group.

The FEP group performed significantly worse than controls on the BACS, N-back and Stroop Colour test but not on the CRDM. Relative spectral power and ACC and DLPFC E/I metabolite levels were associated with performance on these cognitive tasks, whereas MMN was not.

Though not significant the FEP group had reduced MMN amplitudes and longer latency compared to controls. The relative spectral band power in the non-SD condition was slightly but non-significantly increased across all power bands aside from alpha in the FEP group compared to HC. Similarly, in the SD-induced condition there were slightly

but non-significant increases in delta, theta and gamma in the FEP group compared to controls. E/I metabolite levels in the ACC were all non-significantly increased in the FEP group compared to HC. Whereas, the GABA and glutamate levels in the DLPFC were non-significantly increased and the glutamine and combined glutamate and glutamine were non-significantly decreased in the FEP group compared to HC. Moreover, spectral band power was not significantly different in the non-SD and SD condition for either controls or FEP. However, these potential E/I markers had several significant correlations between MMN, relative frontal spectral power and MRS E/I metabolite levels in both the HC and FEP.

Conclusion

There were several trend level, but non-significant findings relating to E/I metabolic differences between FEP and HC groups, and the involvement of SD and cognition. Social defeat is a consistent feature of first-episode psychosis. The lack of significant associations between potential E/I markers and SD in the FEP group could suggest that the association occurs prior to symptom onset or that SD does not directly impact glutamate and GABA. This is supported by SD's correlation with positive and general symptoms, suggesting it's involvement in the glutamate-dopamine pathway posited for these specific symptom sub-types. The non-significant differences between the control and FEP group in the MMN, spectral band power and E/I metabolite levels could suggest that glutamatergic disturbances occur in a prodromal stage prior to psychosis onset. This may also account for the lack of significant association between SD and E/I markers. The findings of an association between spectral band power and E/I metabolite levels with cognition implicates E/I balance in cognitive impairment in FEP. Despite the sample size and other limitations, this thesis established some novel links between E/I markers and SD and cognitive outcomes which could provide significant insights into disease pathology or mechanisms of psychosis.

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Chapter 1

Introduction

1.1 Psychosis

Psychosis describes a set of symptoms that represent a 'break from reality' (Abi-Dargham et al., 2000). A feature of multiple diagnoses, psychosis is seen in schizophrenia, schizoaffective disorder, bipolar, depression, substance abuse disorder, Parkinson's disease, Alzheimer's disease and other dementia, as well as certain neurological conditions (Dwyer et al., 2019). Symptoms of psychosis can be broken down into positive symptoms (such as hallucinations, delusions and thought disorganisation), into negative symptoms (such as affective flattening and alogia), and into cognitive impairments (such as in executive function, and working memory) (Mcguire et al., 2008).

Originally popularised by Krapelin, psychosis fell into two conceptual categories: 'manic-depressive psychosis' what is now referred to as bipolar, and 'dementia praecox' what is now referred to as schizophrenia spectrum disorders. Early on, stressful life situations, especially in childhood, were linked to the onset of psychosis (Bleuler, 1963). This understanding of psychosis has persisted with the development of the bio-psycho-social and stress-vulnerability models of psychosis (Park et al., 2022). Yet, the aetiology of psychosis remains complex and poorly understood (Mcguire et al., 2008). Therefore, those with first-episode of psychosis have highly heterogeneous prognoses (Lee et al., 2022).

There is some variation in the reported prevalence rate of psychosis. Some estimates are that 1.5% -3.5% of the population have psychosis (Van Os et al., 2001), while others reported that only 0.25% -0.75% of a population meet the criteria for schizophrenia or a

related psychotic disorders (Gordillo et al., 2023). Although prevalence of psychosis is stable across cultures, it varies according to age group and sex (Simeone et al., 2015). Age of onset of psychosis for females is typically 3-5 years later than males (Li et al., 2016). Peak onset for males is between 21-25 years of age, and for females it is either between 25-30 years of age or after 45 years of age.

With psychotic disorder being one of the top 20 leading causes of disability, it is associated with high disease burden (Howes et al., 2015; Lee et al., 2022). In fact, within the 20-24 age group schizophrenia is one of the 10 leading causes of increased disability-adjusted life years[1] (Debbane et al., 2015). Those with lived experience have described psychosis as an alienating and painful experience (Fusar-Poli et al., 2022).

Following the serendipitous discovery of chlorpromazine's effect on psychotic symptoms, dopamine D2 receptor blockers became a focus for the development of anti-psychotic medication (Carlsson and Carlsson, 1990). The dopaminergic system has been a central focus in unpacking the underlying biological mechanisms of psychosis. Excessive dopamine activity in the mesolimbic pathway has been attributed to positive symptoms (Abi-Dargham et al., 2000; Carlsson and Carlsson, 1990; Kegeles et al., 2010). Whereas insufficient dopaminergic transmission leads to cognitive and negative symptoms. Despite, anti-psychotics being fairly effective in reducing positive symptoms they are rather ineffective at treating negative and cognitive symptoms (Duarte and Xin, 2019). Moreover, approximately 25-30% of those with psychosis are treatment resistant to anti-psychotic drugs (Plitman et al., 2014). As a result, there has been a shift towards exploring other neurotransmitter and metabolic activities in psychosis that better account for treatment-resistance, and negative and cognitive symptoms (Plitman et al., 2014).

1.1.1 Glutamatergic Hypothesis for Psychosis

With the limitations of the dopamine hypothesis in mind, attention has shifted towards glutamate. Early studies showed that phencyclidine (PCP) and ketamine can induce temporary psychotic like symptoms such as hallucinations and cognitive impairments (Oliver et al., 2020; Plitman et al., 2014). Both drugs are primarily N-methyl-D-aspartate (NMDA) glutamate receptor antagonists, suggesting that dysfunction of the glutamatergic system may be relevant to psychosis (Merritt et al., 2013). Both animal and human studies have demonstrated that these NMDA receptor antagonists increase glutamate levels in the prefrontal cortex (PFC) (Stone et al., 2012), and that abnormal glutamate transmission

[1] Disability-adjusted life years (DALY) is a World Health Organisation metric implemented to measure the number of healthy life years lost as a result of an illness or disability.

in the PFC leads to alterations in mesolimbic dopamine functioning, as well as impaired γ-Aminobutyric acid (GABA) functioning (Oliver et al., 2020). Specifically, fast-spiking parvalbumin (PV) GABAergic interneurons density reduction within the prefrontal cortex and amygdala has been linked with schizophrenia and dopamine abnormalities (Modinos et al., 2018).

It has been proposed that there are higher levels of glutamatergic activity in early stages of psychosis, such as in first-episode psychosis (FEP). This theory corresponds to the neurotoxic effects of excess glutamate over time. It has been hypothesised that NMDA receptor hypo-functioning on GABAergic interneurons leads to disinhibition of downstream glutamatergic projections leading to increased glutamate and excitotoxicity (Oliver et al., 2020). However, over time neurodegeneration is thought to couple with glutamate-mediated excitotoxicity leading to decreased glutamate concentrations in certain brain regions, such as the thalamus and anterior cingulate cortex (ACC) in those with chronic psychosis (Plitman et al., 2014). It has been posited that this neurotoxicity occurs at earlier stages of illness and glutamate levels plateau over time. This has been some supported by proton magnetic resonance spectroscopy (^{1}H-MRS) research demonstrating that glutamatergic neuro-metabolites are significantly decreased in chronic schizophrenia compared to those with FEP and those at high-risk of psychosis (Marsman et al., 2013; Natsubori et al., 2014). Suggesting that excitotoxicity and excess glutamate are present at early stages, but not in the chronic population.

It should be noted that psychosis is not homogeneous. It has been shown previously that those who are treatment resistant seem to have elevated levels of glutamate in the ACC compared to treatment responsive patients (Egerton et al., 2023; Mouchlianitis et al., 2016). This suggests, that mechanisms could vary within the population of psychosis.

Glutamatergic abnormalities have been shown to have downstream effects on other monoanimergic systems (Carlsson and Carlsson, 1990). Therefore, a combined understanding of both glutamatergic and dopaminergic abnormalities in psychosis provides a fuller explanation of psychotic symptoms. A growing number of studies have shown that there are downstream effects in which glutamatergic abnormalities (mostly cortical) lead to dopaminergic abnormalities in psychosis (Howes et al., 2015; Mcguire et al., 2008; Stone et al., 2010b). In fact, dopamine hyper-excitability in the striatum is a known phenomenon in psychosis (Egerton et al., 2017a).

It has been hypothesised that positive psychotic symptoms arise from the following mechanism: a glutamatergic neurons act on GABA interneurons, these GABA interneu-

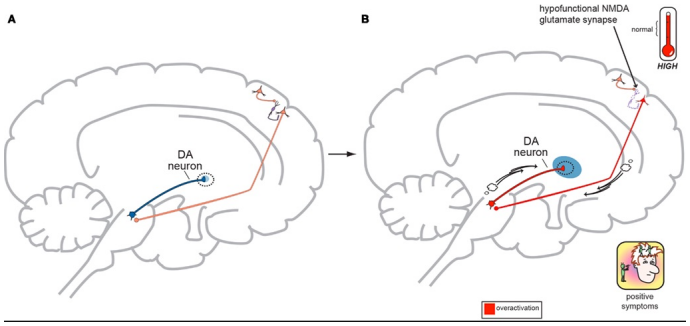

Figure 1.1.1: Proposed glutamatergic mechanism behind positive symptoms of psychosis, a) demonstrates normal functioning, b) demonstrates abnormal mechanism in psychosis(Schwartz et al., 2012)

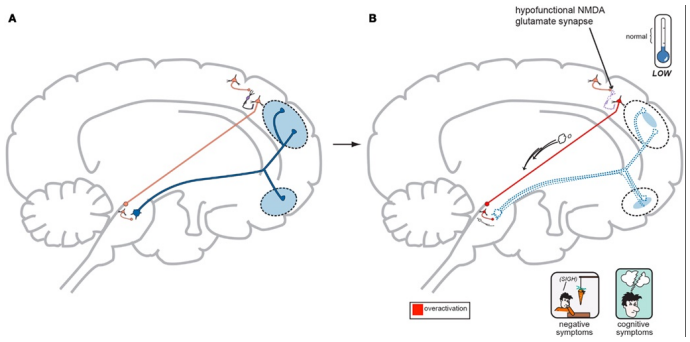

Figure 1.1.2: Proposed glutamatergic mechanism behind negative and cognitive symptoms of psychosis, a) demonstrates normal functioning, b) demonstrates abnormal mechanism in psychosis (Schwartz et al., 2012)

rons have abnormal hypo-functioning NMDA receptors, this leads to decreased GABA interneuron firing and reduced inhibition of glutamatergic neurons, this then causes overactive glutamatergic firing to disrupt mesolimbic dopamine resulting in excessive dopamine levels (Fig. 1.1.1)(Schwartz et al., 2012).

The following mechanism has been suggested for negative and cognitive symptoms: a glutamatergic neurons act on a GABA interneurons, these GABA interneurons have abnormal hypo-functioning NMDA receptors, this leads to decreased GABA interneuron firing and reduced inhibition of glutamatergic neurons, this results in increased glutamatergic firing that acts on a GABA interneurons, this causes increased GABA that impedes the functioning of midbrain dopamine and leads to an over-inhibited and under active mesocortical dopamine that cannot supply the frontal regions with an adequate amount of dopamine resulting in hypofunctional frontal dopamine (Fig. 1.1.2)(Schwartz et al., 2012).

The glutamatergic hypothesis of psychosis can be summarised as: hypofunctioning NMDA

receptors on GABA interneurons lead to an enhancement of pyramidal cell activity which in turn increases glutamate in adjacent and corresponding cortical regions (Moghaddam and Krystal, 2012). These abnormalities are thought to occur in specific networks and are local. In particular glutamatergic abnormalities are thought to occur in the frontal regions, with higher frontal glutamatergic activity leading to downstream effects in mesolimbic and mesocortical brain regions (refer to 1.1.1 and 1.1.2) (McCutcheon et al., 2020; Schwartz et al., 2012).

1.1.2 Excitotoxicity Hypothesis of Psychosis

Elevated glutamate has been hypothesised to lead to anatomical changes and neuronal death through excitotoxicity (Marsman et al., 2013; Plitman et al., 2014; **?**). Excitotoxicity describes the process in which prolonged dysregulation of glutamatergic systems leads to mitochondrial dysfunction, oxidative stress, reactive oxygen species overproduction and calcium influx (Armada-Moreira et al., 2020). In this manner, glutamatergic abnormalities in psychosis are indirectly linked to neuronal death (Olney, 1969).

Glutamatergic neurotransmission occurs via iGluR [2] and mGluR [3]. iGluR channels fall into three classes: NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainic acid (KA) receptors. NMDA receptors are involved in neurotoxicity due to their high permeability to calcium ions (Guo, 2003; Javitt et al., 1996). Extra-synaptic NMDA receptors are thought to contribute to neurotoxic effects due to an influx of calcium, whereas synaptic NMDA receptors are thought to be a protective factor against neurotoxic effects (Armada-Moreira et al., 2020).

Both the glutamatergic hypothesis and its extension, the excitotoxicity hypothesis, can account for the neuro-anatomical structural changes seen in psychosis, such as grey mater loss and volumetric loss (Plitman et al., 2014).

1.2 Excitation/Inhibition Balance

The brain transfers and synthesises information through a complex, finely tuned, functional balance between excitation (activating their target) and inhibition (suppressing their target) of neurons and networks (Gao and Penzes, 2015; O'Donnell et al., 2017). This balance between excitation and inhibition (E/I balance) is largely maintained through

[2] iGluR is a ligand-gated ion channel responsive to cations (such as sodium) that produce excitatory currents.

[3] mGluR is a G protein-coupled receptor that regulates cellular functioning.

a localised relationship between excitatory synapses acting through glutamatergic depolarisation of cells, and inhibitory synapses acting to oppose this through GABA activity (Gao and Penzes, 2015; Missonnier et al., 2020). Therefore, both glutamate and GABA are vital components of the network that coordinates the firing of these pyramidal cells and the brain activity (Missonnier et al., 2020). Disruption in E/I balance would yield to incorrect circuit functioning (Sohal and Rubenstein, 2019; O'Donnell et al., 2017). The hypothesised changes in E/I balance in FEP are thought to occur within specific networks, and with variation across regions. This is supported by MRS studies finding differences in E/I metabolite levels within a psychosis population depending on ROI (Marsman et al., 2013). Further, specific networks have been theoretically and empirically linked with both social defeat and symptoms in psychosis (Selten et al., 2013).

As previously mentioned, glutamate is the primary excitatory neurotransmitter, as well as a precursor to glutamine, GABA, and glutathione, and a necessary component for energy metabolism (Sydnor and Roalf, 2020; Yüksel and Öngür, 2010). Glutamate can be found in approximately 60% of cortical neurons and in 100% of cortical pyramidal neurons (Javitt et al., 1996). Whereas GABA is the primary inhibitory neurotransmitter in the brain and spinal cord, and can be found in approximately 20% of cortical neurons (Tatti et al., 2017).

E/I balance abnormalities, resulting in increased excitability, have been positioned as an intermediate phenotype of circuit aberrations in psychosis (Grent-'t Jong et al., 2018). Reported E/I imbalance does not necessarily reflect the overall ratio between excitation and inhibition, but also refers to the imbalance between subtypes of excitation and inhibition (Liu et al., 2021). The hyperexcitability, glutamatergic hypothesis and NMDA receptor hypofunctioning model of psychosis is in essence an explanation of psychosis via an E/I imbalance lens (Kehrer et al., 2008).

Two major technologies that have been able to push the field forward with *in-vivo* measurements of direct and indirect E/I balance are electroencephalography (EEG) and magnetic resonance spectroscopy (MRS).

1.3 Electroencephalography

Electroencephalography is a non-invasive technique that could serve as a cheaper alternative to MRS for measuring E/I imbalances. EEG picks up voltage changes and network oscillation due to the synchronous firing of large groups of cortical pyramidal neurons

that are perpendicular to the surface of the brain (Britton et al., 2016; Bruining et al., 2020).

1.3.1 Event-related Potentials

Each time there is a sensory, motor or cognitive event, it is met with a measured brain response, this leads to voltage change resulting in what is known as the event-related potential (ERP) (Grimm et al., 2011; Luck, 2014). ERPs can be categorised into early waveforms and late waveforms (Sur and Sinha, 2009). Early waveforms, ERP components in the first 100 milliseconds of stimuli presentation, are more dependent on the physical attributes of stimuli and are often labelled as sensory or exogenous. Whereas later waveforms are thought to reflect information processing and are therefore labelled as cognitive or endogenous.

1.3.2 Mismatch Negativity

The mismatch negativity (MMN) is a cognitive ERP response that has been positioned as a promising potential biomarker for psychosis (Umbricht and Krljes, 2005). MMN is elicited when a series of uniform stimuli (standards) gets interrupted with occasional stimuli that differs according to some parameter (pitch or duration for example). These differing stimuli are referred to as deviants or 'oddballs', giving this stimuli paradigm the name "oddball paradigm". The MMN waveform is the difference between the average response to a standard stimulus and the average response to a deviant stimulus, with the peak of the MMN occurring between 100 to 250 milliseconds following stimuli (Bishop and Hardiman, 2010; Fitzgerald and Todd, 2020). The MMN response is thought to be 'preattentive' as it occurs regardless of whether active attention is paid to the oddball paradigm or not (Shelley et al., 1991).

Using MMN as a biomarker would be helpful in identifying individuals at risk of developing psychosis and to predict prognosis. Therefore, MMN abnormalities should exist prior to onset in those at high-risk or in earlier stages of psychosis (Haigh et al., 2017). MMN abnormalities have been connected to symptom severity and social functioning deficits (Higgins et al., 2021; Murphy et al., 2020). There is also evidence to suggest that MMN abnormalities are linked with disease progression, although others have found no direct association between MMN and duration of illness suggesting the association is non-linear (Erickson et al., 2016). Although there is variation in reported MMN findings, meta-analyses have suggested significant small to medium effects for MMN amplitude

reduction in FEP compared to controls (Erickson et al., 2016; Haigh et al., 2017).

Specifically, duration deviant MMN has been shown to be significantly reduced in psychosis with a stronger effect than frequency deviant MMN (Erickson et al., 2016; Haigh et al., 2017; Michie et al., 2000; Nagai et al., 2013). Moreover, in early stages of psychosis duration MMN has been shown to be significantly reduced, whereas frequency MMN was not (Bodatsch et al., 2011; Nagai et al., 2017). Based on both of these findings duration MMN could be a stronger biomarker for FEP and may be attenuated prior to onset of psychosis (Nagai et al., 2013). Whereas frequency MMN could be reflective of disease progression as it has been linked to reduction in Heschl's gyrus volume seen in chronic psychosis (Nagai et al., 2013). This indicates that different MMN parameters could be used as biomarkers for different aspects of the pathology of psychosis (Koshiyama et al., 2018).

MMN has been explained through several mechanisms, such as neural adaption, deviance detection and predictive coding (Tada et al., 2019). The neural adaption model posits that there is a decrease in response to repeated stimuli, known as adaption, and that in MMN this decrease occurs more for standard stimuli as it is more repeated than deviant stimuli (Tada et al., 2019). There is evidence of neural adaption in both animals and humans, however the theory itself is insufficient in explaining the MMN phenomena as it fails to account for different MMN paradigms (such as missing tone MMN) (Kiebel et al., 2007). This is where the deviance detection hypothesis steps in. Previous literature, employing a 'many standards' paradigm[4], has shown that the deviant tone in the oddball paradigm elicited a much larger response than the same stimuli when presented as a control (Jacobsen and Schröger, 2003). This demonstrates that there is a specific neural process that detects deviant stimuli in context, and that it is this deviance detection, related to predictive error, that can account for MMN abnormalities in psychosis (Koshiyama et al., 2020; Tada et al., 2019). Predictive error is a central feature in the predictive coding hypothesis for MMN abnormalities in psychosis. When there is a mismatch between stimuli and prediction the prediction error creates a feedback loop that alters the predictive model and leads to a reduction of predictive errors and, hence, a reduction of MMN over time (Kiebel et al., 2007; McCleery and Nuechterlein, 2019). Predictive coding is a process in which sensory input is integrated with predictions through hierarchical cortical interactions that involve both the temporal and frontal cortex (Garrido et al., 2009; Huang and Rao, 2011). It has been suggested that those with

[4]A many-standards paradigm has many control tones in addition to the standard and deviant stimuli seen in the traditional oddball paradigm.

psychosis have abnormalities in predictive error detection, rather than issues with memory trace or the ability to code predictions (Fong et al., 2020; McCleery and Nuechterlein, 2019).

The E/I balance hypothesis has also been applied to MMN. All of the suggested mechanisms behind MMN involve the interplay of fast-spiking PV GABAergic interneurons with excitatory neurons. In particular, NMDA receptor activity and MMN response have been strongly associated (Fitzgerald and Todd, 2020; Fong et al., 2020). Corresponding with previous findings, NMDA activity has been linked with deviance detection but not adaption in MMN (Farley et al., 2010). Attenuated MMN response over the course of disease has been linked to chronic NMDA receptor dysfunction and grey matter loss (Liu et al., 2021). Moreover, NMDA antagonists administered to healthy controls have been shown to reduce MMN response mimicking psychosis (Umbricht et al., 2000). Dynamic causal modelling studies have also suggested the involvement of NDMA and AMPA receptor activity in the formation of the predictive coding feedback loop for MMN (Corlett et al., 2009; Garrido et al., 2009; Kiebel et al., 2007; Wacongne et al., 2012). These findings support the hypothesis for both the predictive coding explanation of MMN and the role of NMDA hypofunctioning in MMN abnormalities in psychosis.

As duration MMN is a promising biomarker for FEP, further exploration in conjunction with other factors related to psychosis could provide insight into mechanisms behind onset of psychosis.

1.3.3 Spectral Analysis

Aberrant neural oscillatory activity, in addition to ERP abnormalities, has been implicated in psychosis (Jahangir et al., 2021; Javitt et al., 2020). Abnormalities have been seen across both low and high frequency oscillations and both during task and resting state (Curic et al., 2019; Jahangir et al., 2021). Unfortunately, the exact mechanisms behind these neural oscillations, and therefore the source of their aberration, remains unclear (Buzsáki and Wang, 2012).

Abnormalities in gamma band oscillations in psychosis have been fairly consistently reported (Uhlhaas and Singer, 2010), and they have been linked with symptom severity in FEP (Tada et al., 2016). However, there is inconsistency as to whether gamma activity is increased or decreased in psychosis, especially in FEP (Perrottelli et al., 2021; Reilly et al., 2018; Spencer et al., 2008). Gamma oscillations have been conceptualised through E/I balance with an interplay between excitatory pyramidal neurons and fast-spiking PV

inhibitory interneurons (Buzsáki and Wang, 2012; Gao and Penzes, 2015; Gonzalez-Burgos and Lewis, 2012; Lisman, 2012). Following excitation, there is delayed inhibitory feedback from GABAergic fast-spiking PV interneurons, forming a negative feedback loop (Ahmad et al., 2022). The phase shift that arises from this mechanism determines the frequency of the gamma oscillation.

Gamma band abnormalities in psychosis are thought to be reflective of hyper-excitability and explained by the glutamatergic hypothesis of psychosis (Foss-Feig et al., 2017; Gao and Penzes, 2015; Missonnier et al., 2020). This has been strongly supported by findings that the activation of fast-spiking PV interneurons induces gamma oscillations, whereas the inhibition of fast-spiking PV interneurons suppresses gamma oscillations but increases alpha and beta oscillations (Bartos et al., 2007; Buzsáki and Wang, 2012; Cardin et al., 2009; Uhlhaas and Singer, 2010; Sohal et al., 2009; Wang and Buzsáki, 1996). This was further supported by research that shows that GABA agonist propofol increases gamma band power (Saxena et al., 2013). It has been suggested that there is a shared mechanism between ACC glutamatergic levels and gamma band power as they both decrease with age in schizophrenia (Brandt et al., 2016; Grent-'t Jong et al., 2018; Marsman et al., 2013). However, there are controversial findings concerning the exact mechanism behind gamma oscillations and thus the mechanism behind gamma band abnormalities in psychosis.

Beta oscillations have also been strongly linked to E/I balance and have been shown to be abnormal in psychosis (Gawne et al., 2020; Venables et al., 2009). Beta oscillations are thought to occur as a result of inhibitory interneuron activity and GABAa gating (Ahmad et al., 2022). As previously mentioned, beta activity has been shown to increase as a result of the inhibition of fast-spiking PV interneurons (Jensen et al., 2005; Sohal et al., 2009). Beta oscillations have been divided into subtypes, with one that occurs due to firing of pyramidal cells and inhibitory interneurons in the beta frequency band, and another linked to synchronised pyramidal cells firing in the beta frequency along with interneuron cells firing in the gamma frequency (Ahmad et al., 2022). Machine learning models have positioned beta power abnormalities as a particularly promising biomarker for psychosis (Dvey-Aharon et al., 2015). Beta abnormalities also are associated with cognitive impairments and other clinically relevant features of psychosis (Jia et al., 2022).

Abnormalities in psychosis have also been seen in lower frequencies (delta, theta, and alpha band power) compared to controls (Buzsáki and Wang, 2012; Gawne et al., 2020; Jia et al., 2022; Sohal et al., 2009; Uhlhaas and Singer, 2013; Venables et al., 2009). Although there are fewer findings for low-frequency abnormalities in psychosis, they could be still be relevant for psychosis as they could lead to downstream gamma abnormalities

(Foss-Feig et al., 2017).

There have been other novel EEG markers strongly associated with E/I balance and look like promising biomarkers for psychosis (Ahmad et al., 2022). However, oscillatory activity has been shown to be abnormal in psychosis and is a more conventional and evidence-backed marker of E/I. Further research on the role of both high and low frequency aberrations in psychosis is still required to better understand these mechanisms and how they reflect abnormalities in psychosis.

1.4 Magnetic Resonance Spectroscopy

E/I balance can be measured more directly via magnetic resonance spectroscopy (MRS). MRS is a non-invasive *in-vivo* method by which various neuro-metabolites are measured, including glutamate and GABA, alongside other glutamatergic metabolites such as glutamine or combined glutamate and glutamine (Glx).

MRS E/I metabolite findings are not consistent across psychosis groups and vary according to metabolite. Some meta-analyses have found decreased glutamatergic metabolites in frontal brain regions in schizophrenia compared to controls (Marsman et al., 2013; Merritt et al., 2023, 2021; Smucny et al., 2021; Sydnor and Roalf, 2020). Similarly, it has been shown that NMDA receptor antagonists could alter the glutamine-glutamate cycle by increasing glutamine and decreasing glutamate (Iltis et al., 2009; Marsman et al., 2013). However, another meta-analysis found increased glutamate levels in several brain regions (Merritt et al., 2016). When focusing on the frontal regions, ACC and dorsolateral prefrontal cortex (DLFPC), this and other meta-analyses found no significant difference in glutamatergic nor GABAergic metabolites in neither schizophrenia nor FEP compared to controls (Dempster et al., 2020; Kaminski et al., 2021; Merritt et al., 2016; Nakahara et al., 2022; Poels et al., 2014). Contrarily, some studies found elevated glutamate and glutamine levels in the ACC in early stages of psychosis (Smesny et al., 2015; Squarcina et al., 2017; Théberge et al., 2007), while others found decreased glutamate and glutamine in the ACC in FEP compared to controls (Godlewska et al., 2021; Wang et al., 2019). In high-risk groups Glx concentrations in frontal regions were elevated compared to controls (Merritt et al., 2016; Romeo et al., 2020; Wenneberg et al., 2020). Conversely, in high-risk versus control groups, a similar meta-analysis found elevated Glx in the thalamus only and not in any other regions (McCutcheon et al., 2021). The few studies exploring GABA found no significant differences in GABA concentrations between psychosis and controls (Egerton et al., 2017b; Sydnor and Roalf, 2020). One

meta-analysis found decreased GABA in the midcingulate cortex (MCC) in FEP compared to controls (Nakahara et al., 2022). Thus, the extant literature concerning E/I balance in psychosis is somewhat inconsistent, which could be explained by differences in brain region studied and differences in stage of illness (Merritt et al., 2016; Nakahara et al., 2022).

All meta-analyses noted heterogeneity in study results and attributed the variation in findings to several factors including patient sample differences, MRS methodology differences, and variation in placement of voxels (Egerton et al., 2017b; McCutcheon et al., 2021; Merritt et al., 2023; Sydnor and Roalf, 2020; Wenneberg et al., 2020). It should also be noted that MRS provides a window into total metabolite concentrations and is unable to reflect functionally diverse metabolite levels, which could also contribute to variations in results (Godlewska et al., 2021).

In line with the excitotoxicity hypothesis it has been suggested that glutamate levels decrease with the progression of illness in psychosis. This is supported by cross-sectional study findings of frontal glutamate and glutamine decreasing with age (Marsman et al., 2013). This has been countered by studies finding an association between decreased frontal glutamate and Glx with antipsychotic medication rather than age (Kubota et al., 2020; Merritt et al., 2016, 2023). This has been contested with a study that found no significant differences in ACC glutamate levels in unmedicated recent psychosis compared to the same group after 6 months of anti-psychotic treatment (Jeon et al., 2021). Interestingly, elevated glutamate in the ACC and MCC has been associated with worse symptom severity and treatment-resistance (Dempster et al., 2020; Egerton et al., 2021; Nakahara et al., 2022). These meta-analyses findings and the examination of the role of age and medication generally support the excitotoxicity argument, suggesting that initially in psychosis glutamate is elevated but over time glutamate levels decrease (Moghaddam and Krystal, 2012).

Importantly, it could also be that there is spectrum of glutamatergic abnormalities in psychosis. Variability in glutamatergic levels was shown to be significantly higher in those with schizophrenia compared to controls (Merritt et al., 2023). Specifically, glutamate, glutamine and Glx were more variable in the medial frontal cortex and glutamine and Glx were more variable in the DLPFC in patients, both medicated and unmedicated, than in controls (Kaminski et al., 2021; Merritt et al., 2023). Overall, patients with more severe symptoms had higher rates of variability, and medication did not seem to play a role. This potentially suggests that glutamatergic dysregulation, rather than a uni-directional aberration in glutamate, underlies psychosis.

Given the potential of MRS technology, as well as the pertinence of the hyperglutamatergic and excitotoxic hypotheses for psychosis, further research in FEP groups would provide vital insight into the metabolic mechanisms behind the earlier stages of illness.

1.5 Social Defeat

In addition to biological mechanisms there are social and environmental factors that could play a role in psychosis. The social defeat (SD) hypothesis for psychosis belongs to the stress-vulnerability model and bio-psycho-social model of psychosis, which attributes the development of psychosis to a combination of genetic predisposition and exposure to environmental stressors (both internal and external) (Demke, 2022; Egerton et al., 2017a). Social defeat in humans has been described primarily in depression populations as a sense of losing a fight/struggle and originates from 'resident-intruder' animal models [5], (Gilbert et al., 2002; Luhrmann, 2007). The link between social defeat and schizophrenia has a strong history within anthropology and sociology, dating back to the seminal text "Saints, Scholars, and Schizophrenics: Mental Illness in Rural Ireland" by Nancy Shepher-Hughes (Scheper-Hughes, 2001). Within anthropology SD has been described as an actual encounter in which one person must physically or symbolically lose to another (Luhrmann, 2007).

Within the psychiatric context of psychosis, the definitions of SD have been somewhat loose (Schalbroeck, 2023). In 2005 SD was put forward as an explanatory factor for the associations between social risk factors and psychosis, with SD being described as a feeling of subordination or being the outsider (Selten and Cantor-Graae, 2005). SD has also been described as being socially excluded from the majority (Selten et al., 2016; Vinkers et al., 2021). Recently, the definition of SD has also included the notion of low status (Selten and Ormel, 2023), though, it has been clarified that the most correct definition of SD was the original one proposed in 2005.

SD has also been heavily associated with the social rank hypothesis (Selten, 2023), which claims that there are certain neural information processing systems that identify hierarchy, specifically social hierarchy, in a manner integral for survival (Wood and Irons, 2016). In humans, this competition is not only reserved for physical resources but also insider status and attractiveness (Allan and Gilbert, 1995; Wood and Irons, 2016). This is in line with Marmot's status syndrome that argues that being lower in a hierarchy increases

[5]The 'resident-intruder' animal model describes when a male rodent is put into a cage with another male rodent who already occupies the space.

risk for various diseases via increased activity in the sympatho-adreno-medullary axis and the hypothalamic-pituitary-adrenal axis (Marmot, 2004). Moreover, low social rank has been previously linked with greater feelings of paranoia (Freeman et al., 2005, 2014). Social rank is thought to be highly tied to SD and could act as a component to the SD phenomena and its potential explanatory power for psychosis (Heriot-Maitland et al., 2022; Selten and Cantor-Graae, 2005).

Selten themselves have argued that social defeat is a non-specific and insufficient explanation for psychosis and should be viewed in conjunction with other factors such as genetic vulnerability (Selten et al., 2016).

Given the parsimonious explanation and growing evidence that social defeat offers for several risk factors for psychosis, its potential role in the aetiology and prognosis of psychosis are well worth exploring (Selten, 2023).

1.5.1 Social Defeat and Risk Factors in Psychosis

SD has been positioned as a mediating factor between demographic factors and risk of psychosis (Schalbroeck, 2023; Seo and Choi, 2018; Stowkowy and Addington, 2012; Van Nierop et al., 2014). These demographic features include: ethnic minority status (especially in a low ethnic density area), first- or second-generation immigrant status, urbanicity, and deprivation (Bosqui et al., 2014; Bourque et al., 2011; O'Donoghue et al., 2016; Radua et al., 2018; Tortelli et al., 2015). SD is thought to be specifically tied to minority status, as it has been shown that being a minority within a community is what leads to increased risk of psychosis (Bourque et al., 2011).

Being an ethnic minority has been associated with increased risk of serious mental illness, and particularly psychosis (Bresnahan et al., 2007; Das-Munshi et al., 2012; Eilbracht et al., 2015). Being a minority, particularly black-skinned in a white-skinned community or from a developing nation in a developed nation, has a particularly large effect on the risk of psychosis (Cantor-Graae and Selten, 2005). It was seen that being an ethnic minority in one's community increased the risk of psychotic experience 1.07 times for every 10% reduction in own-ethnicity density, when living within a community of a similar or same ethnic minority this heightened risk was not present (Das-Munshi et al., 2012). This finding has been reported across different ethnic minorities and cultural contexts (Boydell et al., 2001; Kirkbride et al., 2007; Schofield et al., 2011; Selten et al., 2020).

Immigration has been a relatively well-established risk-factor for the development of psychosis, and persists as a risk factor in second generation immigrants (Bresnahan et al.,

2007; Bourque et al., 2011; Kirkbride et al., 2012; Selten et al., 2020). There is also a greater risk for second generation immigrants compared to first generation immigrants, although the number of studies involving second generation immigrant participants was limited (Bourque et al., 2011; Cantor-Graae and Selten, 2005). Risk of psychosis was also increased in those who experience childhood deprivation and immigration status in an environment where the majority were not deprived and were not immigrants (Zammit et al., 2010). Whereas childhood deprivation and immigration status were not risk factors of psychosis in an environment where the majority was also deprived and from an immigrant background. Moreover, perceived relative deprivation has been associated with increased paranoia and hallucination-proneness (Wickham et al., 2014).

The risk of psychosis for these demographic groups have previously been attributed to experiences of discrimination and lack of social support (Anglin et al., 2021; Whitley et al., 2006). Discrimination in particular has been strongly linked with increased risk of psychotic experiences, and has been formulated as a particularly salient form of SD (Anglin et al., 2021; Bardol et al., 2020; Berger and Sarnyai, 2015; Hall, 2022; Oh et al., 2014; Veling et al., 2007). This was similarly found in other proxy markers for SD such as unemployment, unmarried status and low socio-economic background (Werbeloff et al., 2015). Furthermore, ostracism has been strongly associated with negative symptoms of psychosis (Jaya et al., 2022). A large 6646 participant NEMSIS-2 study established SD as a mediating factor between childhood trauma and psychosis (Seo and Choi, 2018; Van Nierop et al., 2014). Similarly, when controlling for SD associations between demographic factors and schizotypy were no longer significant, suggesting that it is SD that mediates the relationship between demographic risk and psychosis (Lincoln et al., 2022).

Overall, SD has been proposed as a potential predictive factor for psychotic experiences and long-term behavioural differences (Schalbroeck, 2023; Schnider et al., 2022; Shovestul et al., 2023; Valmaggia et al., 2015; Vinkers et al., 2021; Wendelmuth et al., 2020).

1.5.2 Physiology behind Social Defeat

The exact mechanism behind SD's involvement in mental illness progression is not yet established. Based on animal studies and emerging research it has been hypothesised that social defeat acts on mesolimbic dopaminergic activity (Selten et al., 2013).

Associations between SD and mesolimbic dopamine activity have been strongly established through both human and animal models (Chaudhury et al., 2013; Egerton et al., 2017a;

Isovich et al., 2001; Martinez et al., 2010; Mizrahi et al., 2012; Morgan et al., 2002; Novick et al., 2011; Pruessner et al., 2004; Selten et al., 2013; Soliman et al., 2008; Tidey and Miczek, 1996; Vassilev et al., 2021), and potentially is a result of E/I imbalance (Olney et al., 1999; Schwartz et al., 2012). There is evidence to support the hypothesis that abnormal dopamine functioning occurs prior to the transition from high-risk status to psychosis (Van Hooijdonk et al., 2022). It has therefore been suggested that SD acts as a risk factor in conjunction with unregulated dopaminergic activity in the midbrain and striatum (Selten and Ormel, 2023).

The involvement of striatal dopamine in SD has been indirectly supported through findings of elevated stress-induced striatal dopamine release and dopamine synthesis capacity in immigrants (a known at-risk group for psychosis) compared to non-immigrants (Egerton et al., 2017a). A similar finding was established in those with childhood adversity (Oswald et al., 2014). This was further supported by a study that reported lower dopamine receptor activity levels in those with lower social status and lower social support (Martinez et al., 2010; Morgan et al., 2002). Additionally, people who have experienced chronic SD also reacted to stress with greater dopamine release compared to controls (Berger and Sarnyai, 2015; Novick et al., 2011). Moreover, exposure to social stress during teenage years in which dopamine axons grow into the PFC, could lead to a particular susceptibility to environmental factors (Vassilev et al., 2021). These studies support the hypothesis of mesolimbic dopaminergic involvement in SD. Further, psychosis and dopamine have been strongly linked with increases in presynaptic dopamine levels seen in psychosis (Bonoldi and Howes, 2014), which could indicate a shared mechanism behind SD and psychosis.

Stress, including social stress, has also been associated with E/I balance changes (Howes and Shatalina, 2022). SD has been suggested to decrease subunits of NMDA and AMPA receptors, linking SD and NMDA hypofunctioning (Novick et al., 2016). Moreover, prefrontal regions, implicated in the NMDA hypofunctioning and anatomical changes in psychosis (Stone et al., 2012; Oliver et al., 2020; Plitman et al., 2014), have also been implicated in SD and environmental risk factors. It has been reported that individuals from an ethnic minority background had higher rates of activation in the ACC compared to controls (Akdeniz et al., 2014). The ACC may be of particular relevance to the SD hypothesis of psychosis due to its association with social exclusion and stress (Théberge et al., 2002; Lederbogen et al., 2011). The extant literature therefore suggests that there is a relationship between social defeat and NMDA hypofunctioning models of psychosis (Kehrer et al., 2008).

The potential biological overlaps between SD and mechanisms behind psychosis suggests

that SD could influence these impacted biological pathways in psychosis. Therefore, research exploring these biological mechanisms and their interactions could clarify the multi-factorial risks associated with psychosis onset and prognosis.

1.6 Cognition in Psychosis

Cognitive impairments in psychosis have been linked with clinical and social outcomes (Baldeweg et al., 2004). Approximately 80% of those with psychotic illness suffer from clinically significant cognitive impairments (McCleery and Nuechterlein, 2019). Meta-analyses have shown that there is a large effect size for differences in cognitive performance across a wide variety of tasks between healthy controls (HC) and schizophrenia groups, with the largest differences being in memory and processing speed (McCleery and Nuechterlein, 2019). Importantly, these cognitive impairments do not seem to be moderated by cultural context, duration of illness or symptom profile (Schaefer et al., 2013). As previously discussed, cognitive impairments remain particularly difficult to treat and are the symptom type that most hinders positive outcomes and functionality within a community (Duarte and Xin, 2019; McCleery and Nuechterlein, 2019).

These cognitive impairments are thought to begin in prodromal stages, with one meta-analysis concluding that those with psychosis already had marked deficits in IQ and motor functioning at the age of 16 (Dickson et al., 2012). It was shown that basic cognitive deficits occur very early on in a prodromal stage, with significant cognitive impairments occurring in ultra-high risk groups and worsen within the first-episode stage (Simon et al., 2007). These cognitive impairments seem to occur independently of other symptom severity (Simon et al., 2007).

Glutamatergic activity and E/I balance have been positioned as central to cognitive functioning and therefore has been linked to cognitive impairments in psychosis (Dauvermann et al., 2017; Howes and Shatalina, 2022). Lower Glx levels are linked with overall cognitive impairment in psychosis (Bustillo et al., 2011). There has also been an association between ACC glutamate levels and composite scores on the BACS in first-episode psychosis (refer to Section 2.4 for more information on the BACS)(Godlewska et al., 2021). Using ^{1}H-MRS technology, working memory has been linked with ACC glutamate (Wang et al., 2019). Additionally, glutamatergic agents have a small yet significant effect size for the improvement of overall cognition and working memory, although improvements may be clinically negligible (Sinkeviciute et al., 2018). Specifically, AMPA site acting agents and memantine are the most promising for improvements in working memory and overall

cognition respectively. Also, NMDA antagonists have been reported to mimic similar cognitive impairments to those seen in FEP (Kraguljac et al., 2021). One study also found associations between medial prefrontal GABA levels and cognition but failed to find a significant interaction between frontal glutamate and cognition (Rowland et al., 2016). This evidence suggests that cognitive impairments in FEP could be accounted for by glutamatergic dysregulation and NMDA hypofunction.

Despite the potential link between cognition and E/I, a systematic review on the topic concluded that the lack of homogeneity in study design and outcomes makes it particularly challenging to draw any strong conclusions in psychiatric populations (Reddy-Thootkur et al., 2022). Therefore, further research within the FEP population, would elucidate the relationship between E/I, cognition and other risk factors.

1.7 Thesis Aims and Objectives

Significant effort has been made to develop predictive models and to understand the risk factors of psychosis. This is especially pertinent as early intervention has been shown to be crucial for positive FEP outcomes (Lee et al., 2022). Few models have combined biological mechanisms with socio-demographic factors (Lee et al., 2022). Driven by the prodromal nature of cognitive impairment and the potential role of SD as a mediator, this thesis aims to investigate how potential biomarkers of E/I balance relate to social defeat measures and cognitive performance in individuals experiencing their FEP.

Divided into three main biological markers: mismatch negativity, relative spectral power bands and MRS spectra of E/I metabolites (glutamate, glutamine, Glx and GABA), this thesis employs two main technologies: EEG and ^{1}H-MRS. Due to the relevance of prefrontal E/I balance in psychosis, MRS measures were acquired in both the ACC and DLPFC, and EEG measures were acquired from the fronto-central (FCz) electrode site. A correlational analysis comparing these various potential proxy E/I markers is also included in order to discuss possible shared biological mechanisms.

SD questionnaires were included with both EEG and ^{1}H-MRS measurement sessions to establish potential associations between SD and these E/I markers. Additionally, a social defeat manipulation was incorporated in the EEG session task to assess the potential oscillatory mechanism behind an induced feeling of SD (refer to Section 2.3). Each measurement session also had different cognitive tasks that tested a wide variety of aspects of cognitive impairments in psychosis including working memory, attention, and

evidence integration (refer to Section 2.4).

It is hypothesised that SD will be increased in the FEP group compared to controls. It is also expected for SD to be correlated with worse symtpomology and cognitive performance. Further, it is hypothesised that the FEP group will be more susceptible to induced SD and will therefore have greater differences in spectral power following the SD manipulation compared to controls. Moreover, there is an expectation that disruptions in E/I balance, shown via MMN, spectral power and MRS results, will be correlated with SD. Specifically, it is expected that reduced MMN amplitudes, increased frontal gamma power and decreased glutamatergic metabolite levels will be correlated with higher SD.

It is hypothesised that these EEG and ^{1}H-MRS measures will reflect the glutamtergic and excitotoxicity hypothesis of FEP. Therefore, based on above-mentioned extant literature, it is expected that the FEP group will have significantly reduced MMN amplitudes and significantly increased gamma power. Despite the literature suggesting the contrary, based on the pilot study it is hypothesised that glutamatergic levels will be decreased in the FEP population compared to controls Godlewska et al., 2021. Glutamatergic metabolite levels, as a direct measure of E/I balance, are hypothesised to share a common mechanism with MMN amplitude and gamma power, therefore, it is expected that these measures will be correlated.

Given the lack and inconsistency of human, *in-vivo* research exploring the biological mechanisms of SD and cognition in FEP, the research presented in this thesis is a novel attempt to elucidate the relationship between these central social and potential E/I biomarker components in the experience of and risk for psychosis.

Chapter 2

General methods

2.1 Electroencephalography

Electroencephalography (EEG) is a non-invasive and *in-vivo* tool that measures changes in extra- and intracellular electrical activity linked with neural activity (Michel and Murray, 2012). EEG is sensitive to voltage changes and oscillations that result from the synchronous firing of a collection of cortical pyramidal neurons which sit perpendicular to the electrode/surface of the cortex (Britton et al., 2016).

EEG has demonstrated its utility in a clinical capacity with its use as a diagnostic tool for epilepsy and other neurological conditions (Collura, 1993). As well as being non-invasive, EEG is relatively inexpensive, simple to use, and is becoming increasingly portable (Casson et al., 2010). This feature of EEG facilitates its wide-spread use, with it being accessible to a greater range of people and across multiple modes (during sleep, during cognition, under anaesthetic etc.). Additionally, as EEG is able to detect electrical activity on a millisecond scale, it offers high temporal resolution and can measure rapid neural responses (Bell and Cuevas, 2012).

2.1.1 The Physiology Behind Electroencephalography

EEG picks up on changes in summations of electrical signals (Beres, 2017). These electrical signals occur as a result of neuronal membrane ion channel activity, such as the sodium potassium channel (Valentine, 2020). When the extracellular space has more positive ions, an electrical gradient forms and the resting potential within the neuronal cell is $\approx -70\mu$V. Depolarisation occurs when ion channels (sodium) open leading to a

change in cell resting potential as a result of positive ions flooding into the cell. Once the membrane potential reaches its peak, another ion channel will open (potassium) that 'flushes' out positive ions and repolarises the cell, returning it to its original state. This process is referred to as an action potential and is how the brain and nervous system transmit information. During an action potential, it is also possible for hyperpolarisation to occur when too many positive ions exit the cell, overshooting the resting potential and leading to the intracellular voltage being more negative than at baseline.

The primary mechanism through which EEG detects neural activity is depolarisation that leads to a relatively negative extracellular voltage and hyperpolarisation that leads to relatively positive extracellular voltage.

Inter-neuronal communication occurs at the synapses of neurons with the postsynaptic binding of neurotransmitters. When the excitatory neurotransmitter, such as glutamate, binds to the synapse, it triggers neuronal depolarization, leading to the propagation of a signal known as an excitatory postsynaptic potential. When the inhibitory neurotransmitter, such as GABA, binds to the synapse, it triggers neuronal hyperpolarisation, leading to a termination of the signal known as an inhibitory postsynaptic potential.

Electrodes detect collective excitatory or inhibitory postsynaptic potentials when they lead to a significant enough extracellular negative or positive potential (Beres, 2017). It is important to note that an EEG electrode, due to the mechanisms behind the technology, is unable to reflect specific spatial activity. It is, however, highly sensitive to temporal changes in both local and distal electric potential both local to and at some distance from the electrode position (Michel and Murray, 2012). EEG is therefore able to reflect both superficial voltage change and deeper electrical signals. As cortical neurons run perpendicular to the surface, like columns going across cortical layers, electrical changes closer to the cortical surface are detected differently to deeper level electrical changes. Surface excitatory potentials look similar to deeper inhibitory potentials and vice versa, due to the relative changes in surface level extracellular polarity, known as dipole[1](Valentine, 2020). Dipoles form an electrical field between the negative charge and the positive charge (Beres, 2017). The direction, magnitude, strength, and complexity of these dipoles determines how these signals are detected by an EEG machine.

EEG electrodes detect collective excitatory or inhibitory postsynaptic potentials when the extracellular potential is sufficiently positive or negative (Beres, 2017). EEG is unable

[1]A dipole refers to the separation of positive and negative charges of equal magnitude and are a feature of any electromagnetic system, including the brain. By creating a negative extracellular potential, an equal positive extracellular potential is formed in a neighbouring area.

to reflect specific spatial changes in activity, but is able to resolve temporal changes in electrical activity with high sensitivity.

2.1.2 Oscillatory Activity

Brain waves are characterised according to their frequency and amplitude properties (Collura, 1993). Different frequency bands are associated with different cognitive processes, with oscillations gating neuron communication (Uhlhaas and Singer, 2013, 2010).

Gamma Frequency

Gamma band activity occurs at 30 Hz until approximately 100 Hz. It is associated with a great deal of both cognitive processes and perceptual integration and has been strongly associated with E/I balance (Buzsáki and Wang, 2012; Perrottelli et al., 2021).

Beta Frequency

Beta activity occurs within the bandwidth of 12-30 Hz. It is associated with top-down attention regulation, working memory (alongside other cognitive processes), and sensorimotor behaviour (Kaczorowska et al., 2017; Perrottelli et al., 2021).

Alpha Frequency

Alpha activity occurs within the bandwidth of 8-12 Hz. It is associated with cognition, relaxation and consciousness as well as sensory, motor and emotional processing (Kaczorowska et al., 2017; Perrottelli et al., 2021).

Theta Frequency

Theta band activity occurs within the bandwidth of 4-8 Hz. It is associated with sensory stimuli detection, attention and working memory, alongside other integral cognitive processes (Perrottelli et al., 2021).

Delta Frequency

Delta activity occurs within the bandwidth of 1-4 Hz. It is associated with unconsciousness (such as sleep), as well as motivation and cognition when responding to external stimuli (Perrottelli et al., 2021).

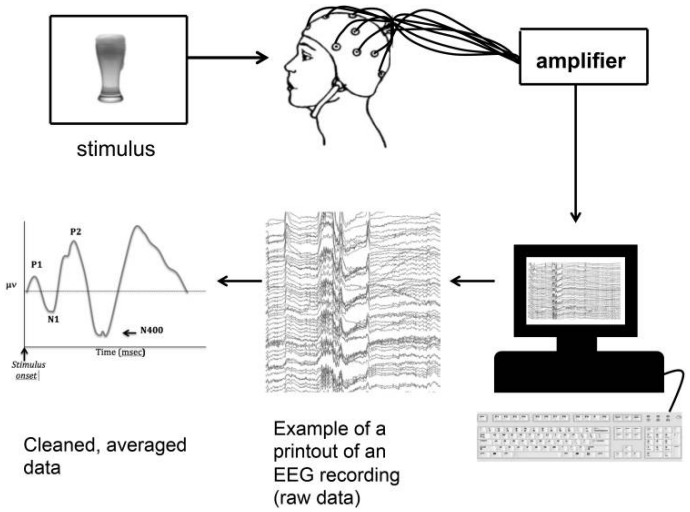

Figure 2.1.1: Example of recording and detecting an event-related potential (Beres, 2017)

2.1.3 Event-related Potentials

External stimuli can elicit neural electrical responses. These responses are known as event-related potentials (ERP). An ERP is a time-locked neural response to a sensory, motor or cognitive event (Grimm et al., 2011; Luck, 2014). ERPs can be conceptually grouped into two categories: early and late waveforms (Sur and Sinha, 2009). Early waveforms (within the first 100 milliseconds post-stimulus) reflect sensory processes that are dependent on the physical properties of stimuli, whereas late waveforms reflect information processing. There are a wide range of ERPs that have been studied as potential biomarkers of pathology, as well as tools to better understand underlying neural processes (Perrottelli et al., 2021).

Mismatch Negativity

Mismatch negativity (MMN) refers to the difference in ERP waveforms in response to 'standard' stimuli and 'deviant' stimuli (Fig. 2.1.2). The auditory MMN is a difference waveform derived from the standard and deviant ERP waveforms which have a negative peak, this negative peak is stronger for the deviant waveform hence leading to a mismatch. It typically occurs between 100 to 250 milliseconds following stimulus onset as a response to the oddball paradigm (Fitzgerald and Todd, 2020). To elicit an MMN response a series of uniform tones are interrupted on a pseudo-random basis by non-uniform stimuli. These 'deviant' stimuli typically differ from 'standard' stimuli in either duration or frequency (Nagai et al., 2013). This tone sequence stimuli is known as the 'oddball' paradigm.

There are several sensory modalities in which MMN can be elicited. Auditory, visual,

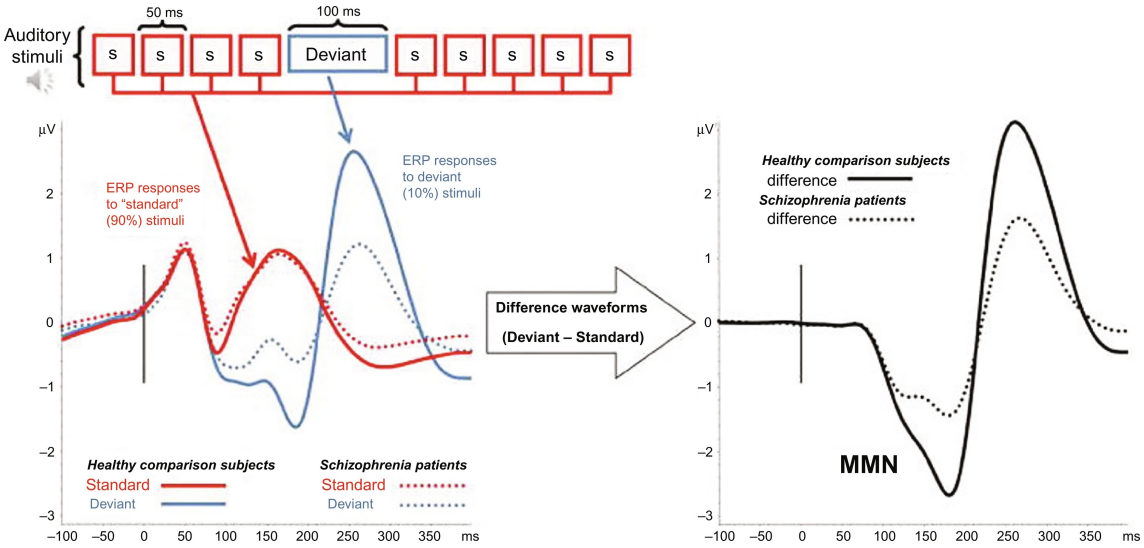

Figure 2.1.2: Example of mismatch negativity (MMN) waveforms based on standard and deviant response waveforms (Light and Swerdlow, 2015)

somatosensory[2] or mixed/multi-sensory modalities.

MMN is considered to be pre-attentive, meaning it occurs regardless of whether attention is being paid to it or not, which is particularly useful for clinical populations or in individuals with limited attention (Shelley et al., 1991).

Auditory Mismatch Negativity

There are several characteristics by which standard and deviant auditory stimuli differ: pitch, intensity, duration and frequency.

The auditory MMN response is generated in the auditory cortex and involves frontal regions of the brain (Garrido et al., 2009; Huang and Rao, 2011). Moreover, the auditory MMN has been used to study perception, sensory memory and cognitive processes specifically in regards to deviance detection (Tada et al., 2019). These processes have been demonstrated to be pertinent to several conditions, including psychosis (Koshiyama et al., 2018).

[2]Tactile stimuli such as light finger stimulation can be used.

2.1.4 EEG Cap Design

Reference Electrode

A reference electrode acts as a relative baseline against which all other electrode signals are measured. It may be best understood through the metaphor of altitude, in the sense that altitude as a concept is measured relative to the somewhat arbitrary baseline of 'sea-level' which is not an absolute measure but provides a common point through which to understand peaks and valleys (Biasiucci et al., 2019). The use of EEG has been subject to criticism due to its 'reference problem,' as it necessitates a reference point to measure voltage. However, since no location on the body is entirely free from electrical input, selecting an appropriate reference can be challenging.

2.1.5 EEG Data Acquisition

Impedances and Impedance Reduction

Impedance is the opposition that an electrical circuit has to the flow of alternating current, and is the sum of both resistance[3] and reactance[4]. It is calculated by running a current (typically 10 Hz) through two or more electrodes and measuring any opposition to this current (Kappenman and Luck, 2010).

Impedance is represented as

$$Z = \frac{V}{I} \tag{2.1.1}$$

where Z is the impedance, V is the voltage and I is the known current.

Impedance in EEG generally refers to the opposition in electrical flow experienced between the electrode on the scalp and the electrical current in the brain. This impedance is variously dependent on hair, skin, skull, other tissue, and humidity. Having high impedance could lead to increased noise and a decreased signal-to-noise ratio in the data, so improving the quality of the connection between the electrode and scalp is an important element of data acquisition (Kappenman and Luck, 2010).

[3]Resistance is the a property of an electrical circuit, caused by its physical properties, that opposes the flow of the current and converts electrical energy into heat.

[4]Reactance is a property of an electrical circuit, caused by capacitors and inductors, that opposes a change in current and stores energy in electric and magnetic fields temporarily.

2.1.6 EEG Analysis

Re-referencing

During data acquisition a reference electrode must be set (Section 2.1.4). However, during computation, it is possible to re-reference the data. Three of the most widely used re-references are an average between the two mastoids (left and right), averaging over all channels, and the Reference Electrode Standardization Technique (REST)[5](Lei and Liao, 2017).

Downsampling

To improve the manageability of EEG data during processing and analysis, it may be downsampled. This can be done without great risk of losing relevant data and can, in fact, improve signal-to-noise ratios (Popescu et al., 2021).

Filtering

Filtering is done to extract relevant data from the overall EEG measurement. EEG data includes signals from noise sources including muscle, eyeblink and environment signals. Frequency bands of interest can be extracted by low-, high-, and band-pass filters. Low-pass filters remove high-frequency noise such as muscle artefacts, and high-pass filters remove low-frequency noise and DC offsets [6].

Epoching

Epoching is a stage of pre-processing in which the continuous data is segmented into shorter time windows. Epoching allows for a time interval of interest to be analysed, and is particularly relevant for ERPs in which time of stimulus onset is relevant to measured responses.

[5]REST is a multi-step process where initially an average re-referencing is done, followed by the generation of a forward model that estimates the distribution of potentials from a known source, this forward model is then applied to understand the contribution of the standard reference location at each electrode, this estimated contribution is then finally used to re-reference. By doing this it is thought that the neural signals that are detected are genuine and do not reflect the fluctuations at the reference electrode itself.

[6]Electrodes have different dc voltage levels, known as input DC offset can be between 1-50 μV.

Time Domain to Frequency Domain

EEG data is recorded in the time domain, meaning that the EEG signal is presented in terms of voltage amplitudes over time. Time-domain EEG allows for the analysis of temporal features of neural patterns as well as patterns in voltage changes.

However, it is also possible to convert the time domain EEG data into frequency domain data. When EEG data is in the frequency domain it represents the signal as a function of frequency instead of as a function of time. Conversion into a frequency domain allows for the analysis of EEG data within specific ranges that are associated with behavioural or cognitive processes. These analyses include spectral band power, ERPs within a specific frequency, and functional connectivity. Moreover, artefact removal can be performed with frequency domain data.

Fast Fourier Transform

There are several methods that be applied to EEG time domain data to convert it to the frequency domain so that spectral analysis can be done (Klonowski, 2009). One of the best established and most commonly used mathematical methods is the Fast Fourier Transform (FFT), which efficiently computes the discrete Fourier transform (Welch, 1967). The Fourier transform converts amplitudes over time into a sequence of sinusoidal components within different frequencies. Using an FFT allows for a power spectrum to be quickly calculated and for the measurement of relative power in specific frequency bands and reflect oscillatory activity.

2.2 Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) is a non-invasive technology that allows for a snapshot of the bio-chemical content within defined and small regions of the brain or body, known as regions of interest (ROI). These ROIs are investigated using voxels which are 3D cubic regions in which the concentration of metabolites are measured. MRS is able to provide *in-vivo* measurements of concentrations of a wide range of metabolites in the ROI based on the unique electron density of each metabolite (VanElzakker et al., 2019). Measuring the concentration of metabolites provides a unique insight into metabolic process and underlying mechanisms. MRS has shown promise for understanding psychiatric disorders, with MRS proving to be a useful tool for the study of psychosis, its disease progression and treatment (Dager et al., 2008). Generalised findings have been

challenging due to small sample sizes, methodological differences in spectrum acquisition, and ROI differences (Dager et al., 2008). However, movement towards more standardised methods and increased accessibility is starting to bridge these gaps (Clarke et al., 2020).

2.2.1 The Physics of Magnetic Resonance Spectroscopy

MRS functions along similar principles as conventional MRI for protons (hydrogen) in water, in which the MRS signal from water and fat hydrogen nuclei are used for imaging. By excluding the signals of water and fat, MRS can detect the chemical composition of a voxel, including metabolites that appear in millimolar concentrations.

Understanding the physics behind nuclear magnetic resonance (NMR) technology helps explain the physics behind MRS. NMR, and therefore MRS, refers to the response of an atomic nucleus to oscillations in an external magnetic field (B_0). This relies on 'spin' properties of the nuclei of these atoms. Quantum spin is an intrinsic property analogous to angular momentum[7]. Atomic nuclei with an odd number of protons or neutrons have a non-zero nuclear spin (and therefore a non-zero magnetic moment[8]) allowing them to be sensitive to magnetic fields, making them NMR active. The magnetic field used to alter the orientation/spin of nuclei is created by superconducting electromagnets. The spin of a nucleus is referred to by a quantum number, known as spin quantum number. In NMR, the most commonly measured atoms, such as hydrogren and phosophorus, have a spin quantum number of $\frac{1}{2}$, meaning that they have two possible spin states (spin-up and spin-down). The spin-up state has a slightly lower energy, as it is aligned with the field, than the spin-down state, as it is anti-aligned with the field, and the difference in these two energy levels is proportional to the strength of the magnetic field, referred to as the Zeeman energy difference. In order to excite the nuclei being measured, a radio-frequency (RF) pulse that matches the Zeeman energy difference is applied to the nuclei. The amplitude and duration of the RF pulse determines the degree of excitation and time required for the spins to return to their original state, hence precise tuning of RF pulses is required to have maximum excitation and MRS signal intensity. The RF pulse generates a magnetic field perpendicular to the external magnetic field and the excitation causes the nuclei to align either parallel or anti-parallel to the field (flipping the magnetic moment), which is equivalent of the nuclei being in a spin-up or spin-down state. These aligned magnetic moments start to precess (rotate) around the direction

[7]Angular momentum is the moment of inertia multiplied by the angular velocity of a rotating object.

[8]Magnetic moment refers to the vector-like quantity describing how a small magnet dipole interacts with an external magnetic field and is proportional to the spin.

of the magnetic field. While the nuclei precess, they interact with their surrounding chemical environment, including other nuclei and electrons, which can cause fluctuations in the local magnetic field (explained in Section 2.2.2). Once the RF pulse is turned off, the nuclei then relax back to their original alignment. As the magnetic moments of the nuclei return to their original state, they emit electromagnetic radiation at their resonance frequency. This is the signal measured by the NMR instrument (in this case, an MRI machine). This resonance frequency is referred to as the Larmor frequency and can be calculated at each field strength (e.g 1.5T or 7T) using Larmor's equation.

Larmor's equation is:

$$f_0 = \gamma B_0 \tag{2.2.1}$$

where f_0 is resonance frequency, γ is the gyromagnetic frequency[9] and B_0 is the external magnetic field.

Spin echo sequences are often used in MRS to generate the MRS signal. A spin echo sequence consists of two RF pulses, separated by a fixed time interval (known as echo time or time to echo (T_E)[10]), where the first pulse is used to perturb the nucleic spin (leading to the above described precess). The signal decays rapidly due to deviations in proton precession frequencies, resulting in a loss of signal intensity and broader spectral lines. To combat this signal decay a second RF pulse, known as the refocusing pulse, is applied after a delay of half of the echo time ($T_E/2$). This refocusing pulse leads to spin echo (which can be detected by the receiver coil), whose signal has higher intensity than the original signal. This spin echo occurs at the same fixed time interval as the time between the two RF pulses.

The unique combination of signal intensity, line width, and position are used to identify molecules (Cecil, 2013). The amplitude and decay of this NMR signal reflects the chemical structure and chemical environment of the nuclei. The area under a spectral peak is a measure of the concentration of nuclei, which can then be used to calculate the concentration of a certain metabolite. There are multiple influencing factors in the quantification of MRS, including the longitudinal relaxation (T_1)[11] and transverse

[9]The gyromagnetic frequency is based on the ratio between the magnetic moment and angular momentum of a particle. This is constant for a nucleus.

[10]Time to echo/echo time (T_E) refers to the time between the delivery of RF pulses and the reception of the echo signal.

[11] T_1 is where the magnetic moments return to their equilibrium position along the direction of the external magnetic field.

relaxation (T_2)[12] values of each metabolite, the B_0 and B_1 inhomogeneity, eddy currents, the type of pulse sequence, repetition time (T_R)[13] and T_E.

The spectrum that results from an MRS scan is the sum of all the frequency profiles found in the ROI (voxel), weighted according to the relative concentrations of the metabolites. Once this spectrum is measured, the known unique frequency profile of each metabolite can be applied to determine the concentration of the metabolites. The prior knowledge of the location and expected spectra for each metabolite is also known as a metabolite basis set and allows for the extraction of spectra from the initially noisy raw data (one such tool is LCModel, further explained in Section 4.2).

2.2.2 Chemical Shift

The chemical environment of an atom influences the resonance frequency, an effect known as chemical shift. On an atomic level, nuclei experience a local magnetic field (B_{loc}) based on the chemical environment surrounding the molecule. This process can be explained by the idea of local shielding. The presence of nearby atoms and the electron density surrounding a nucleus creates a shielding effect that reduces the magnetic field experienced by that nucleus, known as the effective magnetic field. This local shielding is what is meant by chemical shift, and is the component that allows for the differentiation of nuclear spins and therefore of molecules through MRS.

Accounting for chemical shift, Larmor's equation becomes

$$f_0 = \gamma(1 - \sigma)B_0, \tag{2.2.2}$$

where f_0 is resonance frequency, γ is the gyromagnetic frequency, B_0 is the external magnetic field and σ is the chemical shift constant. The value of σ is unique to each type of nucleus.

2.2.3 Water Suppression

Water is a highly abundant molecule in human tissue, accounting for almost 73% of brain tissue composition. Additionally, it has a prominent peak at 4.65 ppm which overlaps

[12] T_2 is where the magnetic moments lose their phase coherence and dephase, which leads to a decrease in the NMR signal.

[13] Repetition Time (T_R) refers to the time between successive pulse sequences being applied to the same slice.

with adjacent metabolites and overwhelms the signal detected from the rest of the spectrum (Mitchell et al., 1945). With proton MRS, the nuclei of interest are non-water hydrogen (^1H) and their spins, which occur in a concentration between 10^3 to 10^4 times less than water. Thus, the overwhelming signal of water is not desirable. To bring out the spectrum of non-water molecules, the water signal needs to be suppressed. There are several methods for the suppression of water in MRS, such as Variable Power and Optimized Relaxation Delays (VAPOR) (Tkac et al., 1999). VAPOR functions by using a series of RF pulses that have varying optimised relaxation delays and power levels that exploits the difference in T_1 relaxation times between water and other metabolites[14].

2.2.4 Proton Magnetic Resonance Spectroscopy

This form of MRS specifically uses hydrogen atoms (protons) that can be found in the body and brain to develop a spectroscopy. Metabolites all have a unique chemical profile, and the positioning and quantity of hydrogens in those metabolites sends back a unique frequency profile. The unique frequency profile (spectrum) of each metabolite can then be used to differentiate and quantify specific neuro-chemicals within a particular voxel. There are approximately 35 metabolites for which this can be done using current 1H-MRS technology, both *in-vivo* and *in-vitro*, with glutamate, NAA and creatine being studied most often (Dager et al., 2008; Govindaraju et al., 2000).

2.2.5 Metabolites

Glutamate

Glutamate (Glu) is the principal excitatory neurotransmitter and non-essential amino acid. It is a precursor for glutamine, and shares a very similar chemical structure. This similarity results in overlapping MRS peaks between 2.1 and 2.4 ppm (from the $^3CH^2$ and $^4CH^2$ protons) and at 3.7 ppm (from the ^2CH proton) and has meant that at lower field strengths (less than or equal to 3 Tesla) glutamate and glutamine have been quantified and reported together as Glx (unless special editing spectra were used). However, recent progress in MRS has led to the development of higher magnetic field strength scanners with the ability to discriminate between Glu and glutamine, allowing for greater insight into their metabolic action in disease (VanElzakker et al., 2019). In ^{1}H-MRS, glutamate can be detected as a peak in the spectrum at a chemical shift of approximately 2.35 ppm.

[14]Water has a shorter T_1 relaxation time compared to the majority of other metabolites. Hence applying optimized relaxation delays between RF pulses attenuated water and preserves other metabolites.

Glutamate acts both in the synaptic cleft and as a building block for several other key metabolites (such as glutamine, GABA and glutathione) and therefore is at the intersection of multiple key metabolic pathways. Glutamate is also central to a plethora of integral CNS functions and neuroplasticity (Pal, 2021). ^{1}H-MRS measures total tissue concentration, meaning that it is unable to differentiate between functionally diverse glutamate (Alger, 2007).

Glutamine

Glutamine (Gln) is an amino-acid that plays a vital role in several processes including protein synthesis, energy production, and cell proliferation. It also acts as a precursor for neuronal glutamate. Gln synthetase, primarily located in astrocytes, is an enzyme that converts Glu to Gln. Glutamine is then transported to neurons where it is converted back into glutamate through glutaminase's enzymatic action. In ^{1}H-MRS, glutamine can be detected as a peak in the spectrum at a chemical shift of approximately 2.45 ppm.

Γ-aminobutyric acid

Γ-aminobutyric acid (GABA) is the principle inhibitory neurotransmitter and an amino-acid. GABA takes multiple functional forms within the brain: cytoplasmic, which plays a role in metabolism; extra-cellular, involved in neuromodulation of cortical inhibition; and vestibular, concerned in inhibitory synaptic neurotransmission (Stagg et al., 2011). MRS is not able to differentiate between these functionally-diverse forms of GABA; however, there is a clear correlation between GABA concentration levels and human behaviour such as motor learning (Stagg et al., 2011).

Another consideration for the quantification of GABA is that it has relatively low concentrations in the brain, and its MRS signal can get contaminated due to overlapping MRS signals from other metabolites and mobile macromolecules that have much stronger resonances (Shungu et al., 2016). In ^{1}H-MRS, GABA can be detected as a peak in the spectrum at a chemical shift of approximately 2.2 to 2.4 ppm.

2.2.6 Single Voxel Magnetic Resonance Spectroscopy

When conducting MRS there is a choice between using a single voxel or multiple voxels. Single voxel MRS measures the biochemical composition of one specific ROI, with a typical voxel measuring 2 cm^3 or more. Multi-voxel MRS allows for the acquisition of MRS data from multiple ROIs within a single acquisition. Both single- and multi-voxel

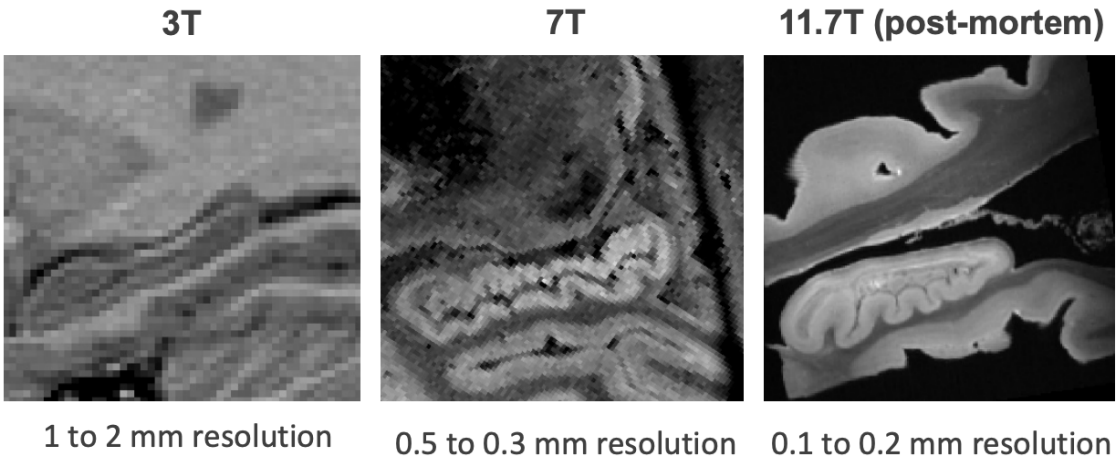

Figure 2.2.1: Human hippocampus imaging on 3T vs 7T and 11.7T. (Vedrine, 2020)

MRS use MR imaging, typically T_1- or T_2-weighted MRI, to position the voxel according to a 2D and 3D array. Multiple voxels provide information for a larger area and tend to have better spatial resolution as the individual voxels are smaller than the single voxels. However, single-voxel MRS presents many benefits. The operator set-up is faster and easier to run, the shim[15] is better, and quantification is easier due to better signal-to-noise ratios, making single-voxel MRS popular in clinical and research fields.

2.2.7 7 Tesla Field Magnetic Resonance Spectroscopy

There are some significant limitations to MRS technology. The main issue for MRS is sensitivity (ability to measure and identify metabolites) and spatial resolution *in-vivo*. In the past this has meant that a combined approach of *in-vivo* MRS with tissue extract, brain slices, cell lines and fluids at higher magnetic field strengths (such as 11.7) would be needed to allow for a fuller picture and a better interpretation of *in-vivo* findings (Tognarelli et al., 2015). However, some of these elements are not feasible in living humans.

Another more parsimonious method for increasing spatial resolution, improving scanning speed, ameliorating chemical shift separation and improving contrast-to-noise ratios is the use of a higher magnetic field strength such as 7 Tesla Magnetic Resonance Spectroscopy (7T MRS) (Barisano et al., 2019). There are remaining technical hurdles to overcome with the 7T, mostly in line with the adaption of lower magnetic field strength protocols (such as 1.5T or 3T) to 7T. This is a result of an increased inhomogeneity in the external

[15]To mitigate the effect of partial volume and magnetic field inhomogeneity, additional small coils are used to subtract or add to the main magnetic field.

magnetic field (the B_0 in Larmor's equation, Equation 2.2.1) and RF pulses. Moreover, there is an increase in specific absorption ratio (SAR) burden, which is the power of the RF pulse experienced by the tissue that it is being applied to. SAR is particularly important to be wary of and account for as it can lead to tissue heating (Kraff and Quick, 2017). In order to facilitate standardised neuroimaging practices, comparison between scanners and sites, and the replicability of findings there has been a movement to increase consistency in 7T protocols, such as the UK7T network (Clarke et al., 2020). Significant strides have already been made and continue to be made in the development and implementation of 7T technology, and it holds a lot of promise for the continual elucidation of metabolic and chemical processes behind various mechanisms and pathologies (Clarke et al., 2020).

2.2.8 The role of grey matter, white matter and cerebro-spinal fluid in MRS quantification

Tissue correction is an important element of the MRS quantification process, to improve the accuracy of MRS data by controlling for the impact of tissue composition and water content (Porges et al., 2017). The chemical environment surrounding the atom measured allows for the differentiation between molecules. This chemical environment refers to the metabolite itself but can also be impacted by the chemical composition of the tissue the metabolite. Moreover, these tissues have different metabolite concentrations, and the relative proportion of these concentrations vary across brain regions as well as across individuals, with brain size, shape, age sex and pathology all being relevant factors (Charles et al., 1994). Therefore, tissue correction allows for comparison across individuals, and differentiates group and pathology differences from individual differences. Previous literature has demonstrated that grey matter (GM) and white matter (WM) proportions are significantly correlated with metabolic concentrations (DeMayo et al., 2023). There has also been research suggesting that there are differences in metabolitc concentrations between GM and WM (Goryawala et al., 2016; Oeltzschner et al., 2019; Schuff et al., 2001; Wang and Li, 1998). Due to the differences in metabolic concentrations between tissue types, and differences in tissue concentrations between individuals, tissue correction remains an integral stage of the MRS quantification process.

2.2.9 STEAM Sequencing

MRS spectra are obtained through specific sequence of RF pulses. Sequencing in MRS refers to the specific RF pulses and gradient fields that are applied to the magnetic field

for spectrum acquisition. The basic components of MRS sequencing include a strong magnetic field (to align protons in the ROI), a series of RF pulses applied to the region (exciting the aligned protons so that they emit radio-frequency signals), a receiver coil (to detect the signals emitted) and processing to compute the signals and measure a spectrum. The way these components are carried out and potentially additional features included in MRS spectrum acquisition are dependent on the type of MRS sequencing conducted.

One of these sequences is the stimulated echo acquisition mode (STEAM) sequence, which was used in the present thesis. STEAM specifically involves three simultaneous RF pulses applied with slice-selected gradients[16] (along the x, y and z-axes). An initial 90-degree excitation pulse creates coherence among the spins in the ROI, a second 90-degree pulse flips the coherence into an observable signal opposite in phase to the first coherence, and a final 90-degree excitation pulse. This final pulse flips the z-components of spin into the transverse plane. Once flipped for this last time, each spin rephases and forms a stimulated echo (STE). A stimulated echo occurs from three or more RF pulses, unlike the echo time that occurs from two pulses, and is a coherent signal detectable at high sensitivity.

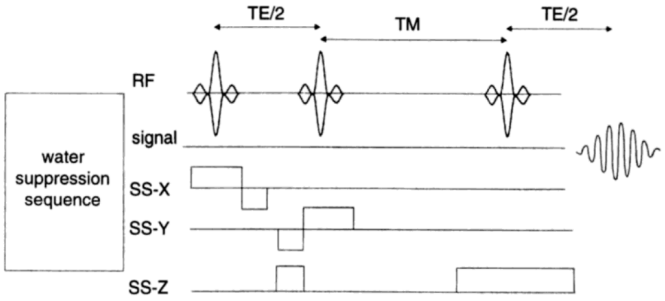

Figure 2.2.2: Example of water suppression and STEAM sequence used for MRS spectrum acquisition (Rajan, 1998)

STEAM sequencing has a shorter echo time (T_E) compared to other commonly used sequences, such as point resolved spectroscopy sequencing. This can be advantageous for detecting glutamate because it has a relatively short T_2 relaxation time. As explained earlier, a short T_2 relaxation time means that its signal decays quickly (Fig. 2.2.2). Therefore, by using a shorter T_E, STEAM sequencing allows for a reduction in the signal decay and improvement of the detection of glutamate. STEAM sequencing has therefore

[16]Slice selection is achieved during the application of an RF pulse by applying a one-dimensional linear magnetic field gradient.

been favoured for metabolites with a short T_2 signal, such as glutamate or myo-inositol. Moreover, STEAM sequencing can also facilitate shorter acquisition times compared to other MRS sequences, which may be a benefit when working with clinical populations or in time-sensitive scenarios. STEAM sequencing also allows for better 3D resolution in comparison to other sequences, as a result of the 90-degree refocusing pulse. Given these advantages, STEAM sequencing has often been chosen over alternative options despite the relatively decreased number of signals that are collected.

2.2.10 Analysis of Magnetic Resonance Spectroscopy

MRS spectra are quantified by the unique chemical shifts and couplings that result in metabolite-specific spectral peaks. With *in-vivo* MRS, there are often overlapping signals, distorted baselines, poor shimming, and incomplete water suppression, along with several other potential artefacts (**?**). To deal with this, several computational tools have been developed, including the Linear Combination of Model Spectra model (LCModel) (Provencher, 1993). LCModel fits measured metabolite spectra with expected spectra based on a pure model for each molecule. The expected MRS spectra are specific to the conditions in which the scan has taken place, being dependent on scanner strength, and pulse sequence. This expected spectra, referred to as the basis set, is derived from known estimates of chemical shifts and coupling for the studied metabolites.

Upon the acquisition and quantification of the MRS spectrum, several steps are taken to ensure the quality of the data. Fit between the acquired MRS spectrum and the expected model spectrum can be visually inspected to ensure that the data acquired is approximately what is expected (baseline and line shapes). Additionally, paying attention to line widths, this refers to the widths of the spectral peaks in the MRS spectrum, (which should be narrow and well-defined), signal-to-noise ratio (peak-signal/root mean square-noise), and metabolite ratios (for example the ratio of NAA to creatine is often used) can be used as indicators for spectral quality (Li et al., 2001).

Furthermore, quantification errors are assessed using the Cramer Rao Lower Bounds (CRLB). The CRLB is an estimate of the lowest possible standard deviation of the measured metabolites. There are various thresholds for CRLB and there is still debate surrounding acceptable CRLB thresholds for MRS analysis; however, less than 30% is generally considered acceptable. Additionally, the signal-to-noise ratio (SNR) and the full width at half maximum (FWHM)[17] are used to assess the quality of data (Kreis, 2016;

[17]FWHM is a common measure of the width of a peak in a spectrum and is the width of the peak

Smucny et al., 2021).

2.3 Social Defeat Questionnaires and Task

2.3.1 The Social Defeat Scale

The Social Defeat Scale (SDS) has been used in many studies exploring social defeat (SD) and is a validated 16 item Likert-type scale (Gevonden et al., 2014; Quijada and Villagrán, 2021; Selten, 2023; Troop and Hiskey, 2013; Valmaggia et al., 2015).

The SDS is particularly well suited for measuring social defeat as it touches upon the subordination element of social defeat (stemming from the social rank hypothesis), as well as the loss of status (Gilbert and Allan, 1998). The higher the score on the SDS the higher the feelings of social defeat, reflecting a greater sense of loss and subordination.

2.3.2 The Social Comparison Rating Scale

The Social Comparison Rating Scale (SCRS) is an 11-item scale that often gets coupled with the Social Defeat Scale to provide a more complete image of feelings of SD in individuals (Gevonden et al., 2014; Selten et al., 2013; Troop and Hiskey, 2013; Valmaggia et al., 2015). Social comparison reflects social rank and is a core aspect of SD (Allan and Gilbert, 1995). The Social Comparison Rating Scale touches on relative feelings of attractiveness, comparison of being accepted by others, and social rank comparisons (in the sense of being better or worse than others) (Allan and Gilbert, 1995; Freeman et al., 2014). The higher the score on the SCRS the better the feeling of social rank in comparison to others, and therefore the lower the feeling of social defeat.

2.3.3 Social Defeat Manipulation using Behavioural Task

A behavioural task was designed for the present study to induce social defeat during an EEG study session. The perceptual decision-making task (CRDM, see Section 2.4.1 and Fig. 2.4.1) played during the MMN and was used to provide false negative feedback on a participant's performance in comparison to the collective performance of other pseudo-participants (who scored significantly better than the participant) in order to

at half of its maximum height. A narrower FWHM implies better spectral resolution and less overlap between peaks.

induce SD. Following this induced SD, a resting state EEG recording was made to determine if any power spectrum changes.

Previous literature has demonstrated that negative feedback regarding performance on a stress-inducing task led to sensitisation of dopamine responses in individuals with a high-risk of psychosis (Mizrahi et al., 2012; Pruessner et al., 2004; Soliman et al., 2008). This dopamine sensitisation has been hypothesised as a potential mechanism for social defeat in psychosis (refer to Section 1.5).

The SD manipulation design used in this thesis was based on a similar manipulation used by Baskak and colleagues that was used to explore neural responses to social defeat in individuals with schizophrenia. In their study, participants played a Box Filling Game in which they would compete with a pseudo-participant. In the social defeat condition, the participant was told that the other participant performed 1.4 times better (shown via the number of boxes filled) and that the other participant had won. Following the task, participants were given a post-task questionnaire that was used to assess whether the task had successfully induced feelings of social defeat (Baskak et al., 2015).

The social defeat condition in this thesis differed slightly from the task just described. Here, the participant was told that they performed significantly worse than the vast majority of participants eliciting a feeling of group outsider status, and that this was reflective of worse academic and work performance eliciting a sense of lower rank and loss (Fig. 2.3.1). These modifications to the feedback were done to better encompass the definition of SD (refer to Section 1.5).

The perceptual decision-making task included financial awards for correct responses (£0.50 per five) and financial punishments for incorrect responses (£0.50 per 10), with this being displayed using a bar at the bottom of the screen. Rewards were used to further the sense of "losing" compared to others.

Following the completion of EEG data collection the participants were debriefed on the task and the false nature of the feedback received. The purpose of the feedback was explained and discussed to ensure participants felt comfortable and understood the SD feedback.

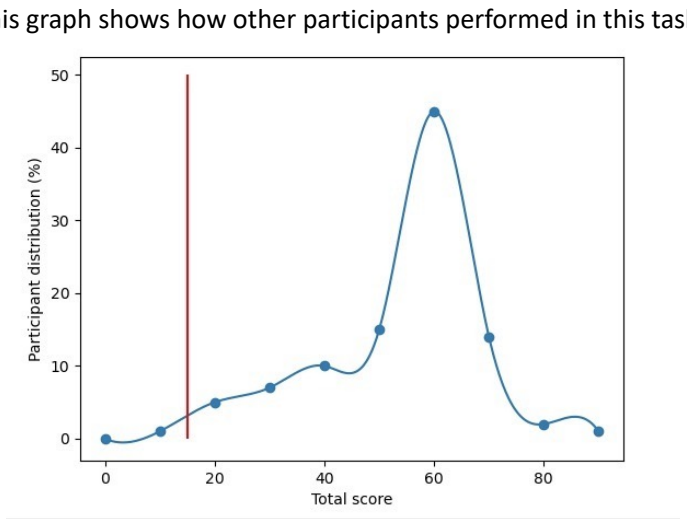

Figure 2.3.1: Example of feedback shown to participants following CRDM cognitive task used to induce a sense of social defeat

2.4 Cognitive Tasks

Cognition is one of the elements of psychosis that remains particularly difficult to treat (Duarte and Xin, 2019). Within treatment-resistant communities it has been noted as being the symptom category that significantly hinders community functioning and positive outcomes (McCleery and Nuechterlein, 2019). Therefore, a key element for the comprehension and treatment of psychosis is further elucidating cognitive symptoms and their neural mechanisms.

2.4.1 Continuous Random Dot Motion Task

The continuous randomised dot motion (CRDM) task used in this study was based on a previously-used task designed by Ruessueler and colleagues (described in (Ruesseler et al., 2022)), and updated for this study by Lilian A Weber (Fig. 2.4.1).

This CRDM is a continuous version of the two-alternative forced choice randomised dot motion task, in which a stream of randomly-moving dots would occasionally coherently move more to the left or more to the right. This coherence refers to the ratio of dots moving in a particular direction to dots moving randomly. A coherence value of 0 would indicate that the dots are moving completely randomly, whereas -1 and 1 would indicate

all dots moving either to the left or right respectively. Mean trial coherence were 0.1 and 0.2 in the low noise/variance condition, and 0.2 and 0.4 in the high noise/variance condition. Coherence variance was 0.3 and refers to the noise around the mean.

Coherence changed constantly, with the average coherence at inter-trial remaining at 0. During a trial the average coherence of dots would consistently veer either to the left or right. The participant was tasked with determining when and in what direction the dots were moving during these trials. Participants would indicate their detection of the average coherence direction using the keyboard button 'A' for a trial moving to the left, and keyboard button 'L' for a trial moving to the right. Each trial was 5 seconds, with the inter-trial period varying to make the task less predictable.

It is possible to determine the degree to which previous stimuli has triggered a participant's response by averaging the noise preceding a response (the participant pressing 'L' or 'A'). This averaged noise prior to a response can then be used to infer the integration kernels participants have across the different conditions.

The CRDM task simulates naturalistic decision-making in a dynamic environment that evolves over time (Hunt et al., 2021). In such environments, more weight tends to be placed on newer information whereas older evidence slowly gets discounted, and one's behaviour adapts to this overall evidence (Veliz-Cuba et al., 2016). This CRDM task allows for the measurement of 'integration kernels' which describes how far back in time evidence is being integrated in order for the participant to make a decision.

2.4.2 The Brief Assessment of Cognition in Schizophrenia

The Brief Assessment of Cognition in Schizophrenia (BACS) is a validated battery of cognitive tasks that focus on deficits that are specifically pertinent to psychosis/schizophrenia and have been most strongly linked to patient outcomes (Keefe, 2004).

The BACS includes: list learning (verbal memory), digital sequencing (working memory), token motor (motor speed), category instances and controlled oral word association test (verbal fluency), symbol coding (attention and information processing), and Tower of London (executive functioning) (Keefe, 2004).

The BACS usually takes approximately 30 minutes to administer and can be administered via pen and paper or via computer/tablet, with a tablet being used in the present thesis. It has been shown to be reliable and valid and have higher completion rates compared to other standard cognitive test batteries (Keefe, 2004).

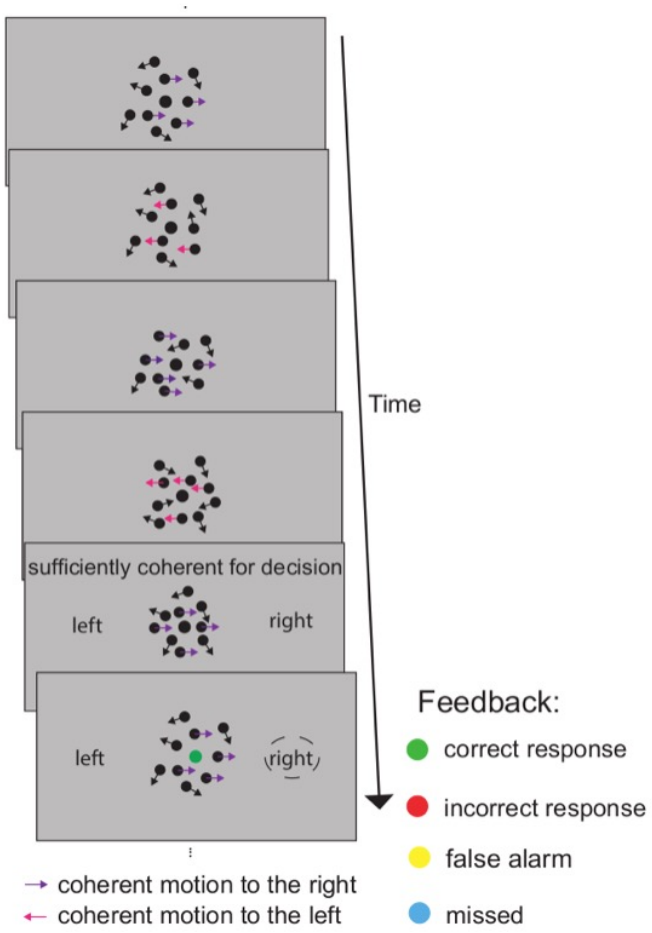

Figure 2.4.1: Illustration of continuous random dot motion (CRDM) task with feedback)

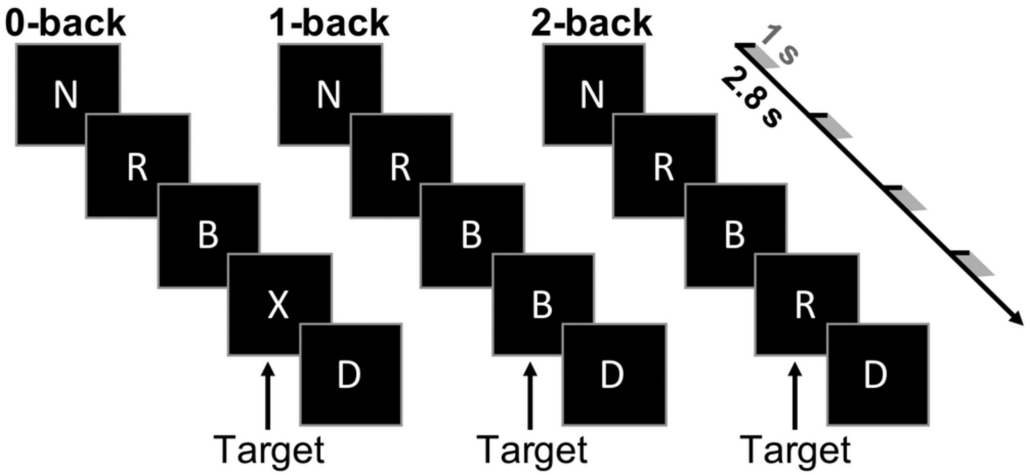

Figure 2.4.2: Exampled of zero to two back N-back task (Costers et al., 2020)

2.4.3 N-Back

The N-back is a working memory task in which the participant is tasked with keeping track of a series of stimuli to determine whether each stimulus matches the stimuli presented N steps back in the series (Fig. 2.4.2)((Moustafa et al., 2021). The N-back is one of the most commonly used tasks for working memory assessment and can vary in the number of N it uses, for this thesis the N-back task went from zero to three back (Lamichhane et al., 2020).

2.4.4 Stroop Colour Test

The Stroop Colour Test (Stroop) is a wide-spread task in which the participant is shown two 'conflicting' pieces of information and is tasked with selecting one option. The Stroop Colour Test is reflective of cognitive inhibition (Krabbendam et al., 2009). Originally designed in 1935 by John Ridley Stroop (**?**). In the version used for this study the Stroop consisted of the words 'red', 'green' or 'blue' flashing upon the screen in either red, green or blue ink. The participant was tasked with selecting the colour of the ink as opposed to what the word said.

There are two conditions within the Stroop: congruent and incongruent. The congruent condition is when the word matches (congruent) the colour of the ink, whereas the incongruent condition is when the word does not match the colour of the ink.

The Stroop is of particular interest within an FEP population as the ACC has been implicated as a location for processing of conflicting information (Krabbendam et al., 2009).

2.5 Clinical Questionnaires

There were several clinical features, such as symptom severity and co-morbidities, that were of interest for this thesis and were measured using relevant validated, self-administered questionnaires or semi-structured interviews.

2.5.1 Positive and Negative Syndrome Scale

The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) has been used widely in clinical practice and research to assess the symptoms associated with schizophrenia and associated psychotic disorders, such as first episode psychosis (Opler et al., 2017). PANSS has been shown to effectively account for wider symptom categories and associated symptoms with a small number of items, suggesting that PANSS can be used to account for the many heterogeneous symptoms associated with psychosis (Lefort-Besnard et al., 2018).

2.5.2 Hamilton Depression Rating Scale

The Hamilton Depression Rating Scale (Ham-D) is a widely used and validated tool of 21 questions used for the assessment depression and depression recovery (Hamilton, 1967; Sharp, 2015).

2.5.3 Young Mania Rating Scale

The Young Mania Rating Scale (YMRS) is a validated 11-item rated scale questionnaire (Young et al., 1978). The YMRS requires the participant to reflect on their condition (core symptoms of mania) over the last 48 hours.

Chapter 3

Analysis of Social Defeat in First-Episode Psychosis compared to Healthy Controls, and interactions with Cognitive Performance

3.1 Introduction

Social defeat (SD) has been positioned as a potential mediating factor between social factors and increased risk of psychosis (Schalbroeck, 2023; Seo and Choi, 2018; Stowkowy and Addington, 2012; Van Nierop et al., 2014). SD is defined as a long-term exposure to being an outsider or put in a subordinate position (Selten, 2023; Selten and Cantor-Graae, 2005).

SD has been hypothesised to lead to sensitisation of mesolimbic dopamine, a system associated with positive symptoms in psychosis and with E/I balance (Howes and Shatalina, 2022; Novick et al., 2016; Olney et al., 1999; Schwartz et al., 2012). It has also been shown that SD leads to worse cognitive performance (**?**Jianhua et al., 2017; Novick et al., 2016; Vassilev et al., 2021).

This study aims to explore feelings of social defeat in first-episode psychosis (FEP) and its association with symptom severity, and with cognitive performance.

It is hypothesised that feelings of social defeat will be increased in the FEP group compared to controls. Moreover, higher SD scores are expected to be correlated with

worse symptomology as measured by the Positive and Negative Syndrome Scale (PANSS), particularly with positive symptoms due to the potentially shared mechanism of sensitised mesolimbic dopamine. SD is also hypothesised to be associated with worse cognitive performance.

3.2 Methods

Social defeat data was acquired during the EEG and MRS study sessions (refer to Section 4.2 and Section 6.2 respectively).

3.2.1 Study Eligibility

22 FEP patients and 21 HC matched for sex and age were included in the study. The FEP group was recruited through direct communication with care coordinators and an Oxford Health Thomas Vaughn ward psychiatrist. Patient participants were eligible if they: had their first episode of psychosis, as defined by Melbourne criteria (i.e. a week or more of psychotic symptoms above a threshold of moderate in severity), within the last three years from study visit date, were between 18 and 40 years of age, were clinically stable[1], were not at risk of suicide, did not have current substance dependency. The age range for the study was 18 to 40, to prevent age related abnormalities (Brandt et al., 2016). Healthy controls were recruited via word of mouth, web advertisements and local newspaper advertisements. Healthy controls were eligible if they are matched to FEP participants, and have no current or previous history of psychiatric disorders according to the DSM-5.

3.2.2 Social Defeat Questionnaires

In order to measure feelings of SD two questionnaires were employed. The social defeat scale (SDS) was used to assess feelings of social defeat, whereas the social comparison rating scale (SCRS) was used to assess feelings of social rank. As the SCRS measures social rank higher scores were associated with feelings of better social rank and therefore less social defeat (refer to Section 2.3 for more information).

[1]Participants could still have symptoms of psychosis however they could not be in a florid state of psychosis, they needed to be deemed well enough and stable enough to participate and understand what the study entailed (provide informed consent).

3.2.3 Inclusion in EEG Study Session

While participants partook in the EEG study session, after providing informed consent participants were asked to complete the SDS and SCRS questionnaires. Demographic information relevant to social defeat was collected following the completion of SD questionnaires.

3.2.4 Inclusion in MRS Study Session

During the three-hour MRS study session, after informed consent was given, participants were given a series of questionnaires including the SDS and SCRS. It was also at this stage that demographic information was collected.

The MRS study visit also included the PANSS questionnaire, which assessed symptomology in participants with psychosis. Therefore, it was this cohort that was used to assess the relationship between symptomology and SD.

3.2.5 Cognitive Performance and Social Defeat

In each of the above-mentioned study sessions SD scores were collected alongside performance on cognitive tasks.

These cognitive tasks included: during the EEG session the continuous random dot motion task (CRDM) assessing evidence integration, and during the MRS session the BACS battery of tests measuring a wide variety of cognitive components, the N-back assessing working memory, and the Stroop Colour test measuring conflicting information processing (for more details on the various cognitive tasks refer to Section 2.4).

3.2.6 Statistical Analysis

Independent t-tests were carried out to compare means between groups (healthy controls, HC vs FEP). Paired sample t-tests were done to compare means between participant SDS and SCRS scores (EEG vs MRS study sessions). Paired sample t-tests found no significant differences between EEG and MRS study session SDS or SCRS scores.

General linear regression models (GLMs) were conducted to determine the effect of SD scores on performance outcomes on the various cognitive tasks. These GLMs were conducted with group (HC or FEP) as a fixed effect, and with the SD scores and PANSS scores as covariates. Moreover, a GLM was conducted to explore the role of social

risk factors (such as ethnicity) on SD questionnaire scores, with group (FEP vs HC), immigration status, ethnicity and education level as fixed factors. An additional GLM was conducted with SD scores and age as covariates, with group and sex as fixed effects and with the PANSS scores as the dependent variable, to explore the role or SD on symptom severity. The main effects of group, ethnicity, education and immigration as main effects, and the interactions between group and ethnicity were explored in both GLMs. Additionally, SD questionnaires were included as main effects for the analysis in the GLM exploring SD's impact on symptom severity.

Paired sample correlations were conducted on repeated measures within participants, who did both the EEG vs MRS study sessions. Whereas Spearman's rho correlations were done to assess the relationship between SD scores and other variables, such as cognitive performance. Spearman's rho correlational analysis was performed as the variables studied were either not normally distributed or the relationship between the variables was better represented with non-linear lines of best fit (tested using scatter plots).

Alpha corrections were done using Šidák corrections for multiple comparisons. Šidák corrections were chosen as they are commonly used for alpha correction, especially for smaller sample sizes, and remains a stringent correction.

3.3 Results

3.3.1 Combined Social Defeat

Demographic Comparisons

Demographic categories considered pertinent to risk for psychosis were measured, and pooled across EEG and MRS study sessions. In cases where the same participant partook in EEG and MRS study session, the MRS study session data was used.

There were no significant group differences in ethnic status or immigration status, but there was a significant difference in education level, with the HC group having more individuals with higher education compared to the FEP group (Table 3.1).

Social Defeat in HC vs FEP

Social defeat data (SDS and SCRS) was collated from both the EEG and MRS study sessions to analyse the relationship of SD scores with other variables with a larger sample size.

	Patients with FEP n= 29	Healthy Controls n= 24	t-value	p-value	Cohen's D effect size
Age	26.93 (5.46)	25.88 (4.44)	-0.761	0.450	-0.210
Sex	13/16	12/12	0.141 (χ^2)	0.707	
Education	14/15	1/23	**12.591 (χ^2)**	**<0.001**	
Ethnicity	9/20	7/17	0.022 (χ^2)	0.883	
Immigration	12/17	14/10	1.510 (χ^2)	0.219	
SDS scores	24.90 (13.01)	11.92 (7.38)	**-4.481**	**<0.001**	**-1.182**
SCRS scores	58.45 (17.14)	64.17 (14.42)	1.297	0.200	0.358

Table 3.1: Means (standard deviations) for pooled EEG and MRS demographic information, SD scores (SDS and SCRS) and group comparison statistics (t-test or chi-square) between FEP and HC. Frequency for the sex variable are female/male, for ethnicity they are non-white/white, for immigration they are immigrant/non-immigrant and for education they are high school/university. Immigration was categorised as 1st Generation if the participant was born outside the UK, whereas 2nd Generation if the participant's family was born outside the UK. Equal variance was assumed for all variables except for the SDS score (based on a Levene's Test of Equality of Variance), a confidence interval (CI) of the difference of 95% was used, and p tests were two-tailed

FEP participants had significantly higher SDS scores compared to HC participants, however there were no group differences in SCRS scores (Table 3.1 and Fig. 3.3.1). The group difference in SDS scores remains significant when applying the Šidák correction for multiple comparisons.

A GLM was conducted to assess the role of group when controlling for ethnicity, immigrant status, and education level as fixed factors. Multivariate testing (Wilk's Λ) revealed that group differences remained significant when accounting for other demographic risk factors ($F(2, 28) = 3.893, p = 0.032$, Wilk's $\Lambda = 0.782$, $\eta_p^2 = 0.218$). Univariate ANOVAs confirmed t-test findings that the significant group effect was on SDS scores ($F(1) = 5.133, p = 0.031, \eta_p^2 = 0.150$), but not on SCRS scores ($F(1) = 0.139, p = 0.712, \eta_p^2 = 0.005$). However, none of these tests survived alpha correction for multiple comparisons.

Interestingly, SDS scores were significantly inversely correlated with SCRS scores (Spear-

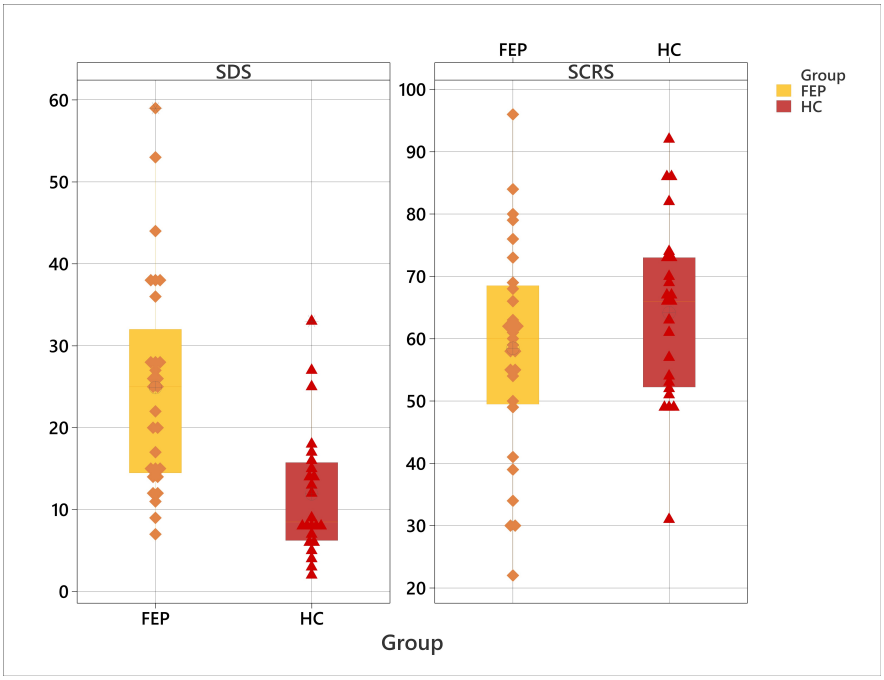

Figure 3.3.1: Boxplots demonstrating group differences in SDS and SCRS scores.

man's rho$= -0.655, p < 0.001$) in the FEP group, but there was no correlation seen in the HC group.

Social Defeat and Demographic Differences

Following the above GLM, SD group differences for ethnicity, education and immigration were explored, in a combined group of FEP and HC.

It was shown that ethnicity and immigration status (majority vs minority) did not significantly differ in SDS nor SCRS scores (Table 3.2). However, education level showed significant group differences in SDS scores with those who had only completed high school scoring significantly higher than those who had a university education. This test did not remain significant after alpha correction.

Education					
	High School n= 15	University n= 38	t-value	p-value	Cohen's D effect size
SDS scores	24.73 (15.06)	16.76 (11.03)	**2.130**	**0.038**	**0.649**
SCRS scores	61.13 (16.51)	59.82 (15.96)	0.879	0.384	0.268
Ethnicity					
	Non-White n= 37	White n= 16	t-value	p-value	Cohen's D effect size
SDS scores	15.63 (7.56)	20.49 (14.18)	1.620	0.112	0.385
SCRS scores	66.94 (16.60)	58.49 (15.37)	-1.794	0.079	-0.537
Immigration					
	Immigrant n= 26	Non-Immigrant n= 27	t-value	p-value	Cohen's D effect size
SDS scores	17.04 (8.86)	20.93 (15.45)	-1.129	0.265	-0.307
SCRS scores	65.23 (14.89)	57.00 (16.41)	1.910	0.062	0.525

Table 3.2: Means (standard deviations) for SD scores between demographic groups (ethnicity, immigration and education). Equal variance was assumed for all variables except for the SDS scores on the ethnicity and immigration t-tests (based on a Levene's Test of Equality of Variance), a confidence interval (CI) of the difference of 95% was used, and p-tests were two-tailed.

3.3.2 Social Defeat and Symptomology in FEP

20 FEP participants had completed both the SD scales (SDS and SCRS) and the PANSS during the MRS study visit (refer to Section 6, and Table 6.1).

There were several significant associations between symptomology and feelings of social defeat (Table 3.3). SDS scores were correlated with positive symptoms and with general symptoms. SCRS scores were only inversely correlated with general symptoms, although there was a trend like inverse association between SCRS scores and positive symptoms (Fig. 3.3.2).

A GLM was also conducted with SD scores and age as covariates, with group and sex as fixed effects and with the PANSS scores as the dependent variable. Multivariate tests ((Wilk's Λ) demonstrated that SDS scores had a significant effect on PANSS scores ($F(3, 28) = 5,692$, $p = 0.004$, Wilk's $\Lambda = 0.621$, $\eta_p^2 = 0.379$). There was no significant

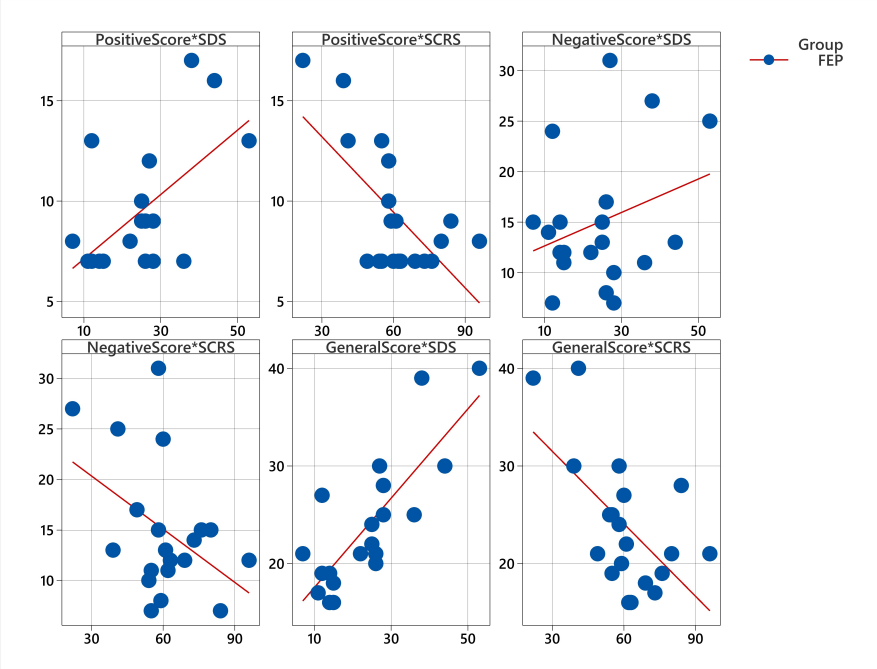

Figure 3.3.2: Scatter plots with the line of best fit for social defeat measures (SDS and SCRS) with PANSS symptom sub-categories

	SDS scores		SCRS scores	
	Spearman's rho	p-value	Spearman's rho	p-value
Positive	**0.470**	**0.036**	-0.439	0.053
Negative	0.071	0.766	-0.265	0.258
General	**0.741**	**<0.001**	**-0.541**	**0.014**

Table 3.3: Spearman's rho correlation coefficients and significance between social defeat measures (SDS and SCRS) with the three sub-categories of symptoms in the PANSS questionnaire.

effect of SCRS scores on PANSS scores. Univariate ANOVAs were then carried out for each symptom subtype. It was shown that SDS scores had an effect on the general symptoms ($F(1) = 13.819, p < 0.001, \eta_p^2 = 0.315$), but not a significant effect on neither positive nor negative scores. It was also shown that SCRS scores had a significant effect on positive symptoms ($F(1) = 4.430, p = 0.044$), but no effect on negative or general symptoms. When correcting for multiple comparisons only the SDS score effect and

general symptoms remained significant.

3.3.3 Social Defeat and Cognition

For the effect of SD scores on cognitive performance GLMs were performed. All GLMs in the following analysis had group and PANSS scores as covariates to control for their effects.

Social Defeat and Cognitive Performance on CRDM task

A total of 19 HC and 14 FEP participants had valid CRDM performance data and SD scores (for information on performance refer to Section 4.3.2).

In just the HCs group there were no significant correlations between feelings of SD and performance on the CRDM task.

Whereas, in the FEP group those with higher SCRS scores (therefore, less social defeat) were significantly correlated with both false alarm rate and number of false alarm, although not with hit rates nor reaction time (Table 3.4).

Healthy Controls				
	SDS scores		SCRS scores	
	Spearman's rho	p-value	Spearman's rho	p-value
FA Rate	-0.083	0.735	-0.015	0.952
FA Number	-0.059	0.809	0.006	0.980
Hit Rate	-0.199	0.413	0.191	0.434
Reaction Time	0.181	0.459	0.146	0.551
Patients with FEP				
	SDS scores		SCRS scores	
	Spearman's rho	p-value	Spearman's rho	p-value
FA Rate	-0.355	0.213	**0.561**	**0.037**
FA Number	-0.451	0.092	**0.748**	**0.001**
Hit Rate	-0.093	0.742	-0.041	0.884
Reaction Time	0.436	0.104	-0.474	0.075

Table 3.4: Spearman's rho correlations between CRDM performance, where FA is false alarm, and social defeat measures (SDS and SCRS scores) in HC and FEP groups

A GLM revealed no significant effects or interactions of SD scores (neither SDS nor SCRS) on performance on the CRDM task (RT, HR and FA). This GLM included mutlivariate testings (Wilk's Λ) as well as between-subject effects tests.

Social Defeat and Cognitive Performance on BACS

A total of 10 HC and 14 FEP participants had both valid BACS performance data and SD scores, both SDS and SCRS (for information on performance refer to Section 6.3.3).

Healthy Controls				
	SDS scores		SCRS scores	
	Spearman's rho	p-value	Spearman's rho	p-value
Verbal Memory	-0.291	0.415	0.333	0.347
Digital Sequencing	0.052	0.887	0.202	0.576
Token Motor	-0.316	0.374	0.243	0.498
Verbal Fluency	-0.304	0.393	0.109	0.763
Symbol Coding	-0.371	0.291	0.578	0.080
Tower of London	-0.105	0.773	0.201	0.578
Composite BACS	-0.199	0.581	0.451	0.191
Patients with FEP				
	SDS scores		SCRS scores	
	Spearman's rho	p-value	Spearman's rho	p-value
Verbal Memory	-0.243	0.403	-0.011	0.970
Digital Sequencing	**0.534**	**0.049**	**-0.570**	**0.034**
Token Motor	-0.426	0.129	-0.194	0.507
Verbal Fluency	0.279	0.357	-0.495	0.086
Symbol Coding	-0.296	0.326	-0.398	0.178
Tower of London	-0.385	0.194	-0.158	0.606
Composite BACS	0.007	0.982	-0.453	0.104

Table 3.5: Spearman rho's correlations between SD scores with cognitive performance battery of BACS tasks and composite BACS scores for HC and FEP groups

There were no significant correlations between SD scores and BACS task performance nor BACS composite score when analysing just the HC group (Table 3.5). On the other hand, the BACS digital sequencing task was significantly correlated with both SDS and SCRS scores in the FEP group (Table 3.5).

A GLM was conducted to further explore the relationship between SD scores and BACS performance. Multivariate testing (Wilk's Λ) showed that there were no effects of SDS nor SCRS on overall performance on the BACS. Univariate ANOVAs revealed that there were no effects of SDS scores on any of the individual BACS tasks. However, there was a significant effect of SCRS scores on digital sequencing performance ($F(1) = 5.326, p = 0.036, \eta_p^2 = 0.262$), although this did not survive alpha correction for multiple comparisons.

Social Defeat and Cognitive Performance on N-Back

A total of 17 HC and 17 FEP participants had both valid N-back task performance results and SD scores (for information on performance refer to Section 6.3.3).

There were no significant correlations between SD scores and performance on the N-back in the HC group, but there was a significant correlation between SCRS scores and reaction time in the 2-back task in the FEP group (Table 3.6).

Healthy Controls				
	SDS scores		SCRS scores	
	Spearman's rho	p-value	Spearman's rho	p-value
RT 0-back	0.323	0.206	-0.068	0.796
RT 1-back	0.233	0.368	0.001	0.996
RT 2-back	0.372	0.142	-0.153	0.559
RT 3-back	0.296	0.249	-0.256	0.322
Acc 0-back	0.171	0.512	-0.208	0.423
Acc 1-back	0.219	0.398	-0.271	0.293
Acc 2-back	0.075	0.775	-0.177	0.497
Acc 3-back	0.008	0.976	-0.066	0.801
Patients with FEP				
	SDS scores		SCRS scores	
	Spearman's rho	p-value	Spearman's rho	p-value
RT 0-back	-0.417	0.096	0.435	0.081
RT 1-back	-0.293	0.254	0.457	0.065
RT 2-back	-0.304	0.236	**0.524**	**0.031**
RT 3-back	-0.343	0.178	0.353	0.164
Acc 0-back	0.384	0.128	-0.288	0.263
Acc 1-back	0.060	0.818	-0.143	0.583
Acc 2-back	0.265	0.305	-0.380	0.132
Acc 3-back	0.055	0.834	-0.218	0.402

Table 3.6: Spearman's rho correlational analysis of SD scores and performance on the N-back task, where RT is reaction time and Acc is accuracy, for HC and FEP participants

Performing GLM highlighted that there were no significant effects or interactions of SD scores, neither SDS nor SCRS, on performance on the N-back task, neither reaction time (RT) nor accuracy (Acc), in any of the conditions. This GLM included mutlivariate testings (Wilk's Λ) as well as between-subject effects tests.

Social Defeat and Cognitive Performance on Stroop

A total of 15 HC and 20 FEP participants had both valid Stroop task performance data and SD scores (for information on performance refer to Section 6.3.3).

There were no significant correlations for HC, but there was a significant correlation between SCRS scores and reaction time on the incongruent condition in FEP (Table 3.7).

Healthy Controls				
	SDS scores		SCRS scores	
	Spearman's rho	p-value	Spearman's rho	p-value
RT cong	0.368	0.177	0.300	0.278
RT incon	0.347	0.205	0.214	0.445
Acc cong	0.023	0.934	0.071	0.803
Acc incon	0.238	0.393	-0.040	0.889
Patients with FEP				
	SDS scores		SCRS scores	
	Spearman's rho	p-value	Spearman's rho	p-value
RT cong	0.044	0.855	0.344	0.138
RT incon	-0.087	0.714	**0.502**	**0.024**
Acc cong	-0.025	0.916	0.146	0.539
Acc incon	-0.216	0.360	0.087	0.715

Table 3.7: Spearman's rho correlational analysis of SD scores and performance on the Stroop task, where RT is reaction time, Acc is accuracy, Con is the congruent condition and Incon is the incongruent condition, for HC and FEP groups

A GLM was done on measures of performance (reaction time and accuracy) on the Stroop task with group as a fixed effect, and with PANSS scores, SDS and SCRS scores as covariates. Multivariate tests (Wilk's Λ) showed significant SCRS effects on performance ($F(4, 24) = 3.554, p = 0.021$, Wilk's $\Lambda = 0.628$, $\eta_p^2 = 0.372$), but no effect for SDS scores. Univariate ANOVAs elucidated that SCRS scores had an effect on reaction time (RT) on congruent Stroop stimuli ($F(1) = 9.988, p = 0.004$, $\eta_p^2 = 0.270$) and RT for in-congruent Stroop stimuli ($F(1) = 4.932, p = 0.035$, $\eta_p^2 = 0.154$). However, when applying alpha corrections for multiple comparisons none of the tests remained significant.

3.4 Discussion

3.4.1 Social Defeat and Psychosis

Main Findings

- There were significant group differences in SDS scores, with FEP participants feeling more socially defeated. There were no significant group differences in SCRS scores.
- Social defeat had significant correlations with both positive and general symptoms of psychosis but not with negative symptoms as measured by PANSS. Social rank was significantly correlated with general symptoms of psychosis, and showed a trend-level (yet not significant) association with positive symptoms.
- SDS scores were also shown to have a significant effect on general symptoms when controlling for the variables of group, age and sex.

Findings in Context

The analysis conducted on repeated SDS and SCRS scores provides further support for the validity and reliability of these measures, especially in an FEP population.

The findings of this thesis support the hypothesis that feelings of social defeat, as measured by SDS, are consistently increased in those with FEP compared to controls. Although interestingly there is no support for feelings of social rank, as measured SCRS, being significantly different between groups. The above finding is in keeping with previous findings of increased social disadvantage and other social defeat proxies in FEP (Morgan et al., 2008). Moreover, the finding of significantly higher scores on the SDS but not on SCRS in FEP suggests a sense of internal defeat being more characteristic of psychosis as opposed to feeling inferior to others. This speaks to the salience of being excluded from the majority group in a way that makes one feel hopeless and powerless as opposed to a sense of feeling worse compared to other individuals (Gilbert and Allan, 1998; Selten et al., 2013). Previous literature on SD has found that associations between SD and depression remained strong when controlling for hopelessness, yet the association between hopelessness and depression was decreased when controlling for SD (Gilbert and Allan, 1998). This suggests that the psychological mechanism in which SD impacts mental wellness is independent of feelings of hopelessness and stands sufficiently on its own. With that being said, scores between SDS and SCRS were correlated in FEP but not in

HC, suggesting that the lack of significant difference in SCRS could be due to differences in interpretation of social rank between the groups, with the FEP group potentially integrating it more into feelings of personal defeat.

Although it did not survive alpha correction, education was the only demographic factor that had significantly different SD scores. Despite not surviving alpha correction, when controlling for demographics SD remained significantly higher in the FEP population compared to HC, suggesting that demographic factors do not influence the association between SD and FEP. Moreover, much like the present study, it has previously been found that associations between demographic features and psychosis-like experiences are no longer significant when controlling for SD scores (Lincoln et al., 2022). These findings suggest that SD could be the mediating factor between demographic risks and psychosis (refer to Section 1.5). Further research with a larger sample size and less variability in the FEP group would allow for a better examination of the relationship between demographic variables, SD and FEP.

This study also found a significant relationship between SD and symptom severity. Specifically, correlations were seen between social defeat and positive and general symptoms, and social rank and general symptoms in FEP. This is in line with previous literature and the hypothesis that SD would be linked to worse symptomology particularly positive symptoms (Freeman et al., 2005; Lincoln et al., 2022). Altered mesolimbic dopamine in psychosis could account for the relationship found between SD scores and positive and general symptoms but not negative symptoms in FEP. Positive symptoms of psychosis have been attributed to altered salience networks particularly through dopamine in the ACC and DLPFC (McCutcheon et al., 2019, 2020; Palaniyappan et al., 2013). Moreover, excessive mesolimbic dopamine has been linked to positive symptoms, whereas cognitive and negative symptoms are associated with mesocortical dopamine (Kesby et al., 2018; Schwartz et al., 2012; Stahl, 2007). The shared mechanism between positive symptoms of psychosis and SD provides a strong theoretical framework to understand the present findings. In contrast with these claims, a study exploring SD and striatal dopamine in autism spectrum disorder saw no significant association between SD and striatal dopamine, though this finding may be unique to autism (Schalbroeck et al., 2021). Although a causal mechanism between SD and psychosis cannot be established at the present stage, these results propose that SD is a feature of psychosis which is closely related to symptoms that have been linked to dopaminergic abnormalities (positive and general symptoms) (Duarte and Xin, 2019).

These findings are a significant replication of SD's linked with psychosis and provide

novel insight into the relationship between symptomology and feelings of SD within an FEP population.

3.4.2 Social Defeat and Cognition

Main Findings

- There was a significant correlation between SCRS scores and CRDM false alarm rates and number of false alarms in the FEP group. There was no correlation between SD and CRDM performance in the HC group.
- There was a significant correlation between SDS and SCRS (inversely) scores and BACS digital sequencing in the FEP group. There was no correlation between SD and BACS performance in the HC group.
- There was a significant correlation between SCRS scores and reaction time in the 2-back condition of the N-back in the FEP group. There was no correlation between SD and N-back performance in the HC group.
- There was a significant correlation between SCRS scores and reaction time on the in-congruent condition of the Stroop Colour test in the FEP group. There was no correlation between SD and Stroop Colour test performance in the HC group.
- GLMs, once alpha corrected, consistently failed to find a significant effects between SD scores and cognitive performance.

Findings in Context

Consistently, there were no associations within the HC group between SD scores and cognitive performance across any of the measured tasks (CRDM, BACS, N-back or Stroop).

In the FEP group, higher feelings of social rank were correlated with higher false alarm rates. Similarly, higher SDS (more SD) and lower SCRS (more SD) were correlated with better performance on digital sequencing in the BACS battery. These results were unexpected and did not fit the initial thesis hypothesis, nor previous findings, that general higher SD would be linked with worse cognitive performance (Da Costa et al., 2023; Wang et al., 2022). Yet, one study has established a link between increased SD and increased cognitive performance that was mediated by NMDA receptor activity in the hippocampus (Yang et al., 2023). This finding implicates NMDA receptor activity and

could be particularly relevant for psychosis and the hypothesised NMDA hypofunctioning mechanism. Despite the contrast with previous literature and the link between higher SD and worse performance on other cognitive tasks in the present thesis, the association between higher SD and better performance on the CRDM and digital sequencing task could possibly be explained by the antifragility hypothesis (Da Costa et al., 2023; Wang et al., 2022). The antifragility hypothesis claims that there may be some benefits, such as resilience, to social adversity and has been used to explain the association between higher SD with better cognitive performance (Yang et al., 2023). Similar to this study, a large scale study (Light and Swerdlow, 2015) found that anyway cognitive performance in psychosis on various tasks often do not correlate with each other.

With that being said, the correlations between SCRS scores and reaction time in the Stroop for the incongruent condition and between SCRS scores and reaction time in the N-back 2-back condition for the FEP group is in line with previous literature (Wang et al., 2022). These correlations point to lower feelings of SD with better cognitive performance. Defeated mice have been shown to perform worse across several cognitive domains (**?**Da Costa et al., 2023; Jianhua et al., 2017; McKim et al., 2016; Novick et al., 2016; Vassilev et al., 2021; Wang et al., 2022). Dendrite loss is a potential mechanism for the role of SD on working memory in particular (Schwabe et al., 2012). Dendrite loss is observed in psychosis and has been associated with dopaminergic abnormalities, particularly in earlier stages of psychosis (Bellon et al., 2022; Moyer et al., 2015). Despite the potential connection between dopamine, SD and cognition, this association was not replicated for E/I balance metabolites. In particular, one study failed to establish glutamate as a mediating factor for the relationship between early life stress and psychosis (Corcoran et al., 2020). This could indicate that SD may act more downstream in the proposed glutamatergic hypothesis of psychosis, specifically on the secondary glutamatergic neuron and mesolimbic dopaminergic pathway.

Additionally, when controlling for group and PANSS scores, SD no longer had an effect on cognitive performance in any task. This could indicate that these associations between SD and cognition are more likely a feature of psychosis as opposed to SD itself.

Further research would be needed to confirm biological mechanisms behind SD's relationship with cognitive impairments in psychosis. Moreover, there is evidence to suggest that E/I balance is involved in cognitive deficits in psychosis (Dauvermann et al., 2017; Howes and Shatalina, 2022). However, the use of *in-vivo*, non-invasive approaches has been limited and further work is needed in this field to elucidate the links between SD, cognition and E/I balance (Grent-'t Jong et al., 2018; Uhlhaas and Singer, 2013).

3.5 Conclusion

The results and analysis from this section of the thesis suggest that SD and social rank are more closely associated in FEP compared to HC. Furthermore, this thesis suggests that SD is particularly linked with general and positive symptoms of psychosis, which are strongly linked with dopaminergic activity. Therefore, the link between SD and these psychotic symptoms could also support the dopaminergic sensitisation hypothesis (Selten and Cantor-Graae, 2005). The limited associations between SD and cognition could further support dopamine involvement in the relationship between SD and psychosis. This could indicate that SD may alter the pathway between secondary glutamategic neurons and mesolimbic dopamine leading to altered E/I in psychosis. It is unclear whether the correlations seen between SD and cognition in the FEP group were due to psychotic symptoms.

Although it did not survive alpha corrections, this thesis also found that the link between SD and psychosis was independent of demographic risk factors. This suggests that SD is a potential mediator for the relationship between demographic risks and psychosis.

Further research would be required to suggest a particular mechanism or demonstrate causal links. A longitudinal study following those at risk of psychosis, those in early stages of psychosis and those with chronic psychosis using PET imaging and SD scales could assess the progression and association between these variables.Moreover, pharmacological studies, particularly using NMDA receptor antagonists could elucidate the potential relationship between E/I balance and the onset of social defeat. In addition, a similar but larger and more powered study in ultra-high risk groups and in the general population may also help elucidate the relationship between social defeat and cognition.

Chapter 4

Analysis of Mismatch Negativity in First-Episode Psychosis compared to Healthy Controls, and interactions with Social Defeat and Cognitive Performance

4.1 Introduction

The mismatch negativity (MMN) response has been positioned as a potential biomarker for psychosis. In particular, the duration MMN could be a promising biomarker for prodomal and first-episode stages (Haig et al., 2017). Reduced MMN response has been reported in FEP (Erickson et al., 2016; Haig et al., 2017; Umbricht and Krljes, 2005)

Kapur (2003) conceptualises psychotic disorders as resulting from aberrations in bottom-up neurochemical drives and top-down psychological processes, claiming that those with psychosis experience the world differently due to aberrant salience. In order to explain this aberrant salience, the mind then provides cognitive compensation such as delusions. A similar notion for understanding the symptomology of psychosis is outlined by the Bayesian model of perception known as unconscious inference. Unconscious inference implies that our understanding of the world,and what we expect, colours our perceptions, which in turn informs our inferences about the world and adjusts future

expectations (Barlow, 1990; Corlett, Frith and Fletcher). It has been suggested that this mechanism involves N-methyl-D-aspartate (NMDA) signalling for feedback, and AMPA signalling for feed-forward that lead to this hierarchical interaction between predictions and the prediction errors which then alter our inferences (Corlett, Frith and Fletcher, 2009). Predictive coding has also been put forward as the mechanism guiding the MMN response.

Given that MMN is thought to reflect information processing, it is reasonable to understand MMN as being reflective of working memory (Javitt et al., 1996). Moreover, MMN outcomes have been asscoiated with cognitive performance (Chitty et al., 2013; Donaldson et al., 2020; Toyomaki et al., 2008). There has also been some limited previous literature to suggest an association between social rank, a component of social defeat, with other ERP amplitudes (Luo et al., 2015; Qui et al., 2010).

This study aims to explore duration MMN outcomes in FEP, in the hopes of replicating previous findings for psychosis in general, compared to HC, and their associations with both SD and cognition.

In this work it has been hypothesised that MMN amplitudes will be significantly decreased in the FEP group compared to controls. Moreover, it is hypothesised that MMN outcomes will be associated with cognitive performance, as a result of shared neural mechanisms (refer to Section 1.3). Finally, SD scores are predicted to be correlated with MMN amplitudes.

4.2 Methods

4.2.1 Study Approval

The aim of this study was to determine whether there was a difference in MMN values (amplitudes and latencies) between HC and FEP patients. Ethical Approval for this study was granted by the Bradford Leeds Research Ethics Committee (Ethics Ref: 19/YH/0090).

4.2.2 Study Eligibility

22 FEP patients and 21 HC matched for sex and age were included in the study. The FEP group was recruited through direct communication with care coordinators and an Oxford Health Thomas Vaughn ward psychiatrist. Patient participants were eligible if they: had their first episode of psychosis, as defined by Melbourne criteria (i.e. a week or

more of psychotic symptoms above a threshold of moderate in severity), within the last three years from study visit date, were between 18 and 40 years of age, were clinically stable[1], were not at risk of suicide, did not have current substance dependency, were not pregnant or breastfeeding and did not have any contraindications to MRI[2]. The age range for the study was 18 to 40, to prevent age related abnormalities (Brandt et al., 2016). Healthy controls were recruited via word of mouth, web advertisements and local newspaper advertisements. Healthy controls were eligible if they are matched to FEP participants, and have no current or previous history of psychiatric disorders according to the DSM-5.

The EEG sample size was calculated using the MMN data from Wynn et al., 2010 using https://clincalc.com/stats/samplesize.aspx with a confidence interval (beta) of 80% and a probability (alpha) of 0.05. For MMN the sample size should be a minimum of 16 participants per group.

4.2.3 EEG Study Session

All EEG recordings and study sessions were carried out at the Oxford Centre for Human Brain Activity (OHBA) building located at the Warneford Hospital site in Oxford. In this session the MMN paradigm was combined with a visual distraction task which in itself functions as a cognitive task of interest. Participants performed a continuous random dot motion task (CRDM, a modified version of a widely used perceptual choice task) in which they made binary decisions about the direction of moving dots presented on the screen, while they passively listened to the sequence of tones that comprised the MMN oddball paradigm. Once informed consent had been received from the participant, they were asked to fill out the Social Defeat Scale (SDS) and Social Comparison Rating Scale (SCRS) questionnaires (outlined in Section 2.3). Once questionnaires were completed, two sets of training sessions were done so that the participant was familiar with the CRDM task and to familiarise the participants with the EEG booth. Following the training sessions, the EEG cap, and additional relevant electrodes (see Section 4.2.7) were applied. The EEG recording included two CRDM task sessions (coupled with the roving oddball paradigm -explained below), and two resting data sessions. Each CRDM session consisted of four five minute long blocks, and each resting state recording lasted five minutes.

[1]Participants could still have symptoms of psychosis however they could not be in a florid state of psychosis, they needed to be deemed well enough and stable enough to participate and understand what the study entailed (provide informed consent).

[2]The same participants were recruited for both the MRS and EEG study sessions, however, if a participant was not MR safe but wanted to take part in the EEG study they were still included.

During the experiment, subjects were comfortably seated in an electrically shielded and sound-attenuated chamber.

4.2.4 Training Session

As the CRDM task aims to measure evidence integration in a dynamic environment (refer to Section 2.4.1) as opposed to learning, all participants went through a training session prior to commencing with the EEG cap placement and actual CRDM task. Each participant did two 10-minute training sessions (20-minutes in total) that included both the low and high noise/variance conditions (replicating the conditions in the CRDM task).

The CRDM task was slightly altered for the first training session, while in the second training session the CRDM task was the same as the actual task. In the first training session the fixation dot would turn white when the 'bees were escaping' to indicate when participants should make a decision. In both training sessions the reward bar at the bottom of the screen was not present, however the fixation dot would still change colour to provide feedback. If the participant was struggling to grasp the task an additional block of each training session was added (a 30-minute training session, 15-minutes of the first training session and 15-minutes of the second training session).

4.2.5 Auditory Oddball Paradigm

A roving duration auditory oddball paradigm (referred to as simply the oddball paradigm through this thesis) was used to induce the mismatch negativity (MMN). The roving paradigm was used to avoid the potential confounding variable of different duration auditory stimuli eliciting different neural responses. A roving paradigm employs identical auditory stimuli as both the standard and deviant. For example what is deviant in one block then becomes the standard in the next block. The tones would either be 50 ms (short tone) or 100 ms (long tone), with 120 tones being played per minute of the task. Each block of tones ranged from 2 to 7 tones, with the initial tone, a deviant tone, being randomised as either short or long, and then flipped for the following block. The tones that follow the initial tone of the block are then considered standard. Deviant and standard tones were pseudo-randomly assigned. The use of the short tone deviant is known as the decrement condition, where the deviant is shorter than the standard. This then gets reversed in a roving paradigm into an increment condition where the deviant is longer than the standard (see Fig. 4.2.1). These tones were played through etymotic research 3C insert earphones, while the participant performed the CRDM.

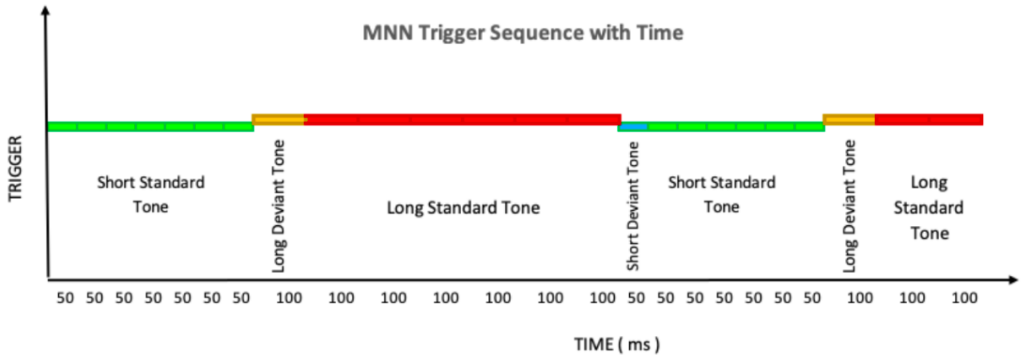

Figure 4.2.1: Example depiction of Roving Oddball Paradigm, green represents short standard tones, red represents long standard tones, blue represents deviant short tone and orange represents deviant long tones

4.2.6 Continuous Random Dot Motion Task

A continuous random dot motion (CRDM) task was done while the oddball paradigm was played in the background. In the CRDM, participants are presented with a stream of moving dots which change their net movement direction over time (Fig. 2.4.1). Their task is to detect short periods (trials of 5 second length) in which the net (average) movement direction is consistently more to one direction than the other, and to indicate the average movement direction via button press. Between trials, average movement coherence was zero ("baseline periods"). In trials as well as baseline periods, average movement direction was hidden in noise, which could be either low ("low variance condition") or high ("high variance condition"). Trials could be easy or hard to detect based on their average motion coherence (low coherence trials versus high coherence trials).

This task was explained using the analogy of bees escaping from the Queen bee, where the Queen bee referred to the fixation dot and the bees referred to the smaller dots that would be buzzing about the fixation dot (for further information please refer to Section 2.4.1).

4.2.7 EEG Cap Design and Acquisition Process

EEG was recorded with 62 electrodes with a sampling rate of 1000Hz with Synamps amplifiers via a Curry 8 system using a customised version of the standard BrainCap with Multirodes (see Fig. 4.2.2). A customised cap was used to reduce set-up time and to keep study sessions as concise as possible. An electrode was also placed on the nasion as a potential additional reference point if needed. Additionally, electrodes were placed

on each wrist to measure ECG values and both horizontal and vertical eye movement were tracked using EOG electrodes beside each eye, and above and below the right eye. EEG was recorded at 1kHz with the left mastoid as the reference, and the POz as the ground. Impedance were all kept under 20 kΩ with the goal being 10 kΩ, in line with the acceptable range (Górecka and Makiewicz, 2019). Curry 8 was used for the EEG data acquisition. A StimTracker Duo device was also employed to send a trigger for the onset of auditory stimuli, meaning it notes the time when stimuli reached the participant's computer as opposed to relying on the timing of when the stimuli was sent.

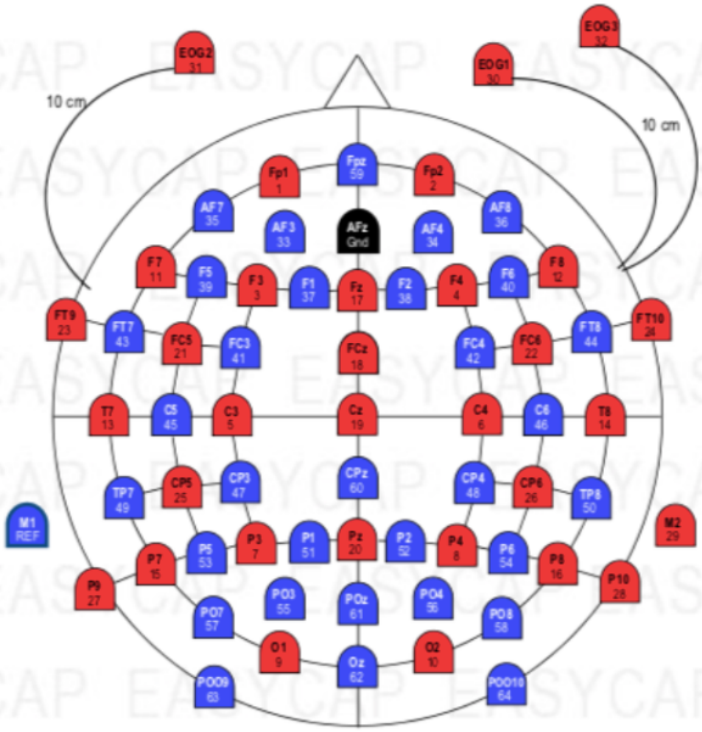

Figure 4.2.2: Customised 62 channel BrainCap with Multirodes as provided by the manufacturer EASYCAP, with POz as the ground and M1 as the reference

4.2.8 EEG Analysis

EEG pre-processing was performed using EEGLAB software for file type conversion, and the remainder of pre-processing was run on Statistical Parametric Mapping (SPM 12) software package (http://www.fil.ion.ucl.ac.uk/spm/) (Litvak et al., 2011), for downsampling, re-referencing, filtering, epoching and artefact removal.

The Curry 8 acquisition files (.cdt) were converted first to .set files using EEGLAB and then .mat files using SPM software. The rest of the pre-processing steps were done on SPM 12 and Matlab. The EEG data was then downsampled to 250 Hz, allowing the data file to be significantly smaller, while allowing for high enough sampling rate to pre-process and analyse evoked responses such as a mismatch negativity. Left mastoid right mastoid (LMRM) referencing refers to an average between both mastoid electrodes and was carried out in the present study. A bandpass filter was used with the high-pass filter cut-off frequency set at 0.1 Hz, and the low-pass filter cut-off frequency set at 30 Hz. Bad trial thresholds were 75 μV and bad channels were detected with the threshold being 0.2. The excision window surrounding a bad trial (jump) was 500 ms. EEG data was then baseline corrected and epoched, with the time frame being between -100 ms and 500 ms around a relevant trigger: either a trigger for standard or deviant oddball auditory stimuli. ERPs were formed using robust averaging, to suppress artefacts while preserving as much data as possible, with weights computed by condition. A Matlab script was then used to calculate the MMN by subtracting the deviant waveform from the standard waveform. Amplitudes were pulled from the 100 to 250ms window following stimuli, using a peak detection method. MMN was calculated at the FCz electrode location. The FCz location, alongside Fz and Cz, has been used in the vast majority of previous literature on MMN in an FEP population (Nagai et al., 2013). The FCz electrode site has also been associated with decreased standard deviations, suggesting it may be more reliable than other electrode locations, both in terms of placement and mapping onto the brain (Scrivener and Reader, 2022). The FCz is thought to correspond with frontal-central regions of the brain, which is a region of particular interest as the anterior cingulate gyrus has been heavily implicated in MMN response generation (Aeberli et al., 2023). MMN were labelled as outliers and excluded in cases where the average ERP to either standard or deviant tones (or both) exceeded $\pm$ 10 μV at any point. The MMN was identified using several parameters including the presence of a negative deflection between 100-250 ms post-trigger, and exhibits a polynomial shape of return to baseline following the negative deflection approximately a few tens of milliseconds.

4.2.9 Statistical Analysis

Statistical analysis was performed using SPSS software version 29. MMN data was analysed using independent sample t-tests and general linear models (GLMs) that include multivariate tests (Wilk's Λ) and between-subject effects tests for both MMN parameters (amplitude and latency).

Associations between variables, such as performance on cognitive tasks or SDS scores with MMN values, were explored using Spearman's rho correlations, and when appropriate GLMs.

General linear regression models (GLMs) were conducted to assess the relationship between MMN and group belonging as well as social defeat and MMN. In the GLM done for the association between MMN and group, – were considered covariates, whereas anti-psychotic and anti-depressant medication, smoking status, age, and sex were considered fixed factors, with MMN amplitudes and latencies as the dependent variables. In the social defeat and MMN GLM both SDS and SCRS questionnaire scores were considered covariates, whereas group, age and sex were considered fixed factors, with the MMN amplitudes and latencies as the dependent variables. In both GLMs main effects were analysed for medication status, smoking status, age, and sex, and SD questionnaire main effects were included in the SD and MMN GLM. Interactions between group, sex and age were also assessed.

Šidák correction was applied for alpha correction of multiple comparisons.

4.3 Results

4.3.1 Mismatch Negativity

Demographic Comparisons

16 HC and 19 FEP participants were included in the MMN analysis . Four HC and one FEP patient were excluded due to issues with trigger timings.

There were no significant differences in age or sex between the HC and the FEP group (Table 4.1).

	Patients with FEP n= 19	Healthy Controls n= 16	t-value	p-value	Cohen's D effect size
Age	25.47 (5.00)	26.44 (4.66)	0.586	0.562	0.199
Sex	7/12	9/7	1.318 (χ^2)	0.251	
Smoking	5/19	2/16	1.036 (χ^2)	0.309	
Antipsychotic drugs	18	n/a			
Antidepressant drugs	7	n/a			
SDS scores	25.79 (14.76)	11.13 (6.05)	**-3.955**	**<0.001**	**-1.256**
SCRS scores	54.42 (16.79)	60.38 (13.83)	1.131	0.266	0.384
MMN Amplitude	-1.49 (1.02)	-1.75 (1.10)	-0.742	0.463	-0.252
MMN Latency	200 (28)	195 (31)	-0.588	0.561	-0.199

Table 4.1: Means (standard deviations) for demographic information, SD scores (SDS and SCRS) and MMN parameters (amplitudes reported in μV and latency reported in ms), and group comparison statistics (t-tests and chi squared) between FEP and HC. Frequency for the sex variable are female/male and for the smoking variable smoker/non-smoker. Equal variance was assumed for all variables except for the SDS scores (based on a Levene's Test of Equality of Variance), a confidence interval (CI) of the difference of 95% was used, and p tests were two-tailed

MMN in HC vs FEP

There were no significant differences between the HC group and the FEP group neither in MMN amplitudes nor in MMN latency (Table 4.1).

A GLM was conducted to explore the relationship between potential confounding variables, for HC and FEP group and MMN values. Multivariate testing demonstrated that there was no significant effect for medication: anti-psychotics and anti-depressants, smoking status, age, or sex, on MMN values. Furthermore, univariate ANOVAs demonstrated that there were no significant between subject effects of group, medication, sex, or age on neither MMN amplitude nor MMN latency.

A Spearman's rho correlational analysis was also performed to establish if there were

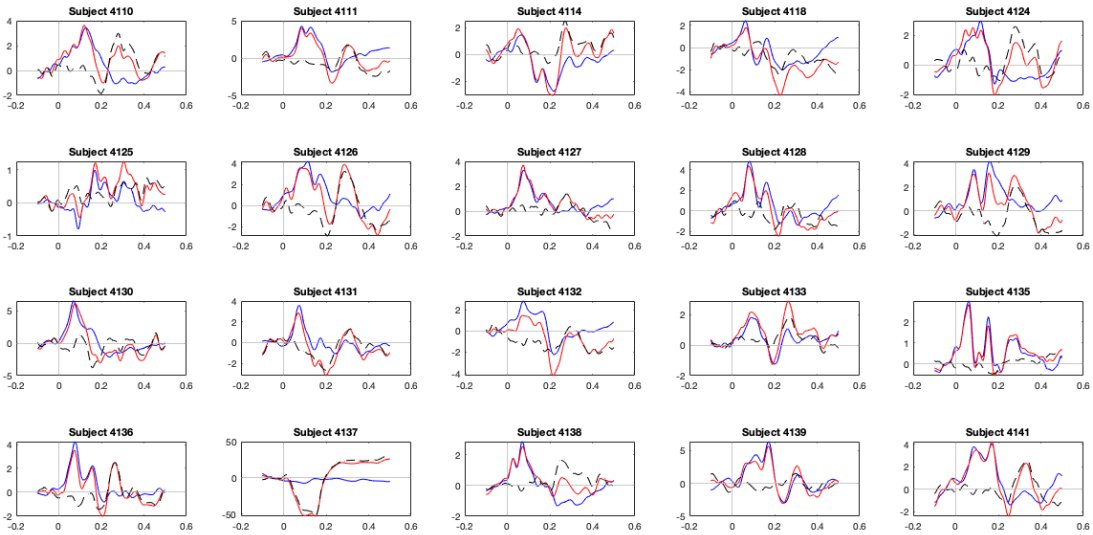

Figure 4.3.1: MMN waveforms for patients with FEP (black = MMN, red = standard, blue = deviant). Participant 4137 was excluded from analysis.

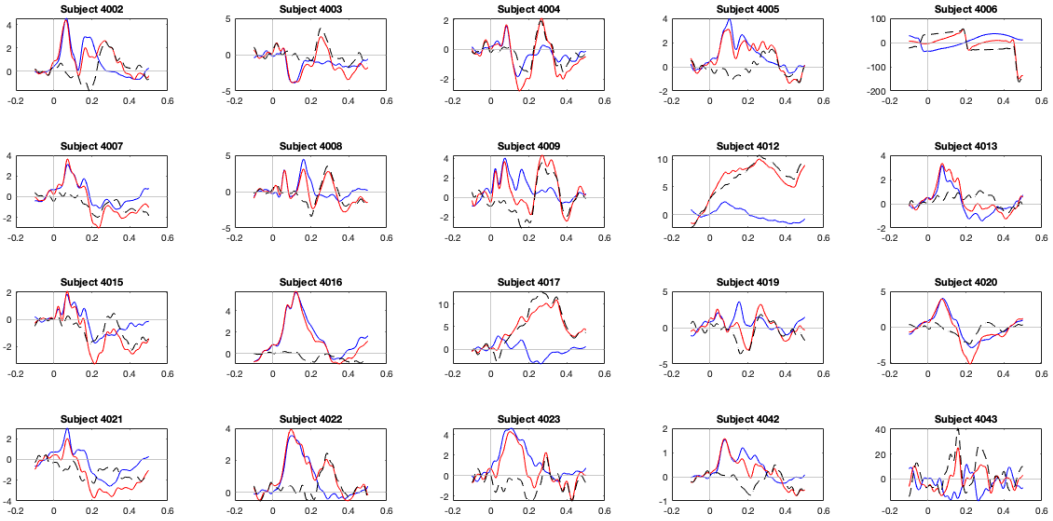

Figure 4.3.2: MMN waveforms for HC participants (black = MMN, red = standard, blue = deviant). Participants 4006, 4012, 4017 and 4043 were excluded from analysis.

any significant associations between MMN amplitude and latency, group, sex, age, or medication status , with anti-psychotics and antidepressants as separate variables. There were no significant correlations between any of the analysed variables.

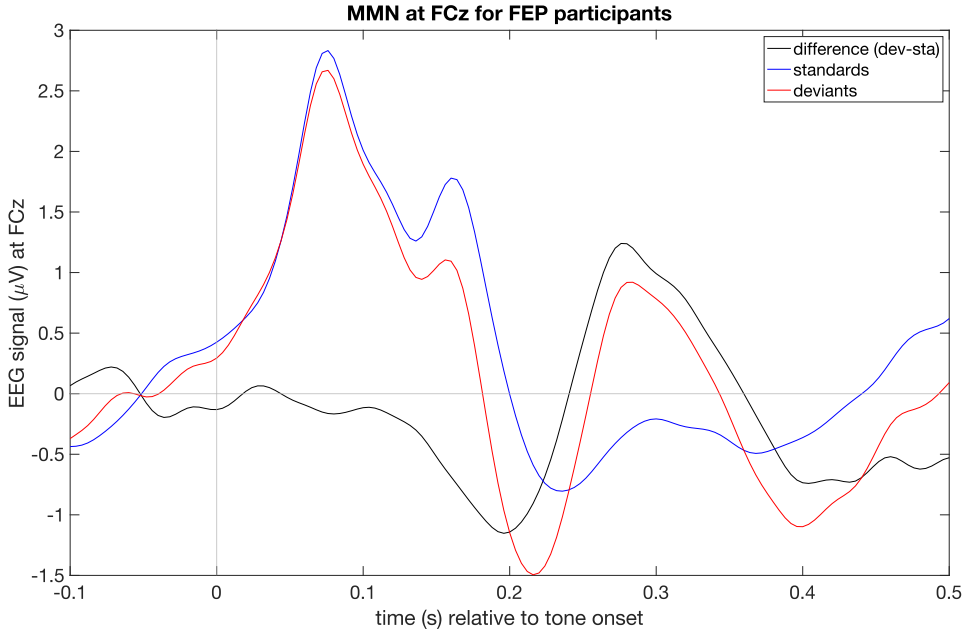

Figure 4.3.3: Averaged MMN waveform for patients with FEP at the FCz electrode location

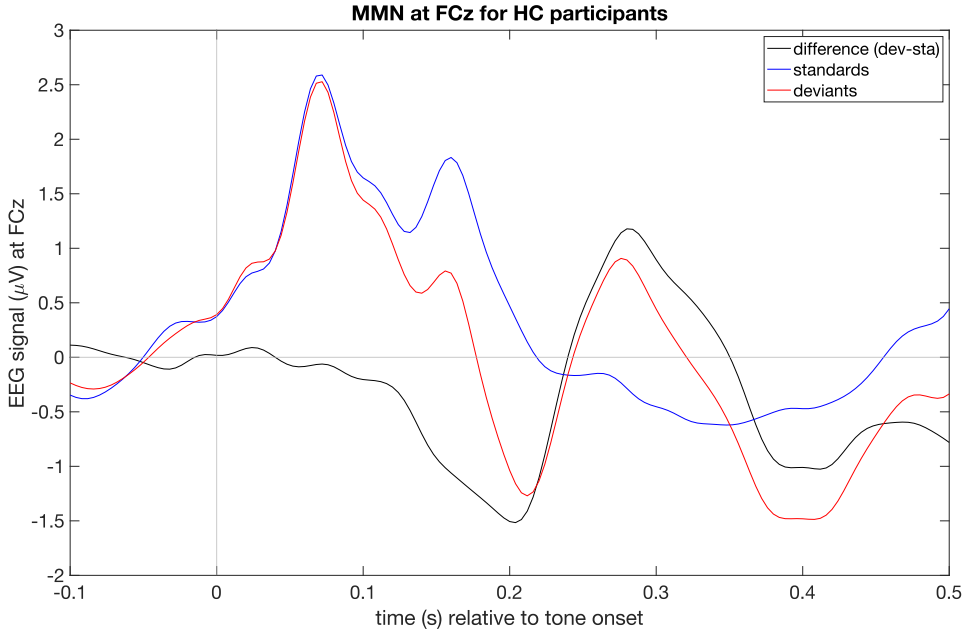

Figure 4.3.4: Averaged MMN waveform for HC at the FCz electrode location

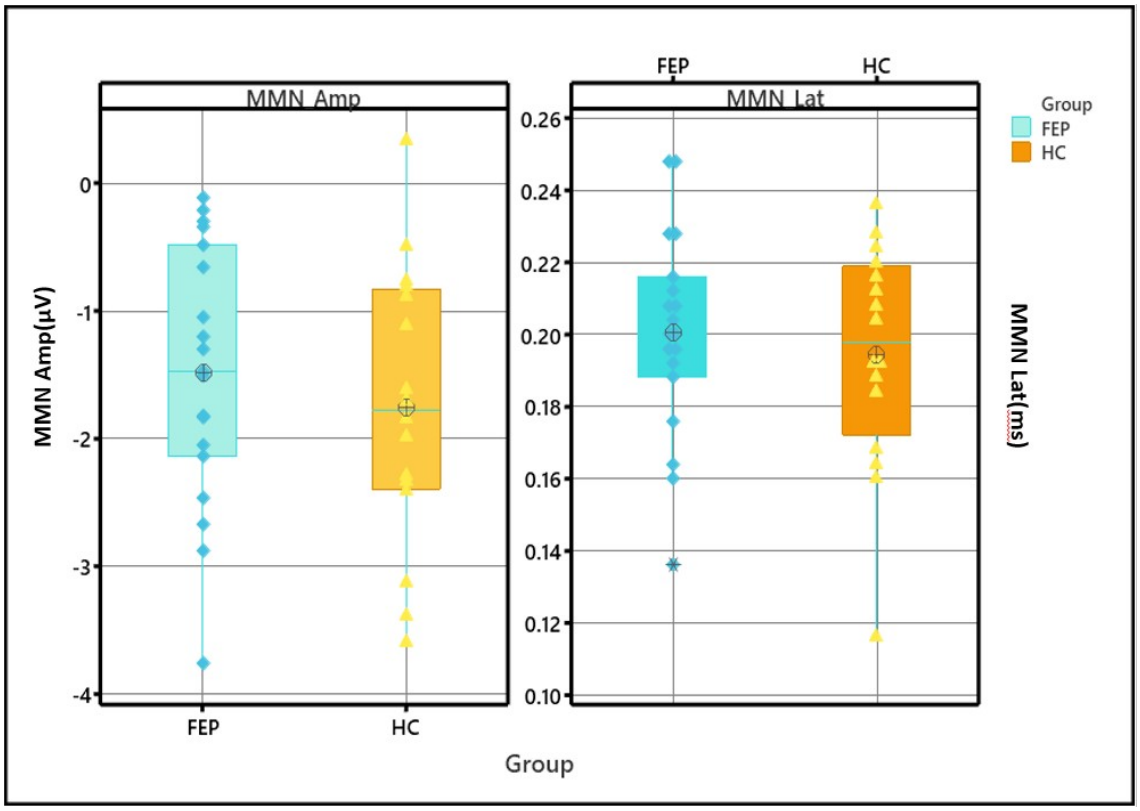

Figure 4.3.5: Boxplot illustrating MMN amplitude and latency values (amplitudes reported in μV and latency reported in ms) for FEP and HC

4.3.2 Mismatch Negativity and Cognition

Performance on Continuous Random Dot Motion task

A total of 16 HC and 14 FEP participants' data was used for the CRDM task performance analysis. Participants with a hit rate of less than 50% were excluded from analysis and those with a false alarm rate of over 75% were excluded from analysis.

There were no significant differences between FEP and HC groups in false alarm rates, number of false alarms, hit rates or reaction time, suggesting that FEP patients did not perform any worse on the CRDM task compared to HC (Fig. 4.3.6). However, the FEP group had slightly more false alarms, a lower hit rate and slower reaction times than controls (Table 4.2)

There were no significant correlations between MMN amplitudes or latencies and false alarm rates, false alarm number, reaction times, or hit rates in FEP or HC groups.

When conducting a GLM, with group as a fixed effect and both MMN amplitude and latency as covariates, it was seen that there were no significant effects or interactions

	Patients with FEP n= 14	Healthy Controls n= 16	t-value	p-value	Cohen's D effect size
Reaction Time	2.35 (0.31)	2.26 (0.25)	-0.933	0.359	-0.341
Hit Rate	0.66 (0.07)	0.70 (0.07)	1.445	0.160	0.529
False Alarm Rate	0.47 (0.05)	0.44 (0.08)	-1.200	0.241	-0.426
Number of False Alarms	59.71 (16.89)	56.50 (22.34)	-0.439	0.664	-0.161

Table 4.2: Means (standard deviations) for CRDM cognitive performance, and group comparison statistics, t-tests and chi squared test, between FEP and HC. Equal variance was assumed for all variables except for the FA rates based on a Levene's Test of Equality of Variance. A confidence interval (CI) of the difference of 95% was used, and p tests were two-tailed

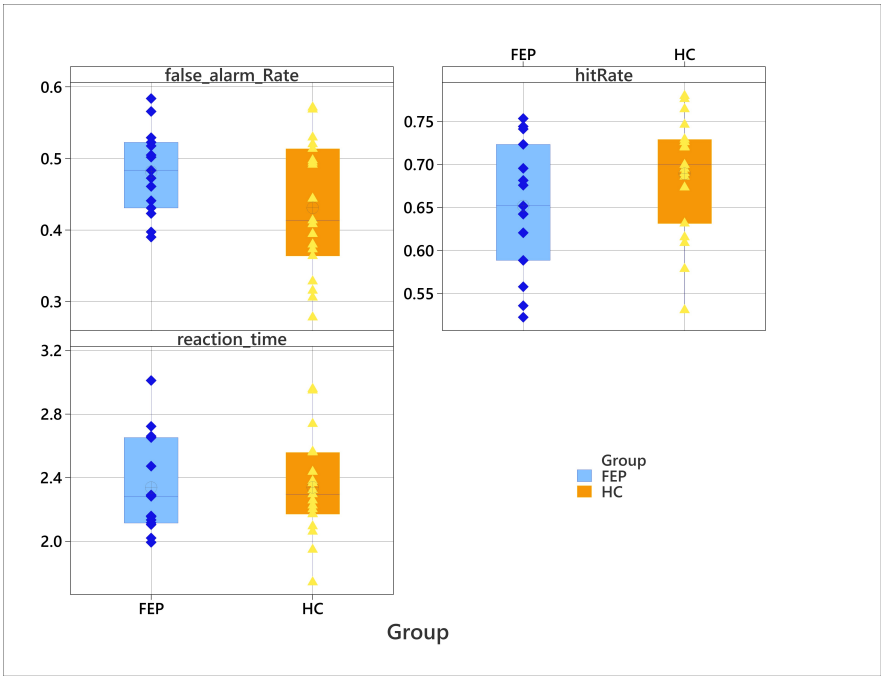

Figure 4.3.6: Box plots representing false alarm rates, hit rates and reaction times in both the healthy control and first-episode psychosis (FEP) group

between the independent variables: MMN amplitude or latency, and false alarm rates, number of false alarms, hit rate nor reaction time. This was the case for both the multivariate tests (Wilk's Λ) and univariate ANOVAs.

4.3.3 Mismatch Negativity and Social Defeat

Social Defeat Questionnaires

There were a total of 22 HC and 21 FEP participants who answered the SD questionnaires, however in this section only the 16 HC and 19 FEP who also had valid MMN data were analysed.

It should be noted that SDS measures social defeat, whereas SCRS measures social rank and is therefore inverse to feelings of social defeat.

There were significant group differences in SDS scores with the FEP group scoring higher than HC group, indicating greater feelings of social defeat (Table 4.1). However, there were no significant differences between groups in SCRS scores. Differences in SDS scores between the two groups remained significant following alpha correction.

Within the MMN subset of SD data there was a strong inverse correlation between SDS scores and SCRS scores in the FEP group (Spearman rho $= -0.695, p < 0.001$), but not in the HC group.

Correlational Analysis between Mismatch Negativity and Social Defeat

HC group had a significant inverse correlation between SDS and MMN amplitudes (Table 4.3 and Fig. 4.3.7), while FEP group had no significant correlation between SD scores and MMN amplitude nor MMN latency (Table 4.3 and Fig. 4.3.8).

Healthy Controls				
	SDS scores		SCRS scores	
MMN Amplitude	**-0.507**	**0.045**	0.130	0.632
MMN Latency	-0.230	0.391	-0.230	0.392
Patients with FEP				
	SDS scores		SCRS scores	
MMN Amplitude	0.256	0.291	-0.121	0.621
MMN Latency	-0.177	0.468	0.015	0.950

Table 4.3: Spearman rho's correlation between SDS and SCRS scores, and MMN amplitude and MMN latency for HC and FEP patients

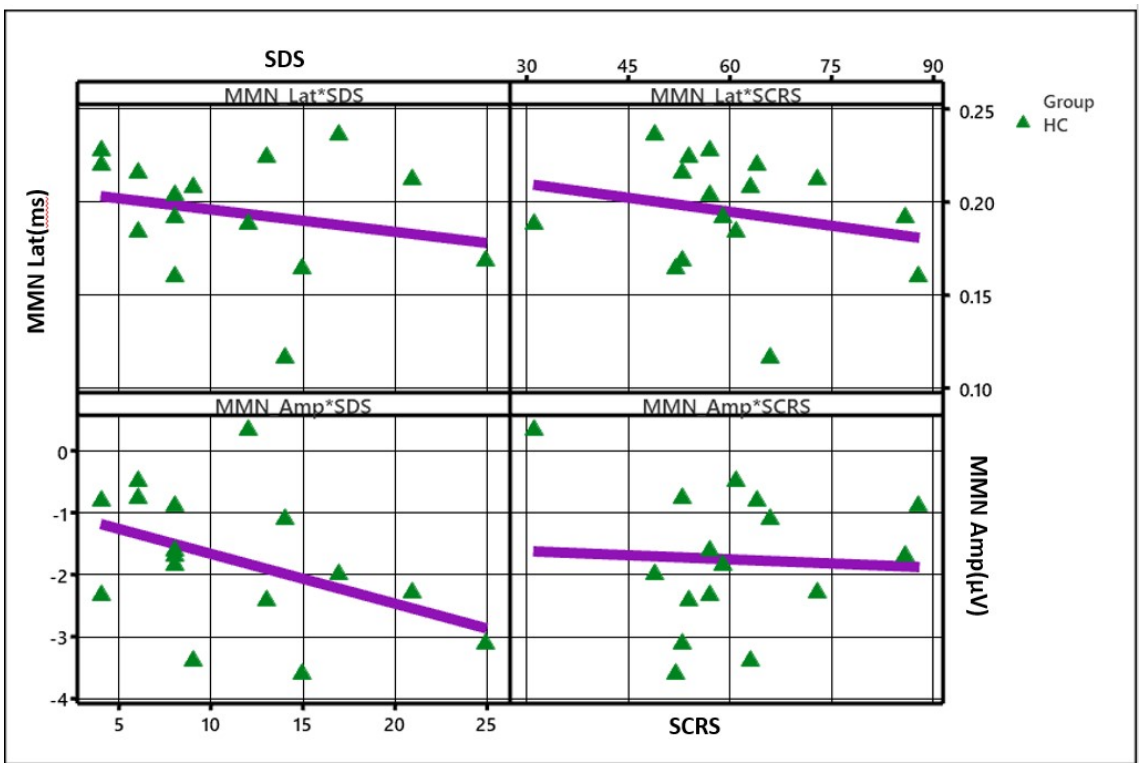

Figure 4.3.7: Scatter plots with the line of best fit for MMN amplitude with SDS and SCRS scores in the HC group

General Linear Model of Mismatch Negativity and Social Defeat

As SD has been positioned as a mediating factor between demographic risk and psychosis, a GLM was conducted.

Multivariate testing (Wilk's Λ) showed significantly different MMN values based on SDS scores ($F(2, 3) = 11.341$, $p = 0.040$, Wilk's $\Lambda = 0.117$, $\eta_p^2 = 0.883$), and SCRS scores ($F(2, 3) = 14.392$, $p = 0.029$, Wilk's $\Lambda = 0.094$, $\eta_p^2 = 0.906$). With no other significant effects or interaction effects. However, none of the multivariate tests survived alpha correction for multiple comparison.

Univariate ANOVAs demonstrated that SDS scores ($F(1, 4) = 30.238$, $p = 0.005$, $\eta_p^2 = 0.883$), SCRS scores ($F(1, 4) = 37.133$, $p = 0.004$, $\eta_p^2 = 0.903$) and group ($F(1, 4) = 15.17$, $p = 0.018$, $\eta_p^2 = 0.791$) all had significant effects on MMN amplitudes, but not MMN latency. However, sex and age did not have any significant effects on MMN values. It is only the effect of SCRS scores and MMN amplitudes that remained significant when applying alpha correction for multiple comparison.

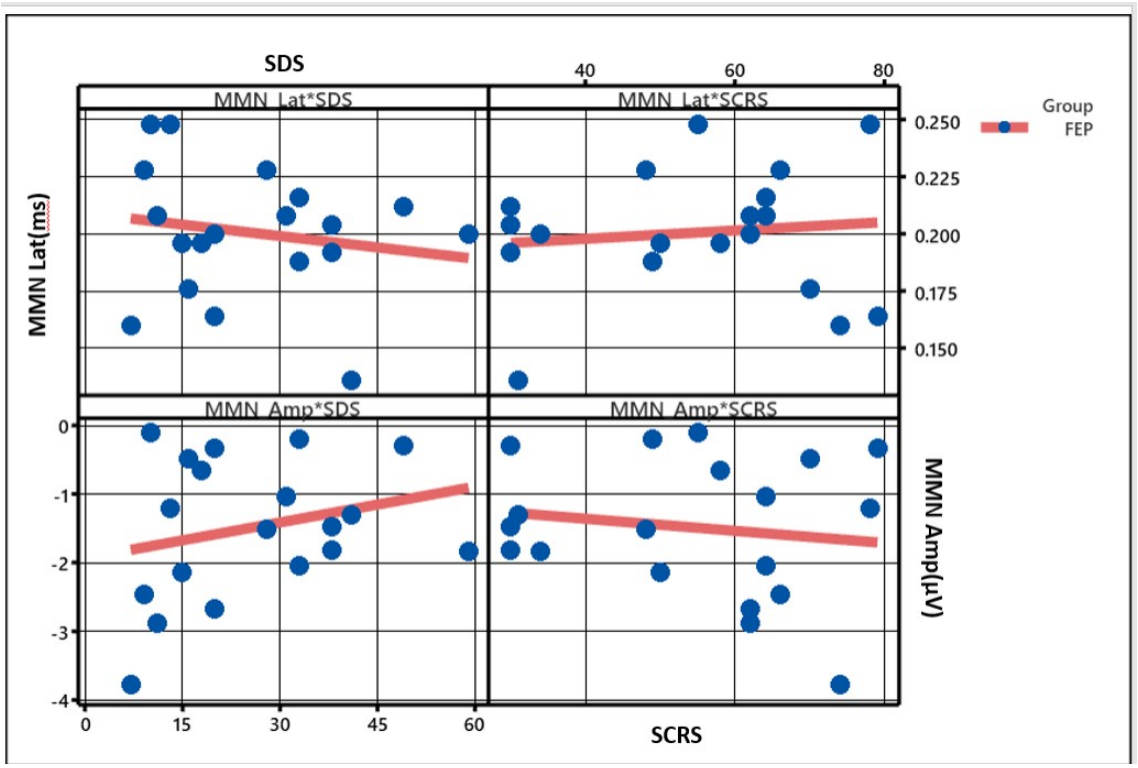

Figure 4.3.8: Scatter plots with the line of best fit for MMN amplitude with SDS and SCRS scores in the FEP group

4.4 Discussion

4.4.1 Mismatch Negativity and Psychosis

Main Findings

- There were no significant group differences between FEP and HC for neither MMN amplitude nor MMN latency.
- There were no significant correlations or effects of: medication, smoking, age or sex on MMN outcomes.

Findings in Context

There were no significant group differences seen in MMN amplitude or latency between groups, however on average the FEP group had decreased MMN amplitudes and increased MMN latencies compared to controls.

Reductions in MMN amplitudes, particularly for duration MMN, in psychosis are a well-

established finding (Erickson et al., 2016; Haigh et al., 2017; Light and Swerdlow, 2015; Light et al., 2015). The present study was not able to replicate this finding. This is most likely due to a relatively small sample size and large heterogeneity within patients, with patients on different medications and symptom profiles. While across many studies MMN on average is consistently impaired in psychotic population (Erickson et al., 2016), there is considerable variability between individuals within patient groups, with some patients even showing intact MMN responses (Light and Swerdlow, 2015). It has been suggested that this variability is what makes the MMN an interesting candidate for stratifying patients (Light and Swerdlow, 2015), but it also means that in small samples, such as the one in the present study, the MMN reduction effect might not be present depending on the individual patients tested (Kapur et al., 2012). In this study, several features of the studied sample could explain the lack of observed MMN impairment. It is thought that MMN worsens with disease progression and that this process is non-linear (Erickson et al., 2016; Koshiyama et al., 2020). Furthermore, it has been suggested that reduced MMN amplitudes are strongly associated with disease prognosis and could be an indicator of treatment resistance in an FEP population (Kim et al., 2023). These findings could explain the lack of significant group differences in MMN amplitudes in the present thesis, as the majority of participants were treatment responsive[3]. Furthermore, all recruited FEP participants were well enough to be out-patients, give informed consent and complete approximately three hours of a study session. This indicates that those who participated in this study would also fall into the category of patients who had a better prognosis compared to the general FEP population. As such, it is possible that the FEP group studied in this thesis are not representative of the broader FEP population.

Although in this study medication had no effect on or correlation with MMN results, previous literature has demonstrated a significant association between medication status and MMN reductions in psychosis (Light et al., 2015). A large scale study, with 824 controls, and 966 schizophrenia patients, concluded that 1st generation anti-psychotics and combined 1st and 2nd generation anti-psychotics lead to significantly reduced MMN compared to 2nd generation anti-psychotics or unmedicated patients (Light et al., 2015). All participants in the present study were on 2nd generation anti-psychotics which could account for the lack of significant medication effect. Medication status could have also contributed to the lack of significant group differences in MMN. Further large scale studies exploring the role of medication type on MMN would help clarify MMN variation with medication.

[3]Treatment resistance is typically referring to cases in which patients have not responded to two trials of anti-psychotics, with the appropriate dosage and time (Pandey and Kalita, 2022)

Moreover, MMN amplitudes have been shown to be potentially dependent on the attentional load of the task accompanying the oddball paradigm. In one study, MMN amplitudes and latency were compared for a visual background task that was highly attentionally demanding compared to one that had low attentional demand (Rissling et al., 2013). The study concluded that MMN responses were greater and FEP and HC group differences were increased in the low attentional demand condition compared to the high demand condition. Moreover, in the high attention demand task the MMN latency was significantly increased, MMN peaks occurring later, suggesting delayed responses and that the MMN response may not be "pre-attentive". Contrary to this, a later study exploring the impact of attentional load of a visual tasks on frequency MMN amplitudes, found no difference between high attentional and low attentional load conditions (Wiens et al., 2019). The present study employed a visual task with high attentional load, and this could therefore impact the MMN amplitudes reported in this thesis. These different findings indicate the need for a more standardised approach across studies (Garrido et al., 2009), as well as the importance for further research to be done to confirm if MMN is "pre-attentive" .

It has been reported that the complexity of the oddball paradigm and deviant stimuli could alter MMN responses. Complex deviants, such as pattern changes employed in the roving paradigm, were used in this study. It was reported that complex deviant stimuli lead to noisier and less impaired MMN responses in schizophrenia (Avissar et al., 2018). This suggests that simpler oddball paradigms may be better for robust measurement of MMN impairment in psychosis. Thus, the lack of significant MMN FEP and HC group differences in this thesis could be a result of both attentional demand from the CRDM task and complex deviant stimuli in the roving duration oddball paradigm.

The present study does not show an association between MMN latency values and FEP. In extant literature MMN latency results in psychosis have been fairly inconsistent (Kärgel et al., 2014; Kathmann et al., 1995; Magno et al., 2008). Some have argued that a short latency could indicate spontaneous dysfunction in psychosis (Grzella et al., 2001). Others argue that MMN latency is thought of as the time needed to recognise deviance (Nishimura et al., 2016), and MMN abnormalities in psychosis in general could be more greatly linked to deviance detection errors (Koshiyama et al., 2020). Deviance detection has been linked to E/I balance, via abnormal NMDA receptor functioning (Gunduz-Bruce et al., 2012; Michie et al., 2016; Nagai et al., 2017; Rowland et al., 2016; Sivarao et al., 2014). Further, the results in this research could once again be due to the study being underpowered or high heterogeneity within the studied sample.

4.4.2 Mismatch Negativity and Cognition

Main Findings

- There were no significant differences between FEP and HC groups in any performance metrics on the CRDM task.
- MMN outcomes were neither correlated with nor had any effect on CRDM performance.

Findings in Context

The lack of significant differences between FEP and HC groups on CRDM performance neither support the hypothesised outcome of this study, nor previous literature findings of worse cognitive performance in psychosis (Chitty et al., 2013).

Furthermore, this study has not shown a significant association between MMN outcomes and CRDM performance. Again, this is contrary to what was hypothesised in this work, and contrary to previous literature findings where an association between MMN and cognitive performance was found (Kärgel et al., 2014; **?**; Lho et al., 2020; Mahmoud et al., 2023). The ACC and prefrontal cortex have been implicated in both cognitive processes and of frontal MMN, suggesting that cognition and MMN generation could have overlapping processes (Mahmoud et al., 2023; Oknina et al., 2005). Furthermore, cognitive impairments in psychosis include poor motor control, which theoretically should have led to worse response times in the FEP group compared to controls (Harvey and Isner, 2020). However, the majority of the previous literature studied cognitive impairments in chronic and comorbid psychosis (Chitty et al., 2013; Donaldson et al., 2020; Kärgel et al., 2014; Toyomaki et al., 2008), and used different oddball paradigms to the one presented in this thesis. Also, none of the literature explored performance on a CRDM or similar evidence integration task. In support of this study, literature using a similar roving paradigm or duration MMN as this study, have failed to find associations between cognitive impairment and MMN in both FEP and schizophrenia patient groups (Kaser et al., 2013; Xiong et al., 2019). Within FEP frequency MMN has been associated with verbal memory performance, however duration MMN was not associated with any cognitive domain (Xiong et al., 2019). Frequency MMN and duration MMN are thought to reflect slightly different processes, with duration MMN being more indicative of early stage neural aberrations (Nagai et al., 2017). Therefore, frequency MMN could potentially be a better indicator of cognitive deficit while duration MMN could reflect other prodromal and early stage processes, at the very beginning of onset

and at an earlier age than the present study. A meta-analysis found that cognitive ability declined over illness duration and severity (Maltais et al., 2015), which suggests that cognitive impairments in FEP may not be severe enough to lead to statistically significant correlations. Therefore, variation in previous study designs and patient groups could account for the discrepancy in findings between the present study and some of the previous literature.

Furthermore, many common proposed neurophysiological markers for psychosis have not been shown to be correlated with each other despite measuring similar processes (Light and Swerdlow, 2015). This could also account for the lack of associations between MMN outcomes and cognitive performance in the present study.

There is a general lack of literature directly exploring associations between MMN response and cognitive performance in FEP. Therefore, further research would be required to better explain and establish any relationship or shared mechanism between MMN and cognition.

4.4.3 Mismatch Negativity and Social Defeat

Main Findings

- There were no significant correlations between MMN outcomes and SD scores in the FEP group.
- There was a significant inverse correlation between MMN amplitudes and SDS scores in the HC group.
- In the GLM only SCRS scores had a significant effect on MMN amplitudes after alpha correction for multiple comparisons.

Findings in Context

This study did not find any correlation between MMN and SD in FEP, while higher feelings of SD, as measured by SDS, were correlated with lower MMN amplitudes in the HC population. Therefore, the hypothesis of SD scores being correlated with MMN amplitudes was only met in the HC group. The findings in the present study suggest that SD leads to MMN reduction in HC that more closely resemble the reduced MMN in FEP. These novel findings suggest that SD plays a role in MMN, and that this relationship may only be present in those who have not developed psychosis. This could also indicate that the mechanism, if there is one, that leads to SD increasing the risk for psychosis occurs prior to the onset of symptoms. Repeating this study, as well as further studies

of the relationship between SD and MMN in high-risk stages, may help elucidate the relationship between these factors in those who have not yet developed symptoms of psychosis.

The present study, alongside previous literature, suggest that SD has an impact on cognitive ERPs (Boksem et al., 2011; Luo et al., 2015; Qiu et al., 2010). In this thesis higher SD was associated with decreased MMN response in HC, while extant literature suggests that SD-like experiences increases ERP responses. This difference in findings could be due to none of the previous studies measuring MMN, and due to differences in SD and ERP assessment and measurement. All of the previous studies that examined SD-like experiences induced SD temporarily and during the study session, while in the present MNN study chronic SD was measured by the questionnaires. Furthermore, previous studies focused more on the social comparison element of SD and therefore may not be a valid measurement of SD (Klucharev et al., 2009). The different approach to measuring and exploring SD means that these previous findings offer limited context for the present study (Klucharev et al., 2009). Therefore, additional study of MMN associations with different aspects of SD is required to confirm and further explain current findings.

With all this said, it is still possible to provide some insight for the findings in this thesis using reported findings from the reaserch in working memory, as MMN has been understood as a working memory task (Javitt et al., 1996). Previous studies reported that ERPs altered by SD have been associated with prediction error, working memory and ACC activity (Boksem et al., 2011; Qiu et al., 2010; Mahmoud et al., 2023; Oknina et al., 2005). Moreover, mice studies have linked sensory processing and SD via altered frontal neural circuit plasticity (Chen et al., 2023). In humans MMN has been linked with frontal inhibitory connectivity and plasticity through NMDA receptor activity (Nishimura et al., 2016; Rosch et al., 2019). This could suggest frontal E/I involvement in SD, but it may not be a direct reflection of MMN deficits. Previous literature has demonstrated decreased prefrontal cortex activity in both schizophrenia and HC, measured by functional near-infrared spectroscopy following induced SD. Schizophrenia patients had significantly decreased right ventrolateral PFC activity compared to HC (Baskak et al., 2015).Other studies have found increased ventral affective network as a response to SD and stress in HC (Buhle et al., 2014; Lee et al., 2014; Oei et al., 2012). Thus, despite the mechanism remaining unclear, the ventral affective network, and more specifically the PFC, have been implicated as a brain region significantly impacted by SD (Baskak et al., 2015; Lee et al., 2014; Oei et al., 2012). Further, the PFC regions have been linked to working memory performance and stress (Oei et al., 2012), as working memory deficits have been shown

to be elicited by SD (**?**Da Costa et al., 2023; Jianhua et al., 2017; McKim et al., 2016; Novick et al., 2016; Wang et al., 2022). The mechanism by which SD influences working memory is attributed to various glutamatergic, dopaminergic and neuroinflammatory alterations (Berton et al., 2006; Da Costa et al., 2023; Novick et al., 2016). Although these inconsistent findings and interpretations of findings limits the understanding of the interaction between MMN and SD, SD has been shown to impact neural activity in a manner that is detectable using ERP responses (Luo et al., 2015). Therefore, further research focusing on frontal EEG ERP activity and SD would elucidate the direction and manner in which SD has an effect on MMN.

4.5 Conclusion

Despite there being no significant group differences, the results of decreased MMN in FEP are somewhat in keeping with previous literature. The lack of significant group differences could be a result of multiple factors such as the use of an attentionally demanding task, complex deviant stimuli in the oddball paradigm, and a patient sample that was treatment responsive and on 2nd generation anti-psychotics. Further research on attentional load and MMN in a larger but similar sample of FEP would need to be conducted to confirm which variables contributed to the MMN findings presented in this thesis.

The present study failed to find any association between cognitive performance and MMN or group. This is in contrast to what was hypothesised, yet given the inconsistencies in previous literature, much more research in larger samples would be required in both FEP and psychosis in general to better establish the relationship between cognitive performance on an evidence integration task and MMN (Kapur et al., 2012).

There was a significant association between SD and MMN amplitudes in HC. This suggests that SD may alter biological mechanisms prior to onset of psychosis. A study exploring SD and MMN in high-risk individuals, as well as HC, would better be able to establish at what stage SD still has a relationship with MMN. Moreover, a combined study using dynamic MRS with duration MMN in these same populations would further clarify if this association may be mediated by glutamategic processes. Alternatively, a combined pharmacological and MMN study using NMDA antagonists in a healthy population would also clarify the potential glutamatergic mechanism for the relationship, if there is one, between SD and MMN.

This study has a small sample size which is in keeping with the majority of other EEG

studies in a psychosis population but could result in it being underpowered (Kapur et al., 2012). Therefore, a similar study with a larger sample size may also assist in elucidating potential relationships between social defeat, cognitive impairment and MMN in FEP.

EEG itself has limitations that must be kept in mind when interpreting findings. EEG relies on the summation of neuronal activity and therefore, it may not reflect the activity of the exact electrode site and could miss electrical changes that are not in the angled non-perpendicularly to the electrode, that are complex or have multiple dipoles (Biasiucci et al., 2019; Michel and Murray, 2012). This is also highly dependent on the specific cap design and decisions surrounding reference electrodes (Biasiucci et al., 2019; Michel and Murray, 2012). Therefore, the interpretation of single site waveforms, such as the MMN phenomena, offers limited information on the exact sources of wave generation (Michel and Murray, 2012). With that being said, it is also possible to explore MMN across all electrodes or perform source localisation in order to provide a more accurate understanding of the source of EEG activity (Michel and Brunet, 2019). Therefore, future research should be conducted with the addition of this analysis to further elucidate the mechanisms and origins of MMN abnormalities in psychosis.

Moreover, EEG has multiple sources of noise such as muscle responses (Whitham et al., 2007). MMN is generally small compared to the noise in EEG data, making pre-processing and cleaning of EEG data critical. This could have been improved in this study with the inclusion of eye-blink removal and principle component analysis which has been shown to the be effective and efficient in EEG signal artefact removal (Kaczorowska et al., 2017). Noise and other technical issues in the acquired EEG data also contributed to the further decrease of the sample size used in analysis further reducing power.

Despite these limitations, the EEG component of this thesis does have particular merit as it has demonstrated that it is possible to record EEG signal, measure cognitive performance alongside an MMN response as well as include a social defeat condition to induce feelings of social defeat and examine their effects, within a 3/3.5 hour study visit per participant. These findings suggest that similar studies would be feasible, and potentially on a larger scale.

Chapter 5

Analysis of Relative Spectral Power in First-Episode Psychosis compared to Healthy Controls, and interactions with Social Defeat and Cognitive Performance

5.1 Introduction

Neural oscillations are a series of rhythmic electrical activity that occurs as a response to internal or external stimuli (Başar, 2013). These neural oscillations can be measured using EEG. Although specific mechanisms remain unknown, abnormalities in oscillatory activity have been shown in psychosis (Buzsáki and Wang, 2012; Jahangir et al., 2021).

Gamma oscillations have been specifically implicated in psychosis, however there are a lack of consistent findings in FEP (Perrottelli et al., 2021; Reilly et al., 2018; Uhlhaas and Singer, 2010). Gamma abnormalities have been linked with hyperexcitability in psychosis, and have been explained using the glutamatergic hypothesis of psychosis (Foss-Feig et al., 2017; Missonnier et al., 2020). Previous literature has demonstrated that activating PV GABAergic inhibitory interneurons induces gamma oscillations, whereas inhibiting these same interneurons suppresses gamma activity, thus providing evidence for gamma involvement in E/I balance (Bartos et al., 2007; Buzsáki and Wang, 2012; Cardin et al.,

2009; Uhlhaas and Singer, 2013; Sohal et al., 2009; Wang and Buzsáki, 1996). The same study reported that inhibiting PV interneurons led to an increase in alpha and beta activity. Beta oscillations have also been shown to be abnormal in psychosis, with the suggestion that this abnormality could be a strong marker for psychosis (Ahmad et al., 2022; Gawne et al., 2020; Venables et al., 2009). Although delta, theta and alpha power have also been reported as abnormal in psychosis, these lower frequency abnormalities have been less studied (Buzsáki and Wang, 2012; Gawne et al., 2020; Jia et al., 2022; Sohal et al., 2009; Uhlhaas and Singer, 2013; Venables et al., 2009).

Given reported abnormal oscillatory activity in psychosis (Başar, 2013), and their potential link with E/I imbalance, this study aims to compare relative spectral band power between FEP and controls. Further, it hopes to elucidate the impact of SD on spectral band power to explore the potential immediate impact of SD on neural processes.

In keeping with the hyperexcitation hypothesis and some of the previous literature, it was expected that the FEP would have increased gamma power in frontal areas compared to controls. It is hypothesised that there will be an increased sensitivity to SD in patients compared to HC as reflected in greater aberrations in resting state evoked gamma in the FEP group, following induced SD from the SD behavioural task. Resting gamma measurements are known to have decreased noise compared to task gamma measurements due to decreased muscle artefacts (Whitham et al., 2007). It is also expected that resting state spectral analyses will indicate increased hyperexcitation following the SD behavioural task compared to baseline resting state.

5.2 Methods

5.2.1 Study Approval

The aim of this study was to determine whether there was a difference in relative spectral band power between HC and FEP patients, and also compare spectral power before and after a SD manipulation. Ethical Approval for this study was granted by the Bradford Leeds Research Ethics Committee (Ethics Ref: 19/YH/0090).

5.2.2 Study Eligibility

22 FEP patients and 21 HC matched for sex and age were included in the study. The FEP group was recruited through direct communication with care coordinators and an

Oxford Health Thomas Vaughn ward psychiatrist at the Oxfordshire NHS Trusts. Patient participants were eligible if they: had their first episode of psychosis, as defined by Melbourne criteria: a week or more of psychotic symptoms above a threshold of moderate in severity, within the last three years from study visit date, were between 18 and 40 years of age, were clinically stable[1], were not at risk of suicide, and did not have current substance dependency. The age range for the study was 18 to 40, to prevent age related abnormalities (Brandt et al., 2016). Healthy controls were recruited via word of mouth, web advertisements and local newspaper advertisements. Healthy controls were eligible if they are matched with FEP participants,and had no current or previous history of psychiatric disorders according to the DSM-5.

5.2.3 EEG Study Session

The EEG recording and entire study session occurred at the Oxford Centre for Human Brain Activity (OHBA) at the Warneford Hospital site in Oxford, England. Following informed consent and the completion of questionnaires, training for the cognitive task was completed by the participant (refer to Section 4.2.3 for more information). EEG cap application was then done, which was followed by the CRDM and MMN session (refer to Section 4.2.3), then a resting state session, followed by the final CRDM and MMN session, and then the presentation of social defeat manipulation coupled with a final resting state recording.

5.2.4 Resting State

Two sets of five minute resting state data were collected, one between the two CRDM/MMN sessions, and the second after the last CRDM/MMN session. The participants were told to close there eyes and try to relax for the next five minutes while their resting state data was collected. They were asked to try and stay awake and to avoid any unnecessary movement. Participants were also informed that the experimenter would re-enter the EEG booth once the recording was over.

[1]Participants could still have symptoms of psychosis however they could not be in a florid state of psychosis, they needed to be deemed well enough and stable enough to participate and understand what the study entailed (provide informed consent).

5.2.5 Social Defeat Manipulation

The social defeat manipulation was done in a manner that was suggested by Selten and colleagues (Selten et al., 2016), who had originally wrote about the social defeat hypothesis of psychosis (Selten and Cantor-Graae, 2005).

As mentioned above, there were two resting states included during the EEG study session. Prior to the second resting state and following the two CRDM/MMN sessions, a screen displaying false failure feedback to induce social defeat was played for 15 second followed by the resting state recording (refer to Section 2.3). Participants were debriefed following the induction of SD.

5.2.6 EEG Cap Design and Acquisition Process

The same cap was used for both the MMN and visual task data acquisition and for the resting state acquisition (refer to Section 4.2.7).

5.2.7 EEG Analysis

File type conversion was performed on EEGLAB software, whereas the remainder of EEG pre-processing: downsampling, re-referencing, filtering, epoching and artefact removal, was run on Statistical Parametric Mapping (SPM 12) software package (http://www.fil.ion.ucl.ac.uk/spm/) (Litvak et al., 2011). Power spectrum analysis was performed using Python 3.11.2 programming.

The EEG data was downsampled to 500 Hz, allowing the data file to be significantly smaller while allowing for high enough sampling rate to pre-process and analyse evoked responses such as a mismatch negativity. LMRM (mastoid references) referencing was then carried out, followed by sensor location identification. A bandpass filter was used with the high-pass filter cut-off frequency set at 0.1 Hz and the low-pass filter cut-off frequency set at 50 Hz. Bad trial thresholds were 75 μV and bad channels were detected with the threshold being 0.2. The excision window surrounding a bad trial (jump) was 500 ms.

The rest of the pre-processing, power spectrum density and calculation of relative spectral power, was then performed using Python. Python based program was applied on frontal (FCz) spectral data selected for analysis.The continuous data was cut at 30 seconds until 270 seconds, to avoid noise that occurred at the beginning of most recordings and then the data was epoched into 2 second lengths, and a Hanning window was applied to

minimise tapering. A Fast Fourier Transform (FFT) was then performed on processed data to get the data in frequency domain.

Relative spectral band power was calculated and used for analysis, to control for individual differences and other potential differences between resting state recording sessions. The bands used for analysis were 1-4 Hz for delta, 4-8 Hz for theta, 8-12 Hz for alpha, 12-30 Hz for beta, and 30-50 Hz for gamma.

5.2.8 Statistical Analysis

T-tests were performed to analyse differences between groups (HC vs FEP). Spearman rho's correlations were used to explore the relationship between SD questionnaire scores, and spectral analysis data.

Three general linear regression models (GLMs) were performed, all had SDS and SCRS scores and age as covariates and sex and group as fixed effects, the first on the non-SD condition spectral data, the second on the SD condition spectral data, and the third on the difference between the second and first sets of spectral data. Main effects for SDS and SCRS questionnaire scores, group, sex and age, and interactions between group and sex were analysed in all three GLMs.

5.3 Results

5.3.1 Spectral Analysis

Demographic Comparisons

A total of 19 HC and 19 FEP participants had measured and valid spectral analysis data. There were no differences in age, sex or smoking status between groups (Table 5.1).

Spectral Analysis Results in HC vs FEP

Non-SD condition Spectral Analysis

There were no significant differences between groups in non-SD condition relative spectral band power measured at the FCz electrode site (Table 5.2 and Fig. 5.3.1).

A GLM was carried out with group and sex as fixed effects and with age as covariates, to examine the impact of group on non-SD condition spectral data. Both multivariate

	Patients with FEP n= 19	Healthy Controls n= 19	t-value	p-value	Cohen's D effect size
Age	25.53 (5.09)	26.26 (4.36)	0.479	0.635	0.155
Sex	7/12	10/12	0.432 (χ^2)	0.511	
Smoking	5/19	3/19	0.633 (χ^2)	0.426	
Antipsychotic Drugs	18/19	n/a			
Antidepressant Drugs	7/19	n/a			
SDS scores	25.26 (14.47)	11.95 (7.24)	**-3.587**	**<0.001**	**-1.164**
SCRS scores	56.11 (15.78)	61.05 (13.53)	1.037	0.306	0.337

Table 5.1: Means (standard deviations) for demographic information, and social defeat measure scores, and group comparison statistics (t-tests and chi squared) between FEP and HC. Frequency for the sex variable are female/male and for the smoking variable smokers/non-smokers. Equal variance was assumed for all variables except for the SDS scores (based on a Levene's Test of Equality of Variance), a confidence interval (CI) of the difference of 95% was used, and p tests were two-tailed

testing (Wilk's Λ) and univariate ANOVAs revealed no group effects on any of the relative spectral band power levels.

SD condition Spectral Analysis

There were no significant differences between the FEP and HC in SD-condition relative spectral band power measured at the FCz electrode site (Table 5.2 and Fig. 5.3.2).

A GLM was again performed with group and sex as fixed effects and with age as covariates, but with the SD condition spectral data as the dependent variable. Once again, both multivariate testing (Wilk's Λ) and univariate ANOVAs revealed no group effects on any of the relative spectral band power levels.

5.3.2 Spectral Analysis and Cognition

To assess the interactions between cognition and spectral band power from the non-SD condition resting state, and CRDM performance during the MMN/CRDM sessions were

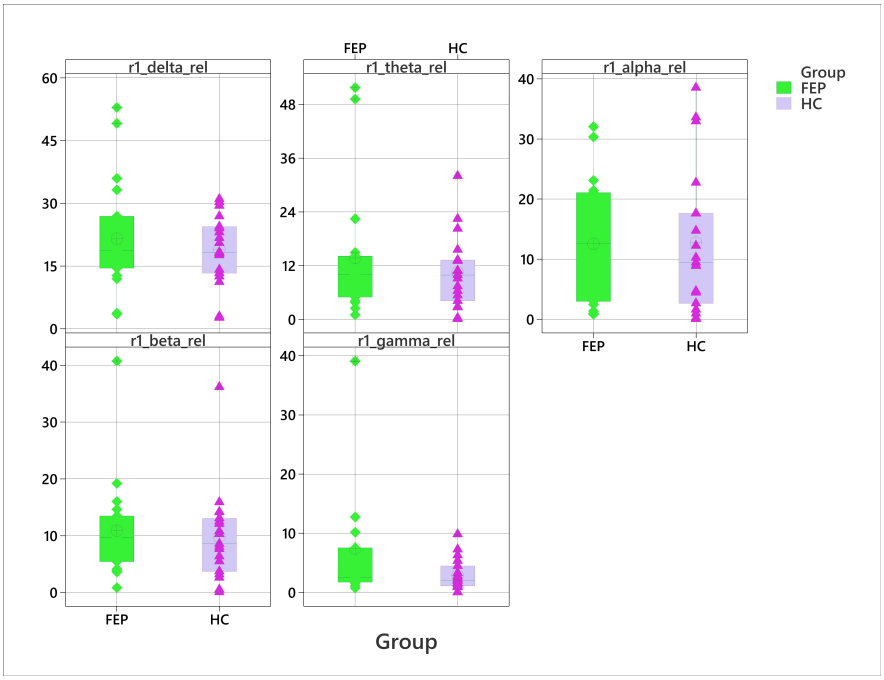

Figure 5.3.1: Boxplot comparing FEP group with HC group on relative frontal (FCz) spectral power in the non-SD (r1) condition, with spectral band power represented as the percentage relative to total power

used.

Cognitive Performance on Continuous Random Dot Motion task

The same CRDM data was used in this analysis as that in the mismatch negativity chapter (refer to Section 4.3.2 and Table 4.1).

There were no significant correlations between relative theta, alpha, beta and gamma power levels and false alarm (FA) rates, reaction time (RT) or hit rate (HR) on the CRDM task for neither FEP nor HC. However, there was a significant correlation between relative delta power and HR in the HC group ($Spearman'srho = -0.472, p = 0.048$) and in the FEP group ($Spearman'srho = -0.535, p = 0.033$).

When conducting a GLM, with group as a fixed effect and all five relative spectral band powers as covariates and FA rate, RT and HR as dependent variables, there were

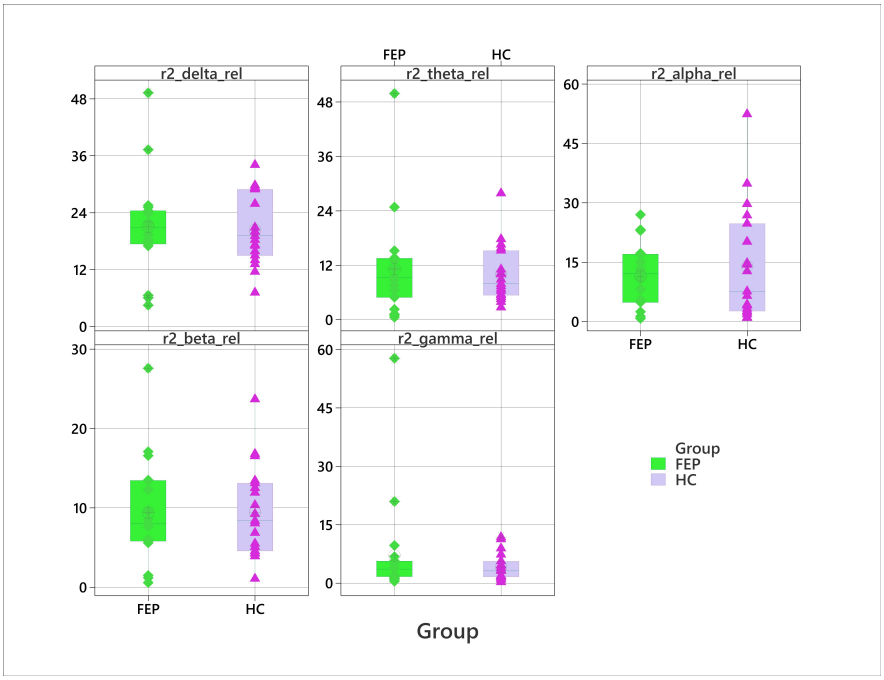

Figure 5.3.2: Boxplot comparing FEP group with HC group on relative frontal (FCz) spectral power in the SD (r2) condition, , with spectral band power represented as the percentage relative to total power

no statistically significant mutlivariate tests´results´ (Wilk's Λ). However, univariate ANOVAs demonstrated that there was a significant effect of delta during the non-SD condition resting state, $F = 5.48, p = 0.027$) on HR, although this did not survived alpha correction for multiple comparisons.

5.3.3 Spectral Analysis and Social Defeat

Social Defeat Questionnaires

There were 19 HC and 19 FEP who had both valid spectral power and SD questionnaire data.

It should be noted that SDS measures social defeat, whereas SCRS measures social rank and is therefore inverse to feelings of social defeat.

There were significant group differences in SDS scores, with the FEP group scoring higher than the HC group. However, there were no significant group differences in the SCRS scores (Table 5.1). The group difference in SDS scores remained significant when correcting for multiple comparisons.

Correlational Analysis between Spectral Analysis and Social Defeat

There were no statistically significant correlations between SD scores and difference in spectral analysis scores for neither the FEP nor HC group.

Moreover, there were no statistically significant correlations between SD scores and non-SD condition spectral data or SD scores and SD condition spectral data for neither the FEP nor HC group.

General Linear Model of Spectral Analysis and Social Defeat

Multivariate testing (Wilk's Λ) did not find any significant effect of SD scores on non-SD condition spectral data. Further, between-subject effects tests, univariate ANOVAs, again found no effect of either SD scores on any of the relative band powers.

SD did not have any signficant effect on SD condition spectral data according to multivariate testing (Wilk's Λ). However, on the univariate ANOVA SDS scores had an effect on the SD condition relative delta power, although this did not survive alpha correction for multiple comparisons.

Finally, the difference between the SD condition and the non-SD condition spectral data did not have any statistically significant multivariate testing results(Wilk's Λ) nor between-subject effects tests with SD scores as an effect.

Comparative Analysis of non-SD condition and SD condition Relative Spectral Band Power

Repeat measures t-tests found no significant difference comparing the non-SD and SD sessions for neither the FEP nor HC group (Table 5.3).

There were significant correlations between non-SD condition and SD condition theta and alpha for the HC group, but delta, beta and gamma were not correlated between conditions for HC (Table 5.4). For the FEP group there were statistically significant correlations between non-SD condition and SD condition delta, theta, alpha, and gamma power, but not beta.

non-SD condition					
	Patients with FEP n= 19	Healthy Controls n= 19	t-value	p-value	Cohen's D effect size
delta	21.57 (13.18)	18.96 (8.21)	-0.733	0.469	-0.238
theta	13.72 (13.96)	10.54 (8.08)	-0.859	0.396	-0.228
alpha	12.57 (9.90)	12.75 (11.84)	0.053	0.958	0.082
beta	10.89 (8.64)	9.76 (7.99)	-0.420	0.677	-0.072
gamma	7.40 (2.93)	2.93 (2.61)	-1.640	0.117	-0.480
SD condition					
	Patients with FEP n= 19	Healthy Controls n= 19	t-value	p-value	Cohen's D effect size
delta	21.02 (10.27)	20.34 (7.31)	-0.235	0.815	-0.076
theta	11.18 (11.10)	9.94 (6.27)	-0.425	0.673	-0.138
alpha	11.43 (8.07)	13.95 (14.22)	0.671	0.508	0.218
beta	9.39 (6.45)	9.44 (5.65)	0.024	0.981	0.008
gamma	7.11 (13.13)	4.13 (3.42)	-0.955	0.346	-0.310
Difference between conditions					
	Patients with FEP n= 19	Healthy Controls n= 19	t-value	p-value	Cohen's D effect size
delta	-0.006 (0.090)	0.014 (0.095)	0.641	0.525	0.208
theta	-0.025 (0.064)	-0.006 (0.071)	0.881	0.192	0.286
alpha	-0.011 (0.078)	0.012 (0.052)	1.088	0.142	0.353
beta	-0.015 (0.103)	-0.003 (0.061)	0.429	0.335	0.139
gamma	-0.003 (0.110)	0.012 (0.036)	0.569	0.287	0.185

Table 5.2: Means (standard deviations) for relative spectral power, represented as a percentage of the total power, for delta, theta, alpha, beta and gamma power bands, and group comparison statistics, t-test or chi-square , between FEP and HC. Difference between conditions refers to the difference between relative spectral power in the SD condition compared to the baseline non-SD condition. Equal variance was assumed for all variables ,based on a Levene's Test of Equality of Variance, a confidence interval (CI) of the difference of 95% was used, and p tests were two-tailed.

Healthy Controls					
	non-SD condition	SD condition	t-value	p-value	Cohen's D effect size
delta	18.96 (8.21)	20.34 (7.31)	-0.631	0.536	-0.145
theta	10.54 (8.08)	9.94 (6.27)	0.368	0.717	0.084
alpha	12.75 (11.84)	13.95 (14.22)	-1.012	0.325	-0.232
beta	9.76 (7.99)	9.44 (5.65)	0.227	0.823	-0.339
gamma	2.93 (2.61)	4.13 (3.42)	-1.477	0.157	0.061
Patients with FEP					
	non-SD condition	SD condition	t-value	p-value	Cohen's D effect size
delta	21.57 (13.18)	21.02 (10.27)	0.266	0.793	0.061
theta	13.72 (13.96)	11.18 (11.10)	1.718	0.103	0.394
alpha	12.57 (9.90)	11.43 (8.07)	0.635	0.534	0.146
beta	10.89 (8.64)	9.39 (6.45)	0.633	0.535	0.145
gamma	7.40 (2.93)	7.11 (13.13)	0.118	0.907	0.027

Table 5.3: Means (standard deviations) for relative spectral power (in percentage) for delta, theta, alpha, beta and gamma power bands, and group comparison statistics ,t-test or chi-square , between non-SD and SD conditions for HC and FEP. Difference between conditions refers to the difference between relative spectral power in the SD condition compared to the baseline non-SD condition. Equal variance was assumed for all variables ,based on a Levene's Test of Equality of Variance, a confidence interval (CI) of the difference of 95% was used, and p tests were two-tailed.

Healthy Controls		
	Spearman's rho	p-value
delta	0.312	0.193
theta	**0.560**	**0.013**
alpha	**0.968**	**<0.001**
beta	0.440	0.059
gamma	0.451	0.053
Patients with FEP		
	Spearman's rho	p-value
delta	**0.621**	**0.005**
theta	**0.818**	**<0.001**
alpha	**0.533**	**0.019**
beta	0.396	0.093
gamma	**0.516**	**0.024**

Table 5.4: Correlations between non-SD and SD condition relative frontal power for each spectral band in FEP and HC

5.4 Discussion

5.4.1 Spectral Analysis and Psychosis

Main Findings

- There were no significant differences between FEP and HC group in relative spectral power neither in the non-SD nor the SD condition.
- There was no group, sex or age effect on relative spectral power.

Findings in Context

The spectral data in this thesis revealed no significant differences in relative spectral band power between groups in neither the non-SD condition nor the SD condition. However, FEP patients did show an average slight increase in relative spectral power for all bands aside from alpha, that was slightly decreased, compared to controls in the non-SD condition. There was a lesser and negligible increase in relative spectral power, aside from alpha and beta that were slightly decreased, in the SD condition for the FEP group compared to HC. However all spectral data had high noise as reflected by standard deviation, especially in FEP group, and especially in SD conditions. This noise could be the reason for insignificant differences, specifically in gamma band power between FEP and HC groups.

Oscillations in both low and high frequency, especially in the gamma band, are known to be aberrant in psychosis patients (Jahangir et al., 2021; Javitt et al., 2020). Although mechanisms remain unclear, elevated gamma band activity ($>$ 30 Hz) is thought to be reflective of hyper-excitability and increased glutamate levels in psychosis (Bartos et al., 2007; Cardin et al., 2009; Ferguson and Gao, 2018; Foss-Feig et al., 2017; Gao and Penzes, 2015; Missonnier et al., 2020; Wang and Buzsáki, 1996). Though this study failed to replicate the finding of significantly aberrant oscillatory activity in an FEP population compared to HC, the trend-level increase of gamma power in FEP could be reflective of hyperexcitability. Moreover, these findings may also suggest excitotoxicity with hyperexcitation already decreasing in the FEP group leading to lack of significant group differences in gamma power. This would suggest that hyperexcitability may occur in prodromal stages and excitotoxic effects can already be observed in FEP. A larger replication study with greater power could help establish the direction and association between oscillatory activity and the early stages of psychosis.

Previous literature has been inconsistently reporting both increased and decreased gamma power in FEP (Kehrer et al., 2008; Reilly et al., 2018; Perrottelli et al., 2021; Wang et al., 2018). With that said, many of these previously reported measurements were taken during an auditory stimuli task, which has been shown to alter gamma compared to resting state (Curic et al., 2019). The discrepancy in findings, could be due to the a lack of consistency in experimental design between studies, including technical factors such as electrode location, stimuli type, data acquisition and processing methods such as latency variation, different tools used, statistical approaches differing and more, as well as diversity in explored gamma power, such as resting gamma vs task evoked gamma, or the gamma range (Gordillo et al., 2023). Moreover, group specifications such as stage of illness or medication status differed between reported studies (Gordillo et al., 2023). This indicates that consistent methodology across studies and sites would be highly helpful in better establishing the level and nature of oscillatory aberrations in the FEP population.

In addition to gamma, there have been reported increases in low-frequency oscillations in those with psychosis, including in FEP (Clementz et al., 1994; Gawne et al., 2020; Uhlhaas and Singer, 2010; Venables et al., 2009). These abnormalities were particularly associated with frontal regions and worse negative symptom severity (Boutros et al., 2008; Gordillo et al., 2023; Kim et al., 2014; Sponheim et al., 2000). These findings were not replicated in the present study, possibly due to differences in studied population, with the majority of studies focusing on chronic schizophrenia, as well as differences in EEG methodology and EEG paradigms analysis as explained above (Perrottelli et al., 2021).

Resting state is aimed to measure resting state and default mode network activity, which has been shown to be disrupted in psychosis, however there are variations in approaches to resting state measurements (Buckner, 2013; Karbasforoushan and Woodward, 2012; Li et al., 2019). There are variations in collecting methods, and thus reporting on resting state with some studies collecting data with eyes closed, others with eyes open or with passive stimuli, such as a film. Additionally, individuals experience resting state diversely with variations in inner experience and network activation (Hurlburt et al., 2015). The inconsistencies in EEG resting-state spectral findings in FEP limit their applicability to clinical contexts and understanding of mechanisms behind oscillatory activity in FEP (Boutros et al., 2008). Therefore, more methologically consistent research in FEP is required to clarify the nature of potential oscillatory abnormalities, mechanisms underlying the onset in early-stage psychosis,and prognosis of psychosis.

The relative spectral band power results are influenced by some challenges in recording EEG at higher frequencies. Gamma frequency band and frequencies over 20 Hz more

generally overlap a great deal with muscle response (Whitham et al., 2007). Muscle artefact are particularly difficult to differentiate from oscillations over 50 Hz. Therefore, higher frequency abnormalities in the FEP group found in previous literature may be a result of increased noise, as opposed to neural aberration, and should be interpreted with caution. Moreover, fairly noisy spectral data in this study, further highlights the importance of effective artefact removal, data cleaning and large sample sizes to avoid underpowered findings (Kaczorowska et al., 2017; Kapur et al., 2012). Thus, the use of principle component analysis and other effective artefact removal techniques and larger sample sizes would increase the validity and power of future findings.

5.4.2 Spectral Analysis and Cognition

Main Findings

- There was a significant inverse correlation between relative delta power in the non-SD condition and hit rate on the CRDM task in both FEP and HC.
- There was no significant effect, that survived multiple comparisons, of non-SD condition relative spectral power on cognitive performance on CRDM.

Findings in Context

The present study found a significant correlation between increased relative delta power in the non-SD condition with lower hit rate in both the FEP and HC groups. There were no other significant correlations or effects between spectral band power and cognitive performance.

Correlations between relative frontal delta power and impaired cognitive performance has been previously established in controls (Posada-Quintero et al., 2019). This finding has been attributed to sleep deprivation and fatigue (Knyazev, 2012). There is a lack of literature focused on delta power and cognitive performance in FEP (Perrottelli et al., 2021). The few studies that explore delta oscillations in association with cognition in psychosis have reported inconsistent findings (Howells et al., 2018; Perrottelli et al., 2021; Zhao et al., 2018). It has been noted that increases in fatigue impact attention during a visual task, specially by decreasing one's ability to suppress irrelevant information (Faber et al., 2012). Given that patients had non-significant increases in false alarms, higher reaction times and a stronger inverse correlation between cognitive performance and delta compared to HC, fatigue could account for the interaction between cognition and delta power.

Although both gamma and beta power have inconsistent reports of associations with cognitive performance in FEP, and beta has not been largely studied within cognitive tasks in psychosis (Perrottelli et al., 2021; Uhlhaas and Singer, 2013), it was expected that there would be associations between gamma and beta power with cognition, as both of these oscillations have been implicated heavily in cognition in the general population (Carr et al., 2012; Mably and Colgin, 2018; Sedley and Cunningham, 2013; Uhlhaas and Singer, 2013). These findings were not replicated in the present study in neither the FEP nor HC group. Unfortunately, neuro-physiological markers map on poorly to cognitive task performance, and the connection between neural EEG phenomena and cognition are not well understood (Seidman et al., 2015). Further research exploring spectral band power during cognitive tasks, particularly within psychosis populations, would greatly assist in elucidating the role of frontal spectral power with cognition in psychosis.

5.4.3 Spectral Analysis and Social Defeat

Main Finding

- There was no significant difference in relative spectral power between the non-SD compared to SD condition within the FEP nor HC group.
- There were no significant correlations between SD scores with neither non-SD relative spectral power, SD relative spectral power nor difference in relative spectral power for neither the FEP nor HC group.
- In the FEP group delta, theta, alpha and gamma power were correlated between the non-SD and SD conditions, while beta was not.
- In the HC group theta and alpha power were correlated between the non-SD and SD conditions, while delta, beta and gamma were not.

Findings in Context

When comparing spectral data in the non-SD condition with the SD condition, there were no significant differences in any power band. This finding is not in keeping with the hypothesis the relative gamma power would be significantly increased following induced SD, particularly for the FEP group. The lack of significant findings of changes in relative power between the non-SD and SD conditions suggest that inducing SD in participants did not significantly alter brain chemistry in the moment. This could suggest that spectral EEG is not sensitive enough to pick-up on neural changes caused by feelings of SD or

that the SD manipulation is not salient enough to induce neural changes in HC or FEP.

In the FEP group there were non-significant decreases in relative frontal theta, beta and gamma band power, and increases in relative frontal delta and alpha band power in the SD condition compared to the non-SD condition. The HC group had decreases in the relative frontal delta, theta, and beta band power, and increases in relative frontal alpha and gamma power in the SD condition compared to the non-SD condition. Increased delta power has been associated with fatigue while decreased frontal gamma has been associated with decreased attention (Borghetti et al., 2021; Knyazev, 2012). Therefore, this difference between groups in both relative delta and gamma power changes, though non-significant, could be suggest that controls engaged more with the SD manipulation, whereas FEP participants do not, which in and of itself could reflect a sense of defeat.

Previous literature in humans has noted that SD does significantly impact neural phenomena, although the nature of this impact was inconsistent. Both hyperactivity and hypo-activity in frontal brain regions have been reported as a response to SD in psychosis (Baskak et al., 2015; Gradin et al., 2012; Lee et al., 2014). Moreover, animal studies have reported inconsistent findings in gamma and delta activity aberrations following SD induction (Abe et al., 2019; Grafe et al., 2020; Henderson et al., 2017; Ito et al., 2020; Wells et al., 2017; Yin et al., 2023). These animal studies attributed these findings of SD induced E/I imbalances through decreased pyramidal neuron firing (Ito et al., 2020; Yin et al., 2023). All studies exploring SD and neural responses in psychosis focused on a chronic schizophrenia group and used different technology such as functional MRI and functional near-infrared spectroscopy, which could account for the discrepancy between the present study and previous literature. The inconsistency and lack of research exploring SD and it's potential neural impact limits the ability to interpret the present study findings. Further, the animal studies also have limited applicability to the present study as they employ different SD manipulations and different data acquisition methods. However, these studies do support the hypothesis that SD impacts frontal neural oscillatory activity (Liu et al., 2022). Therefore, a larger scale replication study exploring spectral power and oscillatory activity changes following SD induction in healthy humans as well as in patients would clarify the potential impact SD may have on neural oscillations.

It is important to note that the results from this thesis focus on the FCz electrode (fronto-central), and other electrode locations could result in different findings. One study exploring the impact of stress in both young and old participants using EEG found that in the younger group absolute power changes differed according to electrode location and oscillatory findings were highly variable for the frontal/fronto-central electrode (Marshall

and Cooper, 2017). This suggests that the inclusion of other brain regions in the study of EEG phenomena and SD could yield useful insights and provide better context for the present findings.

5.5 Conclusion

In this study there were no significant difference in relative spectral power, in neither non-SD nor SD conditions,or between the HC and FEP group.

The lack of significantly increased gamma power in FEP could suggest that hyperexcitation, and therefore gamma power abnormalities, occur in earlier prodromal stages of psychosis. This could support the excitotoxicity hypothesis and potentially suggest that excitotoxicity already begins in FEP leading to a decrease in frontal hyperexcitation. Further large scale research, in both a high risk and FEP group would clarify if and what the potential oscillatory mechanisms behind psychosis onset could be.

However, the spectral data in this study was noisy and had outlier data, especially for the FEP group, which may have impacted statistical conclusions. The leakage of muscle artefacts (EMG) in gamma frequency recording presents a fairly large challenge to accurate interpretation of higher frequency neural activity in FEP (Whitham et al., 2007). To minimise the impact of EMG in the present study gamma band power was cut-off at 50 Hz. Moreover, resting state oscillatory activity, which has less muscle artefacts compared to task-related or attentive EEG, was used for analysis. Additionally, spectral data recorded from a centrally located electrode was used as central electrodes are further from larger muscles and have less noise. To further minimise the impact of noise and provide a clearer image of gamma activity in FEP, future studies should perform careful artefact removal such as principle component analysis (Kaczorowska et al., 2017; Whitham et al., 2007).

EEG recordings can be impacted by many non-technical aspects, such as whether the individual smokes, blood glucose levels, stress levels/emotional state, individual physical activity and mental fatigue, that play a role in EEG signal and relative power band (Blaabjerg and Juhl, 2016; Chin et al., 2019; Li et al., 2020; Xu et al., 2018). This study attempted to control for this by matching controls and FEP participants according to age, sex and smoking status. Additionally, EEG study sessions were booked at approximately the same time for most participants in an attempt to have consistency across other factors across participants.

The present study also did not show significant difference in relative frontal spectral band power between the non-SD and SD condition. This could suggest that SD does not impact oscillatory activity in FEP, which was further supported by the lack of significant correlations or effect of SD scores on spectral power data. As SD has been thought to lead to sensitisation prior to disease onset, it is possible that SD and spectral power would only be associated at prodromal stages. Therefore, a similar study in a high-risk group may better detect potential oscillatory processes behind SD and increased risk of psychosis. As within-subject effects, such as pre-post SD induction spectral power, are less impacted by sample sizes it is unlikely that these findings are merely due to the study being underpowered. However, as previous literature has found SD induced neural responses in chronic psychosis using functional near-infrared spectroscopy and functional MRI (Baskak et al., 2015; Gradin et al., 2012; Lee et al., 2014), it is possible that EEG measured oscillatory power may not be sensitive enough to detect neural changes resulting from SD. Further multi-modal research across stage of illness would be required to determine whether the present findings were due to a lack of SD induced neural response in FEP or due to EEG spectral power not being a sensitive enough tool to measure these neural responses. Moreover, future research should be done with larger samples, consistent spectral/EEG paradigms and more homogeneous within group specification.

Further, the SD induction method in this thesis should be further validated. Conducting a study with a larger sample size, across different patient groups, and the use of questionnaires pre-post SD induction could confirm the validity of the presented SD induction method.

This EEG component of the thesis also has demonstrated the feasibility of efficiently measuring multiple tests with a patient population. This indicates that a similar study would be manageable in the future.

Chapter 6

Analysis of Magnetic Resonance Spectroscopy in First-Episode Psychosis compared to Healthy Controls, and interactions with Social Defeat and Cognitive Performance

6.1 Introduction

An aberration in the fine balance between E/I balance, predominately via glutamate and GABA neurotransmitter activity, has been positioned as a likely mechanism behind many psychiatric conditions, including psychosis (Moghaddam and Javitt, 2012). MRS offers a non-invasive method for *in-vivo* measuring the concentrations of a larger range of neuro-metabolites, including those associated with E/I balance: GABA, glutamate, and glutamine. Other measurable MRS metabolites such as gluthione, N-acetyl-aspartate, myo-inosotol and choline have also been implicated in psychosis (Plitman et al., 2016a; Sydnor and Roalf, 2020; Whitehurst et al., 2020).

The glutamatergic hypothesis of psychosis posits that glutamate levels are increased in prodromal or initial stages of psychosis and lead to excitotoxicity. In keeping with the excitotoxic effects of hyperexcitation it has been suggested that glutamate levels decrease over the course of illness in psychosis. However, findings for glutamatergic abnoramlities

using proton MRS in FEP have been inconsistent (Godlewska et al., 2021; Merritt et al., 2016; Poels et al., 2014; Sydnor and Roalf, 2020; Reid et al., 2019). A major limitation of many of these previous studies is that they were done using 1.5T or 3T MRS, which are unable to assess glutamate with a high level of certainty, with Glx, combined glutamate and glutamine, being a more reliable measure. Recent advancements in MRS technology have allowed for the measurement of neuro-metabolites using higher field strengths and allows for a better differentiation between glutamate and glutamine (VanElzakker et al., 2019). A recent meta-analysis demonstrated that 7T MRS findings differed from those reported at lower field strengths, highlighting the importance of precisely and independently measuring glutamatergic metabolites (Sydnor and Roalf, 2020). The majority of the extant literature was in patients on antipsychotic medication and with the voxel of interest being the ACC. Both the ACC and DLPFC have demonstrated an integral role in cognition and have been associated with abnormalities in the levels of neurochemicals in psychosis. As such they are of particular interest in understanding FEP (McCutcheon et al., 2020; Moustafa et al., 2021; Stevens et al., 2011).

SD have been associated with several neurotransmitters, such as dopamine, glutamate and GABA (Akdeniz et al., 2014; Chaudhury et al., 2013; Egerton et al., 2017a; Isovich et al., 2001; Martinez et al., 2010; Novick et al., 2011; Soliman et al., 2008; Tidey and Miczek, 1996; Vassilev et al., 2021). SD has also been positioned as a significant mediating factor between demographic factors and psychosis (Schalbroeck, 2023; Seo and Choi, 2018; Stowkowy and Addington, 2012; Van Nierop et al., 2014).

The objective of this study is to assess the relationship between SD and MRS E/I related metabolite levels in FEP compared to HC. Furthermore, this study aimed to replicate previous MRS findings seen in the FEP population, including a link between glutamate levels in the ACC and correlations with performance on the BACS (Godlewska et al., 2021).

In keeping with the pilot study (Godlewska et al., 2021), it is hypothesised that the FEP group will have decreased glutamatergic metabolite levels compared to controls. Moreover, FEP patients are expected to perform worse on cognitive tasks compared to controls. Corresponding with the pilot study, it is expected to find a correlation between BACS performance and other cognitive task performance with ACC glutamate levels in the FEP group, but not in the control group (Godlewska et al., 2021). Finally, it is hypothesised that higher SD scores will be associated with increased frontal excitability, higher glutamatergic metabolite levels, in the FEP group.

6.2 Methods

6.2.1 Study Approval

The MRS component of this thesis was approved by National Research Ethics Service Committee (NRES) South Central Oxford (Ethics Ref: 17/SC/0065).

6.2.2 Study Eligibility

20 FEP patient participants and 20 HC, matched for sex and age, were included in the study. The psychosis patient group was recruited through direct communication with care coordinators and an Oxford Health Thomas Vaughn ward psychiatrist. Patient participants were eligible if they: had their first episode of psychosis, as defined by Melbourne criteria (i.e. a week or more of psychotic symptoms above a threshold of moderate in severity), within the last three years from study visit date, were between 18 and 40 years of age, their mental state was stable enough to allow study participation[1], were not at risk of suicide, did not have current substance dependency, were not pregnant or breastfeeding, and had no contraindications to MR imaging. The age range for the study was 18 to 40, to prevent age related abnormalities (Brandt et al., 2016). HCs were recruited via word of mouth, web advertisements and local newspaper advertisements. HCs were eligible if they are matched the patients in age and sex, were able and willing to give informed consent, had no current or previous history of psychiatric disorders according to the DSM-5, were not on any medication that might influence brain neurochemistry, such as benzodiazepines, were not pregnant or breastfeeding and had no contraindications to MR imaging.

The MRS sample size was calculated using data from our pilot study (Godlewska et al., 2021) using https://clincalc.com/stats/samplesize.aspx with a confidence interval (beta) of 80% and a probability (alpha) of 0.05. For the comparisons of MRS glutamate levels a minimum of 10 participants per group was be needed. However, some of the goals depended on between-subject correlations and when this was taken into consideration 20 participants were necessary to reliably detect correlations of SD scores, cognitive testing scores and MRS findings.

[1]Participants were still eligible is they had symptoms of psychosis, however they needed to be deemed well enough to participate and understand what the study entailed by both the care coordinator contacted and the researcher.

6.2.3 MRS Study Visit Session

All MRS study visits were carried out at Oxford Centre for Functional MRI of the Brain (FMRIB) at the John Radcliffe Hospital site in Oxford. Before any procedures were started, participants gave full written consent following the presentation of the appropriate HC or FEP Participant Information Sheet. Upon giving consent participants were asked to complete a series of questionnaires including: the Social Defeat Scale and the Social Comparison Scale, as well as a 7T MRI safety form. The Positive and Negative Syndrome Scale (PANSS), Hamilton Depression Rating Scale (HAM-D) and Young Mania Rating Scale (YMRS) questionnaires were filled out by the researcher based on conversation and a semi-structured interview.

Prior to entering the scanning room the participant was asked to change into scrubs and the radiographer conducting the scan went over the 7T MRI safety form with the participant to ensure eligibility and safety in a 7 Tesla scanner. Once prepared for the scan, the participant was brought into the scanning room, they got their height and weight measured if this was necessary, and were set-up in the 7T scanner. The scanning session consisted of a series of set up scans, two MRS scans, one for the ACC and one for the DLPFC, and a structural MRI scan.

Following the completion of the MRS and MRI scans, a battery of cognitive tests were administered. The N-back was explained verbally, and the participant completed a trial run to ensure that they understood the task. The Stroop Colour test was then set-up, again participants received a verbal explanation of the task (alongside the written instructions), and again they completed a trial run to ensure that they understood the task. Lastly, the BACS was administered using a study dedicated tablet.

6.2.4 MRS Spectrum Acquisition

Glutamate, and other neurometabolites were measured using a Siemens MAGNETOM 7T ^{1}H-MRS scanner at FMRIB in Oxford. The 7T scanner has a Nova Medical 32 channel receive array head coil that was employed to measure neuro-metabolites of two voxels of interest (VOI), one voxel was positioned in the anterior cingulate cortex (ACC, 20 x 20 x 20 mm) and the other was positioned in the dorsolateral prefrontal cortex (DLPFC, 15 x 15 x 30 mm) (Fig. 6.2.1 and Fig. 6.2.2). These voxels were manually placed by referencing a high-resolution 1mm T1-weighted MP RAGE image. The voxel location was set using the coronal, median sagittal and horizontal plane, and were positioned in a manner that would avoid ventricles, skull, and white matter and CSF.

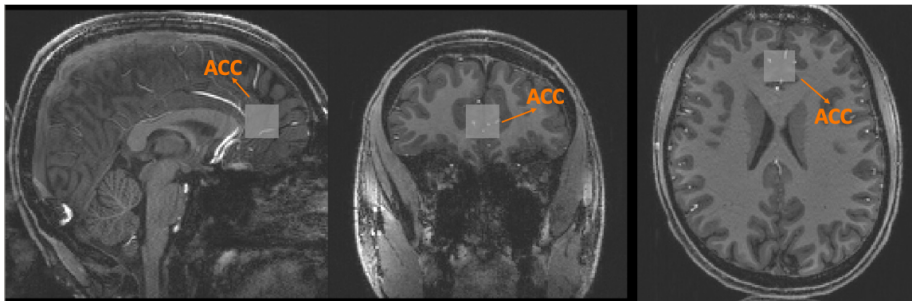

Figure 6.2.1: Representation of the anterior cingulate cortex (ACC) voxel placement

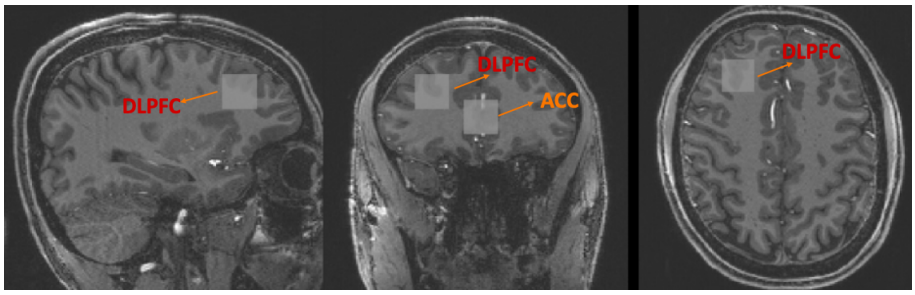

Figure 6.2.2: Representation of the dorso-lateral prefrontal cortex (DLPFC) voxel placement

First- and second- order shims were adjusted using gradient-echo shimming (Shah et al., 2009), and then fine adjustments of first order shims were done with FASTMAP (Gruetter and Tkac, 2000). FASTMAP was used due to having an increased speed and performance, which was of particular concern when scanning the FEP participants and allowed for optimized image quality through greater magnetic field homogeny (Zhang et al., 2009). Spectra was obtained through the use of a stimulated echo acquisition mode (STEAM) pulse sequence ($T_E = 11\,\text{ms}$, $T_R = 5\,\text{s}$, number of transients= 64 for the ACC, and number of transients= 32 for the DLPFC), with variable power radiofrequency pulses and with optimised relaxation delays (VAPOR) water suppression and outer volume saturation (Emir et al., 2012). Correction of residual eddy current effects and reconstruction of the phased array spectra was conducted with unsuppressed water spectra from the same, above-mentioned, voxels. As explained in more detail above, the ACC, and DLPFC were chosen as the regions for metabolite concentration analysis, as they have been implicated in the glutamate abnormalities seen in schizophrenia, specifically first episode patients (Foss-Feig et al., 2017; Mouchlianitis et al., 2016; Stone et al., 2010b). Moreover, a recent study conducted by our group has shown the role of glutamate in cognitive function in early psychosis and the feasibility of conducting 7T MRS study in patients with psychosis (Godlewska et al., 2021).

6.2.5 MRS Analysis

MRS metabolites were quantified using LCModel (Provencher, 1993). Grey matter (GM), white matter (WM) and cerebro-spinal fluid (CSF) were quantified using Statistical Parametric Mapping (SPM 12) software package (for more information on the involvement of GM, WM and CSF in MRS quantification see Section 2.2.8). Voxel locations were checked using using FMRIB Software Library (FSL) (McCarthy, 2023).

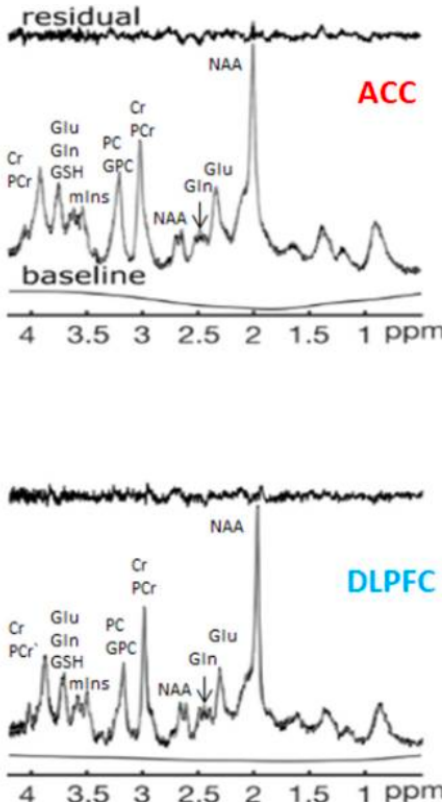

Figure 6.2.3: Example of ^{1}H-MRS spectra of the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC) (Godlewska et al., 2021)

6.2.6 Pre-processing

Neurometabolites were quantified using LCModel, with previously reported chemical shifts and coupling constant used as the basis set for glutamate (Glu), glutamine (Gln), glutathione (GSH), creatine (Cr), phosphocreatine (PCr), ascorbate (Asc), N-acetyl aspartate (NAA), myo-inositol (myo-Ins), phosphocholine (PC) and glycerophosphocholine (GPC). This was done using VESPA's GAMMA/PyGAMMA simulation library to apply density matrix formalism. The simulations were performed using the 7T system RF pulses and sequence timing. The concentration of neurometabolites was established relative to

an unsuppressed water spectrum that was measured in the same voxel location. Water was used as the baseline, as opposed to creatine which is also commonly used, as it is less variable and more consistent in the brain (Goryawala et al., 2016). It should be noted that GABA reported included macromolecules.

SPM 12 software was used to determine the grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) fraction in the two voxels by segmenting the MP RAGE images.

The formula for correcting for GM, WM and CSF was

$$MetConcCorr = AbsMetConc \frac{\frac{(GM \times 43300 + WM \times 35880 + CSF \times 55556)}{1 - CSF}}{55556} \quad (6.2.1)$$

where MetConcCorr is the corrected metabolite concentration, AbsMetConc is the absolute metabolite concentration, GM indicates the fraction of gray matter, WM indicates the fraction of white matter and CSF indicates the fraction of cerebro-spinal fluid in the voxel of interest.

To allow for comparison with other relevant MRS studies, metabolites that were quantified with a Cramer-Rao lower bounds (CRLB) of more than or equal to 30% were classified as not detected. The CRLB is a method used for an estimation of standard deviation since multiple MRS measures are not feasible with in-vivo research. 30% is a standard cut-off point for similar studies, and was considered reasonable for this study (Landheer and Juchem, 2021).

Voxel locations were manually checked after pre-processing of the MRI image using FSL. All MRS scans were deemed to have appropriate voxel placement.

6.2.7 Statistical Analysis

Statistical analysis was carried out using SPSS 29 software. Independent t-tests and chi-square tests were used for group comparisons.

Associations between variables were explored using Spearman's rho correlations, and when appropriate general linear models (GLMs). GLMs that include multivariate tests (Wilk's Λ) and between-subject effects tests (univariate ANOVAs) were also conducted to account relationships between variables while controlling for confounding variables. General linear modelling was performed to assess the interactions between various independent variables on E/I metabolite levels. SDS and SCRS scores, alongside PANSS scores, HAM-D scores and age were entered as covariates, and group and sex were fixed factors. The

main effects for SD questionnaire scores, group, sex, PANSS, and HAMD, as well as interactions between group and sex.

Šidák correction was applied for alpha correction of multiple comparisons.

6.3 Results

6.3.1 MRS E/I Metabolite Levels

Demographic Comparisons

A total of 20 HC and 20 FEP were recruited and completed the MRS study visit. Usable MRS data of adequate quality to be included in the final analysis, varied for each region (17 HC and 20 FEP for ACC refer to Section 6.3.1 and 17 HC and 17 FEP for DLPFC refer to Section 6.3.1). There were no significant differences in age nor sex between the two groups (Table 6.1).

MRS E/I Metabolite Levels in the ACC

A total of 17 HC and 20 FEP were included in the ACC metabolite analysis. Two participants did not have valid MRS spectra (too much variation from the basis set), and one participant's data was excluded due to low signal-to-noise ratio (the SNR was 3 for this participant). The signal-to-noise ratio of 20 was deemed a cut-off value, with the average signal-to-noise ratio for ACC being 34. Any measures with a CRLB of more than 30 were also excluded from the analysis (as described above refer to Section 6.2.6, refer to 6.2).

There were no significant differences in ACC E/I metabolite levels, GABA, Glu, Gln and Glx, between the HC and FEP groups (Table 6.3). Although FEP participant had higher concentrations of all four metabolites compared to HC participants (Table 6.3 and Fig. 6.3.1).

General Linear Model of ACC E/I metabolite levels

General linear modelling was performed to assess the interactions between various independent variables on ACC E/I metabolite levels.

Multivariate testing (Wilk's Λ) demonstrated no significant effects of group nor interactions on E/I related metabolite levels ($F(4, 22) = 1.491, p = 0.239$, Wilk's $\Lambda = 0.787$,

	Patients with FEP n= 20	Healthy Controls n= 20	t-value	p-value	Cohen's D effect size
Age	26.80 (5.52)	25.25 (4.45)	-0.970	0.338	-0.307
Sex	7/13	10/10	0.921 (χ^2)	0.337	
Antipsychotic Drugs	19/20	n/a			
Antidepressant Drugs	8/20	n/a			
SDS scores	23.90 (12.02)	11.67 (8.84)	**-3.604**	**<0.001**	**-1.171**
SCRS scores	60.70 (16.61)	64.11 (15.32)	0.656	0.516	0.213
HAM-D	5.65 (5.28)	2.26 (2.38)	**-2.603**	**0.015**	**-0.819**
Young Mania Rating Scale	1.00 (2.15)	0.42 (0.84)	-1.096	0.280	-0.351
PANSS					
Total	46.30 (17.15)	29.95 (7.35)	**-2.776**	**0.011**	**-0.869**
Positive	9.35 (3.17)	7.32 (0.82)	**-4.733**	**<0.001**	**-1.536**
Negative	14.84 (6.87)	7.32 (0.89)	**-4.382**	**<0.001**	**-1.422**
General	24.05 (7.00)	16.89 (1.33)	**-3.918**	**<0.001**	**-1.239**

Table 6.1: Means (standard deviations) for demographic information, and SD scores, and group comparison statistics (t-test or chi-square) between FEP and HC. Frequency for the sex variable are female/male. Equal variance was assumed for all variables (based on a Levene's Test of Equality of Variance), a confidence interval (CI) of the difference of 95% was used, and p tests were two-tailed.

$\eta_p^2 = 0.213$). Moreover, univariate ANOVAs revealed no significant between-subject effects of group on GABA, Glu, Gln or Glx.

MRS E/I Metabolite Levels in the DLPFC

A total of 17 HC and 17 FEP were included in the DLPFC metabolite analysis. Three participants did not complete the DLPFC voxel specific scan during the MRS visit, two participants did not have valid MRS spectra (too much variation from the basis set), and

	Patients with FEP n= 20	Healthy Controls n= 17	t-value	p-value	Cohen's D effect size
FWHM	0.038 (0.009)	0.034 (0.007)	1.485	0.147	0.490
SNR	31.60 (4.988)	37.18 (3.712)	-3.798	<0.001	-1.253
CSF	0.255 (0.037)	0.217 (0.038)	3.078	0.004	1.015
GM	0.626 (0.039)	0.669 (0.043)	-3.174	0.003	-1.047
WM	0.119 (0.025)	0.114 (0.021)	0.599	0.553	0.198

Table 6.2: Means (standard deviations) for ACC full width at half maximum (FWHM), signal to noise ratio (SNR) values, CSF, GM, and WM volume measures, as well as group comparison statistics between FEP and HC. Equal variance was assumed (based on a Levene's Test of Equality of Variance), and a confidence interval (CI) of the difference of 95% was used

one participant's data was excluded due to low signal-to-noise ratio (signal-to-noise ratio of 20 was deemed a cut-off value, with the average signal-to-noise ratio for DLPFC being 34). Any measures with a CRLB of more than 30 were also excluded from the analysis (see above refer to Section 6.2.6, refer to 6.4).

There were no significant group differences in DLPFC concentrations of GABA, Glu, Gln and Glx (Table 6.3). However, FEP participants on average had higher concentrations of GABA and of Glu compared to HC participants. However, the FEP group had lower Gln and Glx levels compared to the HC group (Table 6.3).

General Linear Model of DLPFC E/I Metabolite Levels

General linear modelling was performed to assess the interactions between various independent variables on DLPFC E/I metabolite levels.

Multivariate testing (Wilk's Λ) demonstrated no significant effects of group nor interactions on E/I related metabolite levels ($F(4, 19) = 0.845, p = 0.514$, Wilk's $\Lambda = 0.849$, $\eta_p^2 = 0.151$).

Moreover, univariate ANOVAs revealed no significant between-subject effects of group on GABA, Glu, Gln or Glx.

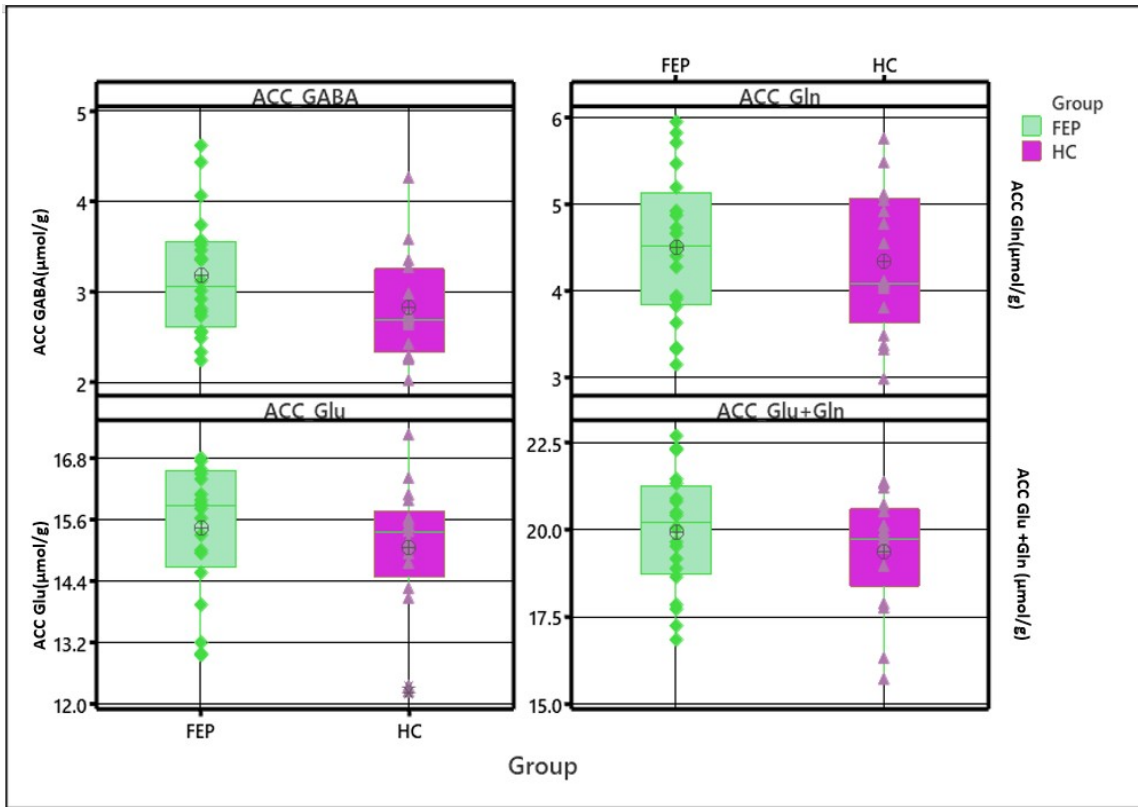

Figure 6.3.1: Boxplot comparing FEP group with control (HC) group on GABA, glutamate (Glu), glutamine (Gln) and Glx-combined glutamate and glutamine (Glu+Gln) concentrations in the anterior cingulate cortex (ACC)

6.3.2 MRS E/I Metabolite Levels and Symptomology

PANSS scores were used to assess the relationship between psychosis symptomology and E/I metabolite levels in the FEP group.

Symptomology and ACC E/I Metabolite Levels

There were no significant correlations between ACC GABA, Glu and Gln with PANSS scores in the FEP group. However, there was a significant moderate correlation between ACC Glx metabolite levels and negative symptoms in the FEP group (Table 6.5).

Symptomology and DLPFC E/I Metabolite Levels

There were no significant correlations between DLPFC E/I related metabolite levels and PANSS scores in the FEP group (Table 6.5).

ACC							
	Patients with FEP n= 20	CRLB	Healthy Controls n= 17	CRLB	t-value	p-value	Cohen's D effect size
GABA	3.19 (0.68)	9.30 (1.57)	2.82 (0.57)	9.00 (0.57)	-1.756	0.088	-0.579
Glu	15.43 (1.29)	2.20 (0.31)	15.04 (1.30)	2.00 (1.00)	-0.906	0.371	-0.299
Gln	4.51 (0.85)	7.85 (1.67)	4.34 (0.82)	6.88 (0.59)	-0.609	0.546	-0.201
Glx	19.94 (1.72)	2.25 (0.41)	19.39 (1.66)	2.06 (1.24)	-0.995	0.327	-0.328
DLPFC							
	Patients with FEP n= 17	CRLB	Healthy Controls n= 17	CRLB	t-value	p-value	Cohen's D effect size
GABA	1.58 (0.18)	14.12 (1.41)	1.43 (0.27)	15.76 (0.14)	-1.864	0.071	-0.639
Glu	9.74 (0.74)	2.76 (0.44)	9.69 (0.55)	2.76 (0.57)	-0.207	0.837	-0.071
Gln	2.57 (0.26)	10.24 (1.20)	2.66 (0.41)	9.76 (0.19)	0.831	0.412	0.285
Glx	12.30 (0.86)	2.94 (0.24)	12.36 (0.74)	2.94 (0.69)	0.189	0.851	0.065

Table 6.3: Means (standard deviations) for ACC and DLPFC E/I metabolite concentration levels (Glu being glutamate, Gln being glutamine, and Glx being Glu+Gln) and the cramer-bao lower bound (CRLB), as well as group comparison statistics between FEP and HC. Equal variance was assumed (based on a Levene's Test of Equality of Variance), and a confidence interval (CI) of the difference of 95% was used

6.3.3 MRS E/I Metabolite Levels and Cognition

BACS and E/I Metabolite Levels

Analysis of BACS data was carried out on the corrected T-scores for each test in the battery and on the composite T-score which accounts for age and sex. Unfortunately, due to technical issues not all participants completed the BACS, and some did not complete every task within the battery of tests therefore N values have been reported alongside the statistic.

	Patients with FEP n= 17	Healthy Controls n= 17	t-value	p-value	Cohen's D effect size
FWHM	0.030 (0.004)	0.031 (0.008)	-0.230	0.820	-0.079
SNR	33.71 (4.012)	35.41 (3.906)	-1.256	0.218	-0.431
CSF	0.588 (0.021)	0.048 (0.016)	1.572	0.126	0.548
GM	0.296 (0.057)	0.291 (0.050)	0.234	0.817	0.081
WM	0.646 (0.075)	0.660 (0.056)	-0.633	0.532	-0.220

Table 6.4: Means (standard deviations) for DLPFC full width at half maximum (FWHM), signal to noise ratio (SNR) values, CSF, GM, and WM volume measures, as well as group comparison statistics between FEP and HC. Equal variance was assumed (based on a Levene's Test of Equality of Variance), and a confidence interval (CI) of the difference of 95% was used

ACC						
	Positive		Negative		General	
	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value
GABA	0.190	0.421	-0.040	0.867	-0.283	0.227
Glu	0.205	0.385	0.360	0.119	-0.026	0.912
Gln	0.356	0.123	0.262	0.265	0.353	0.127
Glx	0.328	0.158	0.444	0.050	0.155	0.513
DLPFC						
	Positive		Negative		General	
	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value
GABA	0.153	0.558	-0.028	0.918	-0.123	0.651
Glu	-0.202	0.437	-0.106	0.695	-0.269	0.314
Gln	0.151	0.562	0.137	0.612	0.179	0.508
Glx	-0.106	0.685	-0.068	0.802	-0.189	0.483

Table 6.5: Spearman's rho correlational analysis between PANSS scores and ACC and DLPFC metabolite levels for FEP participants

Cognitive Performance on BACS

There were significant group differences across all tests included in the BACS as well as the composite score (Table 6.6 and Fig. 6.3.3), with the FEP group scoring worse across

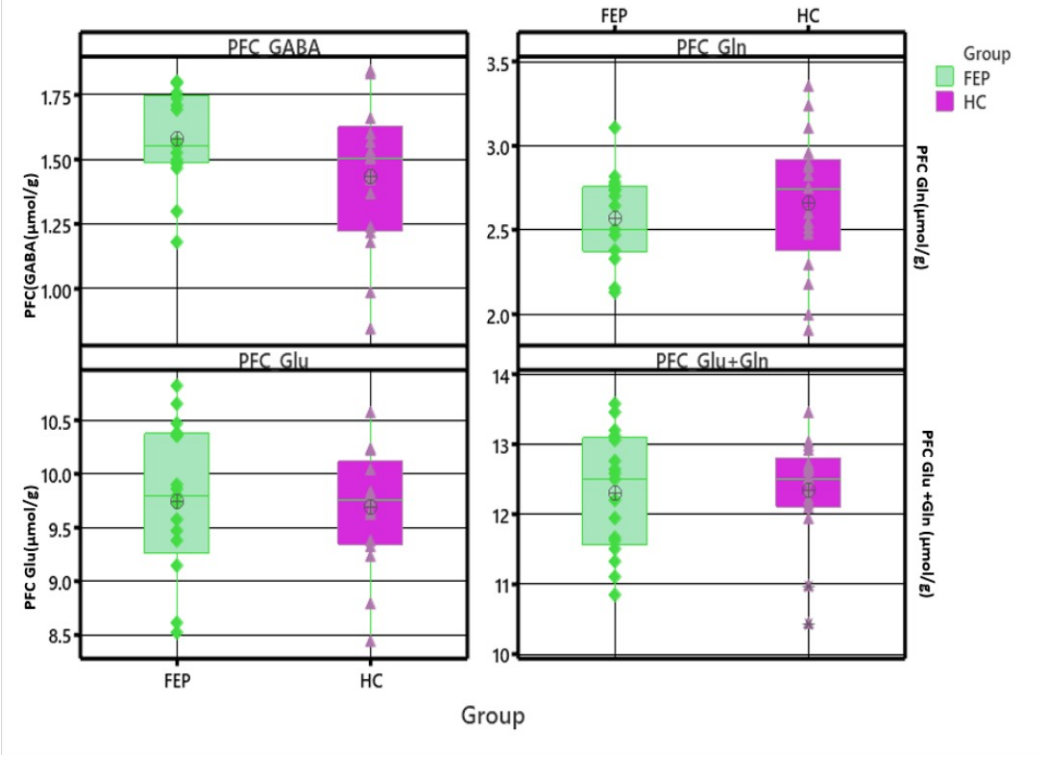

Figure 6.3.2: Boxplot comparing FEP group with control (HC) group on GABA, glutamate (Glu), glutamine (Gln) and Glx-combined glutamate and glutamine (Glu+Gln) concentrations in the dorsolateral prefrontal cortex (DLPFC)

all tests and having a worse composite BACS score. Except for the Tower of London, all BACS tests remained significantly different between groups when correcting for multiple comparisons.

Cognitive Performance on BACS and ACC E/I Metabolite Levels

There were 9 HC and 14 FEP participants with both BACS and ACC E/I metabolite levels.

In the HC group there were significant correlations between performance on verbal memory with GABA and with Glx , token motor performance with GABA and with Glx, symbol coding performance with Glx. Further, there were significant correlations between BACS composite scores with both ACC GABA and ACC Glx (Table 6.7).

Whereas, for the FEP group there were no significant associations between E/I metabolite levels in the ACC and any of the BACS tests nor composite BACS score (Table 6.7).

	Patients with FEP n= 14	Healthy Controls n= 9	t-value	p-value	Cohen's D effect size
Composite BACS	40.64 (11.25)	60.30 (7.59)	**4.788**	**<0.001**	**1.982**
Verbal Memory	42.80 (10.91)	58.06 (7.11)	**3.862**	**<0.001**	**1.599**
Digital Sequencing	39.14 (11.91)	54.80 (7.75)	**3.632**	**0.001**	**1.504**
Token Motor	88.29 (24.01)	134.50 (23.90)	**4.657**	**<0.001**	**1.928**
Verbal Fluency	46.86 (9.14)	58.61 (7.74)	**3.260**	**0.004**	**1.371**
Symbol Coding	41.80 (7.26)	54.91 (12.34)	**3.192**	**0.004**	**1.342**
Tower of London	45.64 (15.39)	59.76 (6.27)	**3.000**	**0.008**	**1.145**

Table 6.6: Means (standard deviations) for BACS cognitive performance, and group comparison statistics (t-test or chi-square) between FEP and HC. Equal variance was assumed for all variables except for the Tower of London score (based on a Levene's Test of Equality of Variance), a confidence interval (CI) of the difference of 95% was used, and p tests were two-tailed.

Cognitive Performance on BACS and DLPFC E/I Metabolite Levels

There were 9 HC and 13 FEP participants that had both BACS scores and DLPFC E/I metabolite concentrations measured.

In the HC group there were significant correlations between DLPFC Gln with performance on verbal memory, token motor performance, symbol coding performance , and performance on the Tower of London. There was a significant correlation between Gln and the composite BACS scores, but there were no other significant correlations between E/I metabolite levels and composite BACS scores in the HC group (Table 6.8).

Contrarily, there were no significant associations between E/I metabolite levels in the DLPFC and any of the BACS tests nor composite BACS score within the FEP group (Table 6.8).

N-Back and E/I Metabolite Levels

There were two performance outcomes assessed reaction time (RT) and accuracy, across four conditions (0-back, 1-back, 2-back and 3-back).

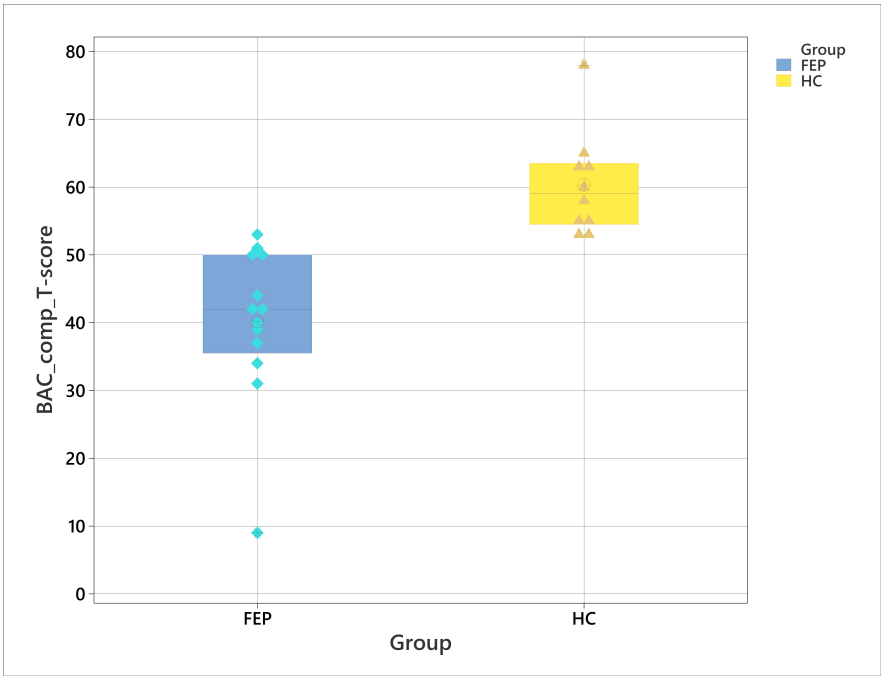

Figure 6.3.3: Boxplot comparing FEP group with control (HC) group on composite T-scores for the BACS.

Cognitive Performance on N-back

There were no significant differences in reaction times (RT) for 1,2, or 3-back conditions nor for accuracy for the 0 or 3-back conditions (Table 6.9 and Fig. 6.3.4). FEP participants had slower RT for 0, 1 and 2 back compared to controls, but slightly quicker RT for 3-back. FEP participants had worse accuracy across all N-back conditions.

When applying alpha correction for multiple comparison only accuracy in the 1-back condition remained significantly different between groups.

Cognitive Performance on N-back and ACC E/I Metabolite Levels

A total of 16 HC and 17 FEP participants completed the N-back task and had valid ACC E/I metabolite levels.

Correlational analysis on N-back performance metrics and ACC E/I metabolites revealed no significant correlations in the HC group but there was a significant correlation between

Healthy Controls								
	GABA		Glu		Gln		Glx	
	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value
Verbal Memory	**-0.849**	**0.004**	-0.429	0.250	-0.588	0.096	**-0.790**	**0.011**
Digital Sequencing	-0.042	0.915	0.513	0.158	-0.605	0.084	-0.286	0.456
Token Motor	**-0.883**	**0.002**	-0.550	0.125	-0.383	0.308	**-0.767**	**0.016**
Verbal Fluency	-0.250	0.516	-0.250	0.516	0.050	0.898	-0.200	0.606
Symbol Coding	-0.600	0.088	-0.650	0.058	-0.383	0.308	**-0.717**	**0.030**
Tower of London	-0.288	0.452	-0.254	0.509	-0.170	0.663	-0.220	0.569
Composite BACS	**-0.700**	**0.036**	-0.447	0.227	-0.574	0.106	**-0.776**	**0.014**
Patients with FEP								
	GABA		Glu		Gln		Glx	
	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value
Verbal Memory	0.490	0.075	0.420	0.135	-0.266	0.358	0.253	0.383
Digital Sequencing	-0.174	0.551	-0.104	0.724	0.057	0.846	-0.040	0.893
Token Motor	0.444	0.111	0.189	0.517	-0.004	0.988	0.189	0.517
Verbal Fluency	0.143	0.642	-0.396	0.181	0.192	0.529	-0.280	0.354
Symbol Coding	0.072	0.815	-0.080	0.794	0.285	0.345	-0.008	0.979
Tower of London	-0.355	0.235	-0.374	0.208	0.080	0.794	-0.197	0.520
Composite BACS	0.137	0.642	-0.097	0.742	0.187	0.522	0.037	0.899

Table 6.7: Spearman's rho correlational analysis between the BACS battery of tasks and BACS composite scores and ACC E/I metabolites for HC and FEP participants

accuracy on the 0-back condition and ACC glutamine levels in the FEP group (Table

Healthy Controls								
	GABA		Glu		Gln		Glx	
	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value
Verbal Memory	-0.034	0.932	0.118	0.763	**-0.681**	**0.044**	-0.210	0.587
Digital Sequencing	0.529	0.143	0.622	0.074	**-0.700**	**0.036**	-0.417	0.265
Token Motor	-0.267	0.488	-0.050	0.898	**-0.700**	**0.036**	-0.417	0.265
Verbal Fluency	-0.300	0.433	0.167	0.668	-0.367	0.332	-0.183	0.637
Symbol Coding	-0.400	0.286	-0.267	0.488	**-0.900**	**<0.001**	-0.650	0.058
Tower of London	-0.305	0.425	-0.271	0.480	**-0.678**	**0.045**	-0.576	0.104
Composite BACS	-0.118	0.762	-0.034	0.931	**-0.937**	**<0.001**	-0.447	0.227
Patients with FEP								
	GABA		Glu		Gln		Glx	
	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value
Verbal Memory	-0.324	0.280	-0.264	0.384	-0.280	0.354	-0.220	0.471
Digital Sequencing	-0.359	0.229	-0.166	0.589	0.295	0.328	-0.036	0.907
Token Motor	-0.005	0.986	-0.176	0.566	-0.451	0.122	-0.242	0.426
Verbal Fluency	0.098	0.762	-0.056	0.863	0.084	0.795	0.007	0.983
Symbol Coding	0.092	0.777	-0.021	0.948	-0.134	0.678	0.014	0.965
Tower of London	-0.452	0.141	0.042	0.896	0.166	0.607	-0.046	0.887
Composite BACS	-0.264	0.383	-0.039	0.900	0.220	0.469	0.022	0.943

Table 6.8: Spearman's rho correlational analysis between the BACS battery of tasks and BACS composite scores and DLPFC E/I metabolites for HC and FEP participants

6.10).

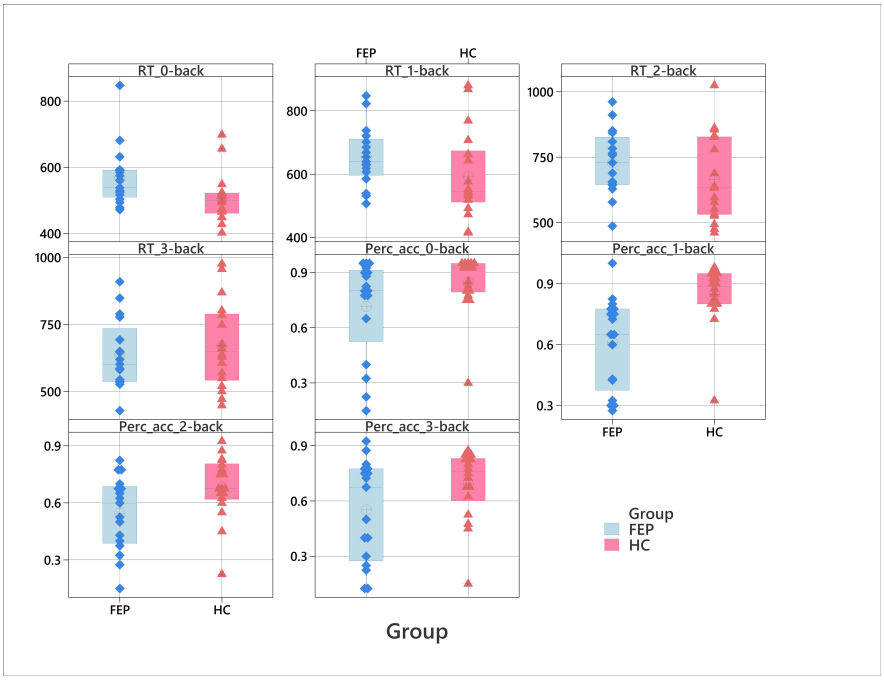

Figure 6.3.4: Boxplot comparing FEP group with control (HC) group on N-back test performance (were RT is reaction time, Acc is accuracy).

Cognitive Performance on N-back and DLPFC E/I Metabolite Levels

A total of 16 HC and 14 FEP participants completed the N-back task and had valid DLPFC E/I metabolite levels.

For the HC group, there were significant correlations between DLPFC GABA levels and RT in the 3-back condition, DLPFC Glu level and RT in the 3-back condition and DLPFC Glu levels and accuracy in the 3-back condition (Table 6.11).

There were significant correlations between DLPFC GABA levels and RT in the 0-back condition for FEP participants (Table 6.11).

Stroop and E/I Metabolite Levels

A total of 17 HC and 20 FEP participants completed the Stroop task during their MRS study visit session. There were two performance outcomes assessed, reaction time (RT) and accuracy, across two conditions (congruent and in-congruent stimuli).

	Patients with FEP n= 17	Healthy Controls n= 16	t-value	p-value	Cohen's D effect size
RT 0-back	567.22 (90.96)	506.94 (75.59)	**-2.173**	**0.037**	**-0.735**
RT 1-back	654.37 (93.73)	592.88 (136.87)	-1.541	0.133	-0.521
RT 2-back	729.15 (123.69)	666.02 (161.45)	-1.293	0.205	-0.437
RT 3-back	636.22 (129.10)	671.36 (157.67)	0.719	0.477	0.243
ACC 0-back	0.72 (0.27)	0.85 (0.16)	1.734	0.095	0.595
ACC 1-back	0.61 (0.22)	0.85 (0.15)	**3.663**	**0.001**	**1.253**
ACC 2-back	0.55 (0.20)	0.68 (0.17)	**2.264**	**0.030**	**0.766**
ACC 3-back	0.55 (0.27)	0.70 (0.19)	1.799	0.083	0.615

Table 6.9: Means (standard deviations) for N-Back cognitive performance, and group comparison statistics (t-test or chi-square) between FEP and HC. 'RT' refers to reaction time and 'ACC' refers to accuracy. Equal variance was assumed for all variables except for accuracy on the 0, 1 and 3-back (based on a Levene's Test of Equality of Variance), a confidence interval (CI) of the difference of 95% was used, and p tests were two-tailed.

Cognitive Performance on Stroop

There were significant group differences in RT for both the congruent and incongruent conditions of the Stroop task, which survived correction for multiple comparison, but no group differences in accuracy in either condition (Table 6.12 and Fig. 6.3.5).

Cognitive Performance on Stroop and ACC E/I Metabolite Levels

A total of 17 HC and 20 FEP completed the Stroop and had valid ACC E/I levels.

Correlational analysis between Stroop task performance and ACC E/I metabolite levels revealed no significant correlations for HC, however there was a significant correlation between ACC GABA levels and accuracy in the incongruent condition for FEP participants (Table 6.13).

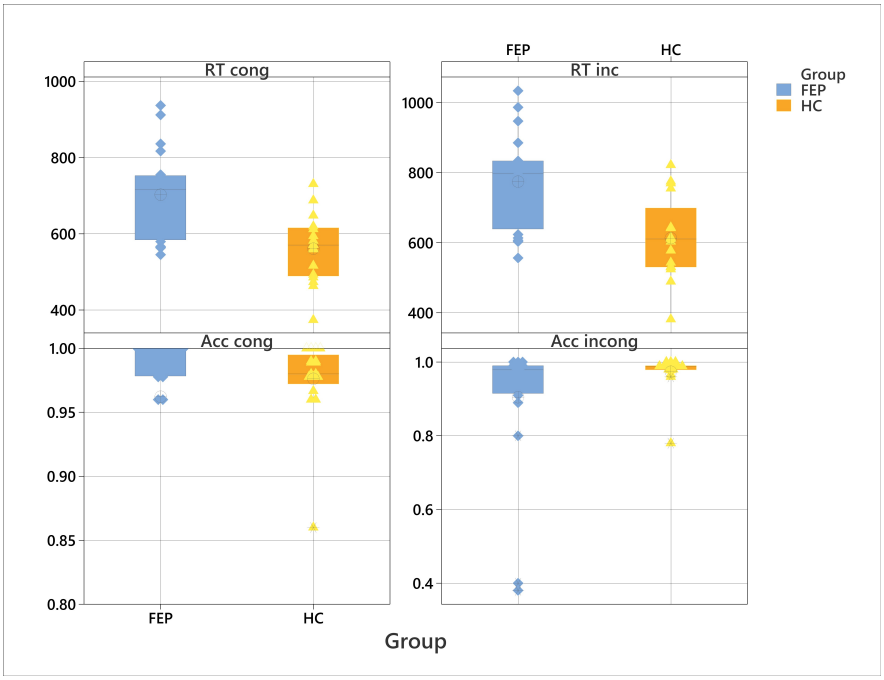

Figure 6.3.5: Boxplot comparing FEP group with control (HC) group on Stroop test performance (were RT is reaction time, Acc is accuracy, cong is congruent, incong is incongrugent).

Cognitive Performance on Stroop and DLPFC E/I Metabolite Levels

A total of 17 HC and 17 FEP participants had both Stroop and DLPFC E/I metabolite levels.

There were no significant correlations within the HC group. However, there were significant correlations between DLPFC Glu and accuracy for incongruent stimuli and Glx and accuracy for incongruent stimuli in the FEP group (Table 6.14).

6.3.4 MRS E/I Metabolite and Social Defeat

A total of 18 HC and 20 FEP had both social defeat measures (social defeat scale (SDS) and social comparison rating scale (SCRS)) during the MRS study sessions. Glutamate (Glu), glutamine (Gln), combined glutamate and glutamine (Glx) and GABA are the metabolites explored that directly reflect E/I balance.

It should be noted that SDS measures social defeat, whereas SCRS measures social rank and is therefore inverse to feelings of social defeat.

Social Defeat in HC vs FEP

There were significant differences in SDS scores with FEP participants scoring higher in SD compared to HC participants. There were no significant differences in SCRS scores between groups (Table 6.1).

The difference in SD scores between groups remained significant when correcting for multiple comparison.

Social Defeat and ACC E/I Metabolite Levels

A total of 17 HC and 20 FEP participants had both social defeat measures (social defeat scale (SDS) and social comparison rating scale (SCRS)) and ACC metabolite levels.

Within this subset (ACC MRS) there were no significant correlations between SDS and SCRS scores and ACC E/I metabolite levels in neither FEP nor HC groups (Table 6.15).

Multivariate testing (Wilk's Λ) demonstrated no significant effects of independent variables nor interactions on E/I related metabolite levels, including SDS scores ($F(4, 22) = 0.464$, $p = 0.078$, Wilk's $\Lambda = 0.922$, $\eta_p^2 = 0.078$) and SCRS scores ($F(4, 22) = 0.465$, $p = 0.078$, Wilk's $\Lambda = 0.922$, $\eta_p^2 = 0.078$).

Moreover, univariate ANOVAs found no significant between-subject effects of group on ACC GABA, Glu, Gln nor Glx concentration levels.

Social Defeat and DLPFC E/I Metabolite Levels

A total of 16 HC and 17 FEP had both social defeat measures (social defeat scale (SDS) and social comparison rating scale (SCRS)) and DLPFC metabolite levels.

Within this subset (DLPFC MRS) there were no significant correlations between SDS and SCRS scores and DLFPC GABA, Glu, Gln and Glx levels for neither the FEP nor HC groups (Table 6.16).

In the GLM multivariate testing (Wilk's Λ) demonstrated no significant effects of independent variables, including SDS scores and SCRS scores, on E/I related metabolite levels. Moreover, univariate ANOVAs found no significant between subject effects.

Healthy Controls								
	GABA		Glu		Gln		Glx	
	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value
RT 0-back	-0.332	0.208	-0.035	0.897	0.076	0.778	0.082	0.762
RT 1-back	-0.150	0.579	0.229	0.393	0.171	0.528	0.244	0.362
RT 2-back	-0.135	0.617	0.194	0.471	-0.003	0.991	0.109	0.688
RT 3-back	0.035	0.897	0.397	0.128	-0.082	0.762	0.191	0.478
Acc 0-back	-0.347	0.188	-0.120	0.659	-0.150	0.580	-0.245	0.360
Acc 1-back	-0.076	0.781	0.016	0.952	-0.081	0.764	-0.013	0.961
Acc 2-back	-0.272	0.309	-0.236	0.379	-0.270	0.312	-0.335	0.205
Acc 3-back	0.038	0.888	0.004	0.987	-0.264	0.323	-0.146	0.590
Patients with FEP								
	GABA		Glu		Gln		Glx	
	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value
RT 0-back	0.211	0.417	0.078	0.765	0.066	0.801	0.098	0.708
RT 1-back	0.181	0.486	0.150	0.567	-0.159	0.541	0.002	0.993
RT 2-back	0.081	0.758	0.250	0.330	-0.108	0.680	0.096	0.715
RT 3-back	0.105	0.687	-0.056	0.830	-0.208	0.422	-0.199	0.445
Acc 0-back	0.185	0.478	0.206	0.429	**0.490**	**0.046**	0.441	0.077
Acc 1-back	0.241	0.352	-0.267	0.301	-0.063	0.811	-0.214	0.410
Acc 2-back	-0.074	0.779	-0.260	0.313	0.065	0.804	-0.114	0.663
Acc 3-back	0.144	0.582	-0.371	0.143	-0.088	0.736	-0.273	0.290

Table 6.10: Spearman's rho correlational analysis between performance on the N-back, as measured by reaction time (RT) and accuracy (Acc), and E/I metabolites in the ACC for HC and FEP participants

Healthy Controls								
	GABA		Glu		Gln		Glx	
	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value
RT 0-back	0.135	0.617	0.076	0.778	-0.032	0.905	0.109	0.688
RT 1-back	0.188	0.485	0.171	0.528	0.156	0.564	0.291	0.274
RT 2-back	0.303	0.254	0.279	0.295	0.071	0.795	0.265	0.322
RT 3-back	**0.524**	**0.037**	**0.509**	**0.044**	-0.112	0.680	0.318	0.231
Acc 0-back	0.105	0.699	0.321	0.226	-0.054	0.843	0.271	0.309
Acc 1-back	0.071	0.794	0.316	0.233	-0.340	0.198	0.037	0.892
Acc 2-back	0.181	0.502	0.323	0.233	-0.272	0.307	0.184	0.495
Acc 3-back	0.279	0.295	**0.604**	**0.013**	-0.121	0.655	0.338	0.200
Patients with FEP								
	GABA		Glu		Gln		Glx	
	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value
RT 0-back	**0.565**	**0.035**	0.160	0.584	0.103	0.725	0.178	0.543
RT 1-back	0.486	0.078	0.341	0.233	0.125	0.670	0.323	0.260
RT 2-back	0.398	0.159	0.393	0.164	0.046	0.876	0.323	0.260
RT 3-back	0.288	0.318	0.411	0.144	0.222	0.446	0.376	0.185
Acc 0-back	0.024	0.934	-0.068	0.816	0.358	0.209	-0.042	0.887
Acc 1-back	-0.265	0.361	0.172	0.557	0.000	1.000	0.198	0.496
Acc 2-back	-0.348	0.223	-0.081	0.782	0.086	0.771	-0.046	0.875
Acc 3-back	-0.315	0.273	-0.178	0.542	-0.022	0.940	-0.156	0.593

Table 6.11: Spearman's rho correlational analysis between performance on the N-back, as measured by reaction time (RT) and accuracy (Acc), and E/I metabolites in the DLPFC for HC and FEP participants

	Patients with FEP n= 20	Healthy Controls n= 17	t-value	p-value	Cohen's D effect size
RT Incong	702.80 (115.32)	561.18 (88.39)	**-4.133**	**<0.001**	**-1.363**
RT Cong	774.79 (132.38)	613.17 (115.42)	**-3.922**	**<0.001**	**-1.294**
Acc Incong	0.96 (0.13)	0.98 (0.03)	0.447	0.658	0.147
Acc Cong	0.90 (0.18)	0.97 (0.05)	1.627	0.118	0.500

Table 6.12: Means (standard deviations) for Stroop Colour cognitive performance, and group comparison statistics (t-test or chi-square) between FEP and HC. 'RT' refers to reaction time, 'Acc' refers to accuracy, 'Incong' refers to incongruent condition, and 'Cong' refers to congruent condition. Equal variance was assumed for all variables except for accuracy on the incongruent condition (based on a Levene's Test of Equality of Variance), a confidence interval (CI) of the difference of 95% was used, and p tests were two-tailed.

Healthy Controls								
	GABA		Glu		Gln		Glx	
	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value
RT Cong	-0.182	0.533	0.332	0.246	0.389	0.169	0.442	0.114
RT Incon	-0.059	0.840	0.354	0.215	0.341	0.233	0.402	0.154
Acc Cong	0.069	0.815	0.196	0.502	-0.280	0.332	-0.004	0.988
Acc Incon	-0.455	0.102	-0.321	0.262	-0.208	0.475	-0.346	0.225
Patients with FEP								
	GABA		Glu		Gln		Glx	
	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value
RT Cong	-0.111	0.640	-0.140	0.556	-0.194	0.413	-0.140	0.556
RT Incon	-0.035	0.885	-0.017	0.945	-0.093	0.696	-0.006	0.980
Acc Cong	-0.087	0.717	0.183	0.440	-0.395	0.085	-0.146	0.539
Acc Incon	**0.548**	**0.012**	0.122	0.609	-0.255	0.277	-0.032	0.894

Table 6.13: Spearman's rho correlational analysis of Stroop performance scores, where RT is reaction time, Acc is accuracy, cong is congruent condition, and incon is incongruent condition, and ACC E/I metabolites for HC and FEP participants

Healthy Controls								
	GABA		Glu		Gln		Glx	
	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value
RT Cong	0.039	0.894	0.174	0.551	0.440	0.115	0.127	0.665
RT Incon	0.028	0.926	-0.124	0.673	0.324	0.258	0.097	0.742
Acc Cong	0.148	0.614	-0.044	0.882	0.426	0.129	0.213	0.464
Acc Incon	-0.064	0.829	-0.256	0.377	0.422	0.133	0.058	0.844
Patients with FEP								
	GABA		Glu		Gln		Glx	
	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value
RT Cong	0.218	0.400	-0.243	0.346	-0.028	0.346	-0.218	0.401
RT Incon	0.223	0.389	-0.141	0.589	-0.089	0.589	-0.148	0.570
Acc Cong	-0.292	0.255	-0.214	0.409	**-0.556**	**0.021**	-0.350	0.168
Acc Incon	-0.467	0.059	-0.395	0.116	-0.312	0.116	-0.433	0.082

Table 6.14: Spearman's rho correlational analysis of Stroop performance scores, where RT is reaction time, Acc is accuracy, cong is congruent condition, and incon is incongruent condition, and DLPFC E/I metabolites for HC and FEP participants

Healthy Controls				
	SDS scores		SCRS scores	
	Spearman's rho	p-value	Spearman's rho	p-value
GABA	-0.012	0.965	-0.198	0.462
Glu	0.427	0.099	-0.223	0.406
Gln	0.171	0.527	-0.232	0.387
Glx	0.336	0.204	-0.290	0.277
Patients with FEP				
	SDS scores		SCRS scores	
	Spearman's rho	p-value	Spearman's rho	p-value
GABA	-0.250	0.287	0.169	0.477
Glu	0.037	0.877	0.062	0.794
Gln	0.332	0.153	-0.209	0.376
Glx	0.146	0.539	0.017	0.945

Table 6.15: Spearman's rho correlational analysis of social defeat measures (social defeat scale- SDS and social comparison rating scale- SCRS) and ACC E/I metabolites for HC and FEP participants

Healthy Controls				
	SDS scores		SCRS scores	
	Spearman's rho	p-value	Spearman's rho	p-value
GABA	0.010	0.970	-0.121	0.656
Glu	-0.060	0.824	-0.265	0.321
Gln	0.137	0.613	0.178	0.509
Glx	0.040	0.884	-0.094	0.728
Patients with FEP				
	SDS scores		SCRS scores	
	Spearman's rho	p-value	Spearman's rho	p-value
GABA	0.117	0.655	-0.164	0.529
Glu	0.054	0.837	0.440	0.866
Gln	0.364	0.151	-0.361	0.155
Glx	0.144	0.582	-0.066	0.801

Table 6.16: Spearman's rho correlational analysis of social defeat measures (social defeat scale- SDS and social comparison rating scale- SCRS) and DLPFC E/I metabolites for HC and FEP participants

6.4 Discussion

6.4.1 MRS E/I Metabolite Levels and Psychosis

Main Findings

- There were no significant group differences in E/I metabolite levels in the ACC nor the DLPFC.
- There was a significant correlation between ACC Glx levels and negative psychosis symptoms.
- There were no significant correlations between DLPFC metabolite levels and across PANSS scores.

Findings in Context

It was hypothesised that there there would be decreases in E/I metabolites in both the ACC and DLPFC in the FEP group compared to controls. The present study found no significant differences between the FEP and control group in E/I metabolite levels. Although the FEP group had both insignificantly higher glutamate and GABA concentrations in both the ACC and DLPFC, as well as insignificantly higher glutamine and Glx levels in the ACC. These findings suggest that hyperexcitation may still be present in FEP but that E/I metabolite levels are not significantly increased compared to controls as they may be already decreasing as a result of excitotoxicity.

Previous literature has demonstrated that unmedicated patients had increased glutamatergic levels compared to controls (Marsman et al., 2013; Plitman et al., 2016b,a; Poels et al., 2014; Théberge et al., 2002), and that glutamatergic levels decreased with the administration of antipsychotics (Kegeles et al., 2012). Antipsychotics have also been shown to impact the GABAergic system, with some evidence for elevated GABA baseline levels in antipsychotic naive psychosis compared to those on medication (Egerton et al., 2017b). This could suggest that the lack of significant differences between groups in the present thesis could be a result of antipsychotic medication that FEP participants had, as well as duration of treatment, and not due to excitotoxcity. Therefore, antipsychotic medication colours the understanding of potential glutamatergic and GABAergic abnormalities explored in the present work. Therefore, further research exploring E/I metabolite levels in both medication-naive and medicated FEP groups compared to controls, would further clarify the role medication and stage of illness have in E/I balance in psychosis.

There are inconsistencies in previously reported frontal, particularly ACC, glutmatergic levels in FEP (Dempster et al., 2020; Merritt et al., 2016; Poels et al., 2014; Reid et al., 2019; Smesny et al., 2015; Squarcina et al., 2017; Sydnor and Roalf, 2020). These studies differed in group specification, with some combining FEP and chronic psychosis or multiple comborbidities with the FEP group, such as schizoaffective disorder or bipolar. Extant literature has demonstrated consistently that region, treatment status, and disease stage played a role in E/I metabolite levels (Marsman et al., 2014; Merritt et al., 2016). Further, despite shared methodology the present study and pilot study (Godlewska et al., 2021) had different results concerning E/I metabolite levels, with the pilot study reporting a significant decrease in glutamtergic levels in the ACC for the FEP group compared to controls. The pilot study did not see a significant difference in DLPFC, matching the present study findings, but found decreases on a trend-level which were not replicated in this study. This differences could be a result of different group specifications, with the pilot study only measuring metabolite levels in males, whereas the present study had both female and male participants. This may be of particular importance as there has been previous research to suggest that sex does play a role in glutamatergic associated metabolites (Tayoshi et al., 2009).

Thus far, the extant literature does not have consistent findings about GABAergic dysfunction in psychosis (Chiapponi et al., 2016; Egerton et al., 2017b). Similar to glutamatergic metabolite levels, GABA has been shown to be increased in unmedicated patients and to decrease with disease progression and pharmacological treatment (De La Fuente-Sandoval et al., 2018; Kegeles, 2016; Kubota et al., 2020; Thakkar et al., 2017). Nonetheless, the exact mechanisms behind E/I balance and particularly GABA's role in psychosis have yet to be elucidated (Liu et al., 2021). Moreover, increases in glutamate could lead to increased GABA, as glutamate is a precursor for GABA synthesis (Yüksel and Öngür, 2010). Thus, given that extracellular and intra-synaptic GABA cannot be differentiated it is possible that these findings reflect non-synaptic GABA activity or could point to GABA neurotransmission being non-significantly increased in FEP population. Further research would be required to provide a more conclusive understanding of GABA's role in psychosis and in frontal E/I balance.

This thesis also failed to find any significant relationship between symptoms of psychosis and E/I metabolite levels in the DLPFC. This is in line with the pilot study that generally were not able to find an association between symptomology and DLPFC E/I metabolite levels in psychosis compared to controls (Godlewska et al., 2021). This is also in line with previous studies (Poels et al., 2014), although it was not a consistent finding (De La

Fuente-Sandoval et al., 2013).

However, there was a moderate significant correlation between ACC Glx levels and negative symptoms of psychosis. Previous literature has found an association between higher ACC glutamate levels and symptom severity (Egerton et al., 2012), although again this is not a consistent finding (Godlewska et al., 2021; Reid et al., 2019; Tarumi et al., 2020). It should also be noted that in aforementioned studies that found an association between sympotomology and DLPFC MRS results (De La Fuente-Sandoval et al., 2013), reported symptom severity was higher across all symptom categories than in the FEP group in the present study. Whereas, in general previous studies that found no significant association between ACC glutamtergic levels and symptomology, reported lower symptom severity in the FEP group compared to the present study. Therefore, the discrepancy in findings could also be due to the patient group in the present study being less florid than in others, with more symptom severity being linked with glutamatergic aberrations. The association between ACC Glx with negative symptoms in the present study should be interpreted with caution as this study could be underpowered and previous literature lacks consistent findings. Longitudinal studies across disease would best detect potential E/I metabolite associations with symptom severity.

6.4.2 MRS E/I Metabolite Levels and Cognition

Main Findings

- FEP participants performed significantly worse on all BACS tasks, except for the Tower of London, and had significantly worse BACS composite scores compared to controls.
- There were significant negative correlations between ACC GABA and Glx with verbal memory, ACC GABA and motor performance, and ACC Glx and symbol coding in the HC group. There were no significant correlations in the FEP group.
- There were significant negative correlations between DLPFC Gln and composite BACS scores, verbal memory, motor performance, and symbol coding, and executive the Tower of London task in the HC group. There were no significant correlations in the FEP group.
- FEP participants performed significantly worse on the 1-back conditions of the N-back compared to controls.
- There was a significant correlation between ACC Gln and accuracy in the 0-back

condition of the N-back in the FEP group. There were no significant correlations in the HC group

- There were significant correlations between DLPFC GABA and DLPFC Glu with reaction time in the 3-back condition, and DLPFC Glu and accuracy on the 3-back condition in the HC group.
- There was a significant correlation between DLPFC GABA and reaction time in the 0-back of the N-back in the FEP group.
- The FEP group had significantly longer reaction times in both the congruent and incongruent conditions of the Stroop task compared to HC. There were no significant group differences in accuracy for either Stroop condition.
- There was a significant correlation between ACC GABA, and DLPFC Gln levels and accuracy in the incongruent condition in the Stroop in the FEP group. There were no significant correlations in the HC group.

Findings in Context

The present study results across the BACS, N-back and Stroop were partially in keeping with previous literature and hypotheses. These previous findings suggest that FEP groups should perform worse on cognitive tasks and that this performance may be correlated with E/I metabolite levels. Impaired cognition is a known and well documented phenomenon in psychosis, and has been associated with disruptions in E/I balance related metabolites (Bojesen et al., 2021). NMDA antagonist models in rodents and humans have implicated NMDA hypofunctioning in cognition, although mechanisms between this association in humans remain unclear (Howes and Shatalina, 2022; Reddy-Thootkur et al., 2022).

FEP participants performing consistently worse across all BACS tasks and on the composite BACS score compared to controls in the present study. This finding is both consistent with previous literature as well as with the pilot study (Godlewska et al., 2021; Oomen et al., 2023). Unlike the pilot study, this study did not find any significant correlations between BACS performance and E/I metabolite levels in either the ACC nor DLPFC for FEP participants. The HC group in this study had ACC GABA and Glx correlated with several BACS tasks and BACS composite scores. Moreover, the HC group in the present study had an association between DLPFC glutamine and all BACS tasks with the exception of verbal fluency. Previous literature has reported inconsistent findings in correlations between DLPFC E/I metabolites and cognitive performance in FEP, particularly in working

memory tasks (Kegeles et al., 2012; Wang et al., 2019). Finding on BACS and E/I metabolites in FEP has been inconsistent across the extant literature (Griffiths et al., 2022; Wang et al., 2019). Further, the existing literature on E/I metabolite levels and cognition in psychosis is inconsistent (Reddy-Thootkur et al., 2022). There were variation in the demographic data (Godlewska et al., 2021), stage of illness (Griffiths et al., 2022), cognitive assessments used (Reid et al., 2019; Wang et al., 2019) and MRS acquisition techniques (Kegeles et al., 2012). It should also be noted that these studies also had different findings to the present study in regards to E/I metabolite levels in those with psychosis compared to controls. All of these factors could contribute to the variation in findings on the relationship between metabolite levels (specifically E/I metabolite levels) and cognition in psychosis.

The N-back task measures several facets of cognition, namely working memory alongside attention and sensorimotor control (Glahn et al., 2005). This thesis demonstrated that the FEP group performed significantly worse in accuracy on the 1-back conditions of the N-back, but saw no significant differences in reaction time or for accuracy on other N-back conditions. Extant literature is inconsistent in terms of expected performance for a psychosis group in the N-back compared to controls (Karatekin et al., 2009). Although, working memory has been shown to be particularly impaired in psychosis (Frydecka et al., 2014). The present study found associations between DLPFC E/I metabolite levels and performance on the 3-back condition in the HC group. Whereas, the FEP group had ACC glutmatergic and DLPFC GABAergic with performance on the 0-back condition. A meta-analysis on N-back performance and neuro-imaging findings has suggested consistently a trend for hypofrontality, with an increase in activation in the ACC and a decrease in the DLPFC (Glahn et al., 2005). This finding is consistent with the theory that one of the driving mechanisms behind psychosis is the disruption in connectivity between frontal and limbic regions. However, previous work directly correlating working memory with glutamatergic metabolite levels in psychosis has failed to find an association between performance and E/I metabolite levels (Corcoran et al., 2020; Kegeles et al., 2012). Given the lack of consistent and robust literature, it is unclear as to whether these findings point to a trend in the association between E/I metabolite levels and working memory (Merritt et al., 2013).

Frontal regions, particularly the ACC, have been implicated heavily in the Stroop effect seen in psychosis (Krabbendam et al., 2009). The finding of worse reaction times in both the congruent and in-congruent conditions in FEP compared to controls, supports previous literature (Kerns et al., 2005). This study saw significant correlations between accuracy

in the in-congruent condition with ACC GABA and DLPFC Gln levels in the FEP group, which was not present in the HC group. These findings could be reflective of disrupted connectivity as exhibited through abnormal E/I balance associations between the ACC and DLPFC in psychosis. Specially, it points to potential increased inhibition in the ACC leading to greater activation in the DLPFC being related to error and conflict activity in FEP. Hypo-functioning of the ACC has previously been associated with schizophrenia and performance on the Stroop in the past (Cadena and White, 2017; Krabbendam et al., 2009; Kerns et al., 2005; Taylor et al., 2015). Although hypo-functioning ACC seems to be a consistent outcome when studying the Stroop effect in psychosis, more research with large sample sizes and replicated methods would be necessary to have a more concrete and coherent understanding. Moreover, the relationship between hypo-functioning and increased inhibition, as assessed through GABA, and cognition in FEP should be further established using combined fMRI and MRS methods.

6.4.3 MRS E/I Metabolite Levels and Social Defeat

Main Findings

- There were no significant correlations between ACC E/I metabolite concentrations and SD scores for neither the FEP nor HC group.
- There were no significant correlations between DLPFC E/I metabolite concentrations and SD scores for neither the FEP nor HC group.
- There were no significant effects of SD scores on E/I metabolite levels in the ACC nor the DLPFC.

Findings in Context

The present study did not find any associations between ACC and DLFPC E/I metabolite levels and SD scores for neither the FEP nor HC group. This is not in keeping with the hypotheses that SD would be linked with E/I balance and previous literature that has demonstrated an association between SD and disruption in mesolimbic dopamine, E/I activity and psychotic symptoms (Schwartz et al., 2012; Selten et al., 2013). This could suggest that SD does not induce detectable neurometabolic changes, or that the SD scales used are not able to accurately detect a unitary and measurable psychological construct.

Previous rodent studies have linked SD with decreased NMDA functioning and E/I

metabolite abnormalities (Novick et al., 2016; Zhang et al., 2016). To the author's knowledge there have not been any studies exploring SD in psychosis using MRS. However, one study explored SD in schizophrenia and controls using functional near-infrared spectroscopy, and found that exposure of SD was associated with decreased activity in the ventromedial PFC in both patients and controls (Baskak et al., 2015). There has also been research exploring proxy-SD in schizophrenia using functional MRI that demonstrated hyperactvivity in prefrontal regions following proxy-SD, such as social rejection or social exclusion, induction (Gradin et al., 2012; Lee et al., 2014). However, previous studies that found a link between SD or proxy-SD and neural activity changes were conducted in chronic schizophrenia, suggesting that stage of illness may impact the relationship between SD and neural activity. Therefore, further MRS studies exploring SD over the course of illness, in high-risk, FEP and chronic schizophrenia, would elucidate the role of stage of illness on the potential interaction between SD and E/I metabolite levels. Additionally, the coupling of MRS with PET imaging would further clarify if dopaminergic activity plays a role in SD, E/I and psychosis.

It is also possible that E/I imbalances in psychosis, which have been demonstrated in extant literature and supports the NMDA hypofunctioning and excitotoxicity hypothesis (Marsman et al., 2013; Poels et al., 2014; Théberge et al., 2002), could lead to a susceptibility for dopamine sensitisation via SD. Previous literature has shown that socially defeated individuals (with severe hearing impairments) had hypersensitivity to dopamine (Gevonden et al., 2014). Moreover, prefrontal cortex glutamate activity has been established to impact midbrain dopamine, and more indirectly GABA interneurons (Jauhar et al., 2018). NMDA hypo-functioning, through ketamine models, have been associated with increased striatal dopamine (Kokkinou et al., 2018). The link between E/I and downstream dopamine abnormalities has been hypothesised, although further research would be required to establish a strong causal link and to explore the potential role of SD (McCutcheon et al., 2019, 2020). Therefore, the coupling of MRS with positron emission tomography (PET) and/or single-photon emission computed tomography (SPECT) imaging, that both use radiotracers to bind and measure dopamine receptors and transporters, would further clarify if dopaminergic activity plays a role in SD, E/I and psychosis.

6.5 Conclusion

The present study provides limited support for the role of frontal E/I imbalance in FEP. Although there were no significant group differences, when considering previous literature and the E/I balance hypothesis of psychosis there seems to be some trend-level support for hyperexcitability in frontal areas. This is somewhat in contrast to the pilot study (Godlewska et al., 2021) but similarly could suggest that hyper-excitability occurs prior to symptom onset and persists into FEP. A longitudinal study, that includes FEP, exploring the role of different regions, neurotransmitters and patient groups would better establish the potential mechanism behind psychosis, cognition and SD.

The findings in this study were not able to provide a clear picture of E/I metabolite levels and cognition. Inconsistencies in previous literature as well as across cognitive tests in the present study mean that there is little evidence to support any given mechanism behind cognitive impairment in FEP, including the glutamatergic hypothesis. However, considering that come tests measure functions that are not based in the ACC or DLFPC regions, there may be no correlations in the present study but if other regions were scanned there may have been more consistently significant correlations between E/I metabolite levels and cognition. A great deal more research would be required, ideally in a collaborative multi-centre approach, with much larger sample sizes and consistent methodologies to better understand cognition and E/I balance in FEP.

The lack of association between E/I metabolites and SD scores could suggests E/I balance may not be directly involved in the relationship between SD and increased risk of psychosis. Given that SD is hypothesised to affect the mesolimbic dopamine system it is possible that potential E/I imbalances create a susceptibility towards SD and aberrant mesolimbic dopamine. This is in keeping with the dopamine sensitisation hypothesis for role of SD in increased risk of psychosis (Selten et al., 2013). A combined MRS and PET study exploring E/I metabolites and dopamine levels, in the relevant regions, with SD in FEP would provide further insight into the potential biological mechanisms behind SD and psychosis. This study design would also further the understanding of the relationship between E/I balance and dopamine, and could clarify the proposed treatment resistant/treatment respondent subtype hypothesis (Hernaus and Van Amelsvoort, 2018).

Alternatively, social defeat could lead to neurochemical shifts in prodromal stages as opposed to during the earlier stages of psychosis (Gevonden et al., 2014; Schnider et al., 2022). This could account for the lack of association between social defeat and MRS in the FEP group in the present study. Therefore, a longitudinal study would be most

appropriate to follow individuals at high-risk and those who go on to develop psychosis while measuring E/I metabolite levels, and sentiments of social defeat at each stage. This type of study would also provide some clarity on the potential causal relationship between social defeat and psychosis that has been posited in previous literature (Selten and Cantor-Graae, 2005).

It should be noted that despite the sample size of this study being similar to those of previous studies (Godlewska et al., 2021), it is small. Despite power being calculated prior to data collection, there is a possibility that the present study is under-powered, especially when taking into account the potential heterogeneity within the FEP group. Therefore this could limit the application of these findings to current approaches or treatments.

Another potential limitation, is that this analysis did not account for the use of cannabis and its potential impact on MRS and other findings. Cannabis use has been reported at much higher rates in those with FEP compared to healthy controls (Ksir and Hart, 2016). However, a previous study looking at immigration (a group thought to be prone to developing social defeat) and dopamine found that cannabis did not make a difference in group effects (Egerton et al., 2017a). More relevantly, a study exploring cannabis use in FEP's impact on glutamatergic levels in the ACC and found no significant group differences nor an effect of cannabis on glutamatergic levels in the ACC (Sami et al., 2020). Interestingly, this study did find an effect of cannabis on glutamate levels in the caudate of FEP participants, suggesting that it could be region specific (Sami et al., 2020). With that being said, the causal relationship between cannabis and psychosis has been disputed, with cannabis use being associated with those who are already more likely to develop psychosis (Ksir and Hart, 2016). As this study focused on the ACC and DLPFC it is unlikely that cannabis use played a role, however controlling for cannabis use would have strengthened the interpretation and contextualisation of the present findings.

Another limitation was the MRS metabolites were only measured during resting state, as opposed to during the cognitive tasks. Therefore, associations between cognitive task performance and resting state MRS data may not be reflective of what occurs *in-vivo* during cognition. With that being said, if E/I balance abnormalities were a trait of psychosis, as opposed to state related, then metabolite levels should be fairly stable. Previous literature has shown that ACC glutamate levels in particular alter between cognition and resting state (Zahid et al., 2023). As such, a study exploring cognitive performance in FEP should be performed using dynamic MRS to better elucidate this relationship.

Moreover, MRS has limitations, particularly it is not possible to distinguish extracellular and vesicular metabolite levels and intra-synatpic levels of metabolites (Kegeles et al., 2012). This is particularly pertinent to this study as both glutamate and GABA perform several roles and glutamate acts as an important precursor to several other metabolites (such as glutamine or GSH) (Yüksel and Öngür, 2010). Therefore, the functional aspects of E/I metabolite levels remain unclear. With that in mind, the evidence tying MRS E/I metabolite levels with actual neurotransmission is fairly strong with carbon-MRS studies pointing to a strong link between neuronal activity and changes in glutamate-glutamine activity and glutamate not readily being able to pass the blood-brain barrier nor are macromolecular assemblies of glutamatergic amino acids measured during MRS (Yüksel and Öngür, 2010). A similar argument has been made for GABA measures in MRS being somewhat reflective of neurotransmission, as there have been links between behavioural measures and MRS measured GABA (Stagg et al., 2011).

Chapter 7

Comparative Analysis of EEG and MRS markers of E/I balance in First-Episode Psychosis and Healthy Controls

7.1 Introduction

Multimodal research is a term that has been applied to both the simultaneous and separate, different times or different study sessions, data acquisition using two or more different methods on the same participant. The brain is incredibly complex and relies on a combination of metabolic, electromagnetic and vascular processes on the molecular to the cortical level (Uludağ and Roebroeck, 2014), hence each method of measuring neuronal activity taps into various aspects of this complex system. As such the comparability of two different methods may be limited, and one can not take the place of another. However, though comparing findings and exploring associations across different methods may not allow for direct comparison they do provide context and a more holistic understanding of the explored phenomena (Bai et al., 2016; Pierce et al., 2021; Uludağ and Roebroeck, 2014).

EEG offers good temporal resolution and MRI technology offers great spatial resolution, therefore a combined approach offers a clearer view of neural activity (Uludağ and Roebroeck, 2014). As such, cross-validation of hypotheses using different methods could

assist in overcoming the particular limitations of each method (Banihashemi et al., 2023).

As this thesis aimed to explore the role of frontal E/I balance and its association with social defeat and cognition in FEP, a multi-modal approach was employed.

There has been evidence linking MMN, specifically duration MMN with NMDA receptor functioning and glutamate levels (Garrido et al., 2009; Nagai et al., 2017). MMN has also been associated with oscillatory power with evidence of an association with theta, alpha and gamma being the most commonly explored (Fuentemilla et al., 2008; Hong et al., 2012; Kaser et al., 2013; Xiong et al., 2019). These oscillations are also tied to glutamatergic and GABAergic activity, although the exact mechanism remains unknown (Buzsáki and Wang, 2012). Specifically, gamma oscillatory activity has been linked to glutamatergic activity and GABAergic activity (Ahmad et al., 2022; Buzsáki and Wang, 2012; Gao and Penzes, 2015; Gonzalez-Burgos and Lewis, 2012; Lisman, 2012).

This study aims to explore the associations between MMN, relative frontal spectral band power and both ACC and DLPFC E/I metabolite concentration levels in FEP.

It is hypothesised that all three measures will indicate hyperexcitation in the frontal regions of the brain in those with FEP. MMN amplitudes are hypothesised to be correlated with E/I related metabolites in both the ACC and DLPFC. It is expected that MMN amplitudes will be related to several power band oscillations, particularly gamma, theta and alpha power. Finally, gamma activity is hypothesised to be correlated with glutamatergic and GABAergic activity in both the ACC and DLPFC. Spectral power was taken during the non-SD condition as both MMN and MRS data was acquired during non-SD conditions.

7.2 Methods

7.2.1 EEG Study Session

All of the EEG recordings used in this comparative analysis (both spectral and MMN) were collected at the Oxford Centre for Human Brain Activity (OHBA) located at the Warneford Hospital site in Oxford. For more detail on the MMN data acquisition and processing refer to Section 4.2 and for more detail on the relative spectral power data acquisition and processing refer to Section 6.2.

7.2.2 MRS Study Session

All of the MRS recordings used in this comparative analysis were recorded at the Oxford Centre for Functional MRI of the Brain (FMRIB) located at the John Radcliffe Hospital site in Oxford. For more detail on the MRS data acquisition refer to Section 6.2.

7.2.3 Statistical Analysis

Pearson correlations were used with data that did not violate the assumptions required, in this chapter it was used for MMN and MRS comparisons. However, Spearman's rho was employed as a non-parametric alternative and was appropriate for the MMN and spectral data comparisons as well as the MRS and spectral data comparisons.

7.3 Results

7.3.1 Mismatch Negativity and Spectral Analysis

Correlational analysis was conducted between MMN values (amplitude and latency) and relative spectral band power data (including delta, theta, alpha, beta, and gamma).

There were no significant correlations in the HC group between spectral data and MMN values (Fig. 7.3.1). However, the FEP group had a statistically significant moderate correlation between MMN amplitude and relative gamma power in the non-SD condition session (Table 7.1 and Fig. 7.3.2).

7.3.2 Mismatch Negativity and MRS Metabolite Levels

Correlational analysis was conducted between MMN values (amplitude and latency) and concentrations of E/I metabolites in both the ACC and DLPFC.

Mismatch Negativity and the ACC E/I Metabolite Levels

A total of 9 HC and 12 FEP participants had both valid MMN values and ACC metabolite data, allowing for an assessment of the potential relationship between these two variables.

There were no significant relationships between ACC E/I metabolite levels and MMN for neither the FEP nor HC group (Table 7.2).

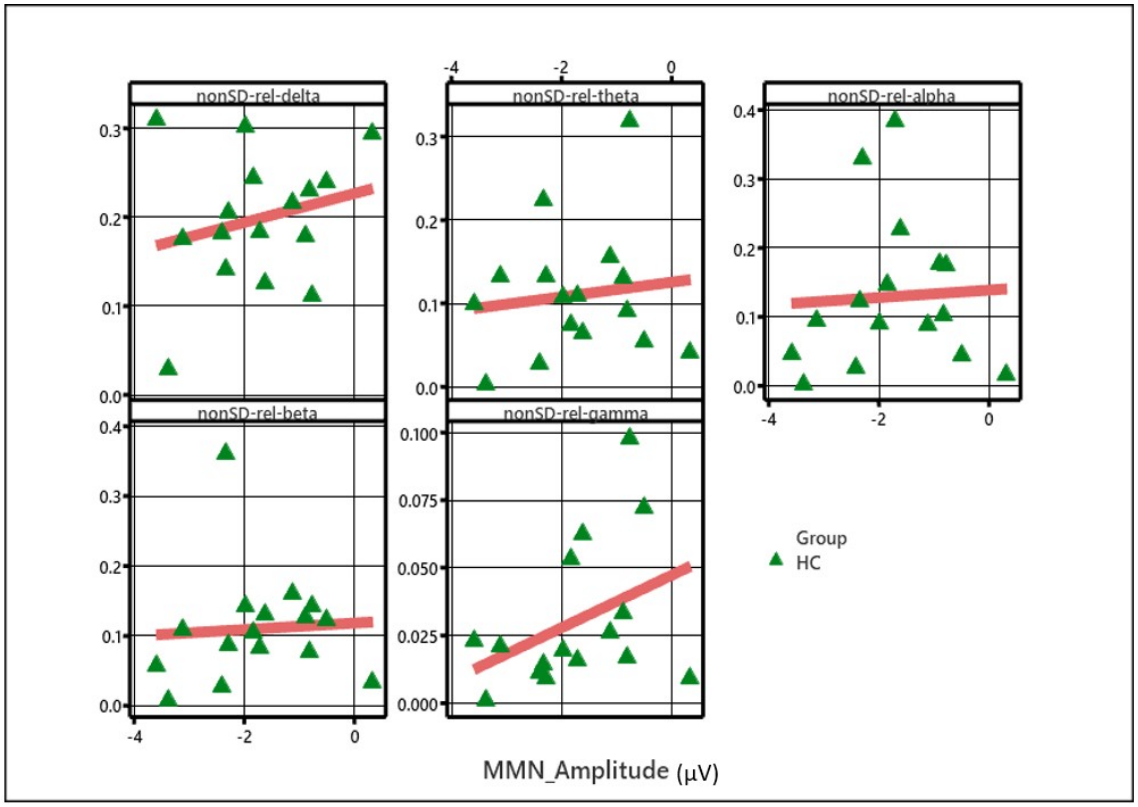

Figure 7.3.1: Scatter plots with the line of best fit for MMN amplitudes with non-SD condition relative frontal spectral band power for the HC group

Mismatch Negativity and DLPFC E/I Metabolite Levels

A total of 8 HC and 12 FEP had data for both MMN values and DLPFC E/I metabolite levels, allowing for the association between these two potential measures of E/I to be compared.

There were no significant correlations between any of the DLPFC E/I metabolite levels with either MMN value for neither the FEP nor HC group (Table 7.3).

7.3.3 Spectral Analysis and MRS Metabolite Levels

Spectral Analysis and ACC E/I Metabolite Levels

A Spearman rho correlation was carried out to assess the relationship between non-SD condition spectral data and ACC E/I metabolites levels.

Within the HC group there were strong significant correlations between ACC GABA and frontal relative delta power (inverse), and between ACC Glx and relative frontal theta

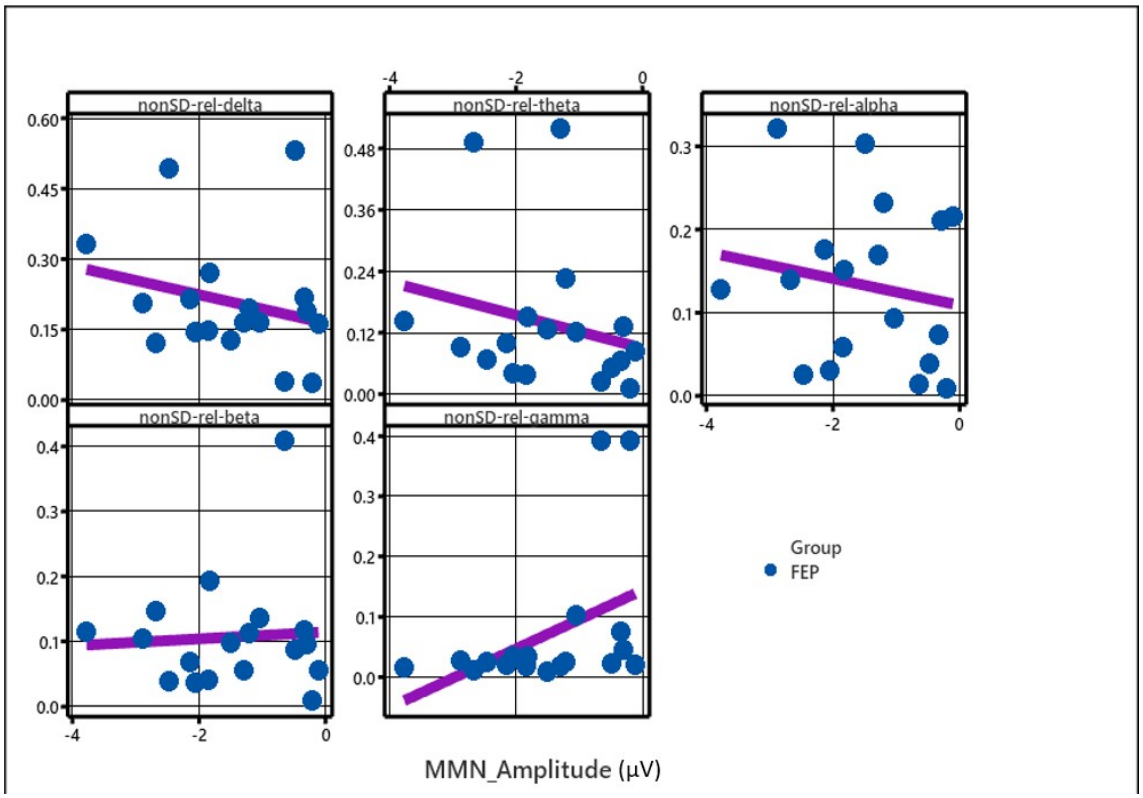

Figure 7.3.2: Scatter plots with the line of best fit for MMN amplitudes with non-SD condition relative frontal spectral band power for the FEP group

power (Table 7.4, Fig. 7.3.3 and Fig. 7.3.4, respectively).

Within the FEP group frontal relative theta power was correlated with ACC Glu and Glx, and frontal relative gamma power was strongly inversely correlated with ACC Glu and Glx levels (Table 7.4, Fig. 7.3.5 and Fig. 7.3.6, respectively). Removing statistical outliers did not change correlational findings for theta and ACC E/I metabolites, however, when removing statistical outliers the gamma correlations were no longer significant. However, given that the FEP participants with outlying gamma values did not differ from other participants based on demographics, medication, or age their data was included in analysis.

Spectral Analysis and DLPFC E/I Metabolite Levels

A Spearman rho correlation was carried out to assess the relationship between non-SD condition spectral data and DLPFC E/I metabolites levels.

The HC group did not have any statistically significant correlations nor trends between DLPFC E/I metabolites and spectral band power. The FEP group had a significant

Healthy Controls				
	MMN Amplitude		MMN Latency	
	Spearman's rho	p-value	Spearman's rho	p-value
delta	0.138	0.610	-0.187	0.488
theta	0.032	0.905	-0.035	0.897
alpha	0.138	0.610	0.069	0.799
beta	0.250	0.350	0.029	0.914
gamma	0.421	0.105	-0.352	0.182
Patients with FEP				
	MMN Amplitude		MMN Latency	
	Spearman's rho	p-value	Spearman's rho	p-value
delta	-0.240	0.336	-0.145	0.566
theta	-0.304	0.219	0.066	0.794
alpha	-0.127	0.616	0.382	0.118
beta	-0.102	0.687	-0.141	0.578
gamma	**0.484**	**0.042**	-0.026	0.919

Table 7.1: Spearman rho's correlation between relative spectral band power and MMN outcomes (amplitude and latency) for HC and FEP participants

Healthy Controls				
	MMN Amplitude		MMN Latency	
	Pearson's correlation	p-value	Pearson's correlations	p-value
GABA	-0.136	0.727	0.268	0.486
Glu	0.218	0.574	0.214	0.580
Gln	-0.087	0.823	0.354	0.350
Glx	0.151	0.698	0.369	0.329
Patients with FEP				
	MMN Amplitude		MMN Latency	
	Pearson's correlation	p-value	Pearson's correlations	p-value
GABA	0.113	0.727	-0.061	0.850
Glu	-0.326	0.301	-0.016	0.960
Gln	-0.178	0.580	-0.310	0.326
Glx	-0.308	0.330	-0.147	0.648

Table 7.2: Pearson correlation coefficients and p-values for correlations between E/I metabolite concentration levels (Glu being glutamate, Gln being glutamine, and Glx being combined Glu and Gln) in the ACC and MMN outcomes for HC and FEP participants

Healthy Controls				
	MMN Amplitude		MMN Latency	
	Pearson's correlation	p-value	Pearson's correlations	p-value
GABA	0.511	0.195	-0.569	0.141
Glu	0.649	0.082	-0.180	0.669
Gln	0.028	0.947	-0.532	0.175
Glx	0.484	0.224	-0.433	0.284
Patients with FEP				
	MMN Amplitude		MMN Latency	
	Pearson's correlation	p-value	Pearson's correlations	p-value
GABA	0.572	0.052	0.101	0.755
Glu	0.392	0.208	0.413	0.182
Gln	0.225	0.481	0.206	0.521
Glx	0.401	0.197	0.415	0.180

Table 7.3: Pearson correlation coefficients and p-values for correlations between E/I metabolite concentration levels (Glu being glutamate, Gln being glutamine, and Glx being combined Glu and Gln) in the DLPFC and MMN outcomes for HC and FEP participants, as well as healthy controls and patients with FEP

strong inverse correlation between relative alpha power and DLPFC GABA levels (Table 7.5).

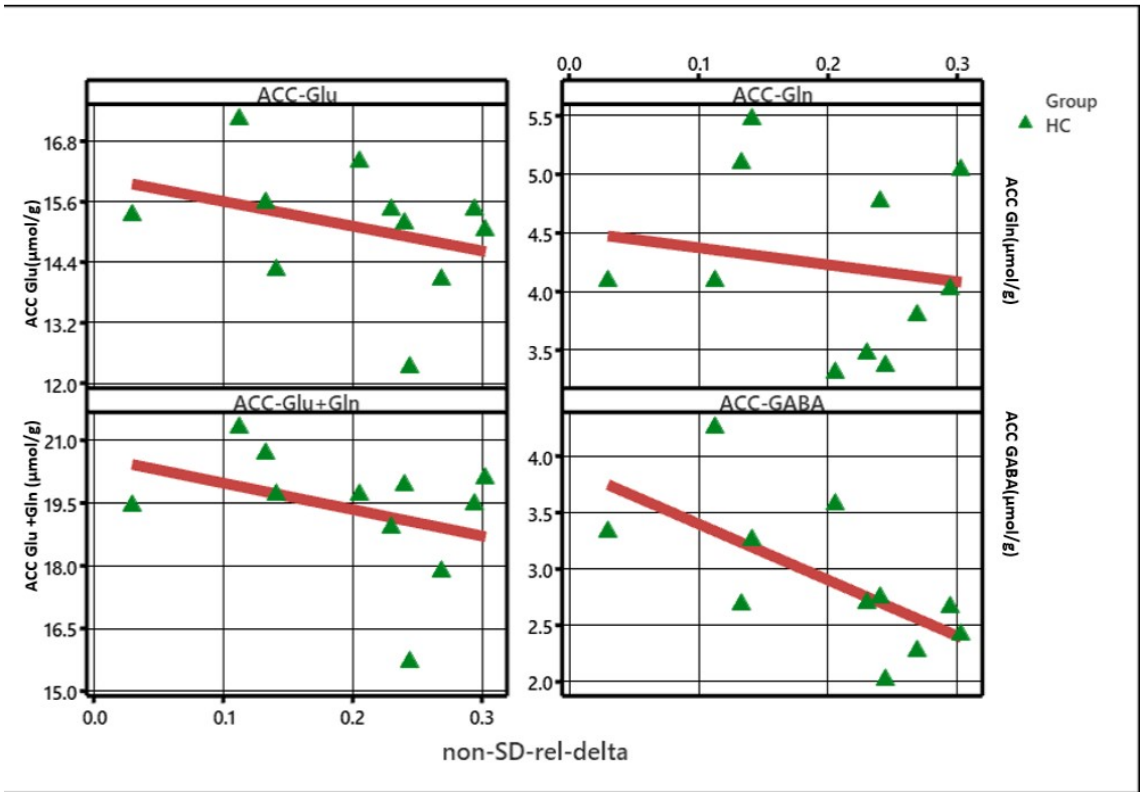

Figure 7.3.3: Scatter plots with the line of best fit for non-SD condition relative frontal delta band power and ACC E/I metabolites for the HC group

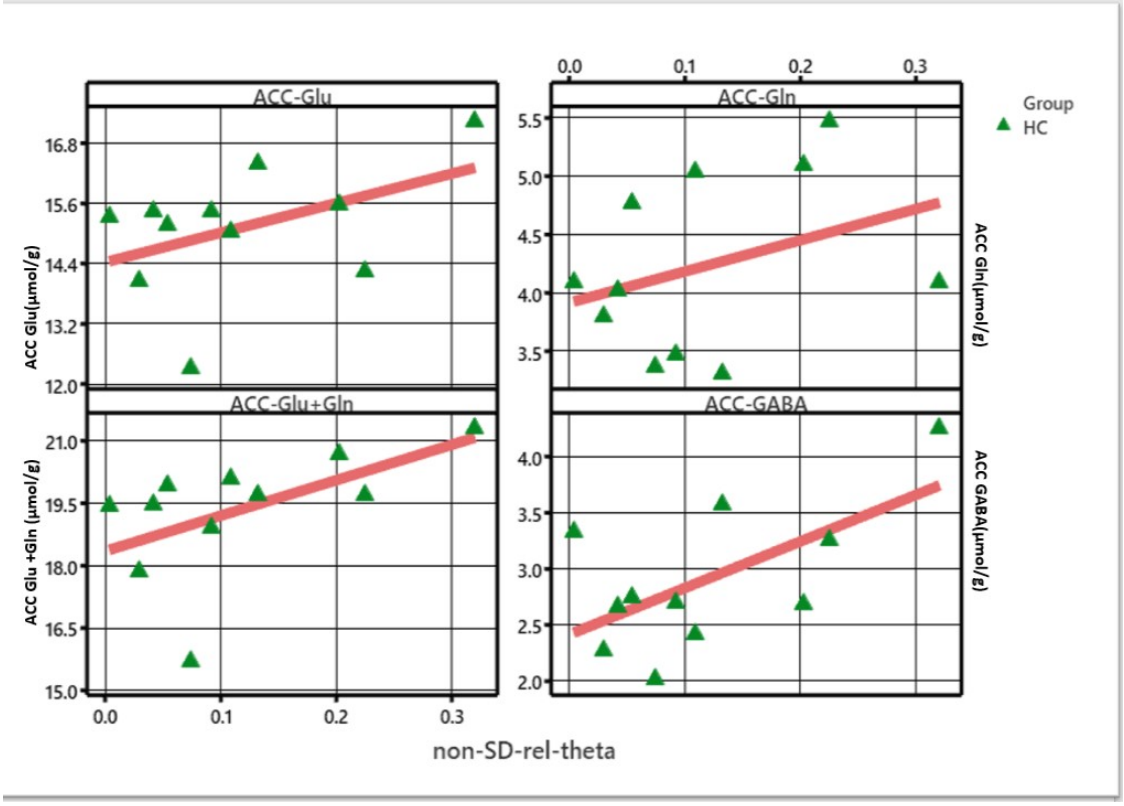

Figure 7.3.4: Scatter plots with the line of best fit for non-SD condition relative frontal theta band power and ACC E/I metabolites for the HC group

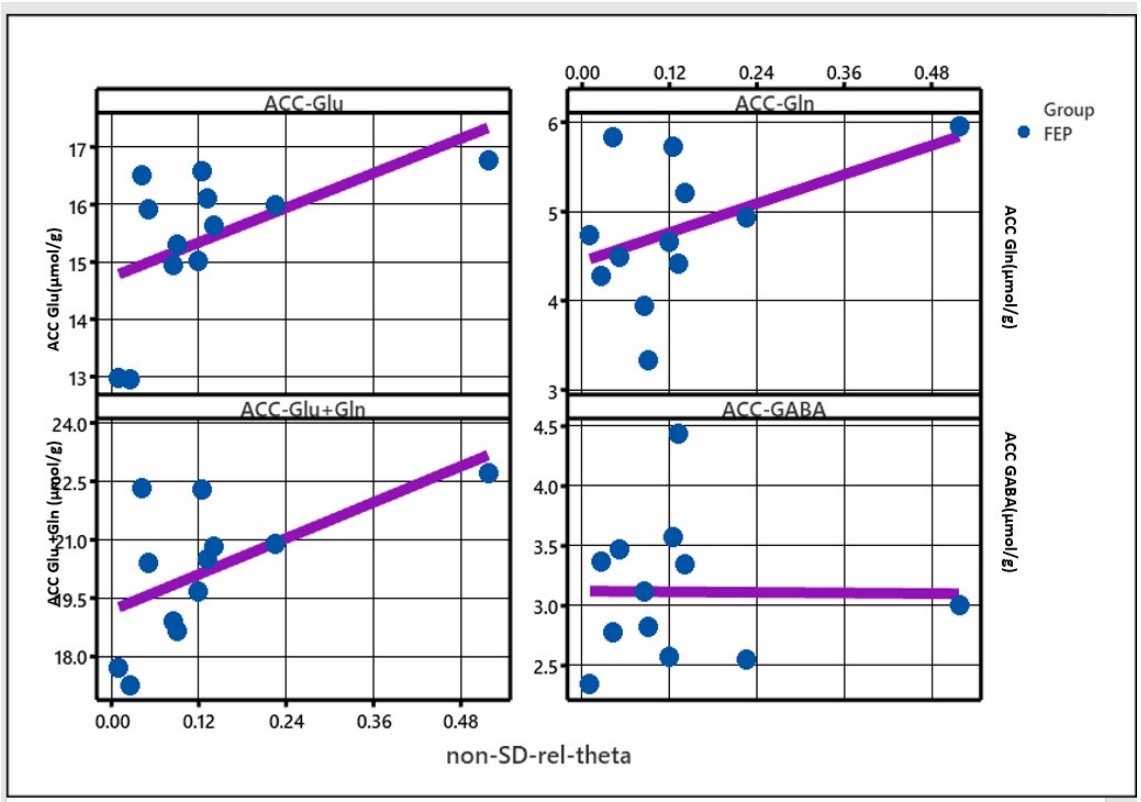

Figure 7.3.5: Scatter plots with the line of best fit for non-SD condition relative frontal theta band power and ACC E/I metabolites for the FEP group

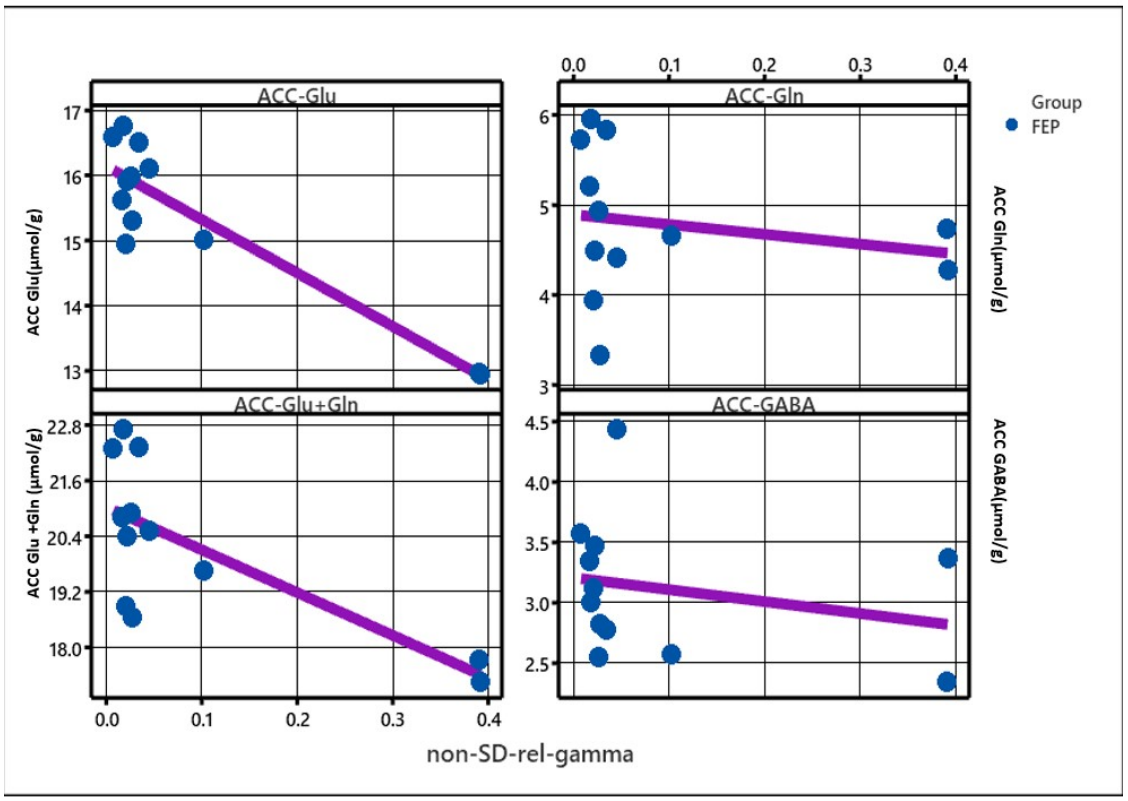

Figure 7.3.6: Scatter plots with the line of best fit for non-SD condition relative frontal gamma band power and ACC E/I metabolites for the FEP group

Healthy Controls								
	GABA		Glu		Gln		Glx	
	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value
delta	**-0.764**	**0.006**	-0.473	0.142	-0.200	0.555	-0.300	0.370
theta	0.409	0.212	0.409	0.212	0.373	0.259	**0.673**	**0.023**
alpha	0.236	0.484	0.427	0.190	0.036	0.915	0.436	0.180
beta	0.155	0.650	-0.164	0.631	0.409	0.212	0.473	0.142
gamma	-0.191	0.574	-0.082	0.811	0.209	0.537	0.327	0.326
Patients with FEP								
	GABA		Glu		Gln		Glx	
	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value
delta	0.196	0.542	0.259	0.417	-0.119	0.713	0.224	0.484
theta	0.140	0.665	**0.622**	**0.031**	0.385	0.217	**0.650**	**0.022**
alpha	0.203	0.527	0.385	0.217	-0.147	0.649	0.273	0.391
beta	0.175	0.587	-0.238	0.457	-0.231	0.471	-0.203	0.527
gamma	-0.336	0.286	**-0.580**	**0.048**	-0.406	0.191	**-0.622**	**0.031**

Table 7.4: Pearson correlation coefficients and p-values for correlations between E/I metabolite concentration levels (Glu being glutamate, Gln being glutamine, and Glx being combined Glu and Gln) in the ACC and relative spectral band power for the non-SD condition for HC and FEP participants

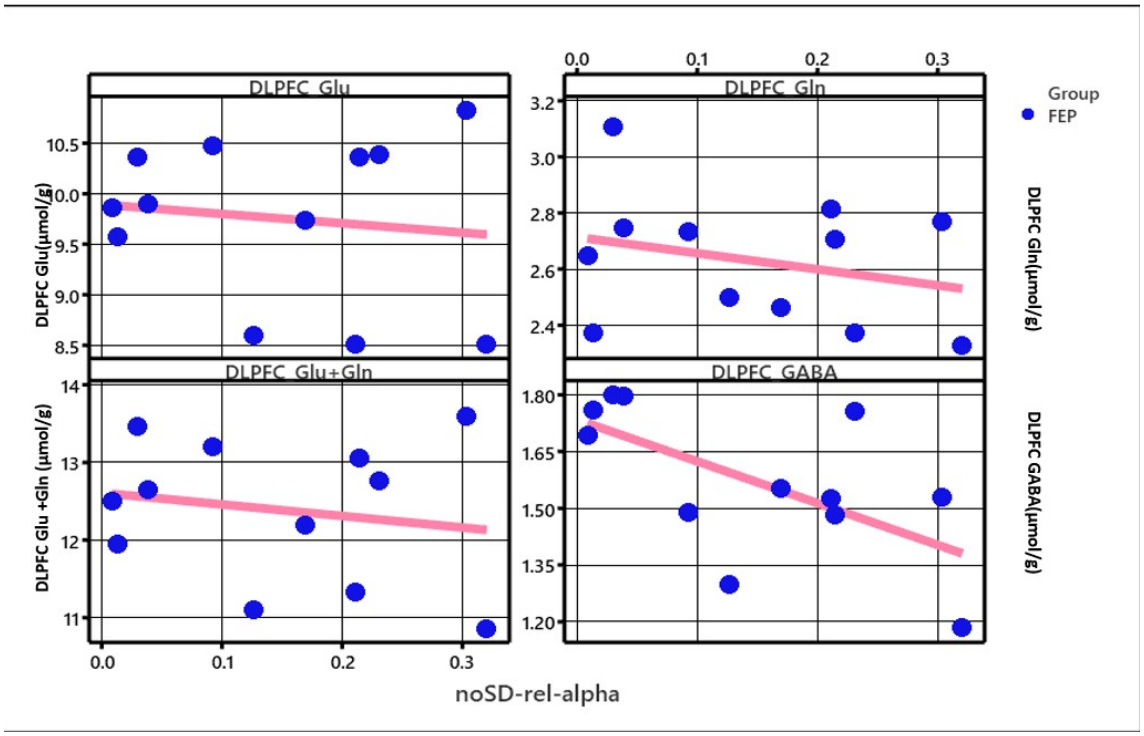

Figure 7.3.7: Scatter plots with the line of best fit for non-SD condition relative frontal alpha band power and DLPFC E/I metabolites for the FEP group

Healthy Controls								
	GABA		Glu		Gln		Glx	
	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value
delta	-0.273	0.417	-0.173	0.612	0.055	0.873	-0.027	0.937
theta	0.218	0.519	0.245	0.467	0.218	0.519	0.236	0.484
alpha	0.427	0.190	0.191	0.574	0.082	0.811	0.182	0.593
beta	-0145	0.670	-0.055	0.873	0.500	0.117	0.236	0.484
gamma	-0.064	0.853	-0.173	0.612	-0.209	0.537	-0.100	0.770
Patients with FEP								
	GABA		Glu		Gln		Glx	
	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value
delta	-0.280	0.379	-0.315	0.319	-0.140	0.665	-0.427	0.167
theta	-0.378	0.226	-0.028	0.931	-0.126	0.697	-0.140	0.665
alpha	**-0.580**	**0.048**	0.042	0.897	-0.168	0.602	-0.042	0.897
beta	-0.266	0.404	-0.063	0.846	-0.434	0.159	-0.259	0.417
gamma	0.287	0.366	-0.196	0.542	-0.084	0.795	-0.147	0.649

Table 7.5: Pearson correlation coefficients and p-values for correlations between E/I metabolite concentration levels (Glu being glutamate, Gln being glutamine, and Glx being combined Glu and Gln) in the DLPFC and relative spectal band power for the non-SD condition for HC and FEP participants

7.4 Discussion

7.4.1 Mismatch Negativity and Spectral Analysis

Main Findings

- There was a significant correlation between relative gamma power in the non-SD condition with MMN amplitude levels in the FEP group.
- There were no other significant correlations between other relative spectral band power and MMN outcomes.

Findings in Context

In order to compare MMN and relative spectral band power data from the non-SD condition was used as this was the spectral analysis data that most closely resembled the in-task MMN paradigm and had the least additional manipulations. It was revealed that there was a significant correlation between relative gamma power and MMN amplitude in the FEP group. There were no significant interactions specific to the control group, nor were the other power bands associated with MMN.

This finding suggests that higher gamma power is associated with increased MMN amplitudes. Despite there being an expectation to find a correlation between gamma and MMN, it was expected that this relationship would be inverse to reflect hyperexcitability and MMN deficits (Erickson et al., 2016; Light and Swerdlow, 2015; Missonnier et al., 2020). There is limited previous literature exploring oscillatory activity and MMN in a psychosis population. Previous research has demonstrated an association between frontal lower frequency abnormalities coincided with MMN responses in schizophrenia (Hong et al., 2012). Frontal theta oscillatory activity has also been associated with the MMN, specifically in deviant trials (Fuentemilla et al., 2008; Xiong et al., 2019), however they are not able to account for MMN deficits in early psychosis (Hua et al., 2023). The literature thus far has had contradictory theta and MMN findings and have pointed to two varying processes being at play: phase alignment and power modulation (Fuentemilla et al., 2008; Hua et al., 2023; Kaser et al., 2013). In this case the power modulation would be more suggestive of firing activity in stimuli relevant networks, whereas phase alignment is more reflective of temporal synchronisation of relevant neurons, although all mechanisms are thought to involve E/I balance disruption (Hua et al., 2023; Kaser et al., 2013). MMN waveform generation have also previously been associated with alpha oscillations pre-stimulus, with the oscillations determining whether the stimuli

will be consciously perceived (Knyazev, 2012). Therefore, the lack of alpha oscillation association could indicate that participants doing the task were not as conscious of the MMN. This explanation could be feasible given how attentionally demanding the visual task was, which has been suggested to impact MMN processing (Rissling et al., 2013). The difference in these findings could be a result of different group specifications, however not enough research has been done to confirm if stage of illness plays a role. Moreover, previous literature measured oscillatory activity simultaneous with MMN, whereas this study used resting state spectral power with MMN. As resting and task state spectral power has been shown to differ, this could also account for the discrepancy between the present study and previous literature (Curic et al., 2019). Moreover, neural region has been shown to play a role in the association between MMN and spectral power, therefore differences in electrode selection could also account for variation in findings (Fuentemilla et al., 2008). Despite the link between ERP composition and oscillatory activity being fairly well established, the extant literature does not seem to paint a clear picture of the nature of the association between oscillatory activity and MMN (Kaser et al., 2013). It should also be noted, that higher frequency oscillatory activity has been associated with a great deal of noise, especially EMG noise. Therefore, much more research in early psychosis measuring both oscillatory activity and MMN activity with stringent artefact removal would be needed to establish the mechanism behind the potential relationship between gamma and other power bands with MMN.

With all that being said, there is not that much evidence of a strong overlap across EEG phenomena (Gordillo et al., 2023). A previous consortium study found that several EEG measurable phenomena, such as P50, prepulse inhibition, and mismatch negativity, did not have a great deal of shared variance, despite theoretically reflecting similar processes (Price et al., 2006; Seidman et al., 2015). A similar study concluded that though some EEG phenomena do show promise for between group differences, between patients and controls, they do not necessarily represent the disorder and therefore, a multi-modal approach may be the most appropriate in creating a fuller picture (Gordillo et al., 2023). Moreover, few studies have focused on combined methods in those with psychosis, including FEP (Hong et al., 2012). Thus, further multi-modal research focused on populations with psychosis or specific symptoms related to psychosis would also further clarify the potential mechanisms behind these abnormalities and how they inter-relate.

7.4.2 Mismatch Negativity and MRS Metabolite Levels

Main Findings

- There were no significant correlations seen between ACC E/I metabolite levels and MMN in neither the FEP nor HC group.
- There were no significant correlations between DLPFC GABA and glutamate with MMN in neither the FEP nor HC group.

Findings in Context

This study did not find any significant associations between ACC or DLPFC E/I metabolite levels and MMN responses in neither the FEP nor HC groups. These findings contrast with previous literature that found associations between glutamate and GABA with MMN, particularly in the ACC (Hall et al., 2015; Kaur et al., 2019; Nagai et al., 2017; Rowland et al., 2016).

However, given the dearth of direct comparison between MMN and ACC metabolite levels in humans, particularly in those with first episode psychosis it is difficult to determine if there actually is no association or if the lack of association found in this study is due to the limitations of methodology such as having a small sample size and a heterogeneous patient group leading to a potentially underpowered study.

MMN is thought to reflect a predictive error process and has been explained using an E/I model (Javitt et al., 1996; Näätänen et al., 2014), with the prefrontal cortex, in particular, being involved (Alho et al., 1994; Chitty et al., 2013). The MMN response has been linked to glutamate activity, specifically NMDA receptor functioning (Fitzgerald and Todd, 2020). This link has been somewhat established through combined EEG and MRS studies finding positive associations between E/I metabolite levels and MMN amplitudes in high-risk and chronic schizophrenia populations (Rowland et al., 2016; Stone et al., 2010a). It has been further suggested that when controlling for the ratio of glutamine to glutamate the association between GABA, which interacts closely with this ratio, and MMN amplitude is no longer significant (Rowland et al., 2016). This suggests that the relationship between E/I balance and MMN amplitude may be more related to glutmatergic abnormalities than GABAergic abnormalities in psychosis. The involvement of glutamatergic abnormalities have further been supported by both human and rodent studies using NMDA antagonists (Ehrlichman et al., 2008; Javitt et al., 1996; Knott V. et al., 2015; Siegel et al., 2017; Thiebes et al., 2017; Umbricht et al., 2000). Importantly,

antipsychotic medication does not seem to impact the MMN greatly, suggesting that dopamine may not play an integral role in MMN generation (Javitt et al., 1996; Nagai et al., 2017). The discrepancy between these findings and the present study could be a result of NMDA antagonists targeting a different population of receptors than the ones relevant to MMN production in psychosis, differences in methodology, especially concerning animal studies, or the limitations associated with EEG technology (covered in Section 4.5 and Section 5.5).

This study did not find any association between MMN latency and E/I related metabolite levels in either the ACC or DLPFC. MMN latency results in psychosis have been fairly inconsistent (Kathmann et al., 1995; Kärgel et al., 2014). MMN latency has been viewed as a marker of the time needed for stimulus recognition in the case of a deviate tone, and may reflect bottom-up sensory processing (Nishimura et al., 2016). One previous study has found a link between temporal lobe Glx levels and peak MMN latency, with higher Glx measures corresponding to shorter latency (Kompus et al., 2015). However, taking into consideration the lack of consistent condition-specific MMN latency findings it could be that latency may not be a strong marker of underlying neural mechanisms of psychosis and therefore, would not have any particular association with E/I in psychosis.

Given the discrepancy in reported findings and the limited number of MMN and MRS research in FEP, a larger scale study with a homogeneous FEP group in which MMN and MRS are recorded simultaneously or during the same study session would be helpful. Moreover, the diversity in findings between the present study and NMDA antagonist studies and the lack of research on the role of stage of illness points to a need to examine MMN and MRS in frontal regions in FEP, chronic psychosis, and healthy controls with and without NMDA antagonists.

7.4.3 Spectral Analysis and MRS Metabolite Levels

Main Findings

- There was an inverse significant correlation between ACC glutamate and Glx levels with both relative gamma and theta band power in the non-SD condition in the FEP group.
- There was significant correlation between ACC Glx and frontal theta power, and an inverse relationship between ACC Glx and relative frontal delta in the HC.
- There was a significant inverse correlation between non-SD relative alpha power

with DLPFC GABA levels in the FEP group.

- There were no significant correlations between spectral power and DLPFC E/I metabolite levels in the HC group.

Findings in Context

The finding of associations between gamma and theta activity with ACC glutamatergic metabolites corresponds with previous literature (Leech and Sharp, 2014). Further, the association between DLPFC GABA and alpha power is in keeping with the limited extant literature (Sohal et al., 2009). Similar results of increased gamma and theta was found in response to the administration of NMDA antagonists (Curic et al., 2021). There has also been evidence to suggest that theta oscillations could modulate gamma activity (Jensen and Colgin, 2007). Both gamma and theta have been specifically associated with glutamatergic activity (Mackintosh et al., 2021).

The inverse correlation between these variables suggests that increased glutamate levels decrease gamma oscillatory activity in FEP. The present findings would suggest that hyperexcitability in frontal regions are associated with decreased gamma activity. This is in contradiction with previous literature as gamma has been particularly associated with elevated excitation as a result of NMDA receptor hypo-functioning and increased glutamatergic levels (Buzsáki and Wang, 2012; Gao and Penzes, 2015; Grent-'t Jong et al., 2018; Uhlhaas and Singer, 2010). However, gamma findings in psychosis across extant literature have been fairly inconsistent and have high levels of noise (Kehrer et al., 2008; Whitham et al., 2007). Moreover, there have been limited studies directly comparing gamma power and E/I metabolite levels in MRS. Therefore, further multi-modal research with stringent data cleaning in FEP would be necessary to establish potential shared mechanisms.

The extant literature has reported inconsistent findings regarding associations between GABA and gamma activity (Chen et al., 2014; Gawne et al., 2020; Grent-'t Jong et al., 2018). This difference in results could be due to regions of interest being different across studies, differences in participant group -as stage of illness and age do play a role-, in stimuli design (for both resting and task related activity), pre-processing approaches and due to limitations of EEG (Kapur et al., 2012; Perrottelli et al., 2021). The evidence does point to E/I involvement and aberrant oscillatory activity in psychosis, although the exact nature remains unclear. Moreover, gamma findings should be interpreted with caution and would necessitate further research with both frontal MRS and oscillatory

band power data with effective noise reduction and artefact removal across stage of illness of psychosis and with a consistent methodology.

The inverse relationship between alpha power and DLPFC GABA found for the FEP group in the present study could be explained through the role of PV interneurons and the E/I hypothesis. Previous literature has demonstrated that inhibition of GABAergic interneurons increases alpha oscillatory activity (Sohal et al., 2009; Uhlhaas and Singer, 2010). There is also literature to suggest that there is cross frequency coupling that occurs, suggesting that alterations in one area in one frequency band could alter another frequency band in that or a corresponding region (Jensen and Colgin, 2007). Therefore, alterations in the ACC that are associated with gamma and theta power could impact alpha activity that is associated with E/I in the DLPFC. However, further research exploring E/I metabolite associations with oscillatory activity across different regions in FEP would be needed to establish how regions may differ and interact with one another. Additionally, more research exploring DLPFC E/I metabolite levels in association with spectral power in FEP would further clarify potential shared mechanisms and abnormalities.

7.5 Conclusion

Overall, this study found that MMN amplitude levels were significantly positively correlated with relative gamma power in the FEP. It also found associations between ACC glutamate and Glx with relative gamma power and relative theta power in the FEP group, between ACC Glx with relative theta power and inversely with relative delta power in the control group, and finally an inverse association between DLPFC GABA and relative alpha power (in the FEP group).

Given the association between ACC E/I metabolites and relative gamma power and discrepancy in the limited previous literature, further research would be needed to establish E/I mechanisms behind gamma power activity in FEP. Moreover, across all of these measures there is an overwhelming lack of previous multi-modal research that allows for direct comparisons within a psychosis group, and more so within an FEP group (Hong et al., 2012). This severely limits the interpretation of these results within a wider context and limits the mechanistic understandings they could provide. Further, there is high variability in oscillatory findings in psychosis, as well as susceptibility to noise in EEG especially at higher frequency bands which further limits the reliability of these results (Gordillo et al., 2023; Whitham et al., 2007). Given the noise in measurements in the present study, future multi-modal research should be conducted with larger sample

sizes and more stringent data cleaning to increase the power of findings.

With that being said, this study has found some significant associations between frontal E/I balance, relative frontal spectral power, and MMN amplitude. This suggests that more research examining these potential markers and their interactions, could prove promising in understanding the mechanisms behind psychosis and the frontal hyper-glutamatergic hypothesis in early psychosis. The relationship between E/I metabolite concentrations, oscillatory activity and MMN in FEP could be better understood by including multi-modal methods, consistent and stringent EEG methodology, a larger sample size, and pharmacological models, such as NMDA receptor antagonists. Moreover, coupling MRS and EEG with more invasive technologies such as microdialysis, or novel multi-modal combinations such as combined fMRI and MRS (Martens et al., 2020) could also enhance the understanding of the involvement of functionally distinct E/I metabolites, oscillatory activity and MMN in FEP.

Chapter 8

General Conclusion and Future Direction

8.1 Summary of Findings

Through EEG and MRS technology, this thesis explored the biological mechanisms underlying the potential roles of SD and cognition in psychosis.

This thesis found significant differences in feelings of SD between groups, with FEP participants feeling significantly more defeated. Although there were no significant difference in feelings of social rank, FEP group scored slightly worse than controls. Further, there was a correlation between social defeat and social rank in the FEP group, but not in the HC group. Moreover, the present thesis found that both social defeat and social rank were associated with symptomology: general and positive symptom categories, in FEP participants .

Feelings of SD were correlated with decreased false alarm (FA) rates in the continuous random dot motion task (CRDM) used alongside the MMN, as well as decreased performance in the digital sequencing task (in BACS) in FEP. Higher feelings of social rank in FEP were associated with faster reaction times in the 2-back condition of the N-back and in the incongruent condition in the Stroop. There were no correlations in the HC group. Moreover, when controlling for group and PANSS scores, there was no significant effect of SD scores on cognitive performance.

There were no group differences between HC and FEP patients for MMN amplitudes or latency, relative spectral power across either condition, nor MRS E/I metabolite levels

in the ACC or DLPFC. However, the comparison between these potential E/I markers revealed several significant associations. It was found that relative frontal gamma power was correlated with MMN amplitudes in the FEP group. Further, ACC glutamate and Glx were correlated inversely with relative frontal gamma and positively correlated with theta power in the FEP group, DLPFC GABA was inversely correlated with relative frontal alpha power in the FEP group, and ACC Glx was correlated with relative theta power and inversely with relative delta power in HC group.

SD was associated with MMN amplitudes, with higher SD being associated with decreased MMN amplitudes in controls, but not in FEP. When controlling for group, age and sex, as well as both social defeat and social rank, only social rank was shown to have a significant effect on MMN amplitudes. There were neither associations between relative spectral power and SD scores, nor associations between ACC or DLPFC E/I metabolite levels with feelings of social defeat or social rank.

Moreover, inducing social defeat through the SD manipulation task did not bring about any changes in relative spectral power for neither controls nor patients with FEP.

There was no significant difference in CRDM performance, nor was MMN associated with cognitive performance on the CRDM task for both FEP and HC group. However, relative delta power in the non-SD condition was inversely correlated with hit rate on the CRDM task in both HC and FEP. Moreover, the FEP group had significantly worse performances across the BACS battery of cognitive tests compared to controls. With several correlations between E/I balance in both the ACC and DLPFC with multiple tasks in the BACS for the control group, but not for the FEP group. The FEP group also had significantly slower reaction times and worse accuracy in some of the N-back conditions, as well as slower reaction times in both conditions on the Stroop task. There were also some significant correlations between both ACC and DLPFC E/I associated metabolites and performance on these tasks.

8.2 Conclusions

This is the first work, to the author's knowledge, to examine social defeat in psychosis *in-vivo* using in parallel EEG and MRS techniques. Additionally, it contributes to the limited research exploring various neuro-cognitive and neuro-physiological markers of psychosis (Seidman et al., 2015).

A significant consistent finding was that first episode psychosis (FEP) participants

experienced significantly higher rates of social defeat (SD) compared to healthy control (HC). This was seen in the social defeat scale (SDS) scores but not in the social comparison rating scale (SCRS) scores. This suggests that social defeat, expressed as SDS scores, is associated with FEP and could be a feature of psychosis.

It is likely that SD does not act directly on glutamate and GABA, but instead could act on the pathway between E/I related metabolites and mesolimbic dopamine. This is supported by the lack of significant findings between E/I related MRS metabolite levels and SD. This theory is further supported in this study by the significant associations between SD and positive and general symptoms of psychosis that are attributed to disrupted mesolimbic dopamine, as reported by previous literature (Corcoran et al., 2020).

On the other hand, it is possible that SD's impact on patients occur prior to FEP at a prodomal stage and persist throughout disease. This would be in keeping with the excitotoxicity hypothesis assuming that hyperglutamatergic abnormalities occur earlier than FEP and the SD hypothesis for psychosis pointing out that SD leads to aberrant neurotransmitter activity prior to onset. This is further supported by the consistent lack of significant HC and FEP group differences in MMN, spectral power and MRS E/I metabolite concentration levels. As well as by the lack of association between potential E/I markers and SD in the FEP group. Although, this could also be due to the regions of interest selected for analysis, and other regions could potentially be more relevant to the SD process in psychosis. However, this could also suggest that EEG spectral power tests as used in this work are not accurate enough measurement method, that the SD induction was not salient enough to induce neural changes or that the SD scales were not a sensitive enough measure of SD.

Moreover, the findings concerning the association between E/I metabolite concentrations and cognitive performance could indicate that glutamatergic and GABAergic abnormalities contribute to these cognitive impairments. However, there are not enough consistent findings in extant literature nor the present thesis to strongly support this specific mechanism.

It has been noted in previous work that patients with psychosis can fall into normal ranges for neuropsychological markers, such as MMN, cognitive markers, or oscillatory markers, leading to additional challenges in examining the relationship between these markers and interaction with other risk factors or symptoms (Light and Swerdlow, 2015). There has also been some research to suggest that within psychosis there are differing clusters of cognitive deficit, those with preserved faculties and those with moderately and severely

altered faculties, that perform distinctively differently on the BACS and other cognitive tasks (Ooman et al., 2023). This points to the issue of potential heterogeneity within patients with psychosis, and studying psychosis based on broader diagnostic criteria.

8.3 Limitations

There are a few limitations to the presented thesis that could influence how representative the findings are for the general first-episode psychosis population, as well as their ability to support the current hypotheses surrounding potential mechanisms underlying psychosis.

Despite the present study having comparable sample sizes in all components to other studies in the field (Godlewska et al., 2021; Kapur et al., 2012), given the sample size and the fairly heterogeneous sample composition, particularly regarding patients,the reported findings could have been influenced by underpowered and noisy results. This thesis attempted to have a consistent group by having FEP participants who all had their first episode of psychosis within the last three years, and that almost all were on 2nd generation anti-psychotics. However, the patient group was somewhat heterogeneous in the sense that there were a few participants over the age of 35, some were on anti-depressants while others were not, a few were also on lithium, and some would perhaps fall into the treatment-resistant category (Pandey and Kalita, 2022). There were several trend level and almost significant findings relating to E/I metabolic differences between FEP and HC groups, and the involvement of SD, suggesting that further research with a more powered study could reveal important interactions or mechanisms for psychosis and risk of psychosis.

The studies in this thesis had a small sample size, this was due to challenges in recruitment, that was particularly challenging due to delays caused by the SARS-COV2 coronavirus strain. Generally, there are several challenges when it comes to patient focused research, leading to underpowered studies, patient heterogeneity, and potentially false comparisons between somewhat 'subjective' assessments, which is further exacerbated by the general replication crisis in psychiatry and psychology (Kapur et al., 2012). Despite the challenges in recruiting and scanning patients, alongside exploring the central theme of SD, cognition and potential E/I markers in FEP, this thesis also demonstrates the feasibility of efficiently recording multiple outcomes (such as MRS, cognitive results and social defeat feelings) in a relatively short time frame with a patient population.

In the design of the present thesis, there was limited formal involvement, input and

feedback of those with lived experience of psychosis. This is particularly relevant given the subjective nature of feeling SD, as well as the importance of upholding the principles of autonomy and dignity for those involved in research, particularly from potentially more vulnerable groups (Sacristan et al., 2016). Moreover, the potential differences in understanding social comparison compared to social defeat and the validity of the social defeat manipulation would have been better understood at an earlier stage with more participant involvement. Hence, future research and/or replications would benefit from involvement of those with lived experience at each stage of the research process.

Another potential limitation is that the definition of FEP varies greatly across studies (Brugger et al., 2011; Lee et al., 2022). This could also limit the generalisation of findings and the ability to find a coherent pattern in existing literature.

Both the EEG and MRS findings were not analysed controlling for cannabis and other illicit substance use. Although there is not a great deal of evidence to demonstrate an *in-vivo* effect of cannabis on frontal glutamate in FEP (Sami et al., 2020), it is possible that illicit substance use did play a role in the presented findings. Cannabis has been shown to potentially play a role in dopamine synthesis, which could suggest that it may be particularly relevant to the proposed social defeat mechanism of psychosis (Bloomfield et al., 2014; Selten et al., 2013). Therefore, future research should take this into account.

There was limited validation of the employed SD condition in the spectral power section (refer to Section 5.2.5), via questionnaires or formal engagement with participants. The lack of previous research in this field adds to the novelty and importance of the work done in this thesis but does mean that more research is required to validate existing SD induction paradigms. This is an element that future SD research should take into account, and could be improved to better establish if such SD manipulations accurately induce feelings of social defeat.

There are also several technical limitations in the present thesis. The EEG results in this study were fairly noisy, which could have been improved with eye blink correction and principle component analysis (Kaczorowska et al., 2017). The noise in the EEG could also have been caused by EMG artefacts, particularly at higher frequency bands (Whitham et al., 2007). More generally, EEG has several limitations as it is based on summations of electrical charge changes that may not reflect region specific or nuanced processes (Biasiucci et al., 2019; Michel and Murray, 2012). EEG reported outcomes also could vary from study to study not only due to the above factors but also choices regarding pre-processing and analysis that are greatly diverse across the field (Gordillo et al., 2023;

Perrottelli et al., 2021). Moreover, there are a great deal of other factors that have been shown to impact EEG recordings such as smoking, blood glucose levels, emotional state, physical activity or mental fatigue (Blaabjerg and Juhl, 2016; Chin et al., 2019; Li et al., 2020; Xu et al., 2018). This calls for a more standardised approach to phenomena of interest, and for the need of more precise replication of previous methodologies.

As the EEG sessions were already slightly longer than the MRS session and were relatively tiring, the questionnaires included were limited to just SD measures. This meant that the PANSS was not included in the EEG study session, and therefore analysis of MMN and spectral band power data with symptom severity was not possible. Given the hypothesised E/I mechanisms of different symptom categories it would have been useful to measure these EEG phenomena in association with specific symptom categories. Moreover, the present thesis analysed relative spectral band power measured during resting state as opposed to during the task, which may have limited the relevance and correlations exploring the association between CRDM cognitive performance and relative spectral band power.

Similarly, the present thesis measured resting-state MRS, which may limit its applicability to cognitive performance, as E/I metabolites have been shown to differ when at rest and during cognition (Zahid et al., 2023). Moreover, as the ROI needs to be predetermined it is possible that associations between E/I and cognition or SD could have been altered due to the region of measurement not being right. ^{1}H-MRS also has its own unique set-backs. Despite, MRS providing information about the concentration of metabolites, it is unable to differentiate between intrasynaptic, extracellular and vesicular metabolite levels, all of which are functionally distinct forms of the same metabolite, as total metabolite concentrations are measured (Kegeles et al., 2012). This is particularly relevant for glutamate and GABA due to their role in other metabolite pathways and neurotransmission (Yüksel and Öngür, 2010). Despite this limitation, the links have been established between metabolite levels and behavioural outcomes which continue to provide novel insights into disease pathology or mechanisms (Stagg et al., 2011; Yüksel and Öngür, 2010). Moreover, MRS results, much like EEG results, are dependent on pre-processing, such as cramer-bao lower bound (CRLB) cut off, which impacts the comparability of study results and could account for some of the variability in previously reported results (Smucny et al., 2021).

Despite these limitations, having a multi-modal method with a FEP patient population exploring potentially highly relevant risk factors has not only been shown to be feasible through this thesis but also points to potentially significant interactions and mechanisms

that would require further research.

8.4 Future Directions

There are multiple ways in which future research could elucidate the role of SD and cognition in first-episode psychosis and how they might interact with potential markers of E/I balance.

A longitudinal study across various demographic backgrounds, would contribute greatly to the findings of this thesis. Employing a longitudinal design would robustly explore the role of SD in psychosis, and could establish a potential causal link. Moreover, research with consistent methodology across different stages of illness, such as prodromal high risk groups, and early stages, would also provide insight into how these potential risk factors may develop and interact with biological mechanisms.

Additionally, induced SD task development, validation and standardisation would allow for more systematic research in the field. The SD task would also benefit from a control condition and random assignment of SD induction, to control for the mis-attribution of neural response due to personal differences or other factors. Moreover, the introduction of a questionnaire, alongside the induced SD task, and integration of qualitative analysis would assist in further task validation. In particular, a qualitative approach would be appropriate for the exploration of how feelings of social defeat and feelings of social rank may be conceptualised differently in a psychosis group compared to a control group. Such a study would further confirm the SD findings in this thesis.

The association between social defeat and the positive and general symptoms of psychosis in this thesis could allude to the dopaminergic sensitisation hypothesis for social defeat in psychosis. Given the implications of dopamine in the social defeat model of psychosis, and the interplay between E/I balance and dopamine in current models of psychotic symptoms further research using PET, MRS and social defeat scales, particularly in a longitudinal methodology, would clarify if these factors interact and their association with psychosis.

Additionally, pharmacological studies focusing on glutamatergic agents such as ketamine or memantine, and dopamine agents such as propofol, would prove valuable in exploring the potential relationship between E/I balance, midbrain dopamine and SD. This would allow for a better framework in which to understand SD and neuro-chemical research in psychosis.

In-vivo high resolution whole cell patch clamp studies in rodents could provide complimentary contributions to EEG research in humans in order to better understand the specific role of E/I in gamma oscillation generation (Bartos et al., 2007). Moreover, there are other EEG measurable phenomena such as aperiodic slope that have been closely associated with E/I balance and would merit exploration, with multi-modal methods, in the context of SD (Ahmad et al., 2022; Medel et al., 2020).

Moreover, though unable to draw clear conclusions concerning mechanism, the associations between E/I metabolite levels, oscillatory power and MMN suggests a need for further research exploring the interactions between these potential markers in early psychosis. Given the potential for social defeat and cognition to be altered in a prodomal stage, their assessment within multi-modal approaches could provide verification and better understandings of the findings in this thesis. It may also be worth coupling these technologies and variables with different technologies to provide a fuller picture of mechanisms such as microdialysis, dynamic MRS, and combined fMRI and MRS for better spatial resolution.

In conclusion, the aim of this thesis was to contribute to the understandings of social defeat and cognition in the context of first-episode psychosis, while providing a basis for exploring the interaction between these factors with neural underpinnings. Better understanding these interactions could potentially explain the mechanisms behind psychosis, which in turn could better inform interventions and prognosis of FEP. Further, for minority groups social defeat has been implicated as a risk for various psychiatric conditions (Hall, 2022), therefore amplifying its potential relevance in disease onset would hopefully lead to more dialogue and research in the field.

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