USING EEG TO FIND ENDOPHENOTYPES OF SCHIZOPHRENIA

by

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ABSTRACT

This dissertation investigates EEG-derived endophenotypes to elucidate the neurophysiological underpinnings of schizophrenia through three interconnected studies.

Study 1: Meta-Analysis of Resting State Microstate Differences in Schizophrenia

The first study is a meta-analysis of EEG-derived microstates in schizophrenia. Microstates are brief, stable patterns of synchronized brain activity. This meta-analysis consolidates data from numerous studies to identify consistent alterations in microstates in individuals with schizophrenia compared to healthy controls. The findings reveal significant differences in microstate classes, particularly an increase in the duration and occurrence of microstate class C and a reduction in class D. These alterations suggest disrupted neural dynamics in schizophrenia, highlighting microstate parameters as a potential endophenotype for the disorder.

Study 2: Resting-State Microstate Differences in Early Psychosis as an Endophenotype Candidate. The second study explores resting-state EEG recordings to examine intrinsic brain activity in individuals with early-phase psychosis. Resting-state conditions reveal baseline brain functions, often associated with the default mode network. The study compares these microstates between individuals with early psychosis (n = 27) and healthy controls (n = 30) to determine if aberrant neural dynamics persist in the absence of external stimuli. The results indicate that individuals with early psychosis exhibit distinct microstate patterns, suggesting fundamental disruptions in brain function that could serve as reliable biomarkers for early diagnosis and monitoring of schizophrenia.

Study 3: Mismatch Negativity as an Endophenotype of Schizophrenia. The third study focuses on auditory processing, a critical domain affected in schizophrenia. Using EEG, this research study investigated event-related potentials (ERPs), particularly the mismatch negativity (MMN) component, which reflects automatic auditory change detection. The study found no group differences. However, MMN measures were associated with clinical symptoms.

General Conclusion: The collective findings of these studies advance our understanding of the neurophysiological abnormalities in schizophrenia. By identifying microstate alterations, this research provides evidence for EEG-derived markers as potential endophenotypes. These biomarkers offer promising avenues for early diagnosis, targeted interventions, and monitoring treatment efficacy, ultimately contributing to improved outcomes for individuals with schizophrenia.

CHAPTER 1 INTRODUCTION

Schizophrenia is characterized by disturbances in thought, perception, and behaviour and has a global prevalence rate of approximately 0.28% (Charlson et al., 2018). Schizophrenia is a heterogeneous illness that often has a strong genetic component in its predisposition and emergence. Schizophrenia symptoms include positive symptoms such as hallucinations in any sensory modality, although most commonly in the auditory domain, and delusions or fixed false beliefs that cause distress and impairment. Negative symptoms include, for example, affective flattening, social isolation, and difficulties in communication. There are also numerous neurocognitive impairments that add to the day-to-day difficulty in functioning that accompanies the illness. Not only are symptoms of schizophrenia debilitating and related to increases in suicidality and depressive symptoms, but psychopharmacological treatment is ineffective in 25-30% of those treated (as cited in Brunelin et al., 2012). The use of a dominant pharmacological treatment paradigm cost public drug plans $421.9 million in 2009 alone (CADITH, 2012). Yearly pharmacological spending increased to $639 million in Canada, and in 2017, pharmacological treatment spending surpassed hospitalizations as the top spending category related to those with schizophrenia (Stewart et al., 2023). Suicide rates are also significantly higher in those with schizophrenia compared to both the healthy population and those with other mental illnesses. It is estimated up to 5% of those with schizophrenia die by suicide compared to .008% in the general population (Hor & Taylor, 2010). Those with schizophrenia are also more likely to suffer from traumatic events, with 30-80% reporting exposure to trauma (Shah et al., 2014; Turner et al., 2019).

Given the significant impact of schizophrenia on individuals and healthcare systems, there is a critical need for improved diagnosis and treatment methods. This thesis aims to investigate potential biomarkers of schizophrenia to enhance early diagnosis and therapeutic interventions to help mitigate some of these negative impacts and facilitate early intervention.

1.1 Schizophrenia on a Continuum

Symptoms of schizophrenia often manifest in varying degrees of severity and combinations. This complexity has led researchers and clinicians to question whether schizophrenia should be viewed as a discrete categorical classification or as part of a broader spectrum of related disorders (Guloksuz & van Os, 2017). At the one end of the schizophrenia spectrum, there are traits and experiences that share certain features with schizophrenia but do not meet the criteria for a clinical diagnosis. This is often referred to as schizotypy, a subclinical set of traits often found in the general population (Vollema & van den Bosch, 1995). Schizotypy does not refer to schizotypal personality disorder, but the subclinical manifestations of the schizophrenia spectrum. These may include sub-clinical experiences like unusual beliefs or mild perceptual distortions. While these experiences are not distressing or impairing enough to warrant a diagnosis, they are important to consider when studying the spectrum, as they are associated with a clinical high risk of developing schizophrenia (Fluckiger et al., 2019). Moving into greater severity along the spectrum, individuals with schizotypal personality disorder exhibit eccentric behaviours, peculiar thought patterns, and social difficulties reminiscent of schizophrenia (Rosell et al., 2014). Although not diagnostically equivalent, this disorder shares a genetic predisposition and overlapping features with schizophrenia, suggesting

similarities in the underlying processes of the illnesses. Included in the spectrum are individuals who may experience brief episodes of psychotic symptoms but do not meet the duration criteria for a diagnosis of schizophrenia.

In addition to schizotypy and schizotypal personality disorder, psychotic-like experiences (PLEs) are conceptualized as a part of the schizophrenia spectrum. PLEs encompass subclinical manifestations such as unusual beliefs, perceptual anomalies, and mild thought disturbances that occur in the general population without meeting the criteria for a psychotic disorder. These experiences are more prevalent than previously recognized, with large-scale epidemiological studies estimating that approximately 5-8% of the general population reports PLEs at some point in their lifetime (Linscott & van Os, 2013). While most individuals with PLEs do not transition to a psychotic disorder, these experiences are associated with heightened levels of distress and impairment, particularly in individuals with additional risk factors. Previous research indicates that PLEs serve as potential indicators of vulnerability to psychosis. For instance, a meta-analysis by Healy et al. (2019) found that children and adolescents reporting PLEs had a fourfold increased risk of developing a psychotic disorder and a threefold risk for other mental health conditions. This exemplifies the importance of monitoring PLEs as part of early intervention strategies and the existence of early symptomatology before a schizophrenia diagnosis. Furthermore, PLEs have been associated with adverse outcomes such as self-harm, violence perpetration, and increased healthcare use. A longitudinal study by Kelleher et al. (2012) demonstrated that adolescents experiencing PLEs were at heightened risk for suicidal behaviour and subsequent mental health issues. Additionally, a study by Yung et al. (2009) found that individuals with PLEs who also exhibited

functional decline were at a higher risk of transitioning to psychosis, suggesting that the combination of PLEs and functional impairment is potentially an important factor in predicting psychosis onset. By recognizing these nuanced predictors, clinicians and researchers can better tailor interventions to those most at risk. By addressing these subclinical symptoms, clinicians and researchers can develop more effective preventive measures and therapeutic interventions, potentially mitigating the progression to full psychotic disorders.

Early in the psychosis progression/spectrum are also individuals with sub-clinical psychotic-like symptoms who may be considered to be at clinical high risk for psychosis (Rossler et al., 2015). Clinical high risk can be defined as those who are in the age range of highest risk for psychosis (adolescence, early adulthood) and have either sub-threshold positive psychotic symptoms during the past 12 months, have clinical psychotic symptoms for less than one week which resolve spontaneously, meet criteria for schizotypal personality disorder, or have a first degree relative with a psychotic disorder (McHugh et al., 2018). Approximately 29-36% of these clinical high-risk individuals will develop a psychotic disorder within a 2- to -3-year follow-up period (Fusar-Poli et al., 2012). The accuracy of predicting schizophrenia development based on clinical high-risk symptoms is not specific enough, as some individuals in clinical high-risk states for psychosis progress to non-psychotic illness or even no illness (Rossler et al., 2015). There is thus a need for sensitive diagnostic tools that will facilitate the identification of psychosis proneness, as early diagnosis and phase-appropriate treatments will lead to better outcomes (Insel, 2010). While several studies have suggested that interventions could delay or prevent conversion to psychosis in those at clinical high risk (Nordentoft

et al., 2006; McGlashan et al., 2006; McGorry, 2002), these interventions are not currently standard in Canada (Nolin et al., 2010). A prime reason for this has involved but is not limited to, the costs of pursuing these treatments in those who will never transition to full psychosis (McGlashan et al., 2006; Fusar-Poli et al., 2013). The availability of sensitive and specific biomarkers could result in more effective identification of risk and thus phase-appropriate treatment for those who need it and the omission of direct interventions for those who do not.

Toward the more severe end of the spectrum lies schizophrenia, characterized by more pronounced and persistent symptoms compared to a brief psychotic disorder or schizophreniform disorder. The Diagnostic and Statistical Manual of Mental Disorders - fifth edition (DSM-5) criteria for schizophrenia define the disorder as the presence of at least two of the following symptoms for a significant portion of time during a one-month period: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behaviour, and negative symptoms (diminished emotional expression or avolition). At least one of the symptoms must be delusions, hallucinations, or disorganized speech. The defined symptoms need to disrupt the level of functioning in one or more major areas including work, interpersonal relationships, or self-care, which is below the level prior to symptoms onset. These individuals typically experience disruptions in daily functioning, and their symptoms are more readily recognizable (Insel, 2010). These core symptoms and definitions have traditionally defined our understanding of schizophrenia. In addition to schizophrenia, schizoaffective disorder represents a condition where symptoms of schizophrenia co-occur with mood disturbances such as depression or bipolar disorders,

but delusions or hallucinations are present for at least 2 weeks in the absence of a major mood episode (Levinson et al., 1999).

Recognizing schizophrenia as a spectrum of disorders has several important implications. It challenges the notion of rigid diagnostic boundaries and encourages a more dimensional approach to assessment. This encourages a focus on symptoms in a broader range, the impact of these symptoms/experiences, their neurodevelopmental origins, and functional outcomes to provide more accurate, early intervention. Understanding the schizophrenia spectrum may also inform treatment strategies. That is, interventions can be tailored to an individual's specific symptom profile and level of impairment; individuals with non-clinical phenomena may benefit from psychoeducation and support, while those with schizoaffective disorder may require a combination of antipsychotic medication and mood stabilizers. Those with schizophrenia are also often regarded in a stigmatized fashion in their ability to function and live with a satisfactory quality of life while having symptoms that are managed and coped with appropriately. However, early identification and patient-specific treatment of those along the schizophrenia spectrum can provide better long-term outcomes (Malla & McGorry, 2019). Therefore, identifying markers involved in the early stages of symptomatology may lead to more effective practices in proactive, preventative, early intervention medicine to better alter their prognostic trajectory.

Early phase psychosis (EPP) refers to the critical phase of the first five years of an individual’s psychotic illness, such as schizophrenia. Schizophrenia is typically associated with a progressive social and functional decline during the early course of the illness if, without early intervention/treatment, progress as pre-onset (prodromal)

progressive symptomatology has been previously demonstrated (Hirayasu et al., 1998; Kasai et al., 2003; Salisbury, 2007). Identification and phase-appropriate treatment of those in the early phase can potentially ameliorate their illness trajectory and severity (Murphy & Brewer, 2011). More time spent in untreated psychosis has been found to predict future time in active psychosis and the severity of symptoms (Melle et al., 2010). The duration of untreated psychosis (DUP) has been extensively studied in relation to its impact on clinical and functional outcomes. Research consistently indicates that a longer DUP is associated with more severe symptoms and poorer functional outcomes. For instance, a meta-analysis by Marshall et al. (2005) found that extended DUP correlates with worse symptomatic and functional outcomes at 6 to 24 months follow-up. Similarly, a study by Penttilä et al. (2014) demonstrated that longer DUP predicts poorer long-term outcomes in schizophrenia, emphasizing the importance of early intervention. This optimally occurs after a period in prodrome or gradually increasing psychosis-like symptoms and functional deficits. This then progresses into the early phase of psychosis, which is often marked by a drop in job performance or academic functioning (Melle et al., 2010). These symptoms often result in significant distress and disruption in daily functioning across multiple aspects of life, such as social, vocational, activities of daily living, and wellbeing. Schizophrenia is often conceptualized within a diathesis-stress model, that is, those with a neurodevelopmental predisposition can reach a threshold for symptom expression through distress/stressful events or significant substance use, such as cannabis or hallucinogens (Walker et al., 1997). Psychotic symptoms from substance-induced psychosis can often persist in those with a predisposition or family history of schizophrenia, developing into a chronic illness (Murray et al.,2013). A comprehensive

Finnish register-based study involving over 18,000 individuals found that 46% of those diagnosed with cannabis-induced psychosis transitioned to a schizophrenia spectrum disorder within eight years (Niemi-Pynttäri et al., 2013). This significant conversion rate underscores the importance of early intervention and monitoring in patients presenting with substance-induced psychotic episodes. Identifying those who have this predisposition or who are having these subclinical symptoms can inform their substance use choices and alter their illness trajectory if identified early.

While psychosis is a core component of schizophrenia, it is not exclusive to this diagnosis, highlighting the need to delineate psychosis as a symptom cluster from the broader syndrome of schizophrenia. Psychosis is a broad construct that encompasses a range of symptoms, such as hallucinations, delusions, and disorganized thinking, which can occur in various mental health conditions, including schizophrenia, mood disorders, and substance-induced states. In contrast, schizophrenia is a specific psychiatric diagnosis characterized by a constellation of symptoms, including persistent psychotic features, negative symptoms, and cognitive deficits, with a chronic course and significant functional impairment. The search for endophenotypes in this context focuses on identifying neurobiological or cognitive markers that reflect the underlying vulnerability to schizophrenia as a neurodevelopmental disorder, rather than symptoms of psychosis. This approach distinguishes endophenotypes from biomarkers, as endophenotypes are intended to provide insight into the heritable and stable traits that contribute to the disorder's etiology, irrespective of symptom state.

Understanding the fluid nature of the schizophrenia spectrum is essential for appreciating how transient episodes and subclinical manifestations contribute to the

trajectory of psychosis. These episodes are not isolated occurrences but rather part of a continuum that offers critical insights into the underlying mechanisms and progression of schizophrenia. By studying this, researchers can better identify patterns of risk, pathways to illness development, and opportunities for intervention. Appreciating the spectrum in its entirety allows for a more nuanced understanding of schizophrenia, moving beyond rigid diagnostic categories to a dimensional approach that acknowledges the diverse presentations and severity levels. This perspective not only advances research but also informs clinical practice, enabling the development of targeted interventions that can potentially alter the illness trajectory and improve outcomes for individuals across the spectrum.

The identification of stable deficits or aberrant biological markers/processes are referred to as endophenotypes. Endophenotypes were introduced by Gottesman and Shields in 1972, who described these as internal phenotypes discoverable by biochemical tests or microscopic examination and were first conceptualized to refer to genetic analysis. The endophenotype is advantageous as it does not rely on subjective measurement and may not be obvious to the unaided eye upon examination. If a phenotype associated with a disorder is a more elementary phenomenon inherently involved in producing the symptoms of the illness state, it would qualify as an endophenotype. The endophenotype represents the downstream effects of genetic variance on traits and disorders and an upstream representation of symptoms observed within the illness. The endophenotype is not only a marker of illness but also a potential marker for predisposition to symptoms or a vulnerability to a specific illness.

The construct of the endophenotype has undergone much development since its conception in 1972 and now encompasses multiple modalities of measurement and investigation. Current methods available for the identification of endophenotypes include neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, and neuropsychological methods of measurement. In general, endophenotypes typically represent the influence of conditions with high genetic loading that contribute to the presentation of symptoms (Gottesman & Gould, 2003). Endophenotypes are typically more stable over time compared to symptoms of a disorder as they are the result of impacted neurological functioning either during development or from active triggers/stressors. The utility of endophenotypes comes from how they often rely on biological measurement that is more stable and less subjective or prone to error. They are also best suited for biomarkers when they are feasible to measure and identify on a large scale (Correa-Ghisays et al., 2022). To qualify as an endophenotype, a trait must meet several specific criteria. First, it should be associated with the disorder in the population, demonstrating a reliable association with the condition of interest. Second, it must be heritable, meaning its variation is influenced by genetic factors. Third, the trait should manifest in unaffected family members of individuals with the disorder at a higher rate than in the general population, indicating familial co-segregation. Fourth, it must be state-independent, meaning it is present regardless of whether the clinical symptoms of the disorder are active or in remission. Finally, the endophenotype must be reliably measurable using objective, quantitative methods, ensuring reproducibility and accuracy across studies. These criteria help differentiate endophenotypes from other biological markers and support their utility in bridging the gap between genetics and clinical

phenomena (Gottesman & Gould, 2003). The identification of an endophenotype in at-risk individuals with either a family history of illness or early observed traits could identify if an individual is at risk for developing psychosis symptoms. The identification and early intervention of those with predispositions to psychosis can decrease suicidality and potentially reducing conversion to psychosis. Some suggested endophenotypes for schizophrenia have been deficits in sensory processing as well as abnormalities in resting state activation observed in EEG (Venables et al., 2009) and abnormalities in neuroanatomy (Chand et al., 2022). Abnormalities in resting-state activation observed in EEG and abnormalities in neuroanatomy are frequently documented in schizophrenia. However, these abnormalities often become more apparent only after the illness has progressed or when other clinical signs are already present. This limitation highlights the need for biological markers that are detectable earlier in the course of the illness. As a result, there has been a surge in brain-based measures aimed at identifying reliable endophenotypes for schizophrenia.

1.2 Resting-State Default Mode Network

One identified brain-based endophenotype for schizophrenia has been aberrations in what is referred to as the resting default mode network. The Default Mode Network (DMN) refers to the pattern and distribution of neurological activation while a subject is at rest and not performing any cognitive task or exposure to stimuli (Smallwood et al., 2021). The DMN primarily encompasses several key regions of the brain, including the posterior cingulate cortex (PCC), the precuneus, the medial prefrontal cortex (mPFC), the lateral parietal cortex, and the hippocampus, as evidenced by fMRI investigations (Utevsky et al., 2014). The default mode network involves the activation of these

different brain regions that are highly interconnected and demonstrate synchronized activity patterns during rest, forming a coherent network (Fan et al., 2021). Resting state refers to brain activity when a person is not engaged in a specific task, highlighting functional networks rather than isolated activation of specific brain regions. Rather than individual brain regions working independently, the resting state reflects coordinated activity across interconnected regions within networks (Rosazza & Minati, 2011). This networked activity emphasizes that brain function arises from the dynamic interaction of regions working together, rather than discrete areas operating in isolation. The DMN has been previously shown to be involved in self-referential processing, introspection, and autobiographical memory retrieval (Whitfield-Gabriele & Ford, 2012). Activity within the DMN often corresponds to the contemplation of one's thoughts, emotions, and personal experiences. The DMN's activation during resting states is also associated with mind-wandering and creative thinking. It facilitates the generation of novel ideas and the integration of information from multiple sources. The DMN also plays a pivotal role in social cognition, enabling individuals to infer the mental states and intentions of others, a process known as theory of mind (Mars et al., 2012). The medial prefrontal cortex, in particular, is implicated in understanding others' perspectives (Krause et al., 2012). The DMN also contributes to memory consolidation, especially during periods of rest after learning. It facilitates the transfer of information from short-term to long-term memory (Sestieri et al., 2011).

The DMN is often measured with EEG by focusing on specific frequency bands associated with at-rest activity, particularly in the alpha (8-12 Hz) and low-frequency (0.01-0.1 Hz) bands. EEG recordings are obtained while the subject is in a relaxed, eyes-

closed state to enhance DMN activation. Data is then analyzed to isolate sources of neural activity and connectivity analysis to identify functional connectivity patterns characteristic of the DMN. By examining coherence and phase synchronization between regions like the medial prefrontal cortex and the posterior cingulate cortex, researchers can infer the activation and interaction of the DMN. Additionally, source localization methods, such as Low-Resolution Brain Electromagnetic Tomography (LORETA), can be applied to map the spatial distribution of DMN activity from the EEG data, providing a more detailed understanding of its dynamics.

Abnormalities in the default mode network (DMN) have been the subject of research interest in schizophrenia, shedding light on the neural underpinnings of this complex psychiatric disorder. The DMN exhibits distinct alterations in individuals with schizophrenia (Hu et al.,2017). These abnormalities contribute to our understanding of the disorder's cognitive and perceptual features. One of the most consistent findings in schizophrenia is altered connectivity within the DMN (Del Fabro et al., 2021). This dysconnectivity disrupts the typical coordination of brain regions within the DMN, leading to cognitive and perceptual impairments. The mPFC, a crucial component of the DMN, often exhibits increased activity in conjunction with the broader network in individuals with schizophrenia. In fMRI studies, mPFC hyperactivity is associated with symptoms such as rumination, excessive self-referential thinking, and impaired self-awareness in schizophrenia (Chai et al., 2011). In healthy individuals, the DMN typically reduces in activity during cognitively demanding tasks (Mak et al., 2017). While some regions of the DMN may exhibit greater connectivity during resting states, other regions may show reduced connectivity with each other (Salgado-Pineda et al., 2011). Relatedly,

individuals with schizophrenia often show impaired task-related activation reduction in the DMN. This failure to disengage the DMN during goal-directed activities can lead to attention and concentration deficits (Pomarol-Clotet et al., 2008).

Schizophrenia has been associated with disruptions in the balance between the default mode network (DMN) and other brain networks, such as the central executive network (involved in cognitive control) and the salience network (responsible for detecting relevant stimuli) (Manoliu et al., 2014). These disruptions can contribute to difficulties in filtering irrelevant information and distinguishing between internally generated thoughts and external stimuli, processes that are impaired and are involved in multiple schizophrenia symptoms (Marino et al., 2022). These alterations thus can affect neurological pathways, potentially leading to unintended activations in regions such as the superior temporal gyrus, known to engage in auditory processing and, when overactive, may contribute to auditory hallucinations (Adams et al., 2022; van Tol et al., 2014). Hallucinations have been previously associated with increased connectivity within the DMN, leading to a heightened sense of self-referential thoughts and perceptual distortions (Sasabayashi et al., 2023). Negative symptoms, characterized by deficits in motivation, emotional expression, and social engagement, are associated with reduced engagement of the DMN during tasks related to self-referential processing (Hu et al., 2017). This reduced activation may contribute to social withdrawal and emotional blunting seen in schizophrenia. Some studies have shown that antipsychotic medications, commonly prescribed for schizophrenia, may influence DMN activity (Deng et al., 2022). While they can partially normalize some DMN abnormalities, the effects can be variable and heterogeneous across treatment recipients.

Understanding these abnormalities in the DMN is critical for advancing our understanding of the neurobiology of schizophrenia. It highlights the intricate relationship between brain network dysfunctions and the diverse symptomatology observed in the disorder. Further research into the DMN and its role in schizophrenia holds promise for the development of early identification, targeted interventions and treatments aimed at addressing specific cognitive and perceptual deficits associated with the disorder.

1.3 Electroencephalography

Electroencephalography (EEG) is a non-invasive neuroimaging technique used to record electrical activity in the brain. It involves placing electrodes on the scalp to detect and measure the electrical signals produced by neurons firing in the brain. EEG measures the summation of post-synaptic potentials generated by neurons and measured on the scalp. EEG has been used as a particularly useful method of measuring and identifying endophenotypes in schizophrenia. EEG recordings can be analyzed in observed frequency across time, or as event-related potentials (ERPs) time-locked to the presentation of stimuli or cognitive event. EEG is advantageous in its measurement of brain activity with extremely high temporal resolution as it can collect electrical signals on a millisecond-by-millisecond basis. Compared to other brain measurement methods like functional magnetic resonance imaging (fMRI), which is limited by the speed of blood flow to active brain areas and can only measure activity on a 1-2 second-by-second basis, EEG is better able to capture cognitive and precognitive processes. EEG can easily measure these processes and identify millisecond changes in processing, however, EEG lacks the spatial resolution that fMRI allows. EEG electrode arrays can include a large number of

electrodes, but due to the nature of collecting neurological activity in the cortex near the scalp, any spatial reconstruction of EEG signals results in a low spatial resolution image.

One field of research that may aid in the identification of biomarkers for psychosis is that of event-related potentials (ERPs). Within the fields of attention and information processing, ERPs provide a sensitive method of indexing brain function that can both complement and clarify behavioural observations. The ERP waveform is elicited in response to a specific stimulus, including tones, light flashes, or cognitive events. Specifically, ERPs represent an average of the brain's activity that follows the onset of a stimulus. ERPs are regularly used in psychological research because they can provide valuable insights into basic cognitive mechanisms as well as higher brain functioning before the performance of an overt response (van der Stelt & Belger, 2007). ERPs are a helpful analysis tool as they can be markers of automatic sensory perception that do not require any behavioural response or cognizant attention to the stimulus (Näätänen, 2003). Due to their relative ease of acquisition, accessibility, and low cost, ERPs could be ideal in elucidating biomarkers of psychosis.

Another EEG analysis strategy to investigate the distribution of processing on a millisecond-by-millisecond basis that includes topographical distribution is referred to as microstates. Microstates refer to the transient, quasi-stable global states or patterns of EEG activation at rest or while performing cognitive operations. Microstates differ in frequency band, like other broadband quantitative EEG analyses, but include topographical distribution. There are four commonly used canonical microstates labelled A, B, C, and D. These microstates classes were first introduced and investigated by Dietrich Lehman in 1987 (Lehman et al.., 1987) and popularized with an analysis

software developed by Koenig et al. (2002), which incorporated spatial and temporal dynamics of brain activity while at rest. These investigation methods found four consistent states that are switched between multiple times a second (Luo et al., 2020). The topography of these different states is commonly observed as right frontal to left posterior activation in class A involved in the underpinnings of language processing; frontal to occipital activation in class B involved in visual imagery and visual processing; in class C involved in interoceptive autonomic processing using left frontal to right posterior activation; and frontomedial patterns of activation in class D involved in attention and orientation aspects of the default mode network (Yuan et al., 2012; Milz et al., 2016). Microstates typically are active for 60-120 ms before changing to a different topography that also remains quasi-stable for a similar period of time. Microstates trade-off in activation and represent the simultaneous activation of large-scale active brain networks. The four canonical microstate classes have been observed to account for 84% of the variance of resting state EEG-derived activity (Michel & Koenig, 2018). These microstates have been found to be closely related to fMRI-derived resting state networks and have been conceptualized as components of the default mode networks. Abnormalities in those with schizophrenia have been identified in default mode networks in both the fMRI-derived resting state and in temporal dynamics of EEG microstates (Britz et al., 2010). These microstates are thought to reflect the basic building blocks of spontaneous cognitive processing and are associated with different functional brain networks, including the DMN. By segmenting the EEG data into distinct microstates, researchers can identify those that correspond to DMN activity based on their spatial and temporal characteristics. The duration, occurrence, and transition probabilities of these

microstates provide insights into the temporal dynamics and stability of the DMN, further enriching our understanding of its functional role in resting-state brain activity.

To contextualize the significance of EEG microstate alterations in schizophrenia, network theory (Borsboom & Cramer, 2013) offers a useful framework for understanding how disruptions in specific neural dynamics might influence broader cognitive and perceptual systems. Microstates, particularly class C and D (as discussed in section 1.4), reflect transient neural states that map onto larger-scale brain networks, including the salience network and default mode network (Koenig et al., 2002). According to network theory, symptoms of schizophrenia are not isolated but arise from the interaction of various disrupted processes, creating a 'dynamic feedback loop' (Isvoranu et al., 2017). Abnormal microstate transitions could contribute to a failure in the coordination of these brain networks, leading to cognitive fragmentation, attentional deficits, and the misattribution of internal stimuli, which are key features of schizophrenia. This theoretical framework highlights the role of microstate abnormalities underpinning and maintaining the psychosis symptom network and suggests that targeting these network disruptions may offer new therapeutic approaches.

Research has identified alterations in the composition of microstate classes in individuals with schizophrenia (Baradits et al., 2020). Those with schizophrenia have been shown to exhibit a decreased occurrence of the typical microstate classes seen in healthy individuals and an increased occurrence of atypical or unique microstates (Murphy et al., 2020). This suggests a disruption in the fundamental building blocks of resting brain activity. In schizophrenia, the duration of microstate class D, associated with attention and orientation, has been observed to be significantly reduced (Luo et al., 2020).

This shortened duration may reflect a potential lack of sustained cognitive processing and could contribute to the cognitive deficits observed in schizophrenia or vice versa. Individuals with schizophrenia have also been shown to have increased or lengthened amounts of microstate class C (da Cruz et al., 2020), indicating heightened brain activity volatility, dysfunctional processing in the underlying areas active in the DMN, or a deficit in switching out of the sensory processing involved in class C. Alterations in topography and occurrence of microstate class C and D have been previously identified as potential candidates for endophenotypes of schizophrenia (da Cruz et al., 2020). Abnormalities in microstate dynamics have been associated with specific symptoms of schizophrenia. For instance, decreased microstate class D has been associated with positive symptoms such as hallucinations and delusions (Kindler et al., 2011), while lengthened microstate class A has been correlated with negative symptoms, including apathy, anhedonia, and asociality (Giordano et al., 2018). These alterations in the resting default mode network suggest that individuals with schizophrenia may display difficulties in coordinating microstates appropriately to form coherent, larger-scale brain networks. The hyperexcitation and lack of inhibition of excitatory processes may be involved in the differing processes underlying schizophrenia symptomatology, processing such as sensory, executive, memory, and self-referential cognitive functioning (Garrity et al., 2007; Hui et al., 2017).

Antipsychotic medications have also been documented in their alterations of EEG microstate abnormalities (Yoshimura et al., 2007). Previous investigations have suggested that medication-naive individuals with schizophrenia may show more pronounced microstate abnormalities than those on medication (Mackintosh et al., 2020). The exact impact of medication on microstate dynamics remains an area of ongoing investigation,

particularly regarding the potential changes or compensatory processes to changes longitudinally.

Schizophrenia is also associated with changes in the topographical distribution of microstates (Stevens et al., 1997). This may represent irregularities in the spatial configuration of EEG scalp maps during specific microstates in those with schizophrenia. This suggests a dysfunction in the normal coordination of neural networks. Recent studies found that individuals with schizophrenia exhibit disrupted connectivity patterns between different microstates (Yan et al., 2023). This implies a dysfunction in the coordinated information processing between brain regions involved in the default mode network, which may contribute to cognitive dysfunction observed in schizophrenia. Schizophrenia has also previously been associated with alterations in the dynamic complexity of microstate transitions (Murphy et al., 2020). These authors found that the patterns and transitions between microstates differed significantly from healthy controls. It is important to note that the specific abnormalities observed can vary among individuals with schizophrenia due to the heterogeneity of the disorder.

Research into EEG microstates has expanded to include early-phase psychosis (EPP), offering valuable insights into the neural alterations that may precede the onset of schizophrenia. Microstate abnormalities, long associated with established schizophrenia, are now being examined in individuals at clinical high risk (CHR) for psychosis and those experiencing first-episode psychosis (FEP). These studies aim to identify potential biomarkers for earlier detection and intervention.

Tomescu et al. (2014) investigated EEG microstates in adolescents with 22q11.2 deletion syndrome, a population at high risk for developing psychosis. They found

deviations in microstate class distribution and duration, resembling patterns typically observed in individuals with schizophrenia. Specifically, these alterations included prolonged microstate class C and reduced occurrence of class D, which are thought to reflect disruptions in neural networks linked to attentional control and cognitive integration. This study underscores the potential utility of microstate analysis as an early indicator of schizophrenia risk. Similarly, Andreou et al. (2014) explored resting-state microstates in CHR individuals and reported disrupted temporal dynamics and connectivity patterns between microstates. For example, they observed reduced connectivity involving microstate classes A and B, which are associated with default mode network activity and language processing, respectively. These disruptions suggest that early neural network dysfunctions are present during the prodromal phase and could contribute to the cognitive and functional impairments observed in schizophrenia. These findings highlight the value of EEG microstates in understanding the progression of psychosis. Detecting such abnormalities during the early stages of illness may facilitate the identification of individuals at higher risk for conversion to schizophrenia and inform phase-specific interventions. By bridging the gap between clinical and subclinical states, EEG microstate research holds promise for improving prognostic models and developing targeted treatments for those in the early phases of psychosis.

1.4 Auditory Dysfunction in Schizophrenia

Auditory dysfunction in schizophrenia plays a significant role in the experience of auditory hallucinations, which are one of the hallmark symptoms of the disorder. Individuals with schizophrenia often exhibit impairments in basic auditory processing (Donde et al., 2023). Auditory hallucinations typically involve the hearing of voices or

sounds that are not actually present in the external environment. Neuroanatomically, auditory hallucinations often implicate regions of the brain associated with auditory processing, such as the superior temporal gyrus (STG) and the auditory cortex (Stahl et al., 2018). Dysfunction in these areas, whether due to structural abnormalities or altered connectivity, can contribute to the perception of auditory stimuli in the absence of external input (Huang et al., 2019). Neurochemically, imbalances in neurotransmitter systems play a significant role in the generation of auditory hallucinations. The neurotransmitter systems primarily implicated in the generation of auditory hallucinations include the dopaminergic and glutamatergic systems (McCutcheon et al., 2020). Hyperactivity of dopamine, particularly in the mesolimbic pathway, is thought to contribute to the abnormal salience and perception of internal thoughts as external voices (Stahl, 2018). Additionally, dysregulation of glutamate, particularly through NMDA receptor hypofunction, may disrupt the balance of excitatory and inhibitory signals in the brain, leading to altered processing that manifests as auditory hallucinations (Jardri et al., 2016). Serotonin and GABA neurotransmitter systems also play a role in modulating the overall neural circuitry involved in these experiences (Mizuno, 2015). In terms of neural connectivity, disruptions in functional connectivity within and between neural networks have been observed in individuals experiencing auditory hallucinations. This can involve both hyperconnectivity, where certain brain regions exhibit abnormally heightened communication, and hypoconnectivity, where communication between regions is reduced. In individuals experiencing hallucinations, hyperconnectivity is often observed in the auditory cortex, particularly the primary auditory cortex, which can lead to the misinterpretation of internal thoughts as external sounds (Shao et al., 2021). There is also

increased connectivity between the auditory cortex and Broca's area, which is involved in speech production, potentially contributing to the perception of hearing voices (Fovet et al., 2022). Additionally, hyperconnectivity is noted in the default mode network (DMN), which may disrupt normal cognitive processes and self-referential thoughts (Hwang et al., 2021).

On the other hand, hypoconnectivity is commonly observed in regions such as the prefrontal cortex, which is crucial for executive function and reality testing (Shao et al., 2021). Reduced connectivity between the prefrontal cortex and the hippocampus can impair memory and contextual processing, further contributing to the formation of hallucinations (Blessing et al., 2020). Reduced connectivity between the prefrontal cortex and the hippocampus can impair memory and contextual processing by disrupting the communication necessary for integrating and retrieving information. The hippocampus plays a critical role in encoding and consolidating memory, while the prefrontal cortex is involved in organizing and contextualizing this information for decision-making and adaptive behaviour. When connectivity is weakened, the coordination between these regions breaks down, leading to difficulties in forming coherent memories and using contextual cues to guide behaviour (Eichenbaum, 2017). Dysfunction in the corollary discharge, a mechanism that helps the brain differentiate self-initiated actions from external events, may exacerbate this issue, as seen in auditory hallucinations where self-generated thoughts are misinterpreted as external auditory stimuli (Ford & Mathalon, 2005). Such connectivity deficits, particularly between the prefrontal cortex and sensory regions, reinforce this misattribution and abnormal sensory processing (Wu et al., 2022). Similarly, diminished connectivity between the prefrontal cortex and the thalamus, a

region involved in sensory information processing, may lead to abnormal sensory experiences and the integration of hallucinations (Wu et al., 2022). These connectivity alterations may lead to the misinterpretation of neural signals, contributing to the perception of auditory stimuli that are not actually present (Shinn et al., 2013).

Understanding the auditory dysfunction underlying hallucinations is essential to their effective treatment. For example, individuals with schizophrenia may have trouble distinguishing between real sounds and internally generated ones, and this may be due to observed alterations in the left insula involved in the salience network (Barber et al., 2021). Previous research has also identified abnormalities in identifying the source of auditory stimuli in those with schizophrenia (Thakkar & Rolfs, 2019). Neuroimaging studies have revealed hyperactivity in the auditory cortex of individuals with schizophrenia, particularly during the experience of auditory hallucinations (Jadri et al., 2011). Schizophrenia has also been previously associated with altered functional connectivity between different brain regions involved in auditory processing (Zhang et al., 2018). Cognitive factors, such as biases in attention and memory, can also play a role in the development and maintenance of auditory hallucinations. The detection of these abnormalities can inform diagnosis and treatment for these individuals with schizophrenia spectrum illness. Individuals with schizophrenia may have a heightened sensitivity to auditory stimuli, selectively attending to and recalling information that is consistent with their delusional beliefs or hallucinatory experiences (Garety et al., 2001). Stress and emotional factors can exacerbate auditory hallucinations in schizophrenia. Elevated stress levels can increase the likelihood and intensity of hallucinations, possibly

through their impact on neural circuits involved in emotion regulation and general heightened neural activity under distress (Lataster et al., 2013).

It has been suggested that dysfunctional coordination of early stages of sensory and information processing may also underlie the characteristic clinical and cognitive deficits of schizophrenia, such as hallucinations, delusions, impaired working memory and attention (Javitt, 2009; Light et al., 2006). One of the most robust neurophysiological deficits of schizophrenia is observed in auditory change detection indexed by the EEG-derived mismatch negativity (MMN). Mismatch negativity is an event-related potential component observed in previous EEG studies, reflecting the brain's automatic response to deviations or mismatches in repetitive auditory stimuli. It is used to assess pre-attentive auditory processing and is often employed in research on various neurological and psychiatric conditions (Fitzgeral & Todd, 2020). The automatic and pre-attentive MMN is commonly generated by randomly inserting rare deviant auditory stimuli into a train of standard sounds. A prediction error model of the MMN suggests that the auditory cortex imputes a pattern of the auditory environment and that deviations from the complex pattern elicit an error signal from primary to secondary cortices used to adjust the model (Winkler, 2007). To elicit MMN, the deviant can be different from the standard in any number of ways, including deviations in frequency, duration, intensity, and location (Näätänen & Alho, 1997).

Research into the MMN in those with schizophrenia has been a major point of interest since the first study linking the two was published (Shelley et al., 1991). In that study, patients with schizophrenia exhibited significantly reduced MMN amplitudes compared to healthy controls. This reduction in MMN was associated with the severity of

cognitive and clinical symptoms in those with schizophrenia. The results suggested that impaired automatic auditory processing, as reflected by the observed decreased MMN, might be associated with the cognitive deficits and symptom severity observed in schizophrenia. In general, individuals with chronic schizophrenia display deficits in sensory information processing, as reflected in the consistent reports of robust MMN amplitude reductions (Javitt et al., 1993; Umbricht et al., 2003; Park et al., 2002), especially to duration deviants (Michie, 2001). As a result of the robust nature of MMN alterations in schizophrenia, the ongoing Consortium on the Genetics of Schizophrenia (COGS) recently endorsed the utility of the MMN as an assessment tool in this disease due to its significant correlations with well-established measures of clinical, cognitive, and psychosocial functioning in those with schizophrenia (Light et al., 2015).

While duration deviants often produce the largest deficits in MMN responses in schizophrenia, other kinds of deviants have also shown notable between-group differences (Umbircht & Krljes, 2005). For example, frequency deviants, which involve changes in the pitch of the stimulus, have been found to elicit smaller reductions in MMN amplitude than duration deviants, indicating that frequency-related auditory processing might be less impaired (Todd et al., 2008). In contrast, MMN deficits in response to intensity deviants, which reflect changes in the loudness of the stimulus, tend to be less robust and more variable (Light & Braff, 2005). These findings suggest that schizophrenia may differentially affect specific neural mechanisms involved in processing different types of auditory changes.

Moreover, location deviants, which involve shifts in the spatial origin of the sound, have also shown reduced MMN amplitudes in individuals with schizophrenia,

though fewer studies have examined this type of deviant compared to frequency and duration (Schall et al., 1999). This diversity in MMN response patterns across different types of deviants underscores the complexity of sensory processing deficits in schizophrenia, with certain pathways, such as those involved in duration processing, being more severely affected than others. Thus, the choice of deviant stimulus can significantly influence the magnitude of MMN reductions observed in schizophrenia.

While there is some evidence that MMN deficits are present at the first psychotic episode and may predate psychosis in clinical high-risk individuals (Atkinson et al., 2012; Jahshan et al., 2012; Nagai et al., 2013; Perez et al., 2014), findings are inconsistent. Brockhaus-Dumke and colleagues (2005) found that prodromal subjects showed a non-significant reduction of MMN amplitude, which ranged between healthy controls and individuals with schizophrenia, while other groups have reported a normal MMN at first psychotic episode (Salisbury et al., 2002, 2007; Umbricht et al., 2006; Magno et al., 2008). Results from genetic high-risk studies have similarly been inconsistent. While some groups have reported reduced MMNs in the first-degree relatives of individuals with schizophrenia (Jessen et al., 2001; Michie et al., 2002; Sevik et al., 2011), others have reported either weak (Ahveninen et al., 2006; Hall et al., 2009) or no familial effects (Schreiber et al., 1992; Bramon et al., 2004). A meta-analysis of 14 MMN studies conducted on those in their first episode of schizophrenia concluded that stimuli that deviate in simple stimulus features from the standard elicited stimuli showed no significant MMN reductions between groups (Haigh et al., 2017).

It is worth noting that most of these studies examining auditory change detection in those with schizophrenia or schizophrenia-like symptoms have elicited MMNs using a

traditional, two-stimulus auditory oddball paradigm. In the oddball paradigm, the standard stimuli are physically identical, and deviant stimuli possess some changed feature (Näätänen, 1990). There has been some criticism that such paradigms do not elicit a true MMN. Jacobsen and Schröger (2001) demonstrated that the MMN that is typically measured in oddball paradigms with frequency deviants contains both the MMN and an overlapping N100 enhancement representative of stimulus evaluation. As the deviant stimulus is presented much less than the standard, the N100 elicited by deviant tones is much larger than the refractory response that is evoked by standard tones, and the difference in their amplitudes is retained in the difference wave. In such cases, the MMN and N100 can overlap and summate, and unravelling their relative contributions to the difference wave is often not possible without careful control procedures. In response to these concerns, as well as in response to the inconsistency between-group findings in the prodrome and early phase of schizophrenia using simple stimulus-feature change paradigms, there has been a shift in interest to explore MMNs that are elicited by more complex stimulation parameters that avoid the sensory refractoriness problem that is inherent in the oddball paradigm.

Another novel paradigm to elicit the mismatch negativity has been recently developed by Salisbury and colleagues (2024). The novel dual rule MMN paradigm consists of tones that alternate between presentation to the left and right ear, as well as alternates between high and low frequency. The standard trial pattern consists of the low-frequency tone played to the left ear, and then the high-frequency tone played to the right ear. Deviant trials consist of two presentations of the standard pattern, followed by the low-frequency tone played to the left ear twice (i.e. a repetition of the first tone in the

standard pattern, or a tone that fails to switch both frequency and location, thus breaking the two established patterns of left/right and high/low frequency). The development of such novel paradigms has the potential to generate additional insights regarding central auditory processing in the schizophrenia spectrum and may yield valuable biomarkers of illness.

1.5 Overview of Studies in Thesis

This doctoral dissertation encompasses a comprehensive investigation of potential candidate endophenotypes of schizophrenia using objective brain-based methods. Electroencephalography is uniquely suited to probe the dynamic and temporal aspects of neural activity. EEG provides a millisecond-by-millisecond measurement of neural activity making it an invaluable asset in the aim to identify subtle yet fundamental differences in brain function associated with schizophrenia.

The research presented in this thesis is divided into three distinct but interrelated studies, each contributing a unique facet to the broader understanding of schizophrenia's neurological underpinnings. The three studies are summarized below but will be described in greater detail in their subsequent chapters.

1.6 Study 1: Meta-Analysis of Resting State Microstates Differences in Schizophrenia

The first study involves a meta-analysis of existing literature, focusing on differences in EEG derived microstates between individuals with schizophrenia and the healthy controls. This meta-analysis seeks to consolidate and critically evaluate the existing body of evidence to identify consistent patterns of microstate alterations in individuals with schizophrenia, potentially providing evidence supporting microstates as an endophenotype.

1.7 Study 2: Resting-State Microstate Differences in Schizophrenia

In the second study, the resting-state EEG recordings of those with schizophrenia were experimentally investigated. Resting-state conditions provide a unique window into the intrinsic baseline activity of the brain, referred to as the default mode network. By comparing resting-state microstates between individuals in the early phase of psychosis and controls, we aimed to determine whether aberrant neural dynamics underlying schizophrenia persist even when the brain is at rest. These findings may elucidate some of the fundamental alterations in brain function associated with schizophrenia, which can be observed in a more objective manner and robust against the confounding effects of external stimuli or cognitive processing.

1.8 Study 3: Auditory Processing Microstates, Event-Related Potentials (ERPs), Mismatch Negativity in Schizophrenia

The third study involves the investigation of potential candidates of endophenotypes in the auditory processing domain, a hallmark area of investigation in schizophrenia research, given the prevalence of auditory hallucinations in the illness. Using multiple types of EEG analyses, auditory processing is investigated through the lens of event-related potentials, with a particular focus on the mismatch negativity (MMN) component.

The findings of these three studies aim to contribute to a more nuanced understanding of the neurophysiological underpinnings of schizophrenia and its endophenotypes. By identifying potential endophenotypes related to microstate dynamics and auditory processing, this research not only adds to the scientific knowledge of the basic understanding of schizophrenia but also offers new avenues for early diagnosis,

intervention, and progress monitoring. Ultimately, our goal is to elucidate the neurophysiological components of schizophrenia, offering new insights into its etiology and pathophysiology that may give credence to early identification of schizophrenia, which results in more effective treatments and improved outcomes for individuals affected by this complex disorder. Of the studies included in this thesis, the meta-analysis presented in Chapter 2 has been submitted for publication. At the time of writing, none of the studies have been presented at conferences. However, future dissemination efforts will focus on presenting the key findings from the experimental chapters at relevant academic conferences to engage with the broader scientific community.

CHAPTER 2 Meta-Analysis of Resting Microstate Differences in Schizophrenia

2.1 Introduction

Research has identified significant alterations in the composition of microstate classes in individuals diagnosed with schizophrenia (Baradits et al., 2020). These microstates, which are brief, stable patterns of brain activity, appear to manifest differently in people with schizophrenia compared to healthy individuals. Specifically, individuals with schizophrenia exhibit a reduced frequency of the typical microstate classes commonly seen in the general population and a higher frequency of atypical or unique microstates (Murphy et al., 2020). This shift suggests a fundamental disruption in the brain's resting state activity, which may underlie many of the cognitive and perceptual disturbances associated with the disorder.

The duration of certain microstates, such as the A or D classes, which are associated with sustained attention and memory, is notably shorter in those with schizophrenia (Luo et al., 2020). This reduced duration indicates a possible deficiency in the ability to maintain cognitive processes over time, which may contribute to the characteristic cognitive deficits observed in schizophrenia. Such deficits include impaired attention, memory, and executive functioning, which are critical for daily functioning and quality of life.

Previous research has observed that individuals with schizophrenia tend to have increased or prolonged occurrences of microstate class C (da Cruz et al., 2020). This increase might indicate heightened brain activity volatility, suggesting that the brain's neural networks are more unstable and prone to erratic functioning. Dysfunctional processing in the brain regions associated with the DMN or an inability to effectively

switch away from the cognitive processes involved in microstate class C could be underlying factors. The DMN is implicated in self-referential thought and mind-wandering, and disruptions in its function are believed to contribute to the cognitive and perceptual symptoms of schizophrenia.

Alterations in the duration, coverage and occurrence of microstate classes C and D have been proposed as potential endophenotypes of schizophrenia, which are heritable traits associated with the genetic risk of the disorder (da Cruz et al., 2020). These changes could serve as biomarkers for identifying individuals at risk or for developing targeted interventions.

Microstate class A has been associated with fMRI-indexed network activation in the bilateral superior and medial temporal lobes, regions involved in memory, emotional processing, speech processing, and auditory perception (Rajkumar et al., 2021; Milz et al., 2015). In schizophrenia, alterations in microstate A may reflect deficiencies in sensory and speech processing, which could contribute to symptoms such as auditory hallucinations and communication difficulties. Similarly, microstate class B has been associated with bilateral occipital activation, reflecting visual processing (Rajkumar et al., 2021; Yuan et al., 2012). Dysfunctional processing in occipital regions could underlie visual disturbances, such as visual hallucinations or impaired visual search, which are common features of schizophrenia (Silverstein et al., 2010; Zmigrod et al., 2016).

The difficulty in transitioning between microstates may be associated with the disorganized thinking and distractibility commonly observed in schizophrenia. Abnormalities in microstate dynamics have been correlated with specific symptoms of the disorder. For example, a decrease in the occurrence of microstate class D has been

associated with positive symptoms, such as hallucinations and delusions (Kindler et al., 2011). In studies investigating fMRI and EEG measures, microstate class D has been associated with right-lateralized dorsal and ventral frontal and parietal systems, regions involved in sensory processing, executive function, and attention (Rajkumar et al., 2021; Yuan et al., 2012). On the other hand, an extended duration of microstate class A has been associated with negative symptoms, including apathy, anhedonia, and asociality (Giordano et al., 2018). These negative symptoms significantly impact the quality of life and social functioning of individuals with schizophrenia.

These observations suggest that disruptions in the resting default mode network could hinder the proper integration of microstates necessary to form coherent, large-scale brain networks. Such integration is crucial for efficient cognitive functioning and the coordination of complex mental activities. The hyperexcitation and insufficient inhibition of excitatory processes in the brain might contribute to widespread disruptions in sensory processing, executive functions, memory, and overall cognitive performance (Garrity et al., 2007; Hui et al., 2017). Understanding these dynamics offers valuable insights into the neural mechanisms underlying schizophrenia and points toward potential avenues for therapeutic intervention.

The latest meta-analysis of abnormalities in EEG-derived microstates in those with schizophrenia examined eight independent studies comparing resting microstate dynamics among the four canonical microstates in those with schizophrenia against a control group (da Cruz et al., 2020). The authors found consistently statistically significant increased time coverage and occurrence of microstate class C in those with schizophrenia compared to healthy controls across studies. The authors also found

consistently statistically significant decreased time coverage and mean duration in microstate class D in those with schizophrenia compared to controls. The authors noted that before correction for multiple comparison, there was also a decrease in mean duration in microstate class B in those with schizophrenia, however, the findings lost significance after correction for multiple comparison. The authors generally found medium effect sizes in their meta-analysis and determined that the robust, altered temporal dynamics of microstate processing are a good candidate for an endophenotype of schizophrenia. The authors also found associations between medication status and altered microstate dynamics. The authors found those with schizophrenia who were taking antipsychotic medication displayed increased duration and coverage of microstate class C, although this finding lost significance after correcting for multiple comparisons. However, previous investigations have found those taking medication displayed more normalized microstate dynamics (Kikuchi et al., 2007). The findings of the latest meta-analysis, in general, suggest that there is increased activation in global patterns between frontal to occipital regions but decreased activation or decreased switching of states in frontomedial systems. This may indicate that more attentional resources are attributed to what is being viewed around the individual with schizophrenia, as well as a reduction in frontal moderating systems to language and auditory processing, resulting in the distribution of functioning that may be inherent in the dysfunction that causes auditory hallucinations in those with schizophrenia.

Together, these microstate abnormalities provide insights into the neural disruptions underlying schizophrenia. The observed alterations across microstate classes (A, B, C, and D) highlight their potential role as biomarkers and endophenotypes,

reflecting heritable traits associated with the genetic risk of schizophrenia. These disruptions, particularly within the default mode network, suggest a broader imbalance between processes of saliency detection, attentional engagement, and sensory integration, contributing to the diverse clinical presentations of the disorder.

2.1.1 Hypotheses

The purpose of this meta-analysis was to accumulate data to represent the current state of the literature surrounding the use of EEG-derived microstates as an endophenotype of schizophrenia to identify if those with schizophrenia have similar reliable abnormalities in resting state microstates compared to the general population. This would confirm that microstates are a good candidate as an endophenotype of schizophrenia for further investigation, replication, and implementation. The most recent meta-analysis on the subject was published in 2020 and encompassed eight total studies; the literature on microstates in schizophrenia has more than doubled in this time, necessitating an update. Previous studies have identified consistent microstate abnormalities in those with schizophrenia pertaining to the increase of the coverage, occurrence, and duration increasing microstate class C and a reduced duration, coverage, and occurrence of class D specifically. Because of this, we hypothesize that across studies observed in the meta-analysis, microstate class C and D will have significant differences in comparison to healthy controls. Specifically, the increase of duration, occurrence and coverage of microstate class C and reduction of the duration, occurrence, and coverage of class D.

2.2 Methods

To identify relevant literature, a search with the meshed term “schizophrenia” and the unmeshed term “microstate” was conducted in the Cochrane Library, PsycINFO, Pubpsych, Pubmed, Science Direct, EBSCO, Web of Science, and Embase databases. The resulting papers were imported into the Covidence meta-analysis software and reviewed for inclusion and exclusion criteria for compatibility of comparison across multiple studies. The criteria were that the paper needed to be peer-reviewed, microstate parameters were available to extract or could be requested, participants in the patient group had a schizophrenia diagnosis, there were at least 12 participants per group of schizophrenia and healthy control, and if there was experimental manipulation, control data was available. The sample size criterion was based on previously used criteria in the field (Francis et al., 2024). Care was taken to exclude duplicate reporting of the same data in different papers. The criteria for inclusion/exclusion were created to identify the broadest common ground to compare studies on microstates in schizophrenia at the time of the paper being written. A complete list of papers can be found in Table 1.

The process of study exclusion is available in Figure 1 below. All papers were reviewed by at least two separate reviewers. All four reviewers were subject to reliability training and included/excluded the same 20 full text papers to identify a baseline of operations. A meeting was first held to review inclusion/exclusion criteria and data collection practices. A random sample of 20 papers was taken during title and abstract screening that all four reviewers rated and reached consensus. All conflicts in exclusion were discussed among reviewers and settled by the author. Any disagreements were sent to an independent reader. The meta-analysis was conducted in accordance with the

PRISMA guidelines/checklist (Page et al., 2021). To evaluate the potential of systematic bias in the review all studies were reviewed, and a Cochrane Risk of Bias score was assigned. This was assigned using the Risk of Bias Scale 2, which considered factors such as risk of bias due to missing outcome data, risk of bias in measurement of the outcome, risk of bias in selection of the reported result, and overall risk of bias. Each category provided ratings of either low, some concerns, or high risk of bias.

Figure 1. PRISMA pipeline of identified studies, screening, and data extraction and review

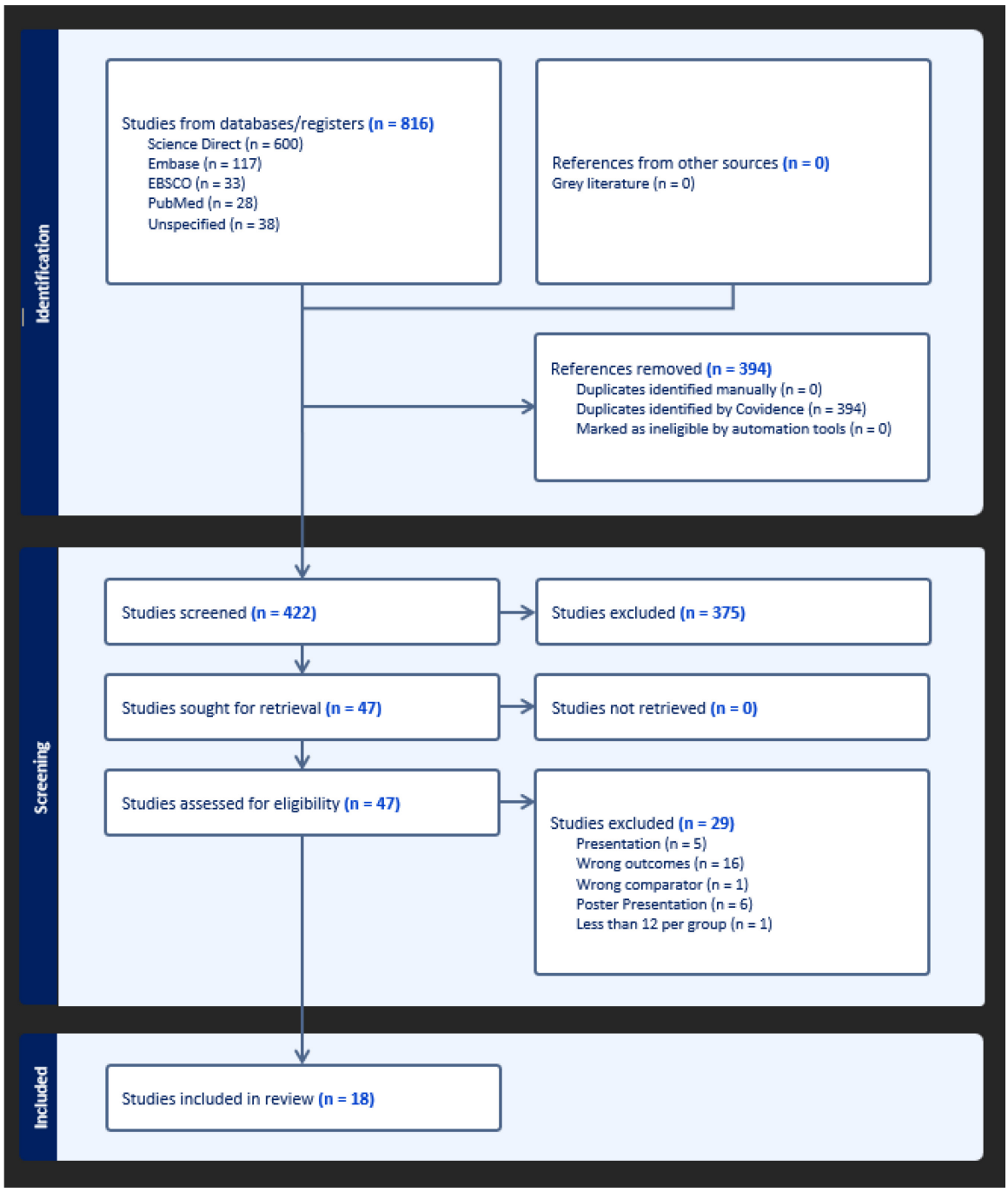


Table 1. List of Articles Included in Data Extraction and Analysis

First Author	Year	Title	Sz N (female)	HC N (female)	Age (SD)	Illness Phase	Medication
Strelets	2003	Chronic Schizophrenics with Positive Symptomatology Have Shortened EEG Microstate Durations	14 (0)	13 (0)	Sz 36.1 (10.2) HC 35.1 (8.2)	Chronic	7 days free
Lehmann	2005	EEG microstate duration and syntax in acute, medication-naive, first-episode schizophrenia: a multi-center study.	27 (9)	27(9)	Sz 23.9 (5.4) HC 24.4 (4.5)	First Episode	Medication Naïve
Kikuchi	2007	Native EEG and Treatment Effects in Neuroleptic-Naïve Schizophrenic Patients: Time and Frequency Domain Approaches	21 (10)	21 (10)	Sz 28.1 (19.1) HC 28.4 (24.6)	First Episode	Anti psychotic Medication
Nishida	2013	Increased Omega Complexity and Decreased Microstate Duration in Nonmedicated Schizophrenic Patients	24 (12)	24 (12)	Sz 25.3 (6.8) HC 24.6 (5.6)	First Episode	Medication Naïve
Andreou	2014	Resting-State Connectivity in the Prodromal Phase of Schizophrenia: Insights from EEG Microstates	18 (2)	20 (5)	Sz 23.6 (4.4) HC 24.35 (5.1)	First Episode	Anti Psychotic Medication

Tomescu	2015	Schizophrenia Patients and 22q11.2 Deletion Syndrome Adolescents at Risk Express the Same Deviant Patterns of Resting State EEG Microstates: A Candidate Phenotype of Schizophrenia	27 (5)	27 (13)	Sz 34.5 (9.5) HC 34.2 (8)	Chronic	Anti Psychotic Medication
Sun	2018	Abnormalities of Electroencephalography Microstates in Drug-Naïve, First-Episode Schizophrenia	23 (7)	23 (10)	Sz 28.04 (5.42) HC 26.39 (6.95)	First Episode	Medication Naïve
Soni	2018	Hyperactivation of Left Inferior Parietal Lobule and Left Temporal Gyri Shortens Resting EEG Microstate in Schizophrenia	34 (NI)	25 (NI)	Sz 27.12 (5.35) HC 32.17 (13.13)	Early Phase	Anti Psychotic Medication
da Cruz	2020	EEG Microstates are a Candidate Endophenotype for Schizophrenia	101 (11)	75 (39)	Sz 36.9 (2.7) HC 35.1 (7.7)	Chronic	Anti Psychotic Medication

Kim	2021	EEG Microstate Features for Schizophrenia Classification	14 (7)	14 (7)	Sz 27.9 (3.3) HC NI	Chronic	NI
Wang	2021	Electroencephalographic Microstates in Schizophrenia and Bipolar Disorder	20 (15)	35 (25)	Sz 25.2 (6.8) HC 24.9 (6.2)	Chronic	Anti Psychotic Medication
Sun	2021	EEG Microstates and its relationship with Clinical Symptoms in Patients with Schizophrenia	46 (10)	39 (14)	Sz 28.7 (7.4) HC 27.2 (6.9)	Chronic	Half Anti Psychotic Medication
Keihani	2022	Bayesian Optimization of Machine Learning Classification of Resting-State Microstates in Schizophrenia: A Proof of Concept Preliminary Study Based on Secondary Analysis	14 (7)	14 (7)	Sz 27.9 (3.3) HC 26.8 (2.9)	Chronic	7 days naïve
Bissonnette	2022	EEG Microstates in Early Phase Psychosis: The Effects of Acute Caffeine Consumption	12 (3)	13 (4)	Sz 29.17 (3.59) HC 23.15 (4.18)	Early Phase	Anti Psychotic Medication

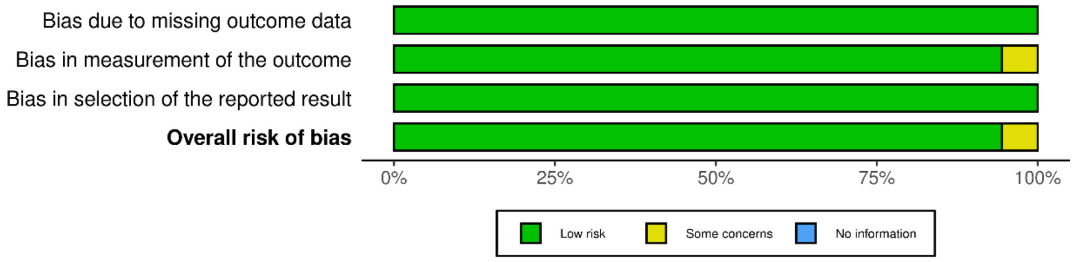
Lin	2022	Altered Microstate Dynamics and Spatial Complexity in Late-Life Schizophrenia	39 (29)	40 (29)	Sz 68.23 (5.43) HC 69.3 (6.93)	Chronic	Neuroleptic Medication
Thiriouz	2023	EEG Microstate Cospecificity in Schizophrenia and Obsessive-Compulsive Disorder	28 (7)	27 (13)	Sz 35.56 (4.6) HC 37.4 (2.4)	Chronic	Anti Psychotic Medication
Chen	2023	Electroencephalographic Microstates are Correlated with Global Functioning in Schizophrenia but Not in Bipolar Disorder	40 (26)	16 (10)	Sz 39.7 (9.5) HC 35.5 (10.1)	Chronic	NI
Iftimovici	2023	Electroencephalography Microstates Imbalance Across the Spectrum of Early Psychosis, Autism, and Mood Disorders	34 (11)	11 (5)	Sz 21.8 (3.8) HC 31 (13)	Chronic	NI

Note. This table includes all articles used in the present meta-analysis. First authors, year of publication, title of article, sample size per group, sex distribution, age of samples, phase of illness, and medication state at testing are offered. NI refers to no information if not provided in the article or by authors.

There was a total of 18 studies meeting our criteria, with dates of publication ranging from 2007 to 2023. All studies were based on a topographically consistent

canonical set of four microstate classes labelled from A to D. The papers were mostly complete in the canonical microstate parameters they reported that were subject to extraction, those canonical parameters being coverage (percent total time covered by an individual microstate class), occurrence (how much each individual microstate class is observed on a per second basis), and mean duration (average duration of an individual microstate class). These parameters have been previously used in microstates analysis that aim to capture each microstate class as they switch on a millisecond basis. From these studies, means and standard deviations were extracted from patient and control data. Only Nishida and colleagues (2013) did not include coverage parameters and Thirioux and colleagues (2023) did not include standard deviations. Both papers did not respond to data requests before the completion of this study. Complete datasets were included in the analysis, while incomplete or missing data were excluded from analysis. The manuscripts examined showed an overall low risk of bias (See Figure 2).

Figure 2. Quality assessment depicted visually which represents the quality of articles included in the meta analysis and their risk of bias evaluated by using the Cochrane Risk of Bias scale. Figure was generated with Robvis.



2.2.1 Statistical Analyses

Summed Cohen's *d* effect sizes were generated from mean difference scores using a custom R script and were used to compare microstate parameters between patient and control conditions. Cohen's d effect sizes can be interpreted as small ($d = .2$), moderate (d

= .5), and large (d = .8). A meta-analysis using the random effects and inverse-variance weighting method was performed utilizing custom R script and the R meta package which used metacont functions (Schwarer & Rucker, 2023). The degree of heterogeneity among studies was evaluated using the I^2 statistic and its corresponding p-values.

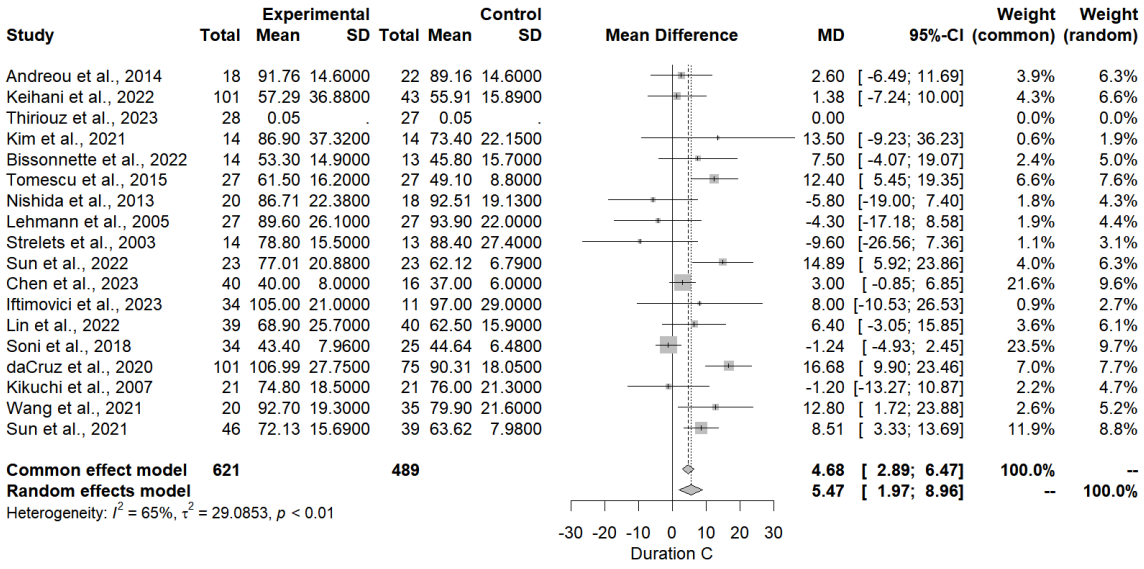
2.3 Results

Forest plots of the mean effect sizes for each microstate parameter (mean duration, time coverage, and occurrence) and microstate class (A, B, C, and D) are shown below (see Figure 3-14). The meta-analysis yielded mean effect sizes with small to large effects of microstate parameter differences between groups.

The meta-analysis focused primarily on microstate classes C and D, given the study's *a priori* hypotheses. Specifically, microstate class C was hypothesized to exhibit increased mean duration, occurrence, and coverage in individuals with schizophrenia, while microstate class D was expected to show reduced mean duration, occurrence, and coverage compared to healthy controls. These hypotheses were largely supported by the findings. For microstate class C, individuals with schizophrenia demonstrated a significant increase in mean duration ($p < .001$, $d = 0.29$, Mean Difference (MD) = 5.47, 95% CI [1.97, 8.96] ; See Figure 3). total proportion of time covered (coverage), and mean number of occurrences per second (occurrence;. However, confidence intervals for the group differences in coverage ($p < .001$, $d = 0.23$, MD = 0.99, 95% CI [-4.19, 6.16]; See Figure 4) and occurrence ($p = .01$, $d = 0.26$, MD = 0.10, 95% CI [-0.19, 0.39]; See Figure 5) of class C spanned zero in the random effects model, suggesting the absence of a true group differences. Microstate class D showed reductions in mean duration ($p = .02$,

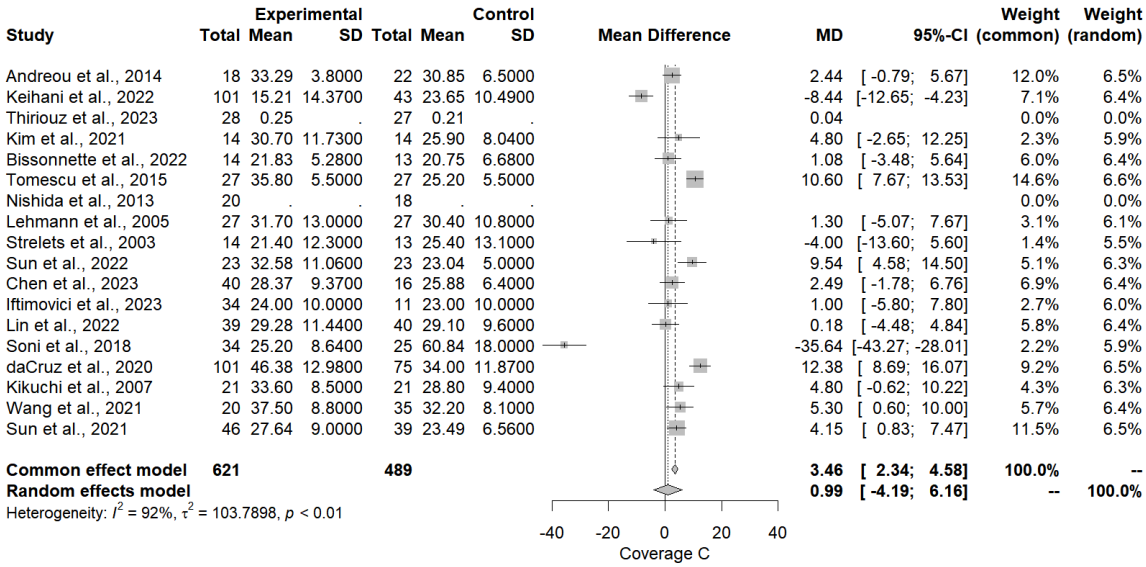
d = 0.23, MD = -3.34, 95% CI [-8.17, 1.50]; See Figure 6), however, was not deemed significant despite p < .05 due to confidence interval values of the mean difference spanning 0. In class D there were statistically significant reductions in total proportion of time covered (coverage; *p* = .02, *d* = 0.42, MD = -3.26, 95% CI [-6.11, -0.41]; See Figure 7), and number of occurrences per second (occurrence; *p* = .03, *d* = 0.36, MD = -0.21, 95% CI [-0.41, -0.02]; See Figure 8). These findings align with the proposed hypotheses and highlight disruptions in salience detection and attentional networks frequently implicated in schizophrenia. Exploratory analyses revealed no statistically significant differences in microstate classes A and B,. While several of these comparisons yielded p-values below p < .05 (e.g., coverage of class A & B), in all cases the 95% CI of the random effects model included zero. Forest plots for microstate duration, coverage and occurrence of class A and B can be seen in figures 9-14.

Figure 3. Forest plot of means, mean differences, and effect sizes for studies measuring mean duration of microstate class C across studies.



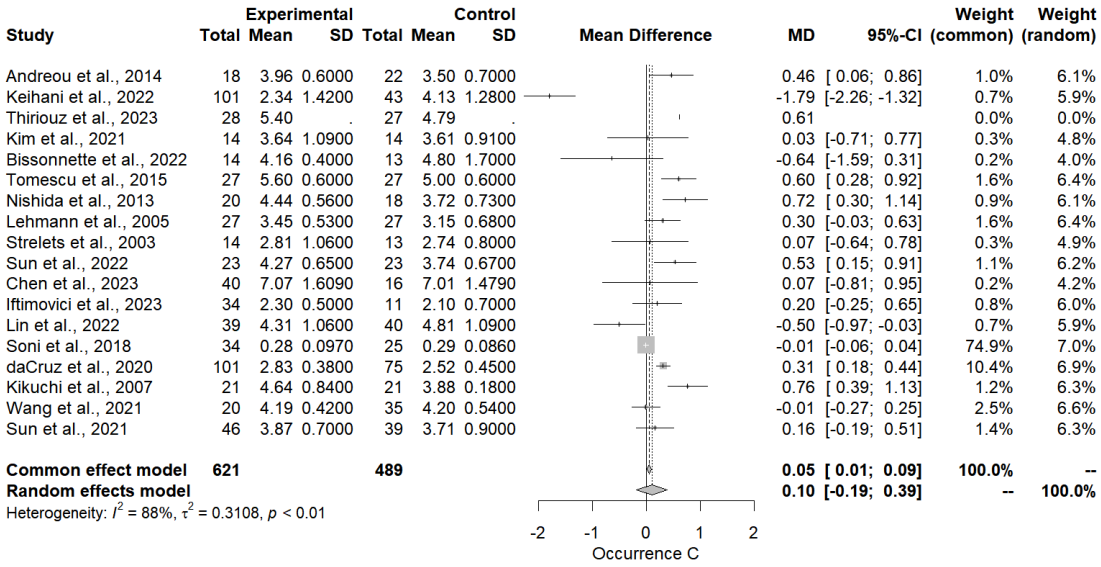
Note. Total sample size, mean duration for microstate class C, standard deviations, mean differences, 95% confidence interval and weighting in the common and random effects m odel displayed per studies measuring duration of microstate class C. Mean differences an d confidence intervals are displayed for random and common effects models. Tests of het erogeneity were passed and displayed via tau squared.

Figure 4. Forest plot of means, mean differences, and effect sizes for studies measuring mean total proportion of coverage of microstate class C across studies.



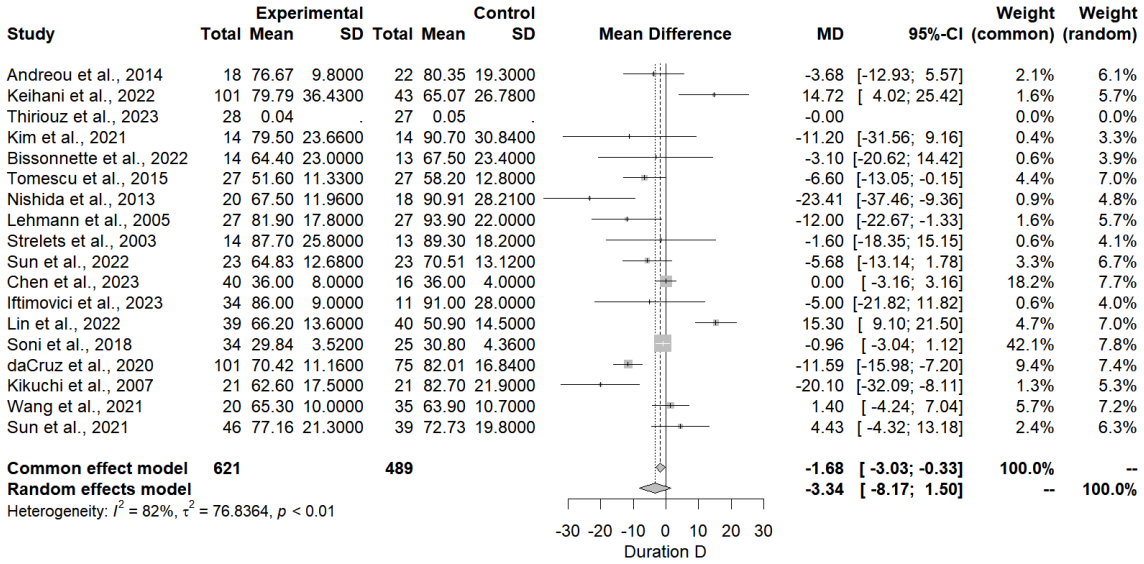
Note. Total sample size, mean coverage for microstate class C, standard deviations, mean differences, 95% confidence interval and weighting in the common and random effects m odel displayed per studies measuring coverage of microstate class C. Mean differences an d confidence intervals are displayed for random and common effects models. Tests of het erogeneity were passed and displayed via tau squared.

Figure 5. Forest plot of means, mean differences, and effect sizes for studies measuring per second occurrence of microstate class C across studies.



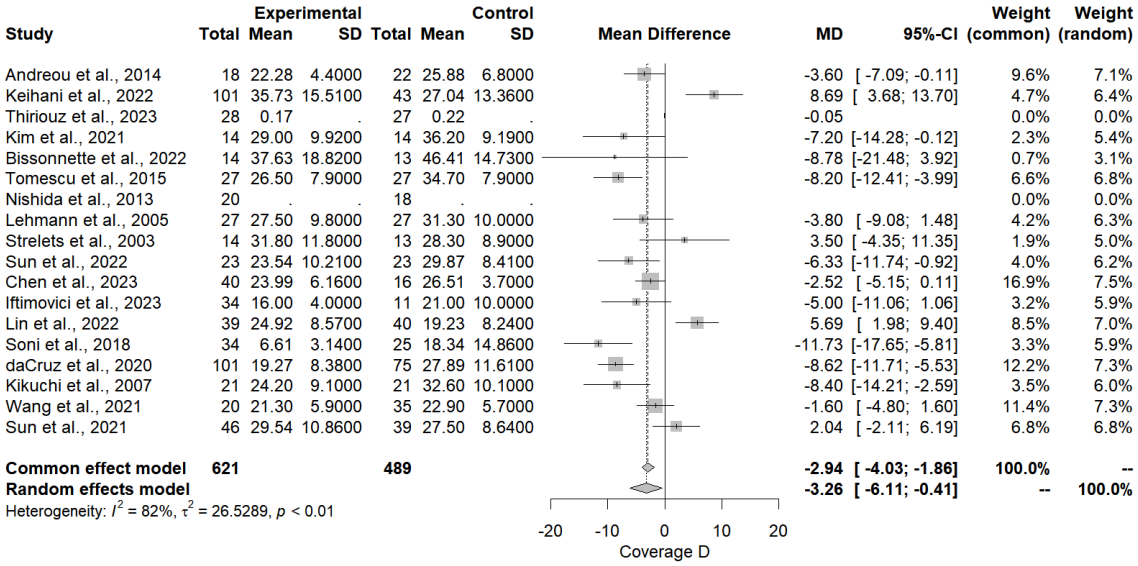
Note. Total sample size, mean occurrence for microstate class C, standard deviations, me an differences, 95% confidence interval and weighting in the common and random effects model displayed per studies measuring the occurrence of microstate class C. Mean differe nces and confidences intervals displayed for random and common effects models. Tests o f heterogeneity were passed and displayed via tau squared.

Figure 6. Forest plot of means, mean differences, and effect sizes for studies measuring mean duration of microstate class D across studies.



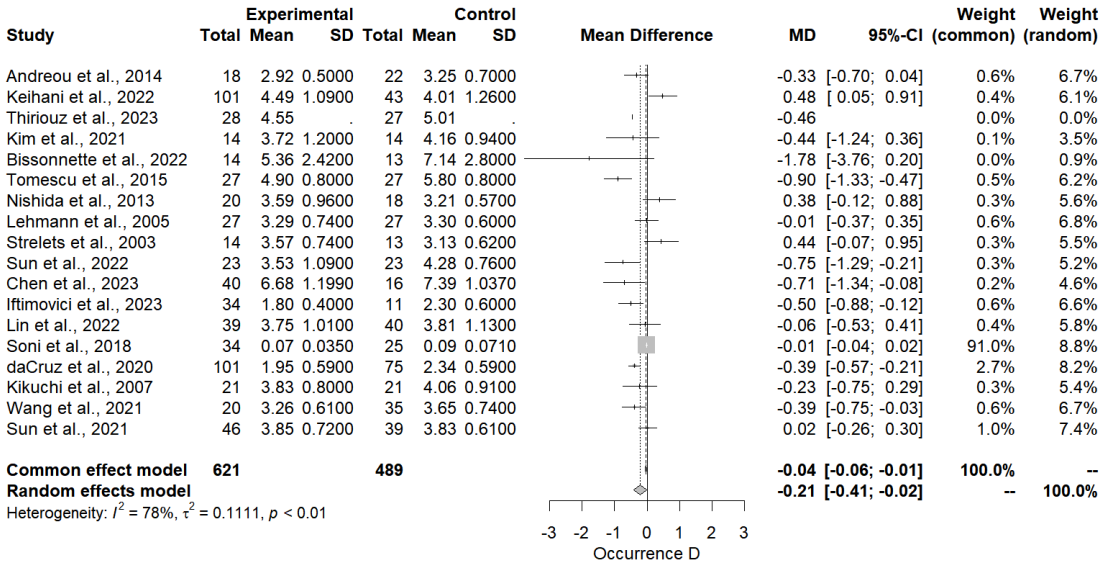
Note. Total sample size, mean duration for microstate class D, standard deviations, mean differences, 95% confidence interval and weighting in the common and random effects m odel displayed per studies measuring duration of microstate class D. Mean differences an d confidences intervals displayed for random and common effects models. Tests of hetero geneity were passed and displayed via tau squared.

Figure 7. Forest plot of means, mean differences, and effect sizes for studies measuring mean total proportion of coverage of microstate class D across studies.



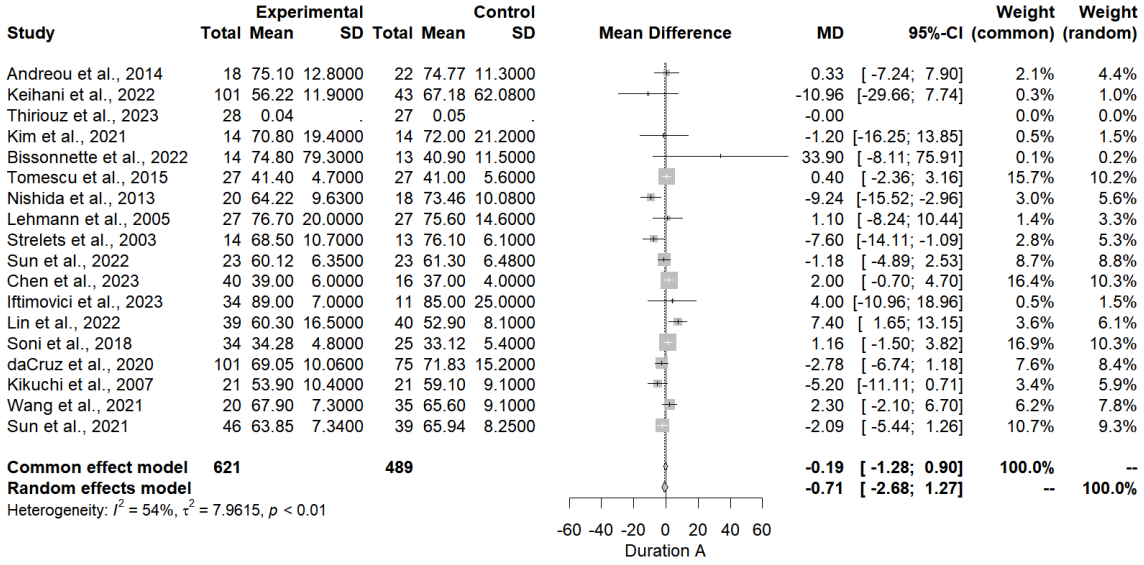
Note. Total sample size, mean coverage for microstate class D, standard deviations, mean differences, 95% confidence interval and weighting in the common and random effects m odel displayed per studies measuring coverage of microstate class D. Mean differences a nd confidences intervals displayed for random and common effects models. Tests of heter ogeneity were passed and displayed via tau squared.

Figure 8. Forest plot of means, mean differences, and effect sizes for studies measuring per second occurrence of microstate class D across studies.



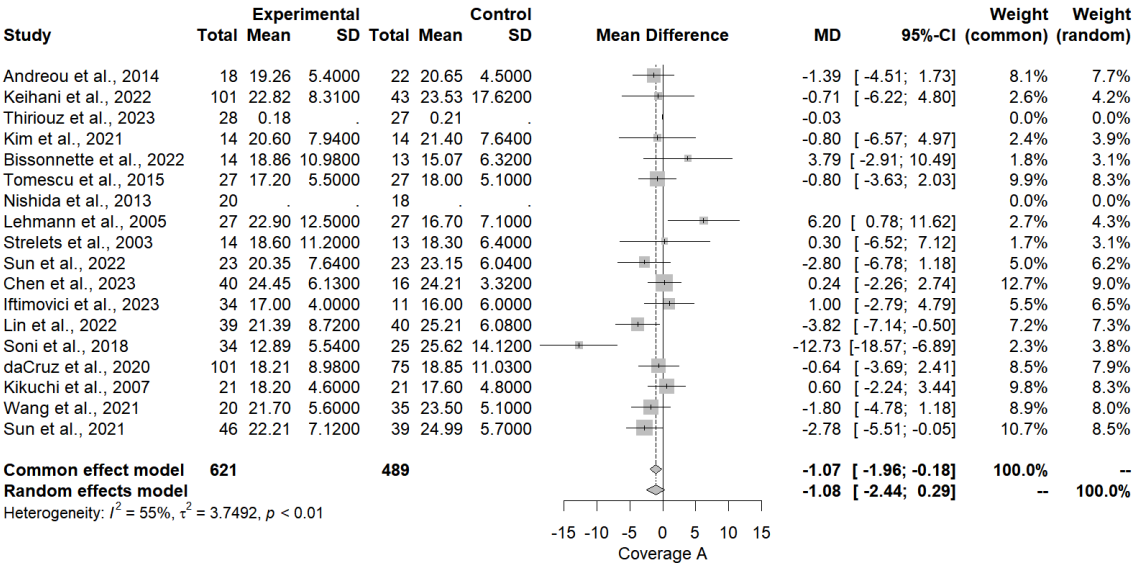
Note. Total sample size, mean occurrence for microstate class D, standard deviations, me an differences, 95% confidence interval and weighting in the common and random effects model displayed per studies measuring the occurrence of microstate class D. Mean differe nces and confidence intervals displayed for random and common effects models. Tests of heterogeneity were passed and displayed via tau squared.

Figure 9. Forest plot of means, mean differences, and effect sizes for studies measuring mean duration (ms) of microstate A.



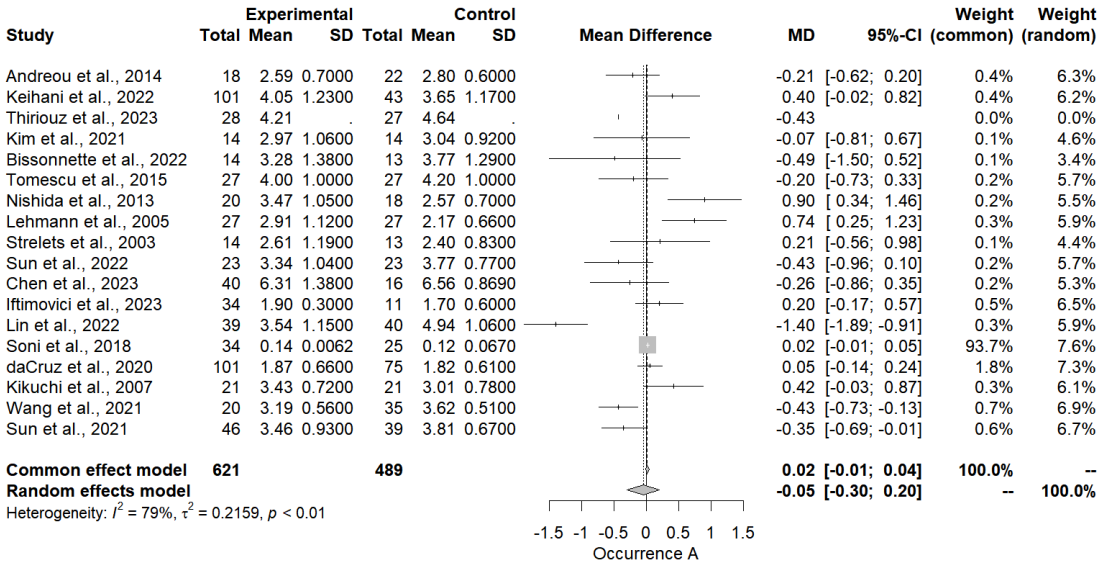
Note. Total sample size, mean duration for microstate class A, standard deviations, mean differences, 95% confidence interval and weighting in the common and random effects m odel displayed per studies measuring duration of microstate class A. Mean differences an d confidence intervals are displayed for random and common effects models. Tests of het erogeneity were passed and displayed via tau squared.

Figure 10. Forest plot of means, mean differences, and effect sizes for studies measuring the proportion of time coverage of microstate A.



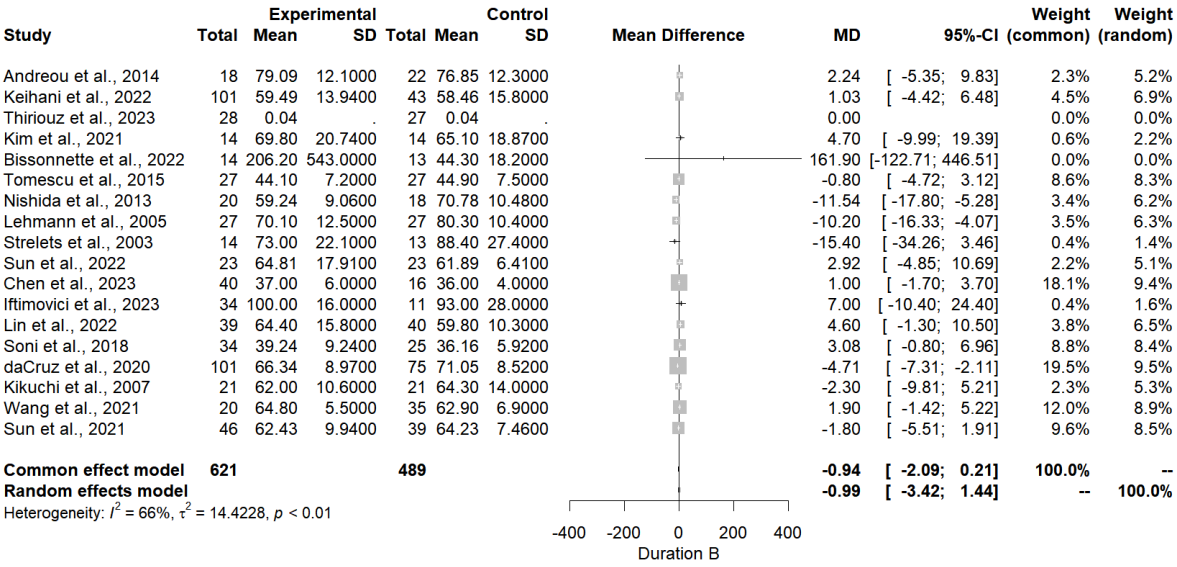
Note. Total sample size, mean coverage for microstate class A, standard deviations, mean differences, 95% confidence interval and weighting in the common and random effects m odel displayed per studies measuring coverage of microstate class A. Mean differences an d confidence intervals are displayed for random and common effects models. Tests of het erogeneity were passed and displayed via tau squared.

Figure 11. Forest plot of means, mean differences, and effect sizes for studies measuring mean per second occurrence of microstate A.



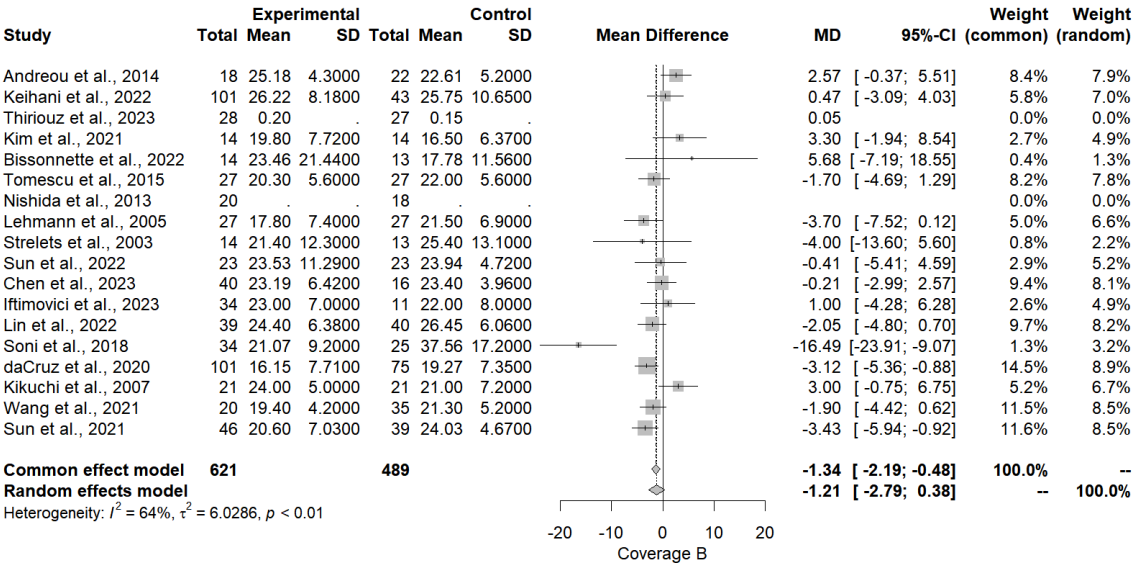
Note. Total sample size, mean occurrence for microstate class A, standard deviations, me an differences, 95% confidence interval and weighting in the common and random effects model displayed per studies measuring the occurrence of microstate class A. Mean differe nces and confidence intervals are displayed for random and common effects models. Test s of heterogeneity were passed and displayed via tau squared.

Figure 12. Forest plot of means, mean differences, and effect sizes for studies measuring mean duration of microstate class B.



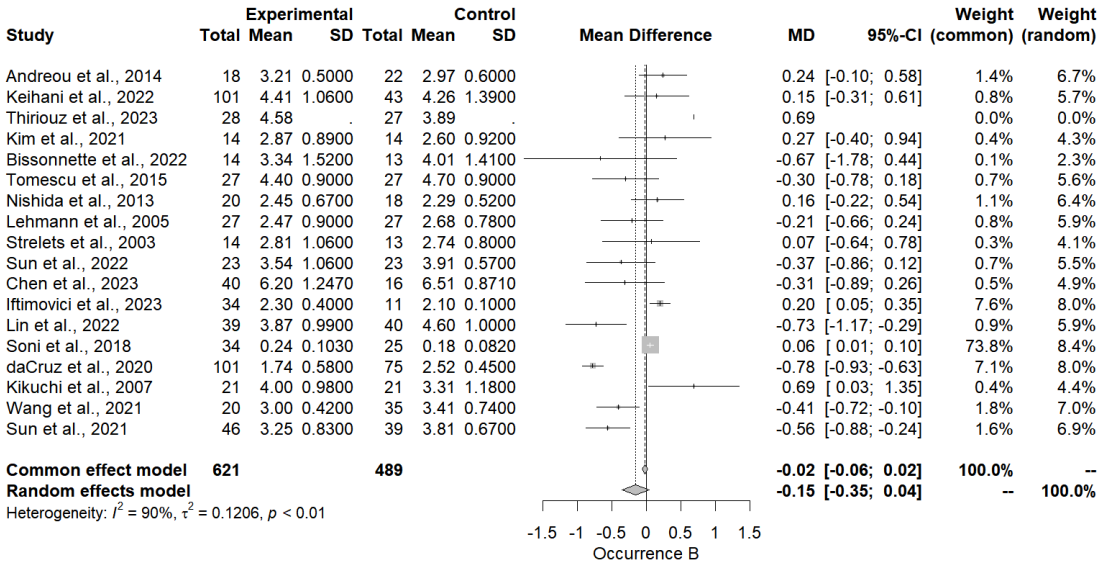
Note. Total sample size, mean duration for microstate class B, standard deviations, mean differences, 95% confidence interval and weighting in the common and random effects m odel displayed per studies measuring duration of microstate class B. Mean differences an d confidence intervals are displayed for random and common effects models. Tests of het erogeneity were passed and displayed via tau squared.

Figure 13. Forest plot of means, mean differences, and effect sizes for studies measuring mean total proportion of coverage of microstate class B across studies.



Note. Total sample size, mean coverage for microstate class B, standard deviations, mean differences, 95% confidence interval and weighting in the common and random effects m odel displayed per studies measuring coverage of microstate class B. Mean differences an d confidence intervals are displayed for random and common effects models. Tests of het erogeneity were passed and displayed via tau squared.

Figure 14. Forest plot of means, mean differences, and effect sizes for studies measuring per second occurrence of microstate class B across studies.



Note. Total sample size, mean occurrence for microstate class B, standard deviations, me an differences, 95% confidence interval and weighting in the common and random effects model displayed per studies measuring the occurrence of microstate class B. Mean differe nces and confidence intervals are displayed for random and common effects models. Test s of heterogeneity were passed and displayed via tau squared.

2.4 Discussion

This meta-analysis involved the collection and analysis of results from 18 peer-reviewed research articles investigating EEG-derived microstate aberrations in those with schizophrenia compared to healthy controls. The most recent meta-analysis we could identify on the topic examined eight total studies and identified an increase in duration, of microstate class C and a decreased occurrence, and coverage of microstate class D (da

Cruz et al., 2020). Due to these consistent findings, it was hypothesized that similar effects would be found in the current meta-analysis. The main findings of the current meta-analysis are consistent with our proposed hypotheses and previous research. There was a significant increase in the duration observed in microstate class C and a reduction of coverage and per second occurrence of microstate class D.

The default mode network differences in individuals with schizophrenia, as indexed through the canonical EEG-derived microstates, suggest non-random and consistent abnormalities in the flow of information through perception of stimuli, cognitive processing, and potential subsequent action (Rajkumar et al., 2021; Yuan et al., 2012). This indicates that aberrant processing involved with perception, cognition, and action in those with schizophrenia is reflected in their default mode network of the brain.

The results of the current meta-analysis are consistent with previous meta-analyses and individual research in the current scientific landscape. The consistent increase in the duration of microstate class C across studies, as well as the reduction in coverage and occurrence parameters for microstate class D, supports their potential utility as endophenotypes of schizophrenia. These parameters appear to reliably differentiate individuals with schizophrenia from healthy controls across diverse samples and methodologies. The heightened duration of microstate C, often associated with salience detection and anterior cingulate activity, may reflect an imbalance in salience attribution, a hallmark of schizophrenia's cognitive and perceptual disruptions. Similarly, the reduced parameters for microstate D, associated with attentional and executive processes, suggest difficulties in integrating sensory inputs with goal-directed action. These findings align with the theoretical framework that endophenotypes must demonstrate reliability,

stability, and state independence (Gottesman & Gould, 2003). Previous meta-analyses of microstate differences involved in schizophrenia identified a reduction in microstate class B but found that the results were only at a trend level after correcting for multiple comparisons across metrics from each microstate. Our exploratory analyses of microstates A & B revealed no significant between group differences. However, as the literature investigating microstates in schizophrenia is still quite limited, further investigation of these microstate classes in future studies may be warranted.

It is also important to note that there was heterogeneity between studies investigating microstates in those with schizophrenia. Some studies suggested there were robust differences, while others did not. The amount of studies that had confidence intervals that spanned zero varied across the different microstate classes and parameters. Generally the proportion of studies with a confidence interval that contained zero in the observed significant group effects across studies in this meta analysis ranged from 38 to 66%. This indicates that even when significant effects are observed across studies there is still heterogeneity in the samples and methodologies contained in the studies. There were also observed differences in the direction of effects across studies with some reporting reductions while others reported increases in the same microstate classes. Continued investigations in this area may bolster the evidence base and provide a more consistent understanding of the alterations of microstate processing of those in schizophrenia. Heterogeneity may also be addressed with future research investigating differing subgroups in schizophrenia or schizophrenia spectrum illnesses. The heterogeneity observed in microstate findings presents a challenge for their use as reliable endophenotypic markers. While the meta-analysis revealed consistent trends for classes C

and D, variability in individual studies highlights potential influences such as sample size, methodological differences, and clinical characteristics. For example, studies with smaller samples may lack the power to detect subtle differences, while variations in participant medication status or symptom severity could contribute to inconsistencies. There was observed heterogeneity across studies observed in the meta analysis in regards to the phase of illness, EEG preprocessing methodologies, sex distribution, EEG recording methods, microstate analysis, recording duration of resting state, epochs used for segmentation, and software used for analysis. Addressing these challenges requires stratifying future analyses by illness phase, symptom profile, and other relevant factors to better isolate the endophenotypic signatures of schizophrenia. Studies specifically investigating the differences in microstate processing in the early phase of schizophrenia or within the first 5 years of first psychotic episode. Continued investigations into how the microstates may differ between the early phase of illness compared to those with chronic illness may help with reducing the heterogeneity in the field. Also further investigations of sex differences in schizophrenia samples may help contribute to understanding and refining the microstate differences and their utility as an endophenotype. While microstates C and D demonstrate promise as endophenotypes, there is still room for further research to determine their candidacy as endophenotypes. The variability in findings across studies highlights the need for standardized methodologies in microstate analysis, including consistent preprocessing techniques and statistical analysis approaches. Additionally, the influence of medication status, comorbid conditions, and other potentially confounding factors should be accounted for to better isolate reliable endophenotypes. Future research would benefit from incorporating

longitudinal studies to assess whether microstate alterations precede illness onset or evolve with symptom progression, further validating their utility as state-independent markers. There also may be a benefit in subgrouping analyses based on the presence of specific symptoms rather than a specific diagnosis. Investigating the microstates in those with auditory hallucinations across differing diagnoses may also provide more nuance and assist in consistency in findings in the field.

The results of the current meta-analysis offer EEG-indexed microstates and their abnormalities, like those observed in microstate Class C and D, as a potential endophenotype for the identification of those with schizophrenia. Previous studies have used microstate abnormalities to find differences observed for other psychiatric conditions. This may aid and be a potential supplement for diagnosis, which can be particularly helpful in determining if a condition has psychosis features or if the illness is primarily psychosis. As previously discussed, microstates differences have been compared between those with schizophrenia and those with a bipolar diagnosis (which often also is accompanied by hallucinatory experiences) to determine if schizophrenia could be uniquely identified compared to controls and other patient populations (Wang et al., 2021). Those with bipolar had alterations in microstate parameters that were significantly different from the observed alteration in microstates of those with schizophrenia. The researchers found reduced microstate class A and B, greater class C and a reduction in class D in those with schizophrenia compared to healthy controls and bipolar groups. Specifically, individuals with bipolar disorder (BD) tend to show altered microstate dynamics that are less pronounced than those observed in schizophrenia. For example, microstate Class C (associated with central-posterior activity) is often

prolonged in schizophrenia but appears to be less altered in BD, indicating differential disruption of cognitive processing and network connectivity (Khanna et al., 2015). Additionally, individuals with schizophrenia frequently exhibit more pronounced reductions in the occurrence of microstate Class D (associated with attention and salience), whereas BD patients may exhibit milder changes or alterations in different microstate classes, suggesting that specific microstate configurations may distinguish between these disorders (Andreou et al., 2014). This tentatively suggests that microstate abnormalities may hold a valuable specificity regarding supplementing diagnostic practice. However, further work is needed to validate this approach regarding the differential diagnostic utility of microstates, including measures of sensitivity and specificity to identify diagnostic categories.

The specificity of microstate findings between bipolar disorder and schizophrenia raises important questions about the underlying neural mechanisms distinguishing these conditions. While both disorders share some overlap in altered microstate dynamics, the extent and nature of these changes appear to differ. In schizophrenia, the prolonged duration of microstate Class C and the reduced occurrence of Class D have been consistently observed, which may reflect more severe disruptions in cognitive control, sensory processing, and attentional networks (Lehmann et al., 2005). In contrast, bipolar disorder seems to involve subtler alterations, with changes in microstates often being more state-dependent, fluctuating between manic, depressive, or euthymic phases (Meyer et al., 2021). This specificity suggests that while both disorders show abnormalities in resting-state brain activity, the degree and type of microstate alteration may provide clues to differential diagnosis and potentially help in distinguishing schizophrenia from

psychotic features present in bipolar disorder. Future research should focus on whether these microstate patterns can be used as reliable biomarkers for diagnostic differentiation and how they might correlate with clinical symptomatology across the spectrum of psychotic disorders.

The identified abnormalities in microstate classes also offer a potential for target and marker for neurologically based treatment modalities. Recent investigation of the use of repetitive transcranial magnetic stimulation (rTMS) on the symptoms and neural deficits of schizophrenia have found that the alterations observed in microstate class C and D were significantly improved by rTMS and that the changes observed in class D differed between active and sham groups (Pan et al., 2021). This suggests that the observed effects were more biological/instrumental in nature than placebo or anticipation-oriented results. rTMS was also previously effective in changing microstates in relationship to decreasing negative symptomatology (Scerak et al., 2021). This indicates that the aberrant default mode network dysfunctional processing is instrumental in the manifestation of both positive and negative symptomatology that can be observed by EEG-derived microstate differences. The use of microstate abnormalities may hold potential as a useful biological/objective metric of symptomatology as well as potentially identifying candidates for treatment. Biologically based metrics may be helpful in the supplementation of early detection of those at risk who may benefit from treatment before their symptoms progress. However future research is necessary to determine the state independence and heritability of these microstate alterations to confirm further endophenotype criteria.

It is important to interpret these differences in network processing with caution. The parameters involved in a microstate analysis are pertaining to the temporal dynamics of the flow of resting state or default information processing in the brain. The microstate parameters are bereft of measures of intensity of processing during these times since the participant is at rest. Because of this, results of microstate parameters often reflect the ability or deficit in switching microstates optimally.

Future research could benefit from the incorporation of the pairing of the intensity of activation of brain regions of the DMN during canonical microstates, potentially via analyses of the amplitude of firings or synchronization of firing within the DMN. This richness of information may allow a more nuanced investigation of the differences in default mode network processing that are more heterogeneous in those with schizophrenia. Investigations involving the microstate differences in those with schizophrenia may also aim to identify symptom clusters involved with the activation and presence of each microstate spatial network. This may involve more concurrent analyses of either fMRI spatial processing, in addition to EEG indexed temporal processing. Source localization of underlying spatial representations may also be investigated and bolstered through processes like sLORETA and fMRI blood oxygen-derived imaging.

This meta-analysis provides some evidence for the potential candidacy of microstates C and D as endophenotypic markers of schizophrenia, given their consistent alterations across studies and alignment with the criteria for endophenotypes. However further research is needed to confirm more conditions and criteria for their use as endophenotypes. For example, research investigating the potential alterations of microstates in unaffected relatives, and those with low to nonexistent symptomatology

would help solidify the heritability and state independence criterion of endophenotypes. While challenges remain in addressing variability and refining methodologies, these findings lay the foundation for integrating microstate analysis into diagnostic and therapeutic frameworks. By bridging the gap between genetic predisposition and clinical manifestation, microstates offer a dynamic and promising avenue for advancing our understanding of schizophrenia.

CHAPTER 3: Transition to Study 2

Chapter 2 provided a detailed exploration of the meta-analysis conducted on resting-state microstate differences in schizophrenia. This analysis showed significant alterations in the microstate dynamics of individuals diagnosed with schizophrenia compared to healthy controls. Specifically, the study highlighted a consistent increase in the duration of microstate class C, coupled with a reduction in microstate class D. These deviations point toward differences in the default mode network (DMN), suggesting aberrant brain activity at rest that may underlie symptoms commonly associated with schizophrenia. The findings support the notion that altered microstate dynamics, particularly the temporal patterns of these brain states, could serve as a potential endophenotype for schizophrenia.

By identifying these consistent patterns, the results of Chapter 2 emphasize the broader significance of microstate dynamics as a marker of disrupted neural functioning in schizophrenia. These disruptions in resting-state brain activity provide a stable, objective measure that may have predictive value for individuals at risk of developing the disorder. Importantly, these abnormalities were observed across various studies and populations, reinforcing the robustness of these neural markers in differentiating individuals with schizophrenia from healthy controls.

The focus of Chapter 3 surrounds the resting-state microstate alterations in early psychosis. Early-phase psychosis represents a critical window in the development of the disorder, as it is often during this time that the earliest signs of neural dysfunction become apparent. In this chapter, we explore whether the microstate alterations observed in chronic schizophrenia, as reported in Chapter 2, are also present in individuals with early

psychosis. By investigating these neural patterns at the onset of the illness, we aim to determine whether these microstate alterations have potential in their utility as endophenotypes, facilitating future research to establish greater evidence in other endophenotype criteria for the purpose of early diagnosis and intervention.

The overarching goal of this thesis is to identify neural biomarkers that can potentially be used to indicate vulnerability to schizophrenia, thus enhancing our ability to detect the disorder in its prodromal and early stages. The concept of endophenotypes is central to this investigation, as it provides a framework for investigating connections between genetic risk factors with observable neural aberrations and symptomatology. The results of Chapter 2 offer a strong foundation for this inquiry by demonstrating the stability and reliability of microstate dynamics as markers of schizophrenia. Now, we turn our attention to early psychosis, where the identification of similar patterns could have profound implications for early detection and treatment strategies.

By building on the findings from the meta-analysis, Chapter 3 delves deeper into the neurophysiological underpinnings of early psychosis, aiming to extend the endophenotype model to individuals who have only started developing schizophrenia symptoms. Through this investigation, we seek to advance our understanding of the early neural markers that may foreshadow the onset of the disorder, ultimately contributing to improved diagnostic and therapeutic approaches for schizophrenia.

CHAPTER 4: Resting Microstate Alterations in Early Psychosis as an Endophenotype Candidate

3.1 Introduction

3.1.1 Early Phase Psychosis

The early phase of psychosis refers to the critical period within five years following an individual's initial psychotic episode. During this early stage of illness, there is often a progressive decline in social and functional abilities (Hirayasu et al., 1998; Kasai et al., 2003; Salisbury, 2007). Proper identification and treatment during this early phase can significantly influence the illness's trajectory and severity. Time spent in active psychosis is predictive of future episodes and symptom severity (Melle et al., 2010). Typically, the early phase follows a prodromal period characterized by gradually worsening psychotic symptoms and functional deficits. This includes decreased job or academic performance, difficulty concentrating, increased suspiciousness, decline in self-care such as personal hygiene, social withdrawal, inappropriate emotional responses, emotional numbness, hallucinations, persistent unusual thoughts or beliefs, and magical thinking (Melle et al., 2010). These symptoms often cause significant distress and disrupt daily functioning. Schizophrenia is often explained using the diathesis-stress model, which suggests that individuals with a neurodevelopmental predisposition can develop the disorder in response to stress or significant substance use, such as cannabis or hallucinogens (Walker et al., 1997). Transient drug-induced psychosis can become persistent in those with a predisposition or family history of schizophrenia (Murray et al., 2013). Individuals with psychosis or prodromal symptoms sometimes self-medicate using substances such as cannabis, nicotine, alcohol, and caffeine (Goswami et al., 2009).

3.1.2 Default Mode Network

One brain-based endophenotype proposed for identifying the presence of schizophrenia that has been discussed is the aberrant resting default mode network. The DMN refers to the pattern and distribution of neurological activation while a person is at rest, not engaged in any cognitive tasks, or exposed to stimuli (Smallwood et al., 2021). The DMN primarily involves several key brain regions in a cohesive network, including the posterior cingulate cortex (PCC), the precuneus, the medial prefrontal cortex (mPFC), the lateral parietal cortex, and the hippocampus (Utevsky et al., 2014). While the DMN is also conceptualized as global processing at rest, these regions are highly interconnected and show synchronized activity patterns during rest, forming a coherent network. The DMN has been shown to be involved in many cognitive processes, including self-referential processing, introspection, and autobiographical memory retrieval (Whitfield-Gabriele & Ford, 2012). DMN activity during resting states is associated with mind-wandering, creative thinking, facilitating the generation of new ideas, and integration of information from various sources. It also plays a crucial role in social cognition, enabling individuals to infer others' mental states and intentions (Mars et al., 2012). The mPFC is particularly involved in understanding others' perspectives, self-referential thinking, and jumping to conclusions, which are often altered in those with schizophrenia (Krause et al., 2012). The DMN contributes to memory consolidation, particularly during rest periods after learning, facilitating the transfer of information from short-term to long-term memory (Sestieri et al., 2011).

Abnormalities in the DMN have been extensively studied in schizophrenia, providing insights into the disorder's neural underpinnings. Altered connectivity within

the DMN is a consistent finding in schizophrenia, which has been associated with cognitive and perceptual impairments (Garrity et al., 2007). In fMRI studies, the mPFC, a component of the broader DMN network, often shows increased activity in individuals with schizophrenia, associated with symptoms such as rumination, excessive self-referential thinking, and impaired self-awareness (Chai et al., 2011). In healthy individuals, DMN activity typically decreases during cognitively demanding tasks (Mak et al., 2017). However, individuals with schizophrenia often show attenuation of these typical decreases, leading to attention and concentration deficits (Pomarol-Clotet et al., 2008). Schizophrenia is associated with disruptions in the balance between the DMN and other brain networks, such as the central executive network and the salience network, contributing to difficulties in filtering out irrelevant information and distinguishing between internal thoughts and external stimuli. This processing abnormality is critical in the generation of hallucinations (Marino et al., 2022). In healthy individuals, while some overlap in DMN alterations can be observed during task-based activity (where task performance typically suppresses DMN activity), the magnitude and persistence of these alterations are much more profound in those with schizophrenia. Specifically, individuals with schizophrenia show not only reduced suppression of DMN during tasks but also heightened activity in the DMN during resting states, which is less commonly observed in healthy individuals (Whitfield-Gabrieli & Ford, 2012). This abnormal engagement and disengagement pattern of the DMN in schizophrenia is thought to reflect an underlying failure to appropriately switch between internally and externally directed attention (Sheffield & Barch, 2016).

Additionally, schizophrenia is characterized by a higher degree of functional connectivity abnormalities within the DMN as evidenced by both fMRI and EEG data. This is particularly noted in the anterior and posterior regions of the DMN network, notably the mPFC and PCC, whereas in healthy individuals, such connectivity fluctuations are more transient and less likely to cause significant cognitive disruption (Anticevic et al., 2012). In schizophrenia, this persistent hyperconnectivity leads to symptoms such as hallucinations and delusions, where there is a breakdown between self-generated internal thoughts and external stimuli. While both healthy individuals and those with schizophrenia can exhibit some DMN changes during tasks, the extent and pathological nature of these changes are what can be used to distinguish the two groups.

3.1.3 Microstates

To investigate the distribution of processing in the default mode network on a millisecond-by-millisecond basis, previous research studies have used microstates as an index of the DMN. Microstates are transient, quasi-stable global states or patterns of EEG activation at rest or during cognitive tasks. They differ in frequency bands, like other broadband quantitative EEG analyses, but include topographical distributions. The four commonly used canonical microstates of at-rest activity, labelled A, B, C, and D (Lehman et al.., 1987; Koenig et al., 2002), and are associated with specific scalp topographies and cognitive networks. These investigations identified four consistent states that switch on a millisecond basis. The topography of these states is typically observed as right frontal to left posterior activation in class A (language processing); frontal to occipital activation in class B (visual imagery); left frontal to right posterior activation in class C (interoceptive autonomic sensory processing and saliency); and frontomedial patterns of activation in

class D (attention and orientation aspects of the DMN) (Yuan et al., 2012; Milz et al., 2016). Microstates are typically active for 60-120 milliseconds before changing to a different topography that remains quasi-stable for a similar time period. These microstates represent the simultaneous activation of large-scale brain networks and account for 84% of the variance in resting state EEG-derived activity (Michel & Koenig, 2018). Microstates have been closely investigated in their relationship with fMRI-derived resting state networks and are conceptualized as measures of components of the DMN. Abnormalities in microstates have been identified in schizophrenia, both in fMRI-derived resting state and EEG microstate dynamics (Honcamp et al., 2022).

In schizophrenia, the duration of specific microstates, particularly those associated with sustained attention and memory (classes A and D), has been reported to be significantly reduced (Luo et al., 2020). This shortened duration may reflect a lack of sustained cognitive processing, contributing to the cognitive deficits observed in schizophrenia. Individuals with schizophrenia also show increased or prolonged microstate class C activity, indicating heightened brain activity volatility, dysfunctional DMN processing, or difficulty switching out of class C processing (da Cruz et al., 2020). Changes in topography and occurrence of microstate classes C and D have been identified as potential endophenotypes for schizophrenia (da Cruz et al., 2020). This dysfunction in state switching may contribute to thought disorganization and distractibility common in schizophrenia's cognitive difficulties. Abnormalities in microstate dynamics correlate with specific schizophrenia symptoms: decreased class D with positive symptoms such as hallucinations and delusions (Kindler et al., 2011) and prolonged class A with negative symptoms like apathy, anhedonia, and asociality

(Giordano et al., 2018). These abnormalities suggest difficulties in integrating microstates to form coherent, large-scale brain networks. Hyperexcitation and lack of inhibitory processes may be involved in general brain processing deficits, such as sensory, executive, memory, and cognitive functions (Garrity et al., 2007; Hui et al., 2017).

Antipsychotic medications also alter EEG microstate abnormalities (Yoshimura et al., 2007). Medication-naive individuals with schizophrenia show more pronounced microstate abnormalities than those on medication, highlighting the need for further investigation into medication's impact on microstate dynamics (Mackintosh et al., 2020). Schizophrenia is also associated with changes in microstate topographical distribution (Stevens et al., 1997), representing irregularities in EEG scalp map spatial configurations during specific microstates. This dysfunction in neural network coordination supports the view of schizophrenia as a neurodevelopmental disorder. Recent studies have found disrupted connectivity patterns between microstates in schizophrenia (Yan et al., 2023), implying dysfunction in coordinated information processing between DMN-involved brain regions. Schizophrenia is also associated with altered dynamic complexity of microstate transitions (Murphy et al., 2020), with patterns and transition predictability differing significantly from healthy controls. The specific abnormalities observed can vary among individuals with schizophrenia due to the disorder's heterogeneity.

EEG microstates offer several methodological advantages in studying early-phase psychosis. As brief, transient states of synchronized brain activity, microstates provide a direct window into the temporal dynamics of large-scale brain networks. This makes EEG an ideal tool for capturing rapid neural state transitions that may underlie the cognitive and perceptual disturbances in schizophrenia (Michel & Koenig, 2018).

Moreover, EEG is non-invasive and allows for continuous, real-time monitoring of brain activity, making it particularly suited for longitudinal studies of early psychosis. The ability to detect subtle changes in microstate class duration and transition patterns offers unique insights into the early neural disruptions associated with schizophrenia. Previous research has demonstrated that these alterations are present in both chronic and early-phase psychosis, supporting the utility of EEG in capturing state-independent biomarkers of the disorder (Rieger et al., 2016).

3.1.4 Current Study

The meta-analysis presented in Chapter 2 identified global differences in microstate parameters of the default mode network at rest. Reduced microstate parameters of class D, as well as increased class C, were observed across the current scientific literature on schizophrenia. However, investigations in microstate differences have been less studied in the early stages of the illness. In the meta-analysis, only two identified microstate investigations of 18 involved the early phase of schizophrenia where early detection is most important and four looked at first episode; other groups kept early phase and chronic schizophrenia in the same sample, or did not report the duration of illness (Lehman et al., 2005; Mackintosh et al., 2020; Murphy et al., 2020; Sun et al., 2022). There were also differences in methodology across studies.

Research groups have predominantly used eyes-closed resting states for their observations of default mode network activity in those with schizophrenia (de Bock et al., 2020; da Cruz et al., 2020; Mackintosh et al., 2020; Murphy et al., 2020; Wang et al., 2021). An understanding of the microstate differences in default mode network patterns of activation in early psychosis in eyes-closed and at rest would benefit in the

identification of robust models of endophenotypes of schizophrenia using EEG-derived microstates. This may be particularly impactful in the early detection stages of the illness, where deficits in neurological function need more sensitive and nuanced tools to be identified appropriately. The current investigation aims to identify differences in those with schizophrenia and healthy controls in eyes-closed microstate indexed default mode network activation. It was hypothesized that microstate class C parameters would be increased, and microstate class D parameters would be reduced in a sample of those with schizophrenia in an early phase of illness compared to their healthy control counterparts.

3.2 Methods

3.2.1 Participants

The early-phase psychosis participants were recruited through the Nova Scotia Early Psychosis Program (NSEPP). We recruited a sample of 28 individuals (21 males, 7 females) between the ages of 18 – 35 (M = 23.2, SD = 3.35) who were within the first five years of onset of their schizophrenia spectrum symptoms. Early-phase psychosis participants were excluded if they had extrapyramidal symptoms resulting in a movement disorder, had epilepsy, or had a moderate or greater DSM-5 diagnosed substance use disorder. The specific diagnoses were as follows: 21 individuals with schizophrenia, three with an unspecified schizophrenia spectrum disorder, and four individuals with schizoaffective disorder. Healthy controls were recruited from the general population through electronic advertisements on social media, paper advertisements and word of mouth. We recruited 31 healthy controls (9 males, 22 females) between the ages of 18-35 (M = 22.7, SD = 2.79). Control participants had negative self-reported histories of psychiatric and neurological illness, no history of significant head injury resulting in the

loss of consciousness within the past year, as well as no first-degree relatives with psychosis as neurophysiological alterations have been observed in unaffected immediate family members of those with schizophrenia (Michie et al., 2002). All participants were required to have normal or corrected-to-normal vision and normal hearing, as determined by self-report, to ensure these were not confounds to the study. Finally, it was mandatory that participants could read and understand both spoken and written English for the informed consent procedures and self-report measures. All procedures described were approved by the Nova Scotia Health Authority Research Ethics Board.

3.2.2 Procedure

Prior to the EEG recording session, participants completed informed consent, were given an opportunity to read the study description, had any questions answered, and completed demographic screening questionnaires. At the same time as the screening, demographic variables of age, sex, level of education, and self-reported weekly average alcohol and cannabis consumption were obtained. Participants attended the BIOTIC Neuroimaging Research Lab at the QEII Health Sciences Centre (Halifax, NS) for an afternoon (i.e., testing beginning between 1:00 -3:00 pm) testing session. Testing sessions were confined to the same time to account for circadian fluctuations in alertness and EEG activity throughout the day. Participants were required to abstain from psychoactive substances, medications, and alcohol beginning at midnight of the previous day. Those with schizophrenia were not asked to halt or pause their current medication regimen. Additionally, participants were asked to abstain from caffeine (including coffee, tea and cola) beginning at midnight prior to the test session to ensure adequate clearance of circulating caffeine (half-life = 2.5-4.5 hours; Ghisolfi et al., 2006). Upon arrival at the

laboratory, questionnaires were completed, and EEG electrodes were applied. Participants were then instructed to sit at rest with for 3 minutes of eyes-closed resting. At the end of the session, a compensation of $25 was given to reimburse them for their time and transportation costs.

3.2.3 Clinical Questionnaires

The selected measures were chosen based on their clinical relevance and utility in capturing key functional and symptomatic aspects of early-phase psychosis. Each measure provides unique insights into the functioning, symptom severity, and trauma history of individuals with psychosis.

Global Assessment of Functioning Scale. The Global Assessment of Functioning Scale (GAF) was employed to quantify broad functional, social and occupational impairments, which are core features of psychotic disorders. The GAF rates an individual's general, social and occupational functioning on a scale from 0 to 100, where higher scores indicate better functioning. The GAF has demonstrated adequate reliability and validity in clinical settings (Hall, 1995). Clinicians use the GAF by evaluating an individual’s overall ability to perform daily activities and maintain interpersonal relationships. This measure provides a snapshot of functioning, considering both psychological and social aspects of well-being. The scale is typically completed through clinician judgment during a structured interview, where the clinician assigns a score based on observed functioning, symptoms and clinical history. This measure was collected in both the early psychosis and healthy control groups**.** By incorporating this

scale, the study aimed to capture the full spectrum of functional impairments essential for tracking illness progression and evaluating treatment efficacy.

Social and Occupational Functioning Assessment Scale. The Social and Occupational Functioning Assessment Scale (SOFAS) is a subjective measure derived from an unstructured interview with a trained member of the research team. SOFAS scores reflect a composite of adaptive living skills, social appropriateness, and interpersonal skills, all subjectively rated by the clinician. Impairments in these areas are considered only if they are not due to lack of opportunity or environmental constraints. Scores range from 1 to 100, with higher scores indicating better social and occupational functioning. The SOFAS is a reliable measure of trait functioning in the general population, separate from the direct impact of psychiatric symptoms (Saraswat et al., 2006). This measure was collected in both the early psychosis and healthy control groups.

Scale of Prodromal Symptoms. The Scale of Prodromal Symptoms (SOPS) is a 19-item scale designed to evaluate prodromal symptoms of psychosis in high-risk populations (Miller et al., 1999). The current study used two subscales of the SOPS: positive and negative symptoms. The positive symptoms subscale includes five items: P1 (unusual thought content/delusional ideas), P2 (suspiciousness/persecutory ideas), P3 (grandiose ideas), P4 (perceptual abnormalities/hallucinations), and P5 (disorganized communication). The negative symptoms subscale consists of six items: N1 (social anhedonia), N2 (avolition), N3 (expression of emotion), N4 (experience of emotion and self), N5 (ideational richness), and N6 (occupational functioning). This tool is a reliable and valid measure of psychosis symptoms in high-risk populations (Miller et al., 2003). Furthermore, SOPS scores show strong correlations with other psychosis symptom

measures, such as the Positive and Negative Syndrome Scale (PANSS) and the Scales for the Assessment of Negative and Positive Symptoms (SANS/SAPS) (Fulford et al., 2014; Tso et al., 2017). The SOPS has also been used in an early psychosis population sample to evaluate the severity of psychosis symptoms (Tso et al., 2017). The SOPS is modelled after the Positive and Negative Syndrome Scale (PANSS), and SOPS scores are highly correlated with PANSS scores. The SOPS is used to gauge early signs of psychosis and is completed based on clinical interviews and behavioural observations. This measure helps identify emerging psychotic symptoms before they fully develop, facilitating early intervention (Tso et al., 2017). Each item on the SOPS is rated by a clinician based on the patient's responses and observed symptoms during the interview. This measure was collected solely in the early psychosis group.

Psychotic Symptoms Rating Scales. The AH-subscale of the Psychotic Symptoms Rating Scales (PSYRATS) (Haddock et al., 1999) was used to assess auditory hallucinations in individuals with early-phase psychosis. The PSYRATS has been validated in early-phase psychosis samples and provides a detailed profile of auditory hallucinations through four subscales: distress, frequency, attribution, and loudness (Drake et al., 2007). The PSYRATS is filled out based on patient interviews, capturing the severity and impact of auditory hallucinations. This scale involves rating the patient's experiences and symptoms as reported during structured clinical interviews, thus complementing other measures of psychosis symptomatology (Woodward et al., 2014). This measure was only administered to the early psychosis group. Additionally, PSYRATS serves as a complement to broader symptom measures, enhancing the overall assessment of psychosis symptomatology (Drake et al., 2007).

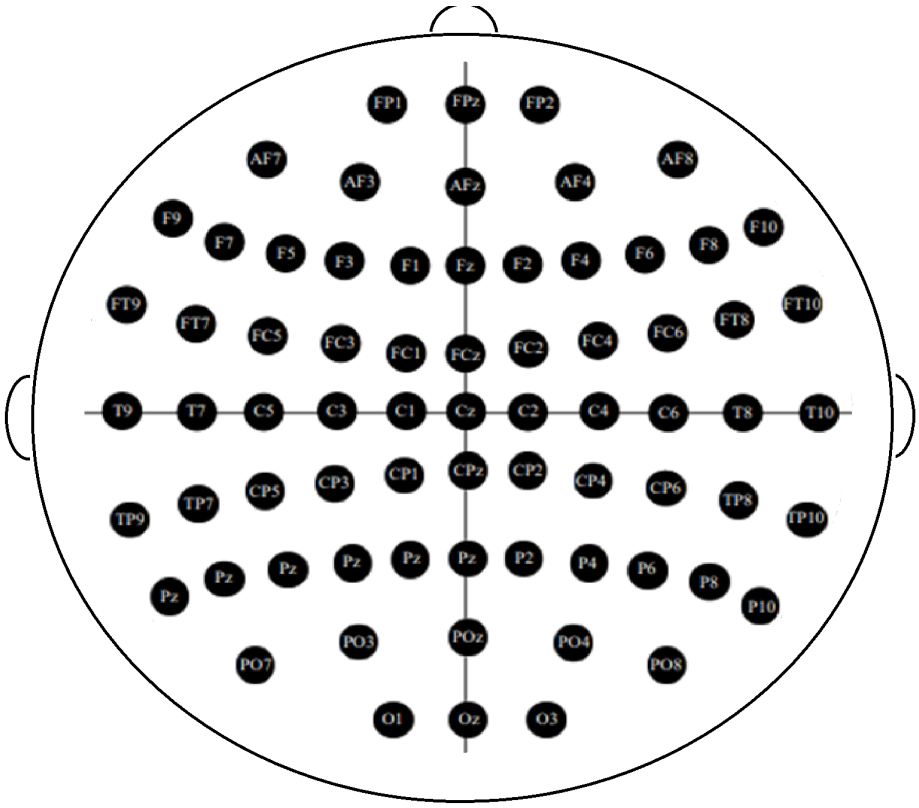
Trauma and Life Events Checklist. The Trauma and Life Events (TALE) checklist is a 21-item self-report questionnaire developed to screen for traumatic or aversive life events, particularly in individuals with schizophrenia. The TALE assesses the occurrence and frequency of various psychologically and physically threatening events, including psychosis-related traumas. It shows acceptable reliability and validity as a trauma measure in psychosis (Carr et al., 2018). Respondents complete the TALE by indicating which events they have experienced and how frequently these events occurred, providing insight into their trauma history and its potential impact on their current mental health. This measure was collected in both the early psychosis and healthy control groups.

3.2.4 EEG Recording

Microstates were extracted from EEG activity recorded from an ActiCap electrode cap (EasyCap GmbH, Wörthsee, DE) with Ag^{+}/Ag^{+}-Cl^{-} active electrodes at 64 scalp sites according to the International 10-10 System of electrode placement, including: three midline sites (frontal [F_z], central [C_z], parietal [P_z]); three left hemisphere (frontal [F_3], central [C_3], parietal [P_3]) and three right hemisphere (frontal [F_4], central [C_4], parietal [P_4]) scalp sites; and bilateral mastoid activity (see Figure 15). Recordings were digitally sampled at 500Hz. An electrode was also placed on the mid-forehead to serve as ground, and an average reference was used. Bipolar recordings of horizontal (HEOG) and vertical (VEOG) electrooculogram activity were taken from supra-/sub-orbital and external canthi sites, respectively. All electrode impedances were kept below 10kΩ. Electrical activity was recorded with an ActiCHamp amplifier (Brain Products, Gilching, DE) bandpass of DC - 250 Hz, digitized at 1000 Hz, and stored on hard disk for later offline analysis. Preprocessing was completed with Brain Vision Analyzer (BrainVision Analyzer, Version

2.2.2, Brain Products GmbH, Gilching, DE), included applying filters from 2 - 20 Hz with a notch filter at 60 Hz, segmentation into 2-second epochs (with no overlap) and artifact rejection of any epochs with electrical activity exceeding ±50μV.

Figure 15. Electrode positions according to the 10-10 system of electrode placement.



Microstate data was then analyzed using the microstates plug-in created for EEGlab by Thomas König (Nagabhushan Kalburgi et al., 2024). First, individual microstate maps were identified by k-means spatial cluster analysis. Each individual microstate map was then sorted according to distributions of scalp potentials from previously established maps and class labelled according to the published template (Koenig et al., 2002). Finally, the resulting class-labeled individual model maps were

exported for statistical analysis. Within each participant, each microstate class yielded the following parameters:

a) Duration: the mean duration of that microstate class in seconds (s).
b) Occurrence: the mean amount of observations of that specific microstate class each second.
c) Coverage: the proportion (%) of total time spent in that specific microstate class while recording.

3.2.5 Statistical Analysis

All statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS; IBM Corp., Armonk, NY). Demographic variables were compared between groups using a general linear model one-way analysis of variance (ANOVA) to determine factors that may need to be covaried and accounted for during the analysis. Sex distribution was compared using Pearsons chi-squared tests. Microstate parameters (duration, coverage, and occurrence for each of the four canonical microstate classes) were subjected to an analysis of covariance (ANCOVA) using the factors of cigarettes smoking, cannabis use, alcohol consumption, sex, and trauma as sources of covariance. Follow-up analyses of significant ($p < .05$; Greenhouse-Geisser-corrected) main or interaction effects found in the ANCOVAs were carried out with pairwise comparisons using separate (vs. pooled) error estimates. Sidak corrections were applied to observed p values to adjust for multiple comparisons. Bi-variate (non-parametric) Spearman's rho correlations were also carried out between the functioning scale scores (GAF and SOFAS total scores), the symptom scale scores (SOPS and PSYRATS scores; only for the early

psychosis group), the demographic variables, and microstate parameters (e.g., duration, occurrence, and coverage).

3.3 Results

3.3.1 Demographic Data

Demographic variables for each group, as well as contrasts between groups, can be found in the table below (See Table 2). Regarding differences between our sample groups, there was a statistically significant difference in cigarettes smoked per day between healthy controls smoking less than individuals, with those in the early phase of schizophrenia smoking more cigarettes per day than healthy controls. Those with schizophrenia also reported smoking significantly more cannabis than their healthy control counterparts. Individuals with schizophrenia also reported significantly more adverse life events on the TALE questionnaire and had significantly lower functioning via SOFAS and GAF scores. Patient and control groups also differed in terms of sex (χ^2 (1) = 12.09, $p < .01$. Due to these group differences, our analysis included using the significantly different group factors as covariates to determine each factor's contribution to neural activity including sex to account for previously discussed differences in sex ratios between groups.

Table 2. Demographic and clinical variables of the early phase psychosis group (SZ) and healthy controls (HC)

	HC *M*(*SD*)	SZ *M*(*SD*)	*F*	*p*
Age (years)	22.76(2.76)	24.23(3.91)	2.47	0.12
Alcohol Consumption (drinks per week)	2.84(3.35)	1.59(3.46)	1.63	0.21
Cigarette Consumption (cigarettes per day)	0.21(0.69)	3.13(3.94)	16.3	<.001
Cannabis Consumption (times consumed per week)	0.73(1.79)	3.69(3.89)	13.04	<.001
TALE	4.22(3.05)	8.69(4.25)	19.44	<.001
SOFAS	91.07(5.68)	64.58(19.50)	37.89	<.001
GAF	93.6(4.90)	61.92(19.15)	37.89	<.001

3.3.2 *Microstate Topographies*

In eyes-closed resting, microstate A in healthy controls exhibited the typical anterior-posterior configuration, with clear frontal positivity (red) and posterior negativity (blue; See Figure 16). This pattern aligns with the canonical microstate A described in previous research (Koenig et al., 2002; Lehmann et al., 2005), where well-defined boundaries and symmetrical hemispheric distribution are characteristic. In individuals with schizophrenia, microstate A retained a similar anterior-posterior orientation but appeared more diffuse, with less pronounced frontal positivity and reduced hemispheric symmetry. Previous studies have reported similar findings of reduced symmetry and diffuseness in microstate A in schizophrenia, potentially indicative of underlying abnormalities in brain network organization (Rieger et al., 2016; Kikuchi et al., 2007).

Microstate B in healthy controls showed strong posterior positivity centred over the occipital cortex, with corresponding frontal negativity, in line with the canonical description of microstate B (Koenig et al., 2002). The boundaries between positive and negative regions were distinct, and the hemispheric symmetry was well-maintained. In the schizophrenia group, microstate B exhibited a similar overall pattern but with blurred boundaries and reduced symmetry. This observation is consistent with findings by Milz et al. (2016) and Kikuchi et al. (2007), who also reported that microstate B in individuals with schizophrenia shows less distinct topography and reduced hemispheric differentiation.

Microstate C in healthy controls closely matched the canonical description, showing a right-frontal positivity and left-posterior negativity, as reported in several previous studies (Koenig et al., 2005). The topography was well-defined, with a clear separation between positive and negative regions. In schizophrenia, microstate C was relatively similar to that of healthy controls, maintaining the expected pattern with only minimal diffuseness. This stability in microstate C topography has been reported in other studies, where microstate C appears to be less affected by schizophrenia compared to other microstates (Rieger et al., 2016; Lehmann et al., 2005).

Microstate D in healthy controls displayed the expected fronto-central positivity and posterior negativity, with strong left-right symmetry, particularly over the frontal and central regions. This is consistent with the canonical description of microstate D (Koenig et al., 2002). In schizophrenia, the same general pattern was observed, but the boundaries between positive and negative regions were more diffuse, and the symmetry was less pronounced. Previous research by Kikuchi et al. (2007) and Lehmann et al. (2005) also

noted these topographical changes in microstate D in individuals with schizophrenia, suggesting potential disruptions in the functional connectivity of brain networks associated with this microstate.

Across all microstates, the healthy controls exhibited topographies that closely resembled the canonical forms described by Koenig and colleagues (2002, 2005). The boundaries were well-defined, and hemispheric symmetry was maintained in microstates A, B, C, and D. In individuals with schizophrenia, microstate topographies were representative of canonical microstates but generally more diffuse, with less distinct transitions between regions of positive and negative fluctuations in topography and reduced hemispheric symmetry, particularly in microstates A, B, and D. These findings align with previous research (Lehmann et al., 2005; Rieger et al., 2016; Kikuchi et al., 2007; Milz et al., 2016) that reports similar alterations in microstate topographies in schizophrenia. Microstate C, however, showed fewer differences between groups, consistent with studies suggesting that topography of microstate C may be less affected in schizophrenia compared to other microstates.

3.3.4 Eyes Closed Resting Microstates

During eyes-closed resting recordings, individuals with in the early phase psychosis group exhibited a statistically significantly different occurrence of microstate C, with those in the schizophrenia group having a lower mean duration than healthy controls. Furthermore, individuals in the early phase psychosis group demonstrated a statistically significantly different occurrence of microstate D, where they had a greater mean occurrence per second and greater coverage relative to healthy controls. These findings are summarized in Table 3, which presents the results of the statistical analyses

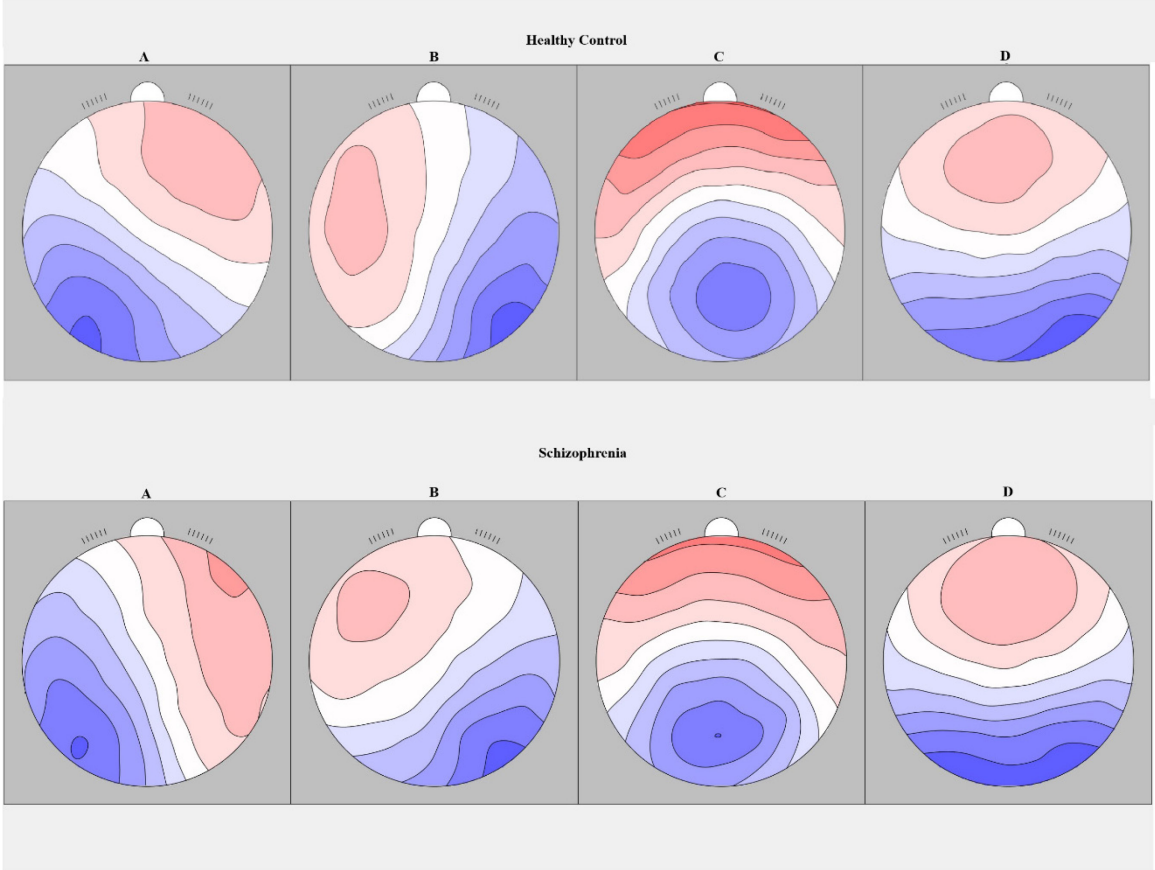
conducted for the resting state recordings. See Figure 16 for microstate maps recorded from healthy controls and early-phase psychosis participants during eyes-closed resting.

Table 3. Mean Differences in Microstate Parameters Between Individuals with Schizophrenia and Healthy Controls During Eyes Closed Resting State

Microstate Parameter	**SZ *M* (SD)**	**HC *M* (SD)**	***p***	***F***	**Cohen's *d***	**95% CI (lower, upper)**
Duration A	35.2 (4.88)	37.37 (8.20)	0.18	1.87	0.32	-9, 2
Duration B	40.40 (8.89)	41.97 (9.72)	0.17	1.92	0.17	-2, 13
Duration C	42.50 (13.63)	51.63 (13.75)	0.02*	6.34	0.38	-25, -3
Duration D	38.65 (9.18)	37.44 (8.54)	0.90	0.02	0.14	-8, 7
Occurrence A	5.47 (1.75)	5.35 (1.68)	0.30	1.11	0.07	-0.69, 2.20
Occurrence B	6.63 (1.46)	6.34 (1.48)	0.22	1.52	0.20	-0.46, 1.90
Occurrence C	7.82 (1.52)	6.89 (1.52)	0.12	4.79	0.61	-0.25, 2.08
Occurrence D	6.30 (1.11)	5.16 (1.66)	0.04*	4.41	0.81	0.05, 2.24
Coverage A	19.48 (5.05)	18.93 (5.26)	0.80	1.78	0.12	-3.90, 5.02
Coverage B	25.54 (4.82)	25.92 (5.34)	0.86	0.33	0.07	-4.63, 3.87
Coverage C	31.70 (6.33)	36.38 (6.03)	0.09	3.09	0.76	-10.01, 0.67
Coverage D	23.33 (5.64)	18.71 (4.10)	0.03*	5.03	0.94	.48, 8.76

Note. This table presents the mean values (M) and standard deviations (SD) for the measured microstate parameters, including duration, occurrence, and coverage, observed in individuals with schizophrenia (SZ) and healthy controls (HC) during resting state conditions. Sidak corrections were applied for multiple comparisons.

Figure 16. Mean microstate maps for each class observed in each group during eyes-closed resting.



Note. Mean Microstate Maps for each canonical class during eyes-closed resting, healthy control are displayed on the top row, those with schizophrenia displayed on the bottom. Red is positive inflection and blue is negative inflection.

3.3.5 Correlations

Cannabis consumption was significantly positively correlated with the duration of microstate class C during eyes-closed resting (r = .33, p = .03). The positive subscale of the SOPS was also positively correlated with the mean duration of class C during eyes-closed resting (r = .44, p = .04). TALES adverse events were also significantly positively associated with increased negative symptoms scores on the SOPS (r = .44, p = .04), and negatively correlated with the proportion of time spent in microstate class D during eyes-

closed resting (r = -.34, p = .02). Proportion of time spent in microstate class D during eyes-closed resting was negatively correlated with number of adverse events on the TALE (r = -.34, p = .03). Functioning via SOFAS scores were also significantly negatively correlated with the General (r = -.8, p < .001), Positive (r = -.64, p < .001) and Negative (r = -.76, p < .001) subscales of the SOPS.

3.4 Discussion

This study examined EEG-derived microstate parameters, including occurrence, duration, and coverage in individuals with early-phase psychosis compared to healthy controls during eyes-closed resting states. By analyzing these specific microstate parameters, we were able to detect microstate differences between groups. These results generally confirm prior findings of altered microstates in schizophrenia (particularly in the early phase) but also offer new perspectives on the nature of microstate alterations in schizophrenia, extending findings into the early phase of the illness and giving credence to the use of microstates as a potential endophenotype of schizophrenia.

This study hypothesized that microstate class C would exhibit an increased duration, occurrence, and coverage, while microstate class D would show a reduction in duration, occurrence, and coverage in individuals in the early-phase psychosis group compared to healthy controls. The results partially supported these hypotheses. For microstate C, individuals in the early phase group exhibited a reduction in duration, which contradicts the hypothesized increase in duration. For microstate D, individuals in the early phase group demonstrated an increased occurrence and coverage in eyes-closed resting state, inconsistent with the hypothesis of reduced occurrence and coverage compared to healthy controls.

In, microstate C, which is often associated with fronto-parietal networks responsible for interoceptive autonomic sensory processing and saliency, showed significant group differences. The early phase psychosis group exhibited a lower mean duration of microstate C compared to healthy controls in the eyes-closed conditions. This reduction in microstate C suggests that the neural networks may be less active or less efficiently engaged in early phase psychosis. Prior studies have produced mixed results regarding microstate C, with some reporting minimal differences between groups (Rieger et al., 2016). However, the findings in this thesis's meta-analysis (Chapter 2) support consistent aberrations in microstate class C among individuals with schizophrenia, showing a significant increase in its duration compared to healthy controls. These results partially align with previous research (e.g., da Cruz et al., 2020) and underscore the role of microstate C alterations in the illness. Our findings also suggest that microstate C may indeed be disrupted in early phase psychosis, particularly in terms of its duration. This supports the idea that salience and sensory processing dysfunction, which is a hallmark of schizophrenia, may be reflected in the temporal dynamics of brain network activity, as seen through reduced activation of microstate C. Moreover, the consistent findings of eyes-closed resting DMN alterations suggest that this disruption is pervasive, affecting brain function while also at rest. Although the disruptions may be heterogeneous in nature, they are consistent in the classes altered.

In the eyes-closed resting state, individuals in the early phase psychosis group demonstrated statistically significantly increased occurrence and greater coverage of microstate D compared to healthy controls. Specifically, early phase participants showed differences in microstate D which activated more often, suggesting that the dynamics of

this microstate, which typically involve fronto-central networks, may be disrupted in early phase psychosis. The increased occurrence of microstate D has been previously associated with impairments in language-related networks (Lehmann et al., 2005), and our results support these findings. The increased occurrence and coverage may reflect a difficulty in transitioning out of this microstate, indicating potential deficits in the flexible switching of brain states, a known characteristic of schizophrenia (Khanna et al., 2015). These disruptions in microstate D could also be indicative of the broader abnormalities in neural oscillations that have been reported in schizophrenia (Rieger et al., 2016). Attentional dysfunction in schizophrenia may manifest as difficulties in sustaining focus, filtering irrelevant information, and engaging attentional networks efficiently, contributing to pervasive cognitive disorganization and challenges in tasks like reading or conversation (Luck et al., 2011; Barch & Ceaser, 2012). Furthermore, these deficits may exacerbate negative symptoms, such as apathy and avolition, by hindering motivation and goal-directed behaviour, leading to greater social withdrawal and functional decline (Kirkpatrick et al., 2006; Strauss et al., 2013).

Since microstate class D has been associated with right-lateralized dorsal, ventral, frontal, and parietal systems in EEG source localization investigations (Mikutta et al., 2024), it is plausible that disruptions in frontoparietal processing may influence the clinical presentation of schizophrenia, particularly symptoms related to hallucinations and perceptual dysfunction. Alterations in parietal sensation-oriented processing and frontal, meaning-based executive processing could theoretically reduce attention reorientation, potentially leading to increased mind-wandering or challenges in inhibiting attentional focus. Some evidence also suggests that microstate D may shorten during active

hallucinations (Kindler et al., 2011), supporting the idea that positive symptoms, such as hallucinations and delusions, could arise from difficulties in transitioning between brain states, although the alteration of class D may be heterogeneous across the development and course of the illness. The fronto-central networks tied to microstate D appear to play a role in attention orientation to self-referential thought in class C, where disruptions may lead to misattributions of internal thoughts as external voices (Jardri et al., 2011). Additionally, challenges in shifting between neural states could foster delusional thinking by limiting cognitive flexibility and belief updating, potentially leading to cognitive rigidity and the persistence of false beliefs (Corlett et al., 2010; Menon, 2011). The increased occurrence may reflect a difficulty in the hyperactivity of this microstate, indicating potential deficits in the flexible switching of brain states, a known characteristic of schizophrenia (Khanna et al., 2015). These disruptions in microstate D could also reflect broader abnormalities in neural oscillations that have been reported in schizophrenia (Bickel et al., 2012). These neural dysfunctions may contribute to core symptoms observed in schizophrenia, which often arise from the brain's inability to efficiently manage information, leading to widespread disturbances in thought, emotion, and behaviour (Javitt, 2009).

The increased occurrence and coverage of microstate D may also contribute to negative symptoms of schizophrenia, such as avolition, anhedonia, and social withdrawal. Negative symptoms are associated with deficits in brain networks involved in attention and motivation (Kirkpatrick et al., 2006). Microstate D, involved in attentional control and executive function, influences goal-directed behaviour (Britz et al., 2010). When individuals with schizophrenia have increased activation of this state without efficient

switching, it may result in cognitive and motivational rigidity, making it difficult to initiate or sustain goal-directed tasks. This could manifest as apathy or reduced engagement in social and occupational activities (Strauss et al., 2013). The inability to shift mental states flexibly may also contribute to blunted affect, where patients display reduced emotional expressivity due to difficulty transitioning between emotional and cognitive states (Kring & Barch, 2014).

The cognitive symptoms of schizophrenia, including impaired attention, working memory deficits, and executive dysfunction, are likely impacted by the increased occurrence and coverage of microstate D. Research has demonstrated that microstate D is associated with preparatory processes in working memory tasks. For example, Muthukrishnan et al. (2016) found that in healthy participants, specific pre-trial configurations of microstate D could predict response accuracy in visuospatial working memory tasks, with EEG activation in the right middle occipital gyrus being particularly influential. This suggests that microstate D supports the allocation of visuospatial processing resources, which is essential for maintaining memory task performance under high cognitive load. In individuals with schizophrenia, these dynamics are notably disrupted. Yao et al. (2021) observed that schizophrenia patients show reduced engagement of frontal and parietal-occipital regions during working memory tasks, areas essential for cognitive control and executive functions. This aberrant activity corresponds with the abnormalities in microstate D and may underlie deficits in sustaining cognitive control, particularly when performing tasks that require attention and working memory. Similarly, Milz et al. (2016) and Seitzman et al. (2017) identified that alterations in microstate D correspond to broader cognitive impairments in schizophrenia, with

hyperactivation of microstate D being associated with reduced attentional control and an impaired ability to adaptively switch between cognitive tasks.

These findings collectively highlight microstates C and D as potential neurophysiological markers, shedding light on how their atypical patterns contribute to the cognitive deficits characteristic of schizophrenia. The consistent disruptions observed across studies suggest that microstates C and D could serve as potential endophenotypes for cognitive dysfunction in schizophrenia, providing insights into the underlying neural mechanisms associated with the disorder's symptoms. However, this study also adds that there may be heterogeneous alterations in these classes, at least in early-phase psychosis and further research is needed to determine how these alterations change along the course of illness to determine their eligibility as endophenotypes.

These observed deficits may be fundamental to the disorder and affect daily functioning and quality of life (Barch & Ceaser, 2012). Difficulty transitioning between cognitive states results in poor attentional control, which is essential for tasks requiring sustained mental effort (Millan et al., 2012). For instance, patients may struggle to maintain attention over extended periods, leading to disorganized thoughts and incoherent speech, both hallmark features of the disorder (Murray et al., 2014). Working memory, which relies on the ability to hold and manipulate information over short periods, also depends on flexible neural transitions. Disruptions in microstate D may exacerbate the cognitive disorganization often observed in patients (Conklin & Iacono, 2002). This disorganization may appear in real-world settings as difficulty following instructions, managing multiple tasks, or tracking daily activities (Reichenberg & Harvey, 2007).

Moreover, executive dysfunction, including challenges with planning, problem-solving, and decision-making, can arise from these microstate dynamics (Chan et al., 2006). The failure to dominance of microstate D suggests that individuals with schizophrenia may become stuck in rigid thought patterns, potentially contributing to disorganized behaviour and delusional thinking (Lesh et al., 2011). This may include inappropriate responses to environmental cues or difficulty adapting behaviour in response to new information, frequently observed in clinical settings (Green et al., 2019). Microstate D is involved in attention to language networks, and impairments in its dynamics may cause disorganized speech characterized by derailment, incoherence, and loose associations between thoughts (Kindler et al., 2011). The prolonged activation of this microstate may lead to difficulty transitioning between different thoughts, contributing to thought disorder, where patients struggle to maintain a coherent flow of conversation or logically connect ideas (Spencer et al., 2004). The differences in microstate class D are observed in previous research in the field of EEG-based endophenotypes in schizophrenia. Specifically, class D alterations in individuals with schizophrenia have been consistently associated with disrupted brain connectivity patterns, particularly those contributing to difficulties in attentional processes and executive function. Additionally, we observed a significant reduction in the duration of microstate C during eyes-closed resting. This finding underscores the potential role of microstate C in the cognitive deficits observed in schizophrenia, particularly in relation to executive function and task switching.

The altered microstate processing in individuals with schizophrenia was associated with deficits in social, occupational, and general functioning. This association

suggests that individuals exhibiting altered microstate dynamics may face challenges in daily interactions and responsibilities, impacting their ability to maintain social relationships, employment, and overall quality of life. For instance, social functioning may decline as microstate alterations interfere with cognitive processes essential for effective communication and interpersonal skills (Harvey et al., 2006; Svirskis et al., 2017). Similarly, occupational functioning could be affected, as impaired microstate dynamics may hinder the cognitive flexibility needed to adapt to changing work environments or tasks. The relationship between altered microstates and these dimensions of functioning underscores the potential real-world implications of neurophysiological changes in schizophrenia, suggesting that interventions aimed at improving microstate dynamics might have beneficial effects on everyday functioning and mental wellness. As much as these differences in microstate dynamics may be potentially related to the underlying symptomatology that is observed with this illness, these underlying brain based differences at rest would still have utility as an endophenotype if they were not directly related to the illness, as endophenotypes do not necessarily need to be self-evident products of symptoms and may be upstream precursors to symptom manifestation.

Our meta-analysis in Study 1 identified group-level differences in microstate classes C and D. In our individual study, we identified statistically significant group differences in multiple microstate classes partially aligning with previous investigations in classes C and D. Individuals in the early phase psychosis group exhibited a greater mean occurrence of microstate class C compared to healthy controls, indicating potential disruptions in the neural processes associated with this microstate. Additionally,

individuals in the early phase group showed a hyperactive microstate D, as indicated by a significantly increased mean occurrence and coverage. This suggests that microstate D, which may reflect disruptions in language or attention-related networks, is more dominant in schizophrenia, further supporting the broader alterations in brain network dynamics observed in the disorder. However, these nuanced differences may be subject to the power of the sample size and factors that are accounted for and measured for statistical modelling.

The findings from this study present both consistencies and divergences when compared to prior research, particularly Study 1, which also explored microstate dynamics in schizophrenia. In Study 1, individuals with schizophrenia exhibited an increase in the mean duration, of microstate C, suggesting heightened engagement with this microstate. In contrast, the present study observed a decrease in the duration of microstate C during eyes-closed resting state. While Study 1 reported a reduction in the mean coverage, and occurrence of microstate D, the current study found that individuals in the early phase psychosis group demonstrated an increased mean occurrence and coverage of this microstate. This divergence could be attributed to differences in the experimental group regarding the clinical phase of the participants, which in the current study focused on early-phase of psychosis. These contradictory findings suggest that the dynamics of microstate class C and D may vary depending on specific contextual factors like illness phase. These differences in microstate engagement, indicate that microstate dynamics in schizophrenia may not be uniform and may fluctuate depending on task demands, the phase of illness, or other individual characteristics, although the presence of abnormalities in these microstate classes remains consistent. Further research is needed to

identify how these alterations change across the illness phases to determine the eligibility of microstate abnormalities as endophenotypes or biomarkers of entering the early phase.

These nuanced alterations of microstate dynamics may also be due to our clinical participants being in the early phase of psychosis. Future investigations may benefit from isolating these more nuanced differences in microstate dynamics as a potentially unique biomarker. Future investigations in the endophenotyping of schizophrenia would benefit from their inclusion of substance use and trauma measures, as well as a reconstruction of canonical microstate patterns that may be present under different states of default mode network activation.

The results of Study 2 elucidate the differences in resting state EEG-derived microstates observed in early-phase of psychosis. These differences may be able to supplement diagnostic assessment and allow access to objective biological screenings for at-risk populations. It is our hope that the early identification of those in this group then facilitates early intervention, which is associated with better prognosis, fewer suicides, and fewer hospitalizations. The results of the study highlight the alterations present in early phase psychosis as they have been observed within five years of their first psychotic episode. This gives some support for the potential candidacy of EEG-derived endophenotypes, particularly in the default mode network during at-rest conditions. However, more research can highlight the potential differences in default mode states and their associated alterations in different psychiatric populations. Previous research has investigated the differences in microstate parameters in those with schizophrenia compared to healthy controls and those with bipolar disorder (Wang et al., 2021). Those with bipolar had alterations in microstate parameters that were significantly different

from the observed alteration in microstates of those with schizophrenia. The researchers found reduced microstate class A and B, greater class C and a reduction in class D in those with schizophrenia compared to healthy controls and bipolar groups.

The observed correlations between cannabis consumption, trauma exposure, symptom dimensions, and microstate dynamics provide important insights into the mechanisms underlying early-phase psychosis and its neural endophenotypes. The correlation between cannabis consumption and the duration of microstate class C during eyes-closed resting suggests that cannabis may exacerbate disruptions in salience network processing, which is implicated in positive symptomatology. This aligns with prior research highlighting cannabis's impact on neural oscillations and salience network activation (D'Souza et al., 2004). As our sample excluded those with a significant cannabis use disorder, heightened or disordered cannabis use may impact more than the duration of class C as the endocannabinoid system is well distributed throughout the brain, however, our sample having more moderate use may be limited in the ability to identify more widespread, cannabis related effects. In early-phase psychosis, when brain networks are still undergoing dynamic reorganization, these disruptions may interact with an already vulnerable salience system, potentially amplifying difficulties in distinguishing relevant from irrelevant stimuli and worsening clinical outcomes. This could explain some of the reduced duration of microstate C observed in this study, as individuals with early-phase psychosis may have a diminished capacity to engage neural networks supporting salience and sensory processing, contrary to the hypothesized increase in class C parameters.

Similarly, the positive correlation between the Positive subscale of the SOPS and the mean duration of microstate class C further supports the role of this microstate in positive symptoms, such as hallucinations and delusions. Reduced duration of microstate C may reflect inefficient engagement of the salience network, which is critical for adaptive attentional shifts and contextual relevance (Menon, 2011). Although increased class C parameters were hypothesized, the observed decrease in its duration may suggest that neural disruptions during the early phase of schizophrenia result in less frequent activation, which could underlie the cognitive rigidity and perceptual disturbances characteristic of the disorder as it undergoes fewer updates to new or incoming information.

Trauma exposure, measured through the TALES, was positively correlated with negative symptom severity and negatively correlated with the proportion of time spent in microstate D. These findings align with previous research showing that trauma disrupts DMN connectivity, particularly in fronto-parietal systems (Whitfield-Gabrieli & Ford, 2012). The increased occurrence and coverage of microstate D in this study suggest a increased recruitment of this state, contributing to cognitive and motivational rigidity. In the early phase of schizophrenia, these disruptions may compound existing deficits, as trauma-related alterations in the DMN could exacerbate negative symptoms such as apathy and avolition. These findings highlight the potential interplay between trauma exposure and neural dysfunction, emphasizing the need to consider co-occurring factors in endophenotyping efforts.

The negative correlations between SOFAS functioning scores and symptom severity (across General, Positive, and Negative subscales of the SOPS) underscore the

real-world impact of symptom burden on functional outcomes and offer some validity in their validity and occurrence in our sample. Impairments in microstate D dynamics, coupled with high negative symptom severity, likely contribute to reduced social, occupational, and general functioning. This is particularly relevant in early-phase psychosis, where functional impairments are predictive of long-term outcomes (Addington et al., 2005). The increased occurrence and coverage of microstate D observed in this study may reflect disruptions in attentional control and executive function, which are critical for daily functioning and goal-directed behaviour. These findings suggest that microstate D abnormalities may be a marker of schizophrenia with alterations across studies, and hold potential as an endophenotype for the disorder pending future work characterizing the nuances of observed changed (albeit in different directions depending on illness state)

One limitation of the current study is the difficulty in disentangling the microstate alterations that may be specific to schizophrenia from those potentially influenced by other common co-occurring factors such as trauma and substance use. Both trauma and substance use are prevalent in individuals with early-phase psychosis and have been shown to affect brain function in ways that overlap with schizophrenia, particularly within networks like the DMN (Whitfield-Gabrieli & Ford, 2012). For instance, trauma is associated with alterations in connectivity within the DMN and can affect cognitive and emotional processing (Bluhm et al., 2009). Trauma, particularly in the form of childhood adversity, has been associated with abnormal default mode network (DMN) function, which could exacerbate or mask microstate alterations from early-phase psychosis (Whitfield et al., 2005). Similarly, substance use, particularly heavy use of cannabis, has

been implicated in disruptions in brain activity, including altered microstate patterns (Brylowski et al., 2019). Cannabis has been shown to impact neural oscillatory dynamics, potentially confounding the interpretation of microstate class C and D abnormalities (Giordano et al., 2018). These factors may independently contribute to the observed abnormalities in microstate dynamics, complicating the ability to attribute the findings solely to schizophrenia.

To address this, future studies would benefit from systematically comparing groups with schizophrenia, trauma, sex based differences, and substance use, both independently and in combination. By examining microstate alterations across these different populations, researchers could identify patterns that are unique to schizophrenia versus those that may be more related to trauma or substance use. Additionally, investigating how these factors interact, such as whether the presence of trauma and substance use exacerbates microstate abnormalities in individuals with schizophrenia, could provide critical insights into the complex interplay between these variables. Incorporating more detailed assessments of trauma history and substance use (e.g., frequency, duration, and type of substances) into future studies would allow for a more accurate understanding of their contribution to brain activity patterns. This is particularly important, as individuals with schizophrenia often have significant substance use histories or trauma exposure, which could confound the results. Furthermore, reconstructing canonical microstate patterns under different DMN activation states could help delineate how these external influences modify or mimic the neural signatures seen in schizophrenia. This approach would help clarify the extent to which the observed microstate differences are driven by schizophrenia itself or are influenced by co-

occurring conditions. A more detailed assessment of trauma and substance use, alongside examining the interaction between these factors and schizophrenia, would enable a more nuanced understanding of the neural mechanisms underlying early-phase psychosis and its potential comorbidities.

Future research would also benefit from a longitudinal approach to the illness course of those with schizophrenia and how those at different time points of the illness may have specific detectable alterations of default mode network activation in its different states, indexed by microstate parameters. Microstates have been previously shown to have good to excellent test-retest reliability in younger and older samples (Popov et al., 2023). However, other research has shown that microstate parameters can change across the lifespan and found altered microstates between age groups from 6-80 (Koenig et al., 2002). Therefore, the utility and application of microstates as an endophenotype may need to take into account age and have normative data for differing age cohorts to be able to effectively be applied as an endophenotype. The groups in our sample were similar in their age and differences were able to be observed within an age cohort. This aligns with the previous investigation which found no differences in microstate in members of the same age cohort (Koenig et al.,. 2002), so age effects may need to be considered in application of microstates as an endophenotype but may not account for the differences observed in those with schizophrenia versus healthy controls. Previous research has also identified differing microstate parameters observed between sexes and noted a prolonged duration of class C in females and increased of occurrence of class D in males (Tomescu et al., 2018). Although we used sex as a covariate as an attempt to account for it in our study sex differences have frequently not been accounted

for in this field and warrant further investigation. Supplemental fMRI spatial data could also help solidify the spatial components of the default mode network and observed alterations in clinical populations, ages and sexes.

The clinical implications of these findings are present, particularly regarding the use of EEG microstates as diagnostic and treatment monitoring supplements. The observed abnormalities in microstate class C and D offer potential biomarkers that could assist in identifying individuals at high risk for developing schizophrenia, even before acute psychosis manifests. Moreover, because microstate dynamics reflect real-time brain function, they can provide valuable insights into how individuals respond to treatments over time (Kindler et al., 2011). For instance, changes in microstate parameters could be used to monitor the efficacy of pharmacological interventions, with normalization of microstate duration and transitions potentially indicating a positive treatment response (Hernandez et al., 2016). This capacity for objective, non-invasive monitoring highlights the potential of EEG microstates to play a key role in personalized medicine approaches for schizophrenia.

CHAPTER 5: Transition to Study 3

In the preceding chapters, we explored the role of resting-state microstates, particularly their involvement in the default mode network (DMN), as potential endophenotypes of schizophrenia. Study 1 provided a meta-analytic overview of the literature, consolidating findings that consistently demonstrated altered microstate patterns in individuals with schizophrenia. Study 2 extended this investigation to an early psychosis sample, examining whether these altered microstates, specifically the increased occurrence of microstate class C and reduced occurrence of class D, were also present in individuals in the early stages of psychosis. This body of work provides some evidence towards the candidacy of resting-state microstate dynamics as endophenotypes for schizophrenia.

However, schizophrenia is not limited to disruptions in resting-state brain function alone. Cognitive and perceptual deficits, particularly in auditory processing, are among the most prominent features of the disorder. Auditory dysfunction plays a crucial role in the manifestation of symptoms such as auditory hallucinations, which are commonly observed in individuals with schizophrenia. As we transition to Chapter 4, our focus shifts to investigating auditory processing deficits, particularly through the lens of the mismatch negativity (MMN), as another potential candidate endophenotype for schizophrenia.

While resting-state abnormalities provide insight into the intrinsic brain dynamics of schizophrenia, auditory processing deficits reflect the disorder's impact on sensory perception and cognitive integration. The MMN is a well-established neural marker used to assess automatic auditory change detection. It is elicited when a deviant auditory

stimulus is presented after a sequence of standard stimuli, creating a negative deflection in the event-related potential (ERP) waveform. This neural response occurs without the need for conscious attention, making it an ideal candidate for studying the pre-attentive auditory processing deficits often observed in schizophrenia.

Studies have shown that individuals with schizophrenia exhibit significantly reduced MMN amplitudes compared to healthy controls, suggesting impaired auditory prediction and error detection mechanisms (Fisher et al., 2018). These deficits may reflect a broader disruption in the brain's ability to process and integrate sensory information, contributing to the auditory hallucinations and other perceptual distortions commonly seen in the disorder. By focusing on MMN in Study 3, we aim to probe these auditory processing deficits in greater detail, investigating their potential as endophenotypes for schizophrenia.

In Study 3, the investigation moves beyond resting-state neural dynamics to explore auditory processing, specifically mismatch negativity (MMN), as a potential endophenotype of schizophrenia. This study builds on existing evidence that individuals with schizophrenia show deficits in auditory change detection, particularly in response to more complex auditory stimuli. By employing various auditory paradigms, including the optimal multi-feature paradigm and the more complex dual rule paradigm, we seek to understand how individuals with schizophrenia process both simple and complex auditory deviations compared to healthy controls.

The MMN serves as a robust index of auditory processing, offering a window into the brain's automatic response to deviations in expected stimuli. In simple paradigms, such as the optimal multi-feature paradigm, participants are exposed to standard tones

that occasionally deviate in frequency, duration, or intensity. However, more complex paradigms, like the dual rule paradigm, introduce subtler violations of expectation, which require more intricate cognitive processing. Given that auditory processing deficits in schizophrenia are often subtle, it is hypothesized that more nuanced differences between individuals with schizophrenia and healthy controls will be observed in the more complex auditory paradigms.

As we move from the resting-state investigations of microstates to the study of auditory processing in schizophrenia, it is essential to recognize the interconnected nature of these neural functions. Both resting-state networks, such as the default mode network, and sensory processing mechanisms, such as those indexed by MMN, are critical to understanding the full spectrum of schizophrenia's neurophysiological underpinnings. By investigating both, we are better equipped to identify robust, multidimensional biomarkers that can aid in the early detection and treatment of schizophrenia.

While the resting-state microstate alterations explored in the first two studies provide valuable insights into the baseline neural dysfunctions in schizophrenia, Study three shifts our attention to the sensory processing deficits that are equally characteristic of the disorder. Through the examination of MMN and its neural generators, this study seeks to identify whether these auditory processing deficits can serve as reliable endophenotypes, further advancing our understanding of schizophrenia's complex neurobiology.

CHAPTER 6: Mismatch Negativity as an Endophenotype of Schizophrenia

4.1 Introduction

Individuals with schizophrenia often show deficits in basic auditory processing, which has been implicated in the generation of hallucinations (Donde et al., 2023). Auditory hallucinations generally involve hearing voices or sounds that are not present in the external world. Neuroanatomically, these hallucinations frequently involve brain regions associated with auditory processing, such as the superior temporal gyrus (STG) and the auditory cortex (Stahl et al., 2018). Dysfunction in these regions, whether due to structural abnormalities or altered connectivity, can lead to the perception of auditory stimuli without external input (Huang et al., 2019). Neurochemical imbalances in neurotransmitter systems also play a significant role in generating auditory hallucinations. Disruptions in functional connectivity within and between neural networks have been observed in those experiencing auditory hallucinations, including both hyperconnectivity (abnormally heightened communication) and hypoconnectivity (reduced communication) between brain regions, potentially causing misinterpretation of neural signals and the perception of non-existent auditory stimuli (Shinn et al., 2013). Investigating the observed auditory dysfunction in schizophrenia is crucial to understanding sensory disturbances in the auditory system and how these may be underlying the experience of auditory hallucinations, a core symptom of the disorder.

Auditory hallucinations in schizophrenia are influenced by a combination of neural, neurotransmitter, cognitive, and emotional factors, which provide insights into their underlying mechanisms. For example, people with schizophrenia may struggle to distinguish between real and internally generated sounds, possibly due to changes in the

left insula involved in the salience network (Barber et al., 2021). Research has also found abnormalities in source identification of auditory stimuli in schizophrenia (Thakkar & Rolfs, 2019), and neuroimaging studies show hyperactivity in the auditory cortex, particularly during hallucinations (Jadri et al., 2011). Additionally, schizophrenia has been associated with altered functional connectivity between brain regions involved in auditory processing (Zhang et al., 2018). Dysregulation of dopamine and glutamate neurotransmission, both associated with schizophrenia, may contribute to auditory hallucinations (Stahl, 2018), while increased dopamine activity in regions involved in the salience network has been previously identified as a significant factor in the positive symptoms of schizophrenia (Howes et al., 2016). Moreover, cognitive factors like attention and memory biases can influence the development and persistence of auditory hallucinations, as those with schizophrenia may have heightened sensitivity to auditory stimuli, selectively attending to and recalling information consistent with delusional beliefs or hallucinatory experiences (Garety et al., 2001). Stress and emotional factors can exacerbate auditory hallucinations, with high stress levels increasing the likelihood and intensity of hallucinations through their impact on neural circuits involved in emotion regulation and general heightened neural activity under distress (Lataster et al., 2013). Auditory hallucinations can also occur in people without schizophrenia during periods of high stress, such as the death of a loved one, kidnapping, or violent interactions (Johns, 2005).

Dysfunctional coordination in the early stages of sensory and information processing may underlie the clinical and cognitive deficits characteristic of schizophrenia (Javitt, 2009; Light et al., 2006). A prominent neurophysiological deficit in schizophrenia

is observed in auditory change detection, indexed by EEG-derived mismatch negativity (MMN). MMN is typically generated by randomly inserting rare deviant auditory stimuli into a series of standard sounds. The MMN is a negative deflection that occurs approximately 200 ms post-stimulus at frontocentral areas of the scalp, with maximal amplitude typically occurring at F_Z. The prediction error model of MMN suggests that the auditory cortex imputes a pattern of the auditory environment, and deviations from this pattern elicit an error signal from primary to secondary cortices, adjusting the model (Winkler, 2007). Deviants can differ from standards in frequency, duration, intensity, and location (Näätänen & Alho, 1997).

Research on MMN in schizophrenia has been a focus of research since the first study finding the relationship between the two was published (Shelley et al., 1991). Generally, individuals with chronic schizophrenia show deficits in basic sensory information processing, evidenced by consistent reports of reduced MMN amplitude (Javitt et al., 1993; Umbricht et al., 2003; Park et al., 2002), especially to duration deviants (Michie, 2001). Due to the robust nature of MMN alterations in schizophrenia, the ongoing Consortium on the Genetics of Schizophrenia (COGS) has endorsed MMN as an assessment tool due to its significant correlations with established measures of clinical, cognitive, and psychosocial functioning in individuals with schizophrenia (Light et al., 2015).

While there is some evidence that MMN deficits are present at the first psychotic episode and may predate psychosis in high-risk individuals (Atkinson et al., 2012; Jahshan et al., 2012; Nagai et al., 2013; Perez et al., 2014), however, results have been inconsistent. Brockhaus-Dumke et al. (2005) found that prodromal subjects showed a

non-significant reduction in MMN amplitude, ranging between healthy controls and individuals with schizophrenia. Other studies reported a normal MMN at the first episode (Salisbury et al., 2002, 2007; Umbricht et al., 2006; Magno et al., 2008). Results from genetic high-risk (GHR) studies have also been inconsistent. Some reported reduced MMNs in first-degree relatives of people with schizophrenia (Jessen et al., 2001; Michie et al., 2002; Sevik et al., 2011), while others found weak (Ahveninen et al., 2006; Hall et al., 2009) or no familial effects (Schreiber et al., 1992; Bramon et al., 2004). A meta-analysis of 14 MMN studies on those in their first episode of schizophrenia concluded that simple stimulus deviations did not show significant MMN reductions (Haigh et al., 2017).

Most studies on auditory change detection in schizophrenia have used the traditional two-stimulus auditory oddball paradigm, where standard stimuli are physically identical to each other, and deviant stimuli possess some changed feature (Näätänen, 1990). This method has been criticized for not eliciting a pure MMN (May & Tiitinen, 2010). Jacobsen and Schröger (2001) demonstrated that MMN measured in oddball paradigms with frequency deviants includes both MMN and an overlapping N100 enhancement. In response to these concerns, as well as in response to inconsistent group findings in the prodrome and early phase of schizophrenia using simple stimulus-feature change paradigms, interest has shifted to explore MMNs elicited by more complex stimulation parameters that avoid sensory refractoriness issues inherent in the oddball paradigm.

One such novel paradigm designed to elicit the MMN uses a ‘dual rule’ pattern that alternates tones between the left and right ear and between high and low frequencies

(Salisbury et al., 2023). The standard pattern is a low-frequency tone to the left ear, then a high-frequency tone to the right ear, while deviant trials involve the presentation of the low-frequency tone twice to the left ear rather than alternating ear and tone, breaking both the left/right and high/low-frequency patterns (i.e., breaking two 'rules'). The development of such novel paradigms has the potential to generate additional insights regarding central auditory processing in the schizophrenia spectrum and may yield valuable biomarkers of illness.

The 'optimal' multi-feature paradigm (Näätänen et al., 2004) has been previously used to investigate auditory processing deficits in schizophrenia (Fisher et al., 2008) and early-phase psychosis (Fisher et al., 2018). The paradigm consists of a string of 15 consecutive standard stimuli that afterwards has a standard tone and then every second tone is deviant that differs in either the frequency, duration, intensity, perceived location, or contains a gap in the middle of the tone. These studies found evidence of MMN reductions in response to deviant stimuli, supporting its utility in identifying sensory processing deficits. However, most prior research has focused on chronic schizophrenia, leaving questions regarding the specific nuances of MMN deficits in early-phase psychosis samples. This study builds upon these prior works by employing the same paradigm to investigate MMN deficits in an early-phase psychosis sample. Furthermore, this study differs in its integration of the dual rule paradigm to probe complex auditory processing in schizophrenia, which could provide complementary insights into sensory processing deficits that may not be fully captured by simple stimulus change paradigms (eg., multi-feature paradigm). By combining these paradigms, this work aims to refine our

understanding of MMN as a potential biomarker and its sensitivity to different aspects of auditory processing deficits in schizophrenia.

There is evidence suggesting that more nuanced changes in auditory processing are more observable in complex auditory processing in those with schizophrenia (Ells et al., 2018; Rudolph et al., 2015; Salisbury, 2012). This study involves the investigation of differing paradigms to probe varying complexities of auditory processing in their potential candidacy as endophenotypes of schizophrenia. It is hypothesized that those with schizophrenia will show reduced mismatch negativity indexed by lesser MMN amplitudes in response to deviant stimuli than healthy controls in response to the deviants generated in the optimal multi-feature paradigm and dual rule paradigm. It is also hypothesized that there will be positive correlations between MMN amplitudes and clinical symptom measures (i.e., as clinical symptoms increase, MMN will approach zero).

4.2 Methods

Chapter six involves the same participant sample and recording parameters of Study 2. However, instead of at rest recording, participants were presented with each of the two MMN paradigms outlined below while watching a silent movie.

4.2.1 Optimal Multi-Feature MMN Paradigm

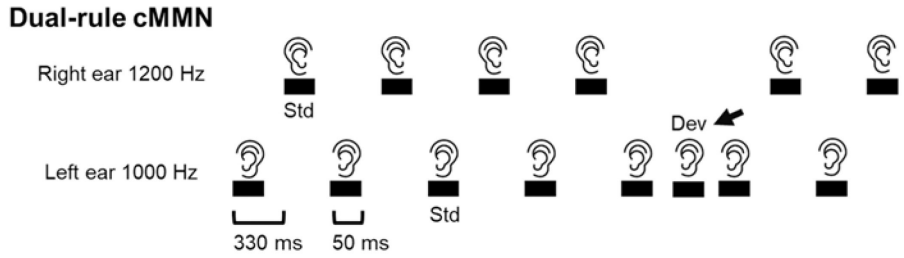
This study employed a multi-feature MMN paradigm referred to as the 'Optimal' Multi-Feature Paradigm (Näätänen et al., 2004) previously used to characterize schizophrenia (Fisher et al., 2008) and early-phase psychosis (Fisher et al., 2018). Following the initial presentation of 15 consecutive standard tones, every second tone was a standard (p = 0.5), and every other presented tone was one of the five deviants (p =

0.1 each); the deviant tones differed from the standard tones in frequency, duration, volume, perceived location, or had a gap in the middle. The standard stimuli were 75 ms in duration and composed of three sinusoidal partials (i.e., sound signals comprised of sine waves with differing frequencies of 500, 1000, and 1500 Hz) presented binaurally at 70 dB. For the frequency deviants, half were 10% higher compared to the standard, and the other half were 10% lower. For the duration deviants, half were 10% shorter compared to the standard, and the other half were 10% longer. For the intensity deviants, half were -10 dB softer compared to the standard, and the other half were +10 dB louder. For the location deviant, a change in the perceived sound-source location was achieved by introducing an interaural time difference of 800 μs, with half of the deviants directed to the right channel and the other half to the left channel. The perceived difference between the standard stimulus and the location deviant was approximately 90°. Finally, the gap deviant was created by removing 7 ms (including 1 ms fall and rise times) from the middle of the standard stimulus, leaving a silent gap. Except for the single feature on which they deviated from the standard, the deviants were otherwise identical to the standards. In each sequence, the initial 15 tones were standards. Following this, the sequence alternated such that every second tone was a standard (P = 0.5), and the remaining tones were divided equally among five types of deviants (P = 0.1 each). The deviants were arranged so that each category appeared once per set of five deviants, with no consecutive presentations of the same category. The stimuli were presented in three blocks of five minutes each for a total of 15 minutes (5535 stimuli). Rest intervals of ~1 minute were inserted between each of the test blocks of the MMN paradigm.

4.2.2 Dual Rule MMN Paradigm

The 'dual rule' MMN paradigm consists of tones that alternate between presentation to the left and right ear, as well as alternate between high and low frequency. The standard trial pattern consists of the low-frequency tone played to the left ear, and then the high-frequency tone played to the right ear. Deviant trials consist of two presentations of the standard pattern, followed by the low-frequency tone played to the left ear twice (i.e. a repetition of the first tone in the standard pattern, or a tone that fails to switch both frequency and location, thus breaking the two established patterns of left/right and high/low frequency). Marked deviant tones were the second presentation of the low-frequency tone to the left ear in this deviant trial. High-frequency tones were composed of 1200 Hz partials (individual sine wave components) delivered to the right ear. Low-frequency tones were composed of 1000 Hz partials delivered to the left ear. Both tones were 75 ms in length with 5 ms rise and fall. The interstimulus interval was 330 ms. Standard trials were presented six times before a deviant trial resulting in deviant tones contributing to 11% of the presented stimuli. The stimuli were presented binaurally through headphones at an intensity of 75 dB SPL in one 8-minute interval (See Figure 17).

Figure 17. Visual Representation of the Dual Rule Complex MMN Paradigm.



Note. The above figure represents the auditory tones played during the dual rule paradigm. Icons of an ear indicate whether tones were delivered to the corresponding left or right ear. Tones labelled '1200 Hz' were high-frequency tones, while those labelled '1000 Hz' were low-frequency tones. The deviant tone is distinguished by "Dev," and the standard is distinguished by "Std." Adapted from Salisbury et al., (2024).

4.2.3 EEG Recording and ERP Computation

EEG recording parameters were the same as those in Chapter 4. Stimuli (and resulting triggers for ERP analysis) were generated by Presentation software (Neurobehavioural Systems, Berkeley, CA). EEG recordings were referenced using an average reference. Preprocessing included applying filters from 0.1 - 20 Hz with a notch filter at 60 Hz, segmentation into 400-millisecond epochs (100ms before stimulus and 300ms post-stimulus) with no overlap and artifact rejection of any epochs with electrical activity exceeding ±50μV. Averages were then taken for each deviant type in each participant. The MMN difference waveforms were derived by digital point-by-point subtraction of the values from the standard stimulus presentations from those elicited by the presentation of the deviant stimuli. MMN amplitudes were obtained by quantifying the averaged activity ±8 ms around peak negative amplitudes (relative to average pre-stimulus baseline activity), defined as the largest negative peak at Fz from 100- 250 ms

after stimulus onset and were confirmed based on visual inspection. Data centered around the peak MMN amplitude was extracted from F3, Fz, F4, C3, Cz, and C4 for ERP analysis.

4.2.4 Statistical Analysis

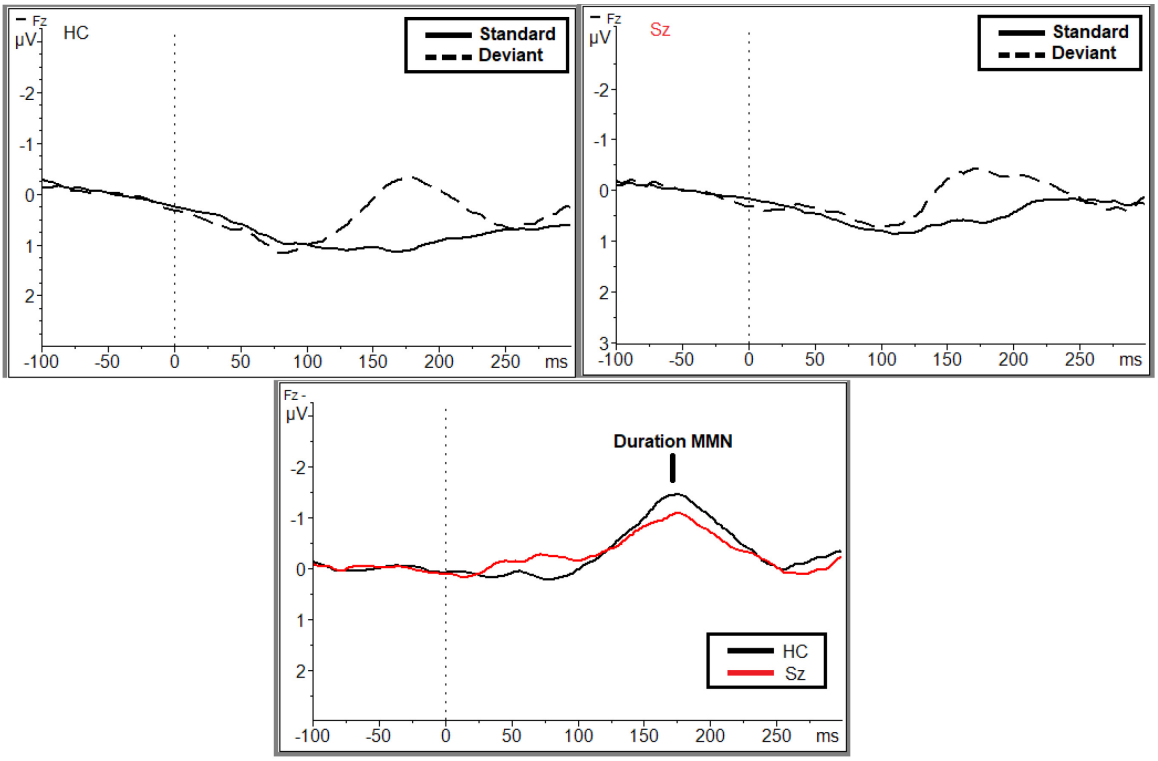
All statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS; IBM Corp., Armonk, NY). Demographic variables were compared between groups using a general linear model one-way analysis of variance (ANOVA) to determine factors that may need to be covaried and accounted for during the main analysis. MMN amplitudes were subjected to separate general linear model mixed measures analysis of variance. Each ANOVA had the between-subjects factor of groups (2 levels: healthy control and early psychosis patient) and two within-subject factors of frontality (2 levels: frontal, central) and laterality (3 levels: right, midline, left) using the factors of cigarette use, alcohol use, cannabis use, and trauma, as sources of covariance. Sex was not included as a covariate due to previous research indicating a lack of MMN differences between sexes (Riel et al., 2022). Follow-up analyses of significant ($p < .05$; Sidak corrected) main or interaction effects found in the ANCOVAs were carried out with pairwise comparisons using separate (vs. pooled) error estimates. Sidak corrections were applied to adjust for multiple comparisons. Bi-variate (non-parametric) Spearman's rho correlations were also carried out between the functioning scale scores (GAF and SOFAS total scores), the symptom scale scores (SOPS scores), demographic variables, and MMN amplitudes.

4.3 Results

4.3.1 Amplitudes

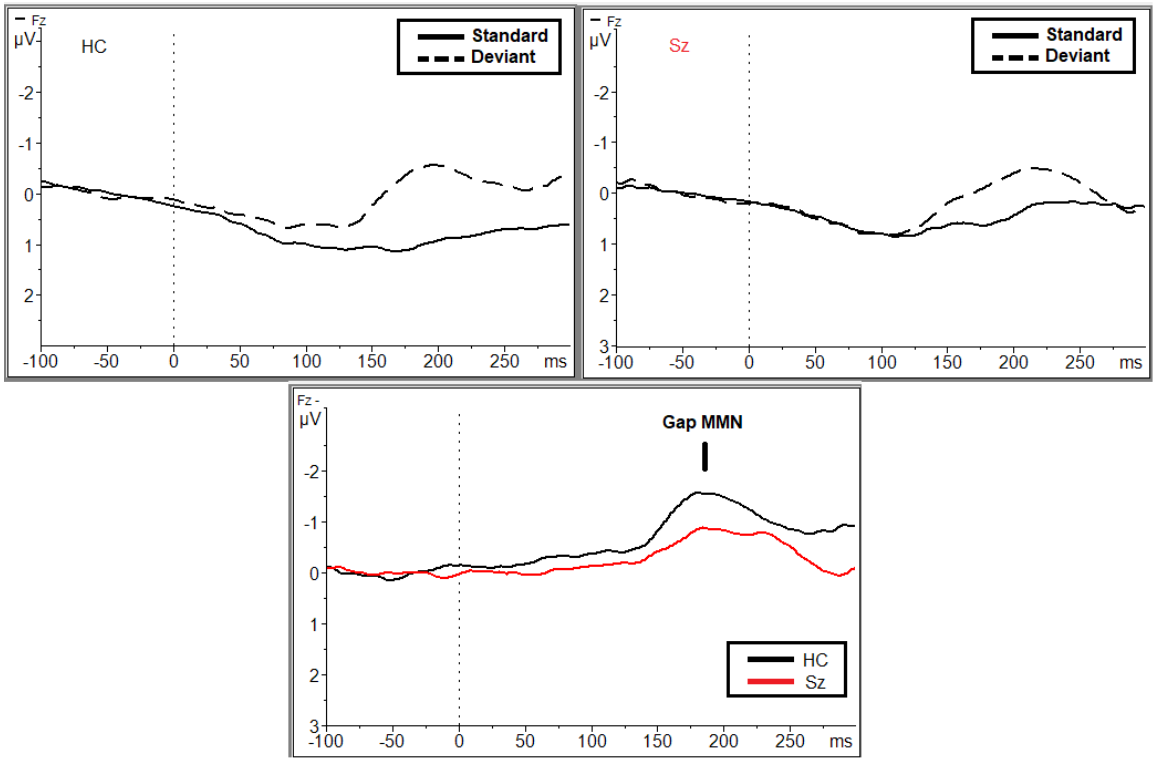
There were no significant group differences between healthy controls and early psychosis patients in MMN amplitudes elicited in response to the duration deviant (see Figure 18), gap deviant (see Figure 19), pitch deviant (see Figure 20), intensity deviant (see Figure 21), and location deviant (see Figure 22) of the optimal paradigm. There were also no observed significant group differences in the dual rule deviant (see Figure 23). Group means p-value, test statistics, effect size, and confidence intervals for each deviant type are provided in Table 4.

Figure 18. Group comparison of the MMN response to duration deviants.



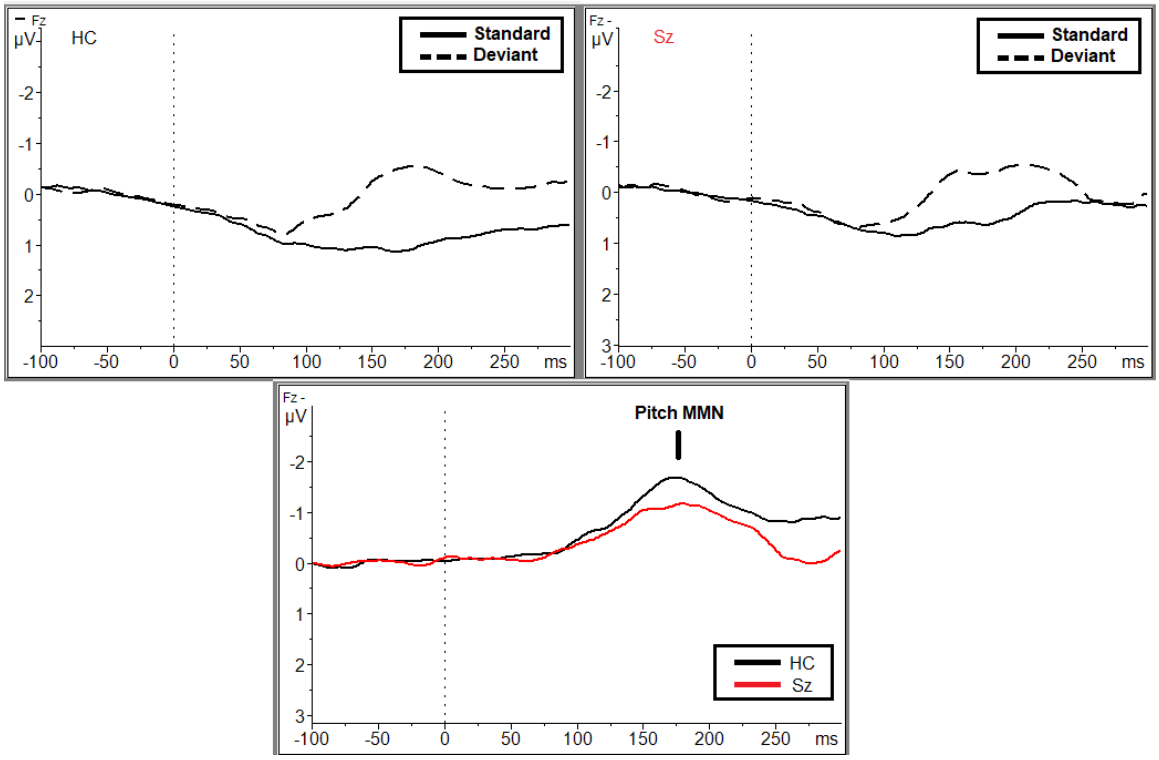
Note. The above figure demonstrates the average response of each group (HC being healthy control and SZ being schizophrenia patients) recorded while being presented with the standard tone (solid black line) and duration deviant (dotted black line) independently, and the difference wave MMN compared between those with early phase psychosis (red solid line) and healthy controls (black solid line). Amplitudes are recorded from Fz, and the MMN is marked with a line.

Figure 19. Group comparison of the MMN response to gap deviants.



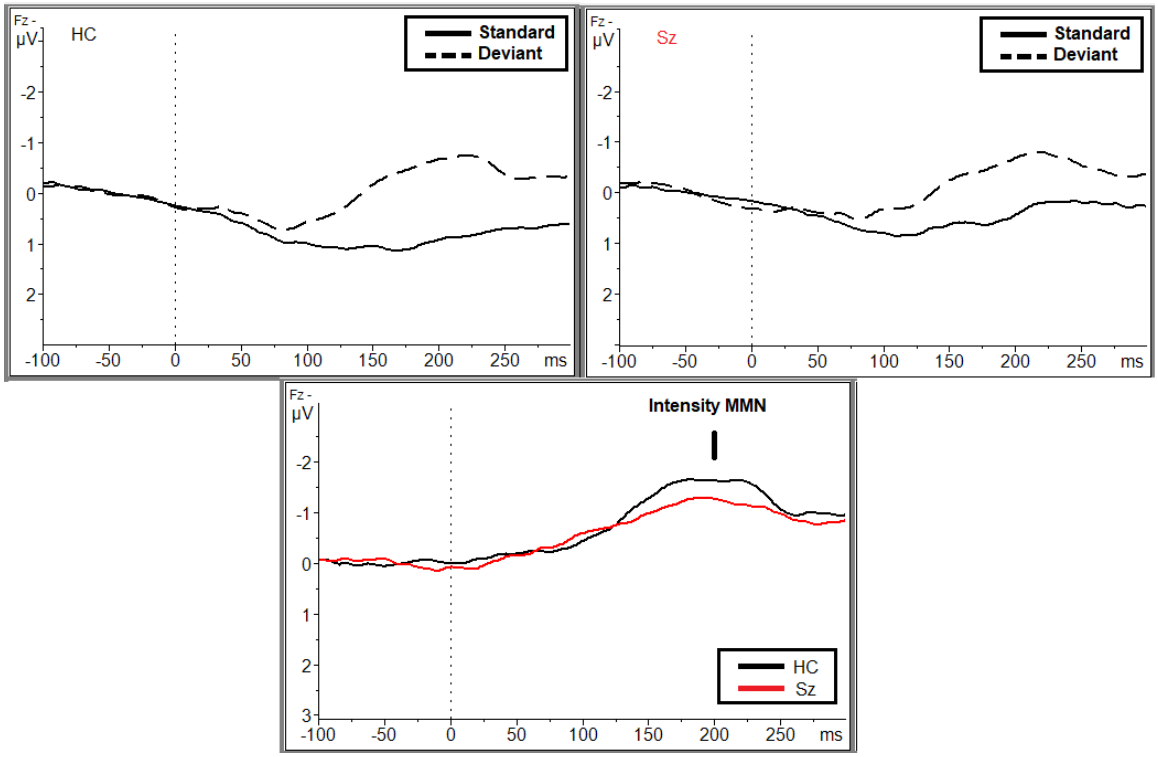
Note. The above figure demonstrates the average response of each group recorded while being presented with the standard tone (solid black line), and gap deviant (dotted black line) independently, and the difference wave MMN compared between those with early phase psychosis (red solid line) and healthy controls (black solid line). Amplitudes are recorded from Fz and the MMN is marked with a line.

Figure 20. Group comparison of the MMN response to pitch deviants.



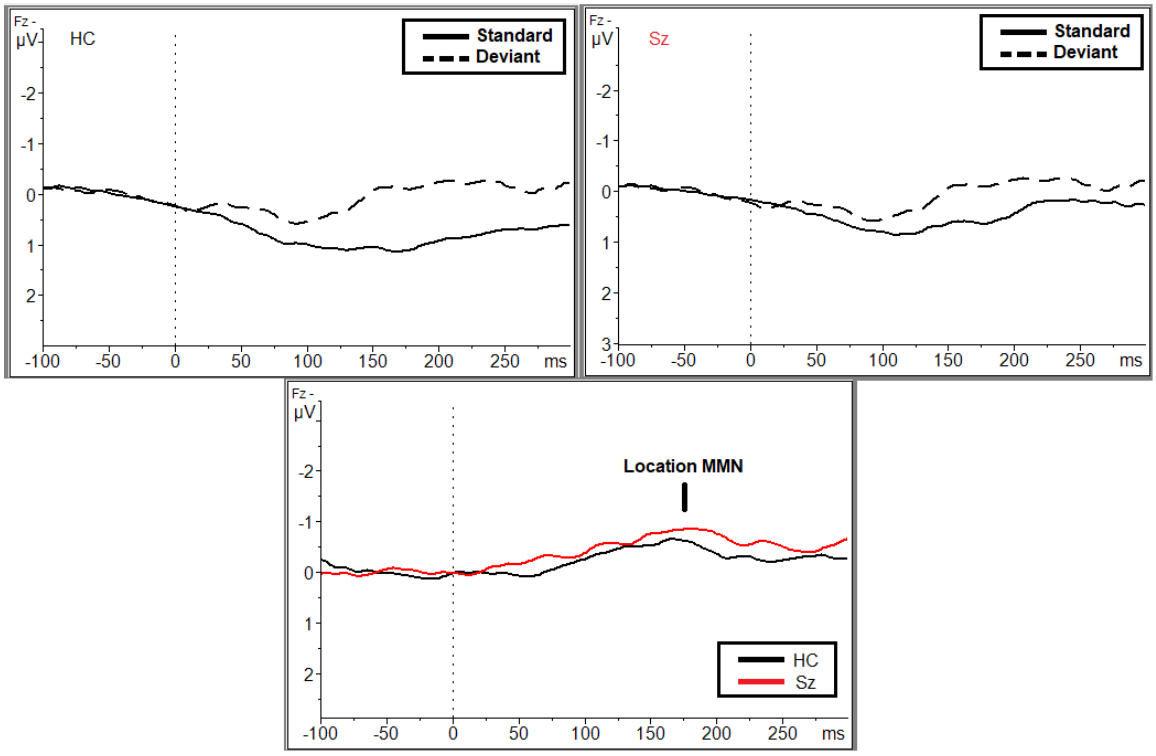
Note. The above figure demonstrates the average response of each group recorded while being presented with the standard tone (solid black line) and pitch deviant (dotted black line) independently, and the difference wave MMN compared between those with early phase psychosis (red solid line) and healthy controls (black solid line). Amplitudes are recorded from Fz, and the MMN is marked with a line.

Figure 21. Group comparison of the MMN response to intensity deviants.



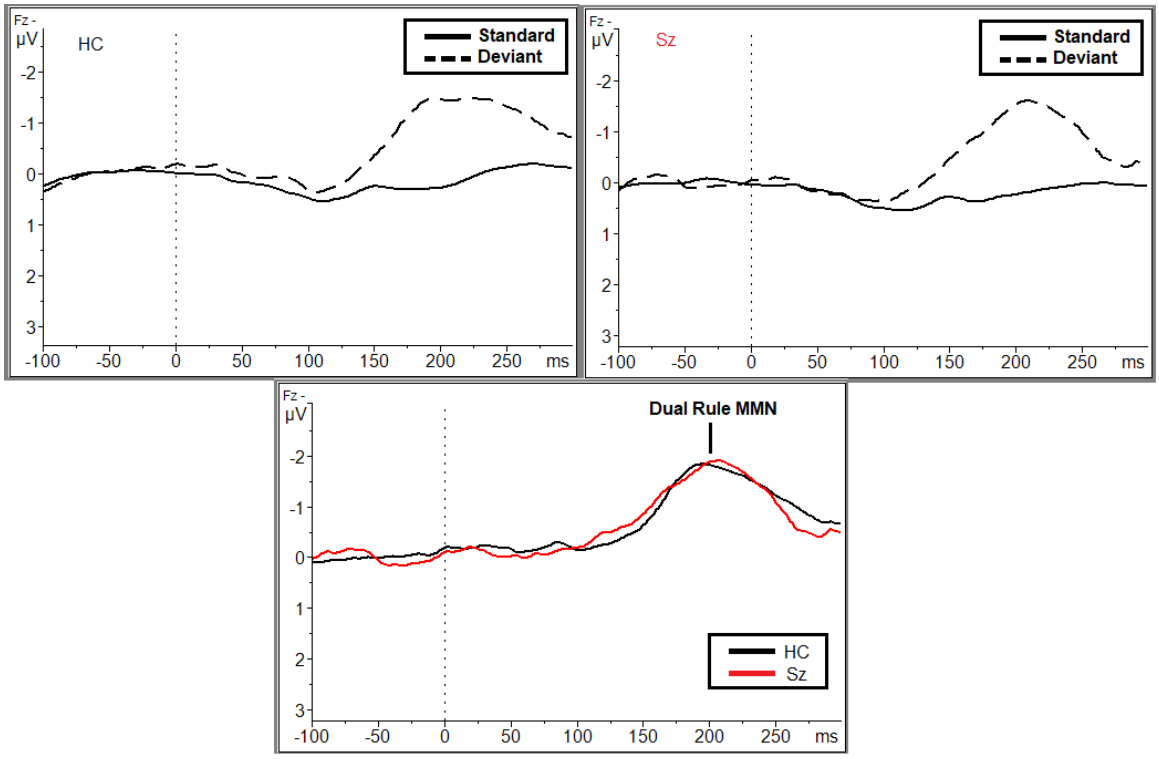
Note. The above figure demonstrates the average response of each group recorded while being presented with the standard tone (solid black line), and intensity deviant (dotted black line) independently, and the difference wave MMN compared between those with early phase psychosis (red solid line) and healthy controls (black solid line). Amplitudes are recorded from Fz and the MMN is marked with a line.

Figure 22. Group comparison of the MMN response to location deviants.



Note. The above figure demonstrates the average response of each group recorded while being presented with the standard tone (solid black line), and location deviant (dotted black line) independently, and the difference wave MMN compared between those with early phase psychosis (red solid line) and healthy controls (black solid line). Amplitudes are recorded from Fz and the MMN is marked with a line.

Figure 23. Group comparison of the MMN response to dual rule deviants.



Note. The above figure demonstrates the average response of each group recorded while being presented with the standard tone (solid black line) and dual rule deviant (dotted black line) independently, and the difference wave MMN compared between those with early phase psychosis (red solid line) and healthy controls (black solid line). Amplitudes are recorded from Fz, and the MMN is marked with a line.

Table 4. Means and results of ANOVA testing MMN response to difference deviant types across parameters.

Deviant Tone Type	EPP *M* (SD)	HC *M* (SD)	*p*	*F*	*Cohen's d*	95% CI (lower, upper)	Mean Difference
Duration	-0.58 (0.16)	-0.80 (0.14)	0.37	0.84	0.3	-0.71, 0.27	-.22
Pitch	-0.42 (0.13)	-0.75 (0.11)	0.11	2.68	0.53	-0.73, 0.08	-.33
Gap	-0.45 (0.12)	-0.59 (0.11)	0.46	0.57	0.25	-0.52, 0.24	-.14
Location	-0.40 (0.11)	-0.45 (0.10)	0.8	0.06	0.09	-0.39, 0.31	-.05
Intensity	-0.44 (0.17)	-0.89 (0.15)	0.09	2.98	0.56	-0.99, 0.08	-.45
Dual Rule	-0.81 (0.16)	-0.90 (0.13)	0.71	0.14	0.13	-0.56, 0.39	-.09

4.3.2 Correlations

It is important to note that when interpreting correlations to a mismatch negativity amplitude, more positive integer values are associated with a lessened mismatch response associated with increases in the second variable (e.g., GAF scores) due to the nature of the negative inflection of the mismatch negativity, because of this, negative and positive correlations should not be equated to lessened and greater response respectively. Correlations that result in a "negative" relationship should be considered associated with a greater mismatch negativity, and those "positive" relationships should be interpreted as a reduced mismatch negativity response.

PSYRATS scores were significantly positively correlated with the latency of the MMN elicited from intensity deviants ($r = .42$, $p = .03$) and duration deviants ($r = .41$, p

= .03). SOPS General scores were significantly positively correlated with the MMN amplitude elicited from location deviants (r = .41, p = .03) and intensity deviants (r = .48, p = .01). SOPS General scores were also significantly positively correlated with the latency of the MMN elicited from intensity deviants (r = .42, p = .03). SOPS Positive Symptoms subscale scores were significantly positively correlated with MMN amplitude elicited from intensity deviants (r = .42, p = .-3). SOPS Negative Symptoms subscale was significantly positively correlated with MMN amplitude from location deviants (r = .44, p = .02) and intensity deviants (r = .51, p < .01). SOPS Negative Symptoms subscale was significantly positively correlated with latency of MMN from intensity deviants (r = .4, p = .04).

4.3.3 Post-Hoc Power Analysis

A post hoc power analysis was conducted using G*Power 3.1.9.7 (Faul et al., 2007) to evaluate the statistical power of the study for detecting the observed effect sizes across the different MMN deviant tones. The analysis revealed variability in the sensitivity of the tests. For the duration deviant, the power was 0.34 (β = 0.66), suggesting the analysis was underpowered, with a 66% likelihood of failing to detect a true effect if present. Similarly, the gap deviant exhibited low power at 0.25 (β = 0.75), reflecting a substantial likelihood of Type II error. The location deviant demonstrated particularly low power at 0.08 (β = 0.92), highlighting the difficulty in detecting effects with the current sample size for this condition. In contrast, the intensity deviant showed sufficient power at 0.83 (β = 0.17), exceeding the conventional 0.80 threshold and suggesting that the sample size was adequate for detecting the observed effect. The pitch deviant exhibited moderate power at 0.79 (β = 0.21), falling slightly below the conventional threshold, indicating that a larger

sample may be necessary to reliably detect similar effects. Lastly, the dual rule deviant had a power of 0.10 ($\beta = 0.90$), reflecting underpowering and a high likelihood of failing to detect true effects.

4.4 Discussion

This third study involved the investigation of potential candidates for the endophenotype of early-phase psychosis using MMN amplitudes in response to different deviant tones from MMN paradigms. The investigation focused on auditory change detection as a possible endophenotype and tested two separate paradigms probing different aspects of audiological processing. These two paradigms differ in both the expected auditory stimuli and the involved changes of aspects of the deviant stimulus. In the multi-feature paradigm, pitch, volume, perceived location, timing, and duration were altered relative to the standard expected stimuli. These all-targeted basic audiological processing of basic characteristics of stimuli. The second paradigm we probed was a novel dual rule paradigm, which increases the complexity of processing by using two simultaneously changing expectations for stimuli and infrequently presenting a stimulus that breaks both of the expected rules of shifting from left to right ear and high to low pitch. In our sample, those with schizophrenia displayed no statistically significant differences in MMN response to duration, pitch, location, intensity, and gap deviants of the optimal paradigm compared to healthy controls. There were similarly no statistically significant group differences in the MMN response to dual rule deviants between our early phase psychosis and healthy control participants. The relatively intact auditory processing implies that the neurological underpinnings of the illness of schizophrenia may not significantly impact attentional and inhibitory auditory processing at this stage of

illness. This is consistent with previous investigations that have found deficits in MMN response are less likely to be observed in the early phase of illness (Haigh et al., 2017; Umbircht & Krljes, 2005). It may also be that the effect of schizophrenia illness/symptomatology on auditory processing deficits may either be so small in the early phase that it is not feasibly detectable or that the reductions in MMN amplitudes observed in prior studies are a consequence of chronic symptomatology rather than their precursor. This would limit the utility of the MMN as a potential endophenotype as it would need symptoms to manifest for a longer duration or more intensity to be detectable. The dual rule paradigm also found no significant group differences between those in the early phase of schizophrenia and healthy controls. This may suggest that regardless of audiological processing complexity, there may not be deficits that are profound enough to be statistically detectable at the early phase of illness, despite deficits in MMN being robust in chronic illness (Haigh et al., 2017; Erickson et al., 2018).

We did observe correlations between MMN amplitude and psychosis symptoms, suggesting that the greater the psychosis symptoms, the greater the observed reduction in MMN amplitude. This may suggest that the MMN may be effective in serving as a biomarker for illness state and chronicity of symptomatology. It should be noted, however, that many in our patient sample were not experiencing hallucinations or aberrant audiological symptoms, and the reductions that would typically be observed in MMN may be more so related to the presence of other auditory processing aberrations like auditory hallucinations. It may be that those with more severe hallucination symptoms display a reduced MMN compared to our sample, even in the early phase. It is also possible that the reductions in MMN are more representative of auditory

hallucinations or other auditory processing deficits rather than the presence of schizophrenia. Previous groups have used NMDA receptor blockers that improved MMN reduction in chronic schizophrenia patients (Lavoie et al., 2008). This suggests that the MMN response may function more as a state marker of psychotic symptoms rather than a trait marker of illness vulnerability. This also limits the use of the MMN as a potential endophenotype but may facilitate its use as a marker of psychosis illness state or illness severity. It is also possible that there were confounds of the presence of antipsychotic medication as most of our patient sample were receiving antipsychotic medication, which may limit the breadth or intensity of observed psychosis symptoms sufficient to detect a neurological difference. Our sample also presented with only mild to moderate symptomatology. If an MMN reduction is only present at moderately severe symptom expression or above, then our sample would not have allowed us to capture the effect.

The observed correlations between mismatch negativity parameters and clinical symptom scales may provide insights into the neurophysiological underpinnings of early-phase psychosis. The hypothesis that positive correlations would be found between MMN amplitudes and clinical symptom measures appears to be supported, as the results suggest that as clinical symptoms intensify, MMN amplitudes tend to approach zero. The positive correlations between PSYRATS scores and MMN latency for intensity and duration deviants may indicate that higher levels of psychotic symptoms are associated with delayed or disrupted neural responses to auditory changes. These delays could reflect deficits in early auditory processing that contribute to the persistence of psychotic experiences. Similarly, positive correlations between SOPS General scores and MMN amplitude for location and intensity deviants, as well as with MMN latency for intensity

deviants, suggest that individuals with a broader range of symptoms in the early phase of schizophrenia may experience more pronounced deficits in auditory change detection. The positive correlations between SOPS Positive Symptoms and MMN amplitude for intensity deviants may reflect the role of impaired auditory processing in the manifestation of positive psychotic symptoms. Finally, the correlations between SOPS Negative Symptoms scores and MMN amplitude for location and intensity deviants, along with MMN latency for intensity deviants, may reflect reduced neural responses and prolonged latencies associated with sensory processing deficits in negative symptomatology.

These findings appear to align with previous research suggesting that reduced MMN amplitude is associated with greater symptom severity in schizophrenia (Light & Braff, 2005). Prior studies have suggested that MMN deficits may also reflect broader impairments in cognition and functioning. MMN attenuation has also been observed in individuals experiencing auditory hallucinations, which may reflect disruptions in auditory processing associated with specific symptom profiles (Fisher et al., 2008). However, the observed correlations with MMN latency in this study may provide additional insights, as research in this area has been less consistent. For instance, some studies have reported unclear relationships between MMN latency and clinical outcomes (Salisbury et al., 2007). The present findings, which demonstrate significant associations between MMN latency and symptom severity, could suggest that delayed neural responses may play a role in the clinical presentation of early-phase psychosis.

When considering the specificity of these findings to the early phase of schizophrenia, it is noteworthy that MMN deficits have been observed across different

stages of the disorder. However, group differences were not statistically significant in the present study, which may be attributed to being underpowered or the effect size being smaller in the early phase compared to later stages. It is also possible that MMN deficits increase over time, with more pronounced reductions in chronic schizophrenia. For example, research has suggested that MMN amplitude reductions are more severe in chronic patients than in those experiencing their first episode of schizophrenia, potentially reflecting progressive neural deterioration (Salisbury et al., 2002). Other studies have reported significant MMN impairments even in first-episode patients, indicating that such deficits may be present from the onset of the disorder (Atkinson et al., 2012). While these findings provide some support for the role of MMN in understanding schizophrenia, the current results do not provide strong evidence for conclusions about its utility as an endophenotype in the early phase. Future research with larger sample sizes and longitudinal designs may help parse apart the nuanced differences in MMN deficits across illness stages, shedding further light on its potential as a biomarker for schizophrenia.

This study has several limitations. First, the sample size was relatively modest. Therefore, these paradigms should be tested again in larger samples. The variability in statistical power across the MMN deviants highlights important considerations for interpreting the results of this study. The intensity deviant, with sufficient power (0.83), was well-positioned to detect the observed effect, suggesting that the findings related to this tone are more likely to be reliable. Similarly, the pitch deviant, with moderate power (0.79), approached the conventional threshold for adequate power, indicating that the results for this tone may still be meaningful, though a larger sample would provide

greater certainty. In contrast, the duration, gap, location, and dual rule deviants were notably underpowered, with power values ranging from 0.08 to 0.34. This low power increases the likelihood of Type II errors, meaning that true effects may have gone undetected. For example, the particularly low power for the location and dual rule deviants (0.08 and 0.10, respectively) suggests that any potential effects in these conditions would be difficult to detect with the current sample size.

The underpowered nature of the study for certain tones likely impacted the ability to detect significant effects, especially for conditions where smaller effect sizes might exist. Although other studies have used smaller sample sizes in their investigations, this limitation underscores the need for caution in interpreting null results, as they may reflect insufficient sensitivity rather than the absence of an underlying effect. Future studies with larger sample sizes are recommended to enhance the ability to detect effects across all deviants and to ensure the robustness and generalizability of the findings. Additionally, given the variability in power across tones, targeted designs that prioritize sufficient sample sizes for underpowered conditions could help clarify the nature of MMN abnormalities in early-phase psychosis.

The measure of psychosis symptoms in the early psychosis group is also a limitation. The SOPS was originally validated in a prodromal population and adapted from the PANSS to include a broader range of symptoms. This measure was chosen to facilitate future comparisons with a high-risk group, which will be collected as a later part of studies in this clinic. Therefore, caution should be exercised when interpreting our correlational analysis with this symptom scale. Lastly, we used self-reported, retrospective measures of cannabis and alcohol use, which may be prone to bias. A more

detailed measure of substance use would have provided more accurate information about substance use in this population. Also, our sample had relatively modest symptomatology, further investigations comparing those with more severe symptoms in early phases may from comparing with chronic symptoms to further determine if MMN reductions are more so related to illness state, than trait vulnerability for developing these symptoms.

Future research should focus on validating the dual-rule paradigm in larger samples of individuals with early psychosis and chronic schizophrenia. Expanding the use of the dual-rule MMN paradigm to include at-risk populations (both clinically and genetically) would help identify whether deficits exist in these groups. Follow-up time points would be necessary to categorize individuals into converters and non-converters, enabling an odds ratio analysis to assess whether the predictive power of the MMN response is superior to traditional methods based on prodromal symptoms alone. Additionally, multiple follow-up assessments could examine how the MMN response is influenced by factors such as antipsychotic treatment, changes in psychosis symptoms, and illness duration. This could lead to further exploration of the potential role of MMN alteration as a marker for treatment efficacy in this population.

Further use of the MMN as a marker of illness state may benefit the inclusion of studies investigating MMN response pre and post-treatment; pharmacological and TMS treatment may be good candidates to test possible alterations based on symptom state and their alleviation.

CHAPTER 7 GENERAL DISCUSSION

7.1 Overview of Dissertation

The three studies comprising this thesis were conducted to investigate potential candidates for endophenotypes of schizophrenia, specifically focusing on identifying abnormalities in auditory processing via MMN and DMN-based microstates in individuals experiencing early phase psychosis. The rationale behind pursuing endophenotyping in this population is rooted in the idea that endophenotypes are stable biomarkers that investigate the relationship between genetic predispositions and observable symptoms, offering a window into the early neurobiological changes that precede full illness manifestation. The identification of reliable endophenotypes, such as disruptions in resting-state microstates or auditory processing deficits, could significantly improve both the early diagnosis and intervention strategies for schizophrenia. Early identification is crucial, as timely intervention can influence the trajectory of the disorder and reduce the severity of long-term outcomes. Schizophrenia is a heterogeneous disorder with a wide range of symptoms that manifest differently across individuals, making it essential to identify biomarkers that can offer insights into the underlying neurophysiological mechanisms driving the illness. By focusing on early phase psychosis, these studies aim to uncover stable, heritable markers that may serve not only as diagnostic tools but also as targets for treatment and monitoring. The hope is that by identifying these neural markers early on, interventions could be developed that are more targeted and personalized, ultimately leading to better outcomes for individuals at risk of or currently experiencing psychosis.

7.2 Meta-Analysis of Microstates in Schizophrenia

The first study involved a meta-analysis of the current state of the existing literature in the field of EEG-derived microstates to identify global differences observed in processing states of the default mode network between those with schizophrenia and healthy controls. This meta-analysis sought to provide a comprehensive overview of microstate abnormalities in schizophrenia, consolidating findings across various studies to reveal consistent patterns. The meta-analysis identified a lengthened class C microstate and shortened class D. Alterations in microstate class C and D were the most consistently reported across studies, but differing microstate parameters were identified in the other classes. The reduced time spent in each individual microstate class may be representative of either dysfunctional processing involved in the spatial nodes of the default mode network and/or an increased difficulty in the switching of microstates. Both of these factors are likely working together to result in the manifestation of altered microstate parameters.

The lengthened microstate class C, which is associated with salience detection, suggests a tendency for hypoactivation in networks involved in error monitoring and cognitive control. In contrast, the reductions in microstate class D, associated with attentional processes, highlight potential deficits in the ability of individuals with schizophrenia to appropriately switch between brain states (Michel & Koenig, 2018). These disruptions in switching may reflect a more general inefficiency in the coordination of large-scale brain networks, particularly those that underlie default mode network function, which is crucial for internal thought and self-referential processing. However, it would be useful for future research to further investigate how much of the

processing in the underlying neuroanatomical underpinnings of the default mode network is dysfunctional and how much of that dysfunction arises from the inability to appropriately switch states, inhibiting previously activated areas, and exciting further processing pipelines. Since previous research has identified the underlying fMRI indexed spatial dynamics of the default mode network and its associated microstate classed. Using these microstate differences may further research areas of interest in relation to hypoactivation in class C areas like dorsal anterior cingulate and inferior frontal systems and potential hyperactivation of class D areas such as right lateralized dorsal and ventral frontal and parietal systems (Michel & Koenig, 2018; Rajkumar et al., 2021).

The results of the meta-analysis of Study 1 indicate that the alterations observed in microstate parameters and default mode network are robust across global samples. This evidence can be used for the advocacy of EEG-derived objective markers of deficits observed in processing innate in schizophrenia. The results of a meta-analysis indicate that these alterations in microstate parameters and DMN activity are consistent across global samples, reinforcing their reliability as biomarkers. These findings help advocate for the use of EEG-derived objective markers to detect and understand the deficits in cognitive processing inherent in schizophrenia. By leveraging microstate analysis, researchers and clinicians can identify subtle neural differences that are not visible through traditional diagnostic methods, thus providing a more detailed and accurate depiction of the disorder.

Using microstates as an endophenotype technique enhances our ability to dissect the neural substrates of schizophrenia. It allows for the identification of intermediate phenotypes that lie between the genetic predisposition and the overt clinical symptoms of

the disorder. This approach not only aids in early detection and more precise diagnosis but also opens avenues for personalized treatment strategies. For example, interventions could be tailored to target specific neural dysfunctions identified through microstate analysis, potentially improving therapeutic outcomes. Microstates provide a dynamic view of brain activity, capturing transient states that reflect underlying neural processes. In schizophrenia, deviations in these microstates can reveal abnormal brain function that corresponds with cognitive and symptomatic manifestations of the disorder. By examining the duration, occurrence, and transition probabilities of different microstate classes, researchers can map out the aberrant neural dynamics specific to schizophrenia. This detailed analysis can uncover how the brain's information processing differs in people with schizophrenia compared to healthy controls, offering insights into the cognitive deficits observed in schizophrenia.

Microstate analysis can highlight the neural impact of genetic and environmental risk factors for schizophrenia. By correlating specific microstate patterns with genetic markers or environmental exposures, researchers can pinpoint how these factors contribute to the development and progression of the disorder. This integrative approach can lead to the identification of biomarkers that are predictive of disease onset, enabling earlier and potentially more effective interventions. The utility of microstates extends to monitoring disease progression and treatment response. By tracking changes in microstate parameters over time, clinicians can be aided in their assessment of how schizophrenia evolves in an individual patient. This longitudinal perspective is invaluable for adjusting treatment plans to better manage symptoms and improve quality of life. Additionally, microstate analysis can be used to evaluate the efficacy of pharmacological

and non-pharmacological treatments, providing objective measures of how interventions impact brain function.

7.3 Microstates in Early Phase Psychosis

The second study built upon the findings from the meta-analysis, aiming to investigate the neural underpinnings of schizophrenia in a more focused, early-phase psychosis sample taking into consideration impacts of trauma and substance use. The study was driven by the need to validate microstate alterations observed in chronic schizophrenia in a group that was in the early stages of the illness, where early intervention is most crucial (Lehmann et al., 2005). One of the primary motivations behind this investigation was to understand whether EEG-derived microstate abnormalities, particularly in classes C and D, are present at the early phase of psychosis and could serve as early biomarkers for diagnosis and intervention. Additionally, the study aimed to determine if these microstate differences could serve as endophenotypes of schizophrenia, connecting genetic vulnerability to observed cognitive and perceptual disruptions in the disorder (Michel & Koenig, 2018).

The results of Study 2 confirmed the presence of significant alterations in microstate classes C and D in eyes-closed resting states in individuals with early phase psychosis. This aligns with previous research that has shown that microstate class C plays a role in aberrations of the salience network, which may contribute to the cognitive and perceptual distortions seen in schizophrenia, such as the misattribution of internal thoughts to external stimuli (Michel & Koenig, 2018; Rajkumar et al., 2021). On the other hand, the increased occurrence and coverage of microstate class D, which is associated with attentional processes, suggests a deficit in attention and switching states

while integrating external information with internal cognitive processes, a hallmark of disorganized thinking in schizophrenia (Lehmann et al., 2005; Northoff & Duncan, 2016). This may be due to processing difficulties inherent in microstate class D that prolong its duration.

The results of Study 2 confirmed significant alterations in microstate classes C and D in individuals with early-phase psychosis, with a reduced duration of microstate class C and increased occurrence and coverage of microstate class D. However, these findings somewhat contrast with the results of our meta-analysis, which identified an increased duration of microstate class C, along with a reduced duration and occurrence of microstate class D among individuals with schizophrenia. This discrepancy may reflect changes in microstate dynamics across the duration of illness or other factors, such as differences in cognitive demands, sex differences, substance use, traumatic history, or symptom severity.

Research suggests that microstate patterns can vary based on illness stage, with early-phase psychosis potentially displaying unique microstate alterations compared to chronic cases. For example, early-phase studies have shown that microstate D may have heightened involvement in attentional processes due to increased demands on cognitive control networks, which could extend its duration in the early stages (Pei et al., 2024). In contrast, microstate C, typically associated with salience network activation (Michel & Koenig, 2018; Rajkumar et al., 2021), might be less activated in its disruption in early phase which may change as the illness progresses and symptoms persist.

This variation aligns with findings that early-phase psychosis often shows transient patterns of neural instability that stabilize or differ in chronic stages (Perrottelli

et al., 2021). Another study suggests that microstate D may serve as a biomarker for abnormal brain state transitions in schizophrenia, with reduced fronto-occipital activity potentially affecting attentional and perceptual integration processes across the illness course (Yan et al., 2024). Additionally, heterogeneity in microstate findings across studies underscores the need for further research exploring symptom-specific or illness-phase-specific effects, which may clarify these inconsistencies and better inform clinical interventions tailored to different schizophrenia stages and help elucidate the potential for microstate differences as either endophenotype or biomarker of different phases.

What is particularly significant about these findings is that they mirror the classes identified as having alterations in microstate dynamics observed in chronic schizophrenia, supporting the hypothesis that these changes are not merely a byproduct of the illness's progression but are intrinsic to its pathophysiology (Lehmann et al., 2005; Michel & Koenig, 2018), although they may change as the illness progresses. This reinforces the potential of microstates, particularly classes C and D, as early markers or endophenotypes of schizophrenia, which could be useful in detecting the disorder before more overt symptoms emerge (Kindler et al., 2011), however as their alterations change across the course of the illness more research is needed to determine their eligibility as a potential endophenotype.

Across the first two studies, the dynamics of microstates in schizophrenia reveal a complex and non-linear pattern of engagement, particularly for microstates C and D,. The consistent finding of disrupted processing with microstates C and D, seen across both studies, reinforces the understanding of attentional and salience impairments as a core feature of schizophrenia. This aligns with broader theories of cognitive dysfunction in the

disorder, where attentional control is frequently compromised. However, the discrepancies between microstate C and D across studies highlight the variability in attention and cognitive processing in schizophrenia as the illness progresses. While Study 1 demonstrated a reduction in microstate D engagement, Study 2 found increased coverage, and occurrence in the same microstate. These differences could reflect context-specific alterations in brain dynamics, such as the effects of resting-state conditions or clinical stage differences. Overall, these findings suggest that while certain microstates, like C and D, show consistent disruption in schizophrenia. Understanding these nuanced microstate dynamics could inform future research and therapeutic approaches, helping to better target the specific neural mechanisms contributing to the cognitive and perceptual disturbances observed in schizophrenia.

Another key contribution of this study was the elucidation of the impact of confounding factors, such as trauma and substance use, which are prevalent in individuals with early-phase psychosis. The findings highlighted the importance of accounting for these factors when investigating microstate abnormalities, as both trauma and substance use have been shown to independently affect brain function and may exacerbate or mask the neurophysiological disruptions specific to schizophrenia (Rundell et al., 2018). This underscores the complexity of identifying endophenotypes in a disorder as heterogeneous as schizophrenia, where multiple factors interact to influence brain function (Giordano et al., 2018).

In terms of its contribution to the broader thesis, Study 2 plays a role in demonstrating that the microstate abnormalities observed in chronic schizophrenia are generally present from the earliest stages of the illness. This finding has potential

implications for supplementing early diagnosis and intervention, as it suggests that microstate analysis could be used as part of a diagnostic toolkit to identify biomarkers of individuals at high risk for schizophrenia before the onset of acute psychosis (Michel & Koenig, 2018). By providing evidence that microstate class C and D abnormalities are present in early-phase psychosis, this study supports the potential utility of these markers as potential endophenotypes, which could be used to track illness progression and treatment response (Michel & Koenig, 2018; Lehmann et al., 2005). However, future research should work to identify if these patterns exist with those who are unaffected by symptoms and in unaffected family members of those with schizophrenia to determine the state independence and heritability criteria of endophenotypes or use as biomarkers.

The limitations of this study, as with any study involving early-phase psychosis populations, include the difficulty of disentangling microstate alterations specific to schizophrenia from those influenced by co-occurring factors, such as trauma, sex differences, or substance use. Given the high prevalence of these factors in early-phase psychosis, future studies would benefit from more detailed assessments of how these variables interact with the neurophysiological changes observed in schizophrenia (Rundell et al., 2018). Additionally, the relatively small sample size may have limited the ability to detect more subtle differences in microstate dynamics, particularly in classes A and B, and larger studies are needed to confirm these findings.

Overall, the results of Study 2 provide evidence for the presence of microstate abnormalities in early-phase psychosis and contribute to the growing body of literature supporting the use of EEG-derived microstates as endophenotypes for the disorder. When taken as part of the broader thesis, this study strengthens the argument for using

microstates to understand the neurophysiological disruptions that underlie schizophrenia, offering a pathway toward earlier and more accurate diagnosis, as well as more personalized treatment approaches.

7.4 Mismatch Negativity as an Endophenotype

Study 3 involved the analysis of auditory processing using mismatch negativity (MMN) paradigms, which probed basic and complex acoustic characteristics, including dual simultaneous streams of auditory changes. The results revealed no statistically significant differences in MMN responses between early-phase psychosis participants and healthy controls across both paradigms. These findings suggest that MMN deficits may not be detectable in the early stages of schizophrenia, aligning with previous research indicating that such deficits are more apparent in the chronic stages of the illness (Näätänen & Kähkönen, 2009; Salisbury et al., 2007). However, while no group differences were found, correlations between MMN amplitudes and psychosis symptoms were observed. This suggests that MMN may serve as a biomarker for the state severity and chronicity of psychotic symptoms rather than as an indicator of vulnerability to schizophrenia.

The lack of significant findings challenges the utility of MMN as an endophenotype for schizophrenia in the early phases of illness. While MMN reductions have been robustly documented in chronic schizophrenia, the subtlety of changes in early psychosis may limit its effectiveness as a diagnostic tool at this stage. Previous research has shown that MMN reductions are associated with greater cortical damage and reduced grey matter in regions such as the temporal and frontal cortices (Kasai et al., 2003; Salisbury et al., 2007). In our study, the relatively mild symptomatology and small

sample size may have contributed to the absence of detectable group differences in MMN responses. Larger studies with more severely affected early-phase participants may better capture these subtle neurophysiological changes.

Furthermore, the dual-rule paradigm, which introduced greater complexity in auditory processing by incorporating two simultaneous rules, also failed to show significant differences between early-phase psychosis and healthy controls. This may suggest that even with more complex auditory stimuli, early-phase psychosis is not characterized by profound deficits in MMN responses. The use of antipsychotic medications in our sample may also have contributed to these null findings, as these medications can modulate symptom severity and potentially limit the detection of neurological differences. Future studies with medication-naïve participants or comparisons across different medication regimens could help clarify the role of MMN in early-phase psychosis.

In light of the findings discussed throughout the thesis, it becomes apparent that EEG-derived microstates and mismatch negativity (MMN) provide distinct insights into different stages and aspects of schizophrenia. While MMN has long been considered a potential biomarker of sensory processing deficits and psychosis-related hallucinations, the data from our early-phase psychosis sample suggest that its sensitivity to detecting vulnerabilities in the pre-psychosis phase may be limited. In contrast, microstate analysis, particularly within the resting-state default mode network (DMN), has proven to be a more promising indicator of early vulnerability to schizophrenia.

Previous studies have demonstrated that MMN deficits are closely tied to illness chronicity and the severity of psychotic symptoms, particularly in auditory processing

(Näätänen et al., 2014). However, in early psychosis, these deficits were not as pronounced in our sample, which aligns with earlier research suggesting that MMN reductions are more consistently observed in later stages of the illness, especially when psychosis symptoms like hallucinations are more severe (Salisbury et al., 2012). This supports the theory that MMN may be more reflective of illness state rather than vulnerability to schizophrenia. The presence of hallucinations, particularly auditory ones, has been strongly associated with decreased MMN amplitude, which may explain the lack of significant findings in our early-phase participants, who exhibited milder symptoms compared to chronic schizophrenia samples (Javitt et al., 1996).

On the other hand, the alterations in microstates were observed even in our early psychosis sample. These findings align with a growing body of research highlighting the sensitivity of resting-state brain activity, particularly within the DMN, to early disruptions in schizophrenia (Michel & Koenig, 2018). These microstate alterations are thought to reflect broader disruptions in brain network connectivity and integration, which are present even before the full onset of clinical symptoms. This makes microstates a potential candidate for an endophenotype of schizophrenia, as they appear to capture the neurobiological vulnerability to developing the disorder in the early stages compared to MMN. However, further research is necessary to confirm these alterations in those without symptoms and unaffected relatives of those with schizophrenia to provide evidence for other endophenotype criteria of state independence and heritability.

The lack of significant MMN differences in our early psychosis sample suggests that MMN might serve better as a marker of illness severity, particularly in patients with more pronounced sensory processing abnormalities like hallucinations (Fisher et al.,

2018). This is consistent with findings that MMN reductions are tied to cortical thinning and grey matter loss in the temporal and frontal lobes, which become more pronounced as the illness progresses (Rasser et al., 2011). In contrast, microstates, particularly those associated with the DMN, may represent a more state-independent marker of underlying neurophysiological vulnerability to schizophrenia, given their presence even in individuals with less severe symptoms and at earlier stages of the illness.

These observations suggest that while MMN remains a valuable tool for understanding the sensory and cognitive deficits associated with chronic schizophrenia, its utility as an endophenotype for early diagnosis may be limited. Microstate analysis, particularly within resting-state networks like the DMN, may provide a more sensitive and stable marker for identifying individuals at high risk of developing schizophrenia before more overt symptoms, such as hallucinations, manifest. This distinction is crucial for refining our approach to early diagnosis and intervention in schizophrenia, as it underscores the need for multidimensional biomarkers that capture both the early vulnerability (as indexed by microstate alterations) and the later symptomatology (as indexed by MMN deficits) of the disorder.

7.5 Limitations and Implications for Future Research

Given the limitations observed in using MMN as an endophenotype in early-phase psychosis, other methods may offer more promise in identifying early biomarkers of the illness or to provide greater nuance in the underpinnings of the robust MMN findings. For example, differences in EEG microstates and alterations in the DMN have shown potential as markers of early-phase psychosis and may be more effective at capturing subtle neurophysiological disruptions. Microstate abnormalities, particularly in

the resting state, have been implicated in early-phase psychosis and could serve as a more sensitive tool for identifying endophenotypes. Similarly, disruptions in the DMN, which is involved in self-referential and internal thought processes, may provide insights into the early neurocognitive changes associated with schizophrenia.

A key limitation of the studies in the thesis was the modest sample size, particularly among early-phase participants, which reduced the statistical power necessary to detect subtle MMN differences. The relatively mild symptom severity in our sample could also explain the lack of significant findings, as more severe cases of early psychosis may exhibit more pronounced MMN deficits. Additionally, the self-reported retrospective measures of substance use (cannabis and alcohol) in our study are prone to bias and could have affected our results. A more detailed and objective assessment of substance use would provide a clearer understanding of how these factors interact with MMN responses.

Moreover, the use of antipsychotic medications in most participants poses a potential confound. These medications can alter neurophysiological responses, possibly masking the MMN reductions typically seen in schizophrenia. Antipsychotic medications are known to influence neurophysiological responses, which can affect measurements of mismatch negativity (MMN) and EEG microstates in individuals with schizophrenia. For instance, Kiang et al. (2009) observed that antipsychotic treatment can modulate MMN amplitudes, potentially masking the reductions typically observed in untreated schizophrenia patients. Specifically, they found that medicated individuals showed less pronounced MMN abnormalities compared to unmedicated patients, suggesting that dopamine modulation might normalize some aspects of auditory processing deficits. In

the context of EEG microstates, Kikuchi et al. (2007) demonstrated that antipsychotic medications can significantly alter the temporal dynamics of microstates. Their study found that medicated patients exhibited longer durations and altered occurrence patterns of certain microstate classes (e.g., Classes C and D) compared to unmedicated patients. These changes suggest that antipsychotics might stabilize neural network activity, potentially impacting the detection of the typical microstate abnormalities associated with schizophrenia, such as increased duration or altered transitions. The potential effects of antipsychotic medications on MMN and EEG microstates should be considered when interpreting the results of this study. Medicated participants may exhibit stabilized microstate dynamics or normalized MMN amplitudes, which could potentially mask the extent of neurophysiological deficits commonly associated with schizophrenia. This might lead to underestimations of group differences or the severity of neural dysfunction. Additionally, variability in medication status across participants could introduce confounding effects, particularly in group comparisons. Including medication status as a covariate or conducting subgroup analyses could help clarify the influence of antipsychotics on the observed neural activity. These considerations may be important for accurately contextualizing the findings within the broader framework of schizophrenia research. Future research should investigate MMN responses in medication-naïve populations or stratify participants based on their medication status to disentangle the effects of the illness from those of the treatment.

Our observations in Chapters 4 and 6 suggest future research should focus on larger sample sizes and include participants with more severe early-phase symptoms to better understand whether MMN reductions are more pronounced at greater levels of

symptomatology. Microstate parameters may also serve as a better endophenotype and benchmark for vulnerability to developing the illness rather than the illness state observed in the MMN. Further testing on the observed alterations in at-rest DMN function in clinical or genetic high-risk populations at risk for developing schizophrenia may further bolster the use of at-rest microstate parameters as an endophenotype.

Integrating MMN and microstate analysis with other imaging modalities, such as fMRI and MRS, could provide deeper insights into the neurochemical and functional disruptions associated with early-phase psychosis. For instance, combining MMN paradigms with resting-state fMRI could allow researchers to examine how disruptions in the DMN or other networks interact with auditory processing deficits. Similarly, MRS could be used to measure glutamate levels in temporal and frontal regions, helping to clarify whether MMN reductions are related to NMDA receptor dysfunction, as has been suggested in previous research.

7.7 General Conclusions

Throughout this thesis, the alterations observed in microstate classes in schizophrenia suggest a more nuanced understanding than previously thought. Traditionally, differences in microstate classes C and D have been well-documented and replicated in our experimentation. This suggests that they may be components of illness presence, which are abnormal across different stages of schizophrenia. Additionally, there are more nuanced components that may evolve as the disorder progresses and becomes more chronic or severe.

The changes like those found in class C and D, which might be detectable irrespective of the illness stage, could serve as potential biomarkers for the identification

and diagnosis of schizophrenia, while MMN responses may be more impacted by change as the disease develops. This nuance might offer valuable insights into the progression of schizophrenia and the effectiveness of treatments over time. By recognizing both the stable and evolving aspects of microstate alterations, we can improve the precision of diagnostic tools and develop more targeted therapeutic interventions. This dual approach enhances our ability to identify schizophrenia early and monitor its progression, ultimately leading to better patient outcomes. When considering the criteria of endophenotype candidates, microstates address many of the criteria:

Association with the disease: Abnormalities in microstate class C and D dynamics have been associated with schizophrenia.

Association in Relatives: There has also been observed microstate differences in relatives and siblings of individuals with schizophrenia.

State independence: Those in the early phase of illness display similar abnormalities in microstates as those with chronic schizophrenia. This indicates that microstate abnormalities may be underpinning schizophrenia, however, they may change as the illness progresses.

Practicality: Resting state EEG is easily recorded within a 5-minute recording session, and as little as 19 electrodes can be used for microstate analyses.

Explicability: The abnormal microstate dynamics in schizophrenia are conceptualized as an imbalance between processes that determine saliency (microstate class C), and processes that inhibit and integrate contextual information (microstate class D), are impacted in schizophrenia.

Heritability: Although the research investigating the heritability of altered microstate dynamics is scant, there have been significant associations between altered microstate temporal dynamics and relatives of those with schizophrenia (da Cruz et al., 2020), future research could also potentially investigate heritability. However, further research into unaffected relatives of those with schizophrenia may be needed to determine heritability and state independence criteria of endophenotypes.

Results across all studies give credence to the use of EEG-derived endophenotypes of schizophrenia and potential objective biological markers for monitoring illness severity and treatment monitoring. The abnormalities in default mode network activation may be used to identify those at risk of entering the early phase of psychosis, and MMN may be useful in tracking the dysfunctional processing involved in the presence of clinical symptoms. These properties can be useful in the provision of diagnoses, other psychiatric conditions elicit different alterations to microstate and mismatch parameters than those with schizophrenia do. This can be used as a diagnostic supplement when the diagnosis is unclear or if there are disagreements about potential diagnoses. Resting and mismatch negativity paradigms are feasible short protocols of EEG data collection in comparison to diagnostic interviewing and other brain imaging modalities. Future investigations could improve upon the field by identifying more nuanced differences in processing while eyes are open compared to closed while at rest and the proportionate impact of trauma, substance use, schizophrenia symptoms, and general functioning on the alterations in processing observed in this population. A more nuanced understanding of the spatial dynamics of the resting state under differing

conditions and which are optimal in the evocation of endophenotypes would benefit the effectiveness of the identified potential endophenotype candidates in practice.

References

Adams, R. A., Pinotsis, D., Tsirlis, K., Unruh, L., Mahajan, A., Horas, A. M., ... & Anticevic, A. (2022). Computational modelling of electroencephalography and functional magnetic resonance imaging paradigms indicates a consistent loss of pyramidal cell synaptic gain in schizophrenia. *Biological psychiatry*, *91*(2), 202-215.

Addington, J., Saeedi, H., & Addington, D. (2005). The course of cognitive functioning in first episode psychosis: changes over time and impact on outcome. *Schizophrenia research*, *78*(1), 35-43.

Andreou, C., Faber, P. L., Leicht, G., Schoettle, D., Polomac, N., Hanganu-Opatz, I. L., ... & Mulert, C. (2014). Resting-state connectivity in the prodromal phase of schizophrenia: insights from EEG microstates. *Schizophrenia research*, *152*(2-3), 513-520.

Atkinson, R. J., Michie, P. T., & Schall, U. (2012). Duration mismatch negativity and P3a in first-episode psychosis and individuals at ultra-high risk of psychosis. *Biological psychiatry*, *71*(2), 98-104.

Baradits, M., Bitter, I., & Czobor, P. (2020). Multivariate patterns of EEG microstate parameters and their role in the discrimination of patients with schizophrenia from healthy controls. *Psychiatry research*, *288*, 112938.

Barber, L., Reniers, R., & Upthegrove, R. (2021). A review of functional and structural neuroimaging studies to investigate the inner speech model of auditory verbal hallucinations in schizophrenia. *Translational psychiatry*, *11*(1), 582.

Blessing, E. M., Murty, V. P., Zeng, B., Wang, J., Davachi, L., & Goff, D. C. (2020). Anterior hippocampal–cortical functional connectivity distinguishes antipsychotic naïve first-episode psychosis patients from controls and may predict response to second-generation antipsychotic treatment. *Schizophrenia Bulletin*, *46*(3), 680-689.

Britz, J., Van De Ville, D., & Michel, C. M. (2010). BOLD correlates of EEG topography reveal rapid resting-state network dynamics. *Neuroimage*, *52*(4), 1162-1170.

Brunelin, J., Mondino, M., Gassab, L., Haesebaert, F., Gaha, L., Suaud-Chagny, M. F., ... & Poulet, E. (2012). Examining transcranial direct-current stimulation (tDCS) as a treatment for hallucinations in schizophrenia. *American Journal of Psychiatry*, *169*(7), 719-724.

Chai, X. J., Whitfield-Gabrieli, S., Shinn, A. K., Gabrieli, J. D., Nieto Castañón, A., McCarthy, J. M., ... & Öngür, D. (2011). Abnormal medial prefrontal cortex resting-state connectivity in bipolar disorder and schizophrenia. *Neuropsychopharmacology*, *36*(10), 2009-2017.

Charlson, F. J., Ferrari, A. J., Santomauro, D. F., Diminic, S., Stockings, E., Scott, J. G., ... & Whiteford, H. A. (2018). Global epidemiology and burden of schizophrenia: findings from the global burden of disease study 2016. *Schizophrenia bulletin*, *44*(6), 1195-1203.

Chen, Y. H., Edgar, J. C., Huang, M., Hunter, M. A., Epstein, E., Howell, B., ... & Cañive, J. M. (2013). Frontal and superior temporal auditory processing abnormalities in schizophrenia. *NeuroImage: Clinical*, *2*, 695-702.

Correa-Ghisays, P., Sánchez-Ortí, J. V., Balanzá-Martínez, V., Fuentes-Durá, I., Martinez-Aran, A., Ruiz-Bolo, L., ... & Tabarés-Seisdedos, R. (2022). MICEmi: A method to identify cognitive endophenotypes of mental illnesses. *European Psychiatry*, *65*(1), e85.

da Cruz, J. R., Favrod, O., Roinishvili, M., Chkonia, E., Brand, A., Mohr, C., ... & Herzog, M. H. (2020). EEG microstates are a candidate endophenotype for schizophrenia. *Nature communications*, *11*(1), 3089.

Curic, S., Leicht, G., Thiebes, S., Andreou, C., Polomac, N., Eichler, I. C., ... & Mulert, C. (2019). Reduced auditory evoked gamma-band response and schizophrenia-like clinical symptoms under subanesthetic ketamine. *Neuropsychopharmacology*, *44*(7), 1239-1246.

Deng, M., Liu, Z., Shen, Y., Cao, H., Zhang, M., Xi, C., ... & Pu, W. (2022). Treatment effect of long-term antipsychotics on default-mode network dysfunction in drug-naïve patients with first-episode schizophrenia: a longitudinal study. *Frontiers in Pharmacology*, *13*, 833518.

Deouell, L. Y. (2007). The frontal generator of the mismatch negativity revisited. *Journal of Psychophysiology*, *21*(3-4), 188-203.

Del Fabro, L., Schmidt, A., Fortea, L., Delvecchio, G., D'Agostino, A., Radua, J., ... & Brambilla, P. (2021). Functional brain network dysfunctions in subjects at high-risk for psychosis: a meta-analysis of resting-state functional connectivity. *Neuroscience & Biobehavioral Reviews*, *128*, 90-101.

Dondé, C., Kantrowitz, J. T., Medalia, A., Saperstein, A. M., Balla, A., Sehatpour, P., ... & Javitt, D. C. (2023). Early auditory processing dysfunction in schizophrenia: Mechanisms and implications. *Neuroscience & Biobehavioral Reviews*, 105098.

Drake, R., Haddock, G., Tarrier, N., Bentall, R., & Lewis, S. (2007). The Psychotic Symptom Rating Scales (PSYRATS): their usefulness and properties in first episode psychosis. *Schizophrenia research*, *89*(1-3), 119-122.

D'Souza, D. C., Perry, E., MacDougall, L., Ammerman, Y., Cooper, T., Wu, Y. T., ... & Krystal, J. H. (2004). The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology*, *29*(8), 1558-1572.

Eichenbaum, H. (2017). Prefrontal–hippocampal interactions in episodic memory. *Nature Reviews Neuroscience*, *18*(9), 547-558.

Fan, F., Liao, X., Lei, T., Zhao, T., Xia, M., Men, W., ... & He, Y. (2021). Development of the default-mode network during childhood and adolescence: a longitudinal resting-state fMRI study. *NeuroImage*, *226*, 117581.

Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior research methods*, *39*(2), 175-191.

Fitzgerald, K., & Todd, J. (2020). Making sense of mismatch negativity. *Frontiers in psychiatry*, *11*, 468.

Fisher, D. J., Labelle, A., & Knott, V. J. (2008). The right profile: mismatch negativity in schizophrenia with and without auditory hallucinations as measured by a multi-feature paradigm. *Clinical neurophysiology*, *119*(4), 909-921.

Fisher, D. J., Campbell, D. J., Abriel, S. C., Ells, E. M., Rudolph, E. D., & Tibbo, P. G. (2018). Auditory mismatch negativity and P300a elicited by the "optimal" multi-feature paradigm in early schizophrenia. *Clinical EEG and Neuroscience*, *49*(4), 238-247.

Fisher, D. J., Rudolph, E. D., Ells, E. M., Knott, V. J., Labelle, A., & Tibbo, P. G. (2019). Mismatch negativity-indexed auditory change detection of speech sounds in early and chronic schizophrenia. *Psychiatry Research: Neuroimaging*, *287*, 1-9.

Flückiger, R., Michel, C., Grant, P., Ruhrmann, S., Vogeley, K., Hubl, D., ... & Schultze-Lutter, F. (2019). The interrelationship between schizotypy, clinical high risk for psychosis and related symptoms: Cognitive disturbances matter. *Schizophrenia Research*, *210*, 188-196.

Francis, A. M., Knott, V. J., Labelle, A., & Fisher, D. J. (2020). Interaction of background noise and auditory hallucinations on phonemic mismatch negativity (MMN) and P3a processing in schizophrenia. *Frontiers in Psychiatry*, *11*, 540738.

Ford, J. M., & Mathalon, D. H. (2005). Corollary discharge dysfunction in schizophrenia: can it explain auditory hallucinations? *International Journal of Psychophysiology*, *58*(2-3), 179-189.

Fovet, T., Yger, P., Lopes, R., de Pierrefeu, A., Duchesnay, E., Houenou, J., ... & Jardri, R. (2022). Decoding activity in Broca's Area predicts the occurrence of auditory hallucinations across subjects. *Biological psychiatry*, *91*(2), 194-201.

Fusar-Poli, P., Smieskova, R., Kempton, M. J., Ho, B. C., Andreasen, N. C., & Borgwardt, S. (2013). Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. *Neuroscience & Biobehavioral Reviews*, *37*(8), 1680-1691.

Garety, P. A., Kuipers, E., Fowler, D., Freeman, D., & Bebbington, P. E. (2001). A cognitive model of the positive symptoms of psychosis. *Psychological medicine*, *31*(2), 189-195.

Garrity, A. G., Pearlson, G. D., McKiernan, K., Lloyd, D., Kiehl, K. A., & Calhoun, V. D. (2007). Aberrant "default mode" functional connectivity in schizophrenia. *American journal of psychiatry*, *164*(3), 450-457.

Guloksuz S, van Os J. The slow death of the concept of schizophrenia and the painful birth of the psychosis spectrum. *Psychological Medicine*. 2018;48(2):229-244. doi:10.1017/S0033291717001775

Giordano, G. M., Koenig, T., Mucci, A., Vignapiano, A., Amodio, A., Di Lorenzo, G., ... & Maj, M. (2018). Neurophysiological correlates of Avolition-apathy in schizophrenia: A resting-EEG microstates study. *NeuroImage: Clinical*, *20*, 627-636.

Goswami, S., Mattoo, S. K., Basu, D., & Singh, G. (2004). Substance-abusing schizophrenics: do they self-medicate? *American Journal on Addictions*, *13*(2), 139-150.

Gottesman, I. I., & Shields, J. (1972). Schizophrenia and genetics. A twin study vantage point. In *Acad. Press, New York, NY*.

Gottesman, I. I., & Gould, T. D. (2003). The endophenotype concept in psychiatry: etymology and strategic intentions. *American journal of psychiatry*, *160*(4), 636-645.

Haddock, G., McCarron, J., Tarrier, N., & Faragher, E. B. (1999). Scales to measure dimensions of hallucinations and delusions: the psychotic symptom rating scales (PSYRATS). *Psychological medicine*, *29*(4), 879-889.

Hall, R. (1995). Global Assessment of Functioning. *Psychosomatics*. 1995;36(3):267-275. doi:10.1016/S0033-3182(95)71666-8

Healy, C., & Cannon, M. (2020). Psychotic-like experiences in the general population. In *Risk factors for psychosis* (pp. 119-141). Academic Press.

Hernandez, L., Rieger, K., Baenninger, A., Brandeis, D., & Koenig, T. (2016). Towards using microstate-neurofeedback for the treatment of psychotic symptoms in schizophrenia. A feasibility study in healthy participants. *Brain topography*, *29*, 308-321.

Hirayasu, Y., Asato, N., Ohta, H., Hokama, H., Arakaki, H., & Ogura, C. (1998). Abnormalities of auditory event-related potentials in schizophrenia prior to treatment. *Biological Psychiatry*, *43*(4), 244-253.

Hor K, Taylor M. Suicide and schizophrenia: a systematic review of rates and risk factors. J Psychopharmacol. 2010 Nov;24(4 Suppl):81-90. doi: 10.1177/1359786810385490. PMID: 20923923; PMCID: PMC2951591.

Hu, M. L., Zong, X. F., Mann, J. J., Zheng, J. J., Liao, Y. H., Li, Z. C., ... & Tang, J. S. (2017). A review of the functional and anatomical default mode network in schizophrenia. *Neuroscience bulletin*, *33*, 73-84.

Huang, J., Zhuo, C., Xu, Y., & Lin, X. (2019). Auditory verbal hallucination and the auditory network: From molecules to connectivity. *Neuroscience*, *410*, 59-67.

Hwang, M., Roh, Y. S., Talero, J., Cohen, B. M., Baker, J. T., Brady, R. O., ... & Shinn, A. K. (2021). Auditory hallucinations across the psychosis spectrum: Evidence of dysconnectivity involving cerebellar and temporal lobe regions. *NeuroImage: Clinical*, *32*, 102893.

Insel, T. R. (2010). Rethinking schizophrenia. *Nature*, *468*(7321), 187-193.

Jardri, R., Pins, D., Bubrovszky, M., Lucas, B., Lethuc, V., Delmaire, C., ... & Thomas, P. (2009). Neural functional organization of hallucinations in schizophrenia: multisensory dissolution of pathological emergence in consciousness. *Consciousness and cognition*, *18*(2), 449-457.

Jardri, R., Pouchet, A., Pins, D., & Thomas, P. (2011). Cortical activations during auditory verbal hallucinations in schizophrenia: a coordinate-based meta-analysis. *American Journal of Psychiatry*, *168*(1), 73-81.

Jardri, R., Hugdahl, K., Hughes, M., Brunelin, J., Waters, F., Alderson-Day, B., ... & Denève, S. (2016). Are hallucinations due to an imbalance between excitatory and inhibitory influences on the brain? *Schizophrenia bulletin*, *42*(5), 1124-1134.

Johns, L. C. (2005). Hallucinations in the general population. *Current psychiatry reports*, *7*(3), 162-167.

Jones, S. R., & Fernyhough, C. (2007). Thought as action: Inner speech, self-monitoring, and auditory verbal hallucinations. *Consciousness and cognition*, *16*(2), 391-399.

Kasai, K., Shenton, M. E., Salisbury, D. F., Hirayasu, Y., Lee, C. U., Ciszewski, A. A., ... & McCarley, R. W. (2003). Progressive decrease of left superior temporal gyrus gray matter volume in patients with first-episode schizophrenia. *American Journal of Psychiatry*, *160*(1), 156-164.

Kiang, Michael, David L. Braff, Joyce Sprock, and Gregory A. Light. "The relationship between preattentive sensory processing deficits and age in schizophrenia patients." *Clinical Neurophysiology* 120, no. 11 (2009): 1949-1957.

Kikuchi, M., Koenig, T., Wada, Y., Higashima, M., Koshino, Y., Strik, W., & Dierks, T. (2007). Native EEG and treatment effects in neuroleptic-naive schizophrenic patients: time and frequency domain approaches. *Schizophrenia research*, *97*(1-3), 163-172

Krause, L., Enticott, P. G., Zangen, A., & Fitzgerald, P. B. (2012). The role of medial prefrontal cortex in theory of mind: a deep rTMS study. *Behavioural brain research*, *228*(1), 87-90.

Kelleher, I., Keeley, H., Corcoran, P., Lynch, F., Fitzpatrick, C., Devlin, N., ... & Cannon, M. (2012). Clinicopathological significance of psychotic experiences in non-psychotic young people: evidence from four population-based studies. *The British Journal of Psychiatry*, *201*(1), 26-32.

Kikuchi, M., Koenig, T., Wada, Y., Higashima, M., Koshino, Y., Strik, W., & Dierks, T. (2007). Native EEG and treatment effects in neuroleptic-naïve schizophrenic patients: time and frequency domain approaches. *Schizophrenia research*, *97*(1-3), 163–172. https://doi.org/10.1016/j.schres.2007.07.012

Kindler, J., Hubl, D., Strik, W. K., Dierks, T., & König, T. (2011). Resting-state EEG in schizophrenia: auditory verbal hallucinations are related to shortening of specific microstates. *Clinical Neurophysiology*, *122*(6), 1179-1182.

Koenig, T., Tomescu, M. I., Rihs, T. A., & Koukkou, M. (2017). Eeg indices of cortical network formation and their relevance for studying variance in subjective experience and behavior. *In Vivo Neuropharmacology and Neurophysiology*, 17-35.

Koenig, T., Prichep, L., Lehmann, D., Sosa, P. V., Braeker, E., Kleinlogel, H., ... & John, E. R. (2002). Millisecond by millisecond, year by year: normative EEG microstates and developmental stages. *Neuroimage*, *16*(1), 41-48.

Langdon, R., Jones, S. R., Connaughton, E., & Fernyhough, C. (2009). The phenomenology of inner speech: comparison of schizophrenia patients with auditory verbal hallucinations and healthy controls. *Psychological medicine*, *39*(4), 655-663.

Lataster, T., Valmaggia, L., Lardinois, M., Van Os, J., & Myin-Germeys, I. (2013). Increased stress reactivity: a mechanism specifically associated with the positive symptoms of psychotic disorder. *Psychological medicine*, *43*(7), 1389-1400.

Lehmann, D., Ozaki, H., & Pál, I. (1987). EEG alpha map series: brain micro-states by space-oriented adaptive segmentation. *Electroencephalography and clinical neurophysiology*, *67*(3), 271-288.

Lehmann, D., Faber, P. L., Galderisi, S., Herrmann, W. M., Kinoshita, T., Koukkou, M., ... & Koenig, T. (2005). EEG microstate duration and syntax in acute, medication-naive, first-episode schizophrenia: a multi-center study. *Psychiatry Research: Neuroimaging*, *138*(2), 141-156.

Levinson, D. F., Umapathy, C., & Musthaq, M. (1999). Treatment of schizoaffective disorder and schizophrenia with mood symptoms. *American Journal of Psychiatry*, *156*(8), 1138-1148.

Light, G. A., & Braff, D. L. (2005). Mismatch negativity deficits are associated with poor functioning in schizophrenia patients. *Archives of general psychiatry*, *62*(2), 127-136.

Linscott, R. J., & Van Os, J. (2013). An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. *Psychological medicine*, *43*(6), 1133-1149.

Luo, Y., Tian, Q., Wang, C., Zhang, K., Wang, C., & Zhang, J. (2020). Biomarkers for prediction of schizophrenia: Insights from resting-state EEG microstates. *IEEE Access*, *8*, 213078-213093.

Mak, L. E., Minuzzi, L., MacQueen, G., Hall, G., Kennedy, S. H., & Milev, R. (2017). The default mode network in healthy individuals: a systematic review and meta-analysis. *Brain connectivity*, *7*(1), 25-33.

Malla A, McGorry P. (2019). Early Intervention in Psychosis in Young People: A Population and Public Health Perspective. *Am J Public Health*. 2019;109(S3):S181-S184. doi:10.2105/AJPH.2019.305018

Manoliu, A., Riedl, V., Zherdin, A., Mühlau, M., Schwerthöffer, D., Scherr, M., ... & Sorg, C. (2014). Aberrant dependence of default mode/central executive network interactions on anterior insular salience network activity in schizophrenia. *Schizophrenia bulletin*, *40*(2), 428-437.

Marino, M., Spironelli, C., Mantini, D., Craven, A. R., Ersland, L., Angrilli, A., & Hugdahl, K. (2022). Default mode network alterations underlie auditory verbal hallucinations in schizophrenia. *Journal of Psychiatric Research*, *155*, 24-32.

Mars, R. B., Neubert, F. X., Noonan, M. P., Sallet, J., Toni, I., & Rushworth, M. F. (2012). On the relationship between the "default mode network" and the "social brain". *Frontiers in human neuroscience*, *6*, 189.

Marshall, M., Lewis, S., Lockwood, A., Drake, R., Jones, P., & Croudace, T. (2005). Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Archives of general psychiatry*, *62*(9), 975-983.

Marzouk, T., Winkelbeiner, S., Azizi, H., Malhotra, A. K., & Homan, P. (2020). Transcranial magnetic stimulation for positive symptoms in schizophrenia: a systematic review. *Neuropsychobiology*, *79*(6), 384-396.

May, P. J., & Tiitinen, H. (2010). Mismatch negativity (MMN), the deviance-elicited auditory deflection, explained. *Psychophysiology*, *47*(1), 66-122.

McCutcheon, R. A., Krystal, J. H., & Howes, O. D. (2020). Dopamine and glutamate in schizophrenia: biology, symptoms and treatment. *World Psychiatry*, *19*(1), 15-33.

McGlashan, T. H., Addington, J., Cannon, T., Heinimaa, M., McGorry, P., O'Brien, M., ... & Yung, A. (2007). Recruitment and treatment practices for help-seeking "prodromal" patients. *Schizophrenia Bulletin*, *33*(3), 715-726.

McGorry, P. D., & Killackey, E. J. (2002). Early intervention in psychosis: a new evidence based paradigm. *Epidemiology and Psychiatric Sciences*, *11*(4), 237-247.

McGuire, P. K., Silbersweig, D. A., Wright, I., Murray, R. M., Frackowiak, R. S. J., & Frith, C. D. (1996). The neural correlates of inner speech and auditory verbal imagery in schizophrenia: relationship to auditory verbal hallucinations. *The British Journal of Psychiatry*, *169*(2), 148-159.

Melle, I., Johannessen, J. O., Friis, S., Haahr, U., Joa, I., Larsen, T. K., ... & McGlashan, T. (2010). Course and predictors of suicidality over the first two years of treatment in first-episode schizophrenia spectrum psychosis. *Archives of Suicide Research*, *14*(2), 158-170.

Menon, V. (2011). Large-scale brain networks and psychopathology: a unifying triple network model. *Trends in cognitive sciences*, *15*(10), 483-506.

Michel, C. M., & Koenig, T. (2018). EEG microstates as a tool for studying the temporal dynamics of whole-brain neuronal networks: a review. *Neuroimage*, *180*, 577-593.

Mikutta, C. A., Knight, R. T., Sammler, D., Müller, T. J., & Koenig, T. (2024). Electrocorticographic activation patterns of electroencephalographic microstates. Brain topography, 37(2), 287-295.

Miller, T. J., McGlashan, T. H., Woods, S. W., Stein, K., Driesen, N., Corcoran, C. M., ... & Davidson, L. (1999). Symptom assessment in schizophrenic prodromal states. *Psychiatric quarterly*, *70*, 273-287.

Milz, P., Faber, P. L., Lehmann, D., Koenig, T., Kochi, K., & Pascual-Marqui, R. D. (2016). The functional significance of EEG microstates—Associations with modalities of thinking. Neuroimage, 125, 643-656.

Mizuno, T. (2015). Auditory Hallucinations and Its Mechanism. *J Neurol Disord*, *3*(230), 2.

Molholm, S., Martinez, A., Ritter, W., Javitt, D. C., & Foxe, J. J. (2005). The neural circuitry of pre-attentive auditory change-detection: an fMRI study of pitch and duration mismatch negativity generators. *Cerebral Cortex*, *15*(5), 545-551.

Murphy, B. P., & Brewer, W. J. (2011). Early intervention in psychosis: strengths and limitations of services. *Advances in psychiatric treatment*, *17*(6), 401-407.

Murphy, M., Stickgold, R., & Öngür, D. (2020). Electroencephalogram microstate abnormalities in early-course psychosis. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *5*(1), 35-44.

Murray, R. M., Paparelli, A., Morrison, P. D., Marconi, A., & Di Forti, M. (2013). What can we learn about schizophrenia from studying the human model, drug-induced psychosis?. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *162*(7), 661-670.

Muthukrishnan, S.-P., Ahuja, N., Mehta, N., & Sharma, R. (2016). Functional brain microstate predicts the outcome in a visuospatial working memory task. *Behavioural Brain Research, 313*, 92–99. https://doi.org/10.1016/j.bbr.2016.08.020

Näätänen, R., & Alho, K. (1995). Generators of electrical and magnetic mismatch responses in humans. *Brain topography*, *7*, 315-320.

Näätänen, R., Pakarinen, S., Rinne, T., & Takegata, R. (2004). The mismatch negativity (MMN): towards the optimal paradigm. *Clinical neurophysiology*, *115*(1), 140-144.

Näätänen, R., Paavilainen, P., Rinne, T., & Alho, K. (2007). The mismatch negativity (MMN) in basic research of central auditory processing: a review. *Clinical neurophysiology*, *118*(12), 2544-2590.

Näätänen, R., & Kähkönen, S. (2009). Central auditory dysfunction in schizophrenia as revealed by the mismatch negativity (MMN) and its magnetic equivalent MMNm: a review. *International Journal of Neuropsychopharmacology*, *12*(1), 125-135.

Nagabhushan Kalburgi, S., Kleinert, T., Aryan, D., Nash, K., Schiller, B., & Koenig, T. (2024). MICROSTATELAB: the EEGLAB Toolbox for resting-state Microstate Analysis. *Brain topography*, *37*(4), 621-645.

Niemi-Pynttäri, J. A., Sund, R., Putkonen, H., Vorma, H., Wahlbeck, K., & Pirkola, S. P. (2013). Substance-induced psychoses converting into schizophrenia: a register-based study of 18,478 Finnish inpatient cases. *The Journal of clinical psychiatry*, *74*(1), 20155.

Nordentoft, M., Thorup, A., Petersen, L., Øhlenschlæger, J., Melau, M., Christensen, T. Ø., ... & Jeppesen, P. (2006). Transition rates from schizotypal disorder to psychotic disorder for first-contact patients included in the OPUS trial. A randomized clinical trial of integrated treatment and standard treatment. *Schizophrenia Research*, *83*(1), 29-40.

Okuneye, V. T., Meda, S., Pearlson, G. D., Clementz, B. A., Keshavan, M. S., Tamminga, C. A., ... & Keedy, S. K. (2020). Resting state auditory-language cortex connectivity is associated with hallucinations in clinical and biological subtypes of psychotic disorders. *NeuroImage: Clinical*, *27*, 102358.

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., ... & Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *International journal of surgery*, *88*, 105906.

Pan, Z., Xiong, D., Xiao, H., Li, J., Huang, Y., Zhou, J., ... & Wu, K. (2021). The effects of repetitive transcranial magnetic stimulation in patients with chronic schizophrenia: insights from EEG microstates. *Psychiatry Research*, 299, 113866.

Pascual-Marqui, R. D., Lehmann, D., Koenig, T., Kochi, K., Merlo, M. C., Hell, D., & Koukkou, M. (1999). Low resolution brain electromagnetic tomography (LORETA) functional imaging in acute, neuroleptic-naive, first-episode, productive schizophrenia. *Psychiatry Research: Neuroimaging*, *90*(3), 169-179.

Penttilä, M., Jääskeläinen, E., Hirvonen, N., Isohanni, M., & Miettunen, J. (2014). Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: systematic review and meta-analysis. *The British Journal of Psychiatry*, *205*(2), 88-94.

Pomarol-Clotet, E., Salvador, R., Sarro, S., Gomar, J., Vila, F., Martinez, A., ... & McKenna, P. J. (2008). Failure to deactivate in the prefrontal cortex in schizophrenia: dysfunction of the default mode network?. *Psychological medicine*, *38*(8), 1185-1193.

Popov, T., Tröndle, M., Baranczuk-Turska, Z., Pfeiffer, C., Haufe, S., & Langer, N. (2023). Test–retest reliability of resting-state EEG in young and older adults. *Psychophysiology*, *60*(7), e14268.

Rajkumar, R., Farrher, E., Mauler, J., Sripad, P., Régio Brambilla, C., Rota Kops, E., ... & Neuner, I. (2021). Comparison of EEG microstates with resting state fMRI and FDG-PET measures in the default mode network via simultaneously recorded trimodal (PET/MR/EEG) data. *Human brain mapping*, *42*(13), 4122-4133.

Rieger, K., Diaz Hernandez, L., Baenninger, A., & Koenig, T. (2016). 15 years of microstate research in schizophrenia–where are we? A meta-analysis. *Frontiers in psychiatry*, *7*, 22.

Riel, H., MacPhee, C., Rudolph, E. D., Tibbo, P. G., & Fisher, D. J. (2022). MMN and P3a elicited by a novelty paradigm in healthy controls: An investigation of sex differences. *Neuroscience Letters*, *781*, 136654.

Rosazza, C., & Minati, L. (2011). Resting-state brain networks: literature review and clinical applications. *Neurological sciences*, *32*, 773-785.

Rosell, D. R., Futterman, S. E., McMaster, A., & Siever, L. J. (2014). Schizotypal personality disorder: a current review. *Current psychiatry reports*, *16*, 1-12.

Rudolph, E. D., Ells, E. M., Campbell, D. J., Abriel, S. C., Tibbo, P. G., Salisbury, D. F., & Fisher, D. J. (2015). Finding the missing-stimulus mismatch negativity (MMN) in early psychosis: altered MMN to violations of an auditory gestalt. *Schizophrenia research*, *166*(1-3), 158-163.

Salgado-Pineda, P., Fakra, E., Delaveau, P., McKenna, P. J., Pomarol-Clotet, E., & Blin, O. (2011). Correlated structural and functional brain abnormalities in the default mode network in schizophrenia patients. *Schizophrenia research*, *125*(2-3), 101-109.

Salisbury, D. F., Shenton, M. E., Griggs, C. B., Bonner-Jackson, A., & McCarley, R. W. (2002). Mismatch negativity in chronic schizophrenia and first-episode schizophrenia. *Archives of general psychiatry*, *59*(8), 686-694.

Salisbury, D. F., Kuroki, N., Kasai, K., Shenton, M. E., & McCarley, R. W. (2007). Progressive and interrelated functional and structural evidence of post-onset brain reduction in schizophrenia. *Archives of general psychiatry*, *64*(5), 521-529.

Salisbury, D. F. (2012). Finding the missing stimulus mismatch negativity (MMN): emitted MMN to violations of an auditory gestalt. *Psychophysiology*, *49*(4), 544-548.

Salisbury, D. F., López Caballero, F., & Coffman, B. A. (2024). Development of Biomarkers Potentially Sensitive to Early Psychosis Using Mismatch Negativity (MMN) to Complex Pattern Deviations. *Clinical EEG and Neuroscience*, 15500594241254896.

Salisbury, D. F., Kuroki, N., Kasai, K., Shenton, M. E., & McCarley, R. W. (2007). Progressive and interrelated functional and structural evidence of post-onset brain reduction in schizophrenia. *Archives of general psychiatry*, *64*(5), 521-529.

Sasabayashi, D., Takahashi, T., Takayanagi, Y., Nemoto, K., Ueno, M., Furuichi, A., ... & Suzuki, M. (2023). Resting state hyperconnectivity of the default mode network in schizophrenia and clinical high-risk state for psychosis. *Cerebral Cortex*, *33*(13), 8456-8464.

Schwarzer, G., & Rücker, G. (2023). *meta: General package for meta-analysis (Version 6.5-0) [Computer software]*. https://CRAN.R-project.org/package=meta

Sestieri, C., Corbetta, M., Romani, G. L., & Shulman, G. L. (2011). Episodic memory retrieval, parietal cortex, and the default mode network: functional and topographic analyses. *Journal of Neuroscience*, *31*(12), 4407-4420.

Seitzman, B. A., Abell, M., Bartley, S. C., Erickson, M. A., Bolbecker, A. R., & Hetrick, W. P. (2017). Cognitive manipulation of brain electric microstates. *NeuroImage, 146*, 533–543. https://doi.org/10.1016/j.neuroimage.2016.10.002

Shah, S., Mackinnon, A., Galletly, C., Carr, V., McGrath, J. J., Stain, H. J., ... & Morgan, V. A. (2014). Prevalence and impact of childhood abuse in people with a psychotic illness. Data from the second Australian national survey of psychosis. Schizophrenia research, 159(1), 20-26.

Shao, X., Liao, Y., Gu, L., Chen, W., & Tang, J. (2021). The etiology of auditory hallucinations in schizophrenia: from multidimensional levels. *Frontiers in neuroscience*, *15*, 755870.

Shinn, A. K., Baker, J. T., Cohen, B. M., & Öngür, D. (2013). Functional connectivity of left Heschl's gyrus in vulnerability to auditory hallucinations in schizophrenia. *Schizophrenia research*, *143*(2-3), 260-268.

Silverstein, S. M., Berten, S., Essex, B., All, S. D., Kasi, R., & Little, D. M. (2010). Perceptual organization and visual search processes during target detection task performance in schizophrenia, as revealed by fMRI. *Neuropsychologia*, 48(10), 2886-2893.

Smallwood, J., Bernhardt, B. C., Leech, R., Bzdok, D., Jefferies, E., & Margulies, D. S. (2021). The default mode network in cognition: a topographical perspective. *Nature reviews neuroscience*, *22*(8), 503-513.

Stahl, S. M. (2018). Beyond the dopamine hypothesis of schizophrenia to three neural networks of psychosis: dopamine, serotonin, and glutamate. *CNS spectrums*, *23*(3), 187-191.

Stanghellini, G., & Cutting, J. (2003). Auditory verbal hallucinations–breaking the silence of inner dialogue. *Psychopathology*, *36*(3), 120-128.

Stewart, A., Patten, S., Fiest, K., Williamson, T., Wick, J., & Ronksley P. 10-Year Trends in Healthcare Spending among Patients with Schizophrenia in Alberta, Canada. *Can J Psychiatry*. 2022 Sep;67(9):723-733. doi: 10.1177/07067437221082885. Epub 2022 Mar 4. PMID: 35244485; PMCID: PMC9449136.

Strelets, V., Faber, P. L., Golikova, J., Novototsky-Vlasov, V., Koenig, T., Gianotti, L. R. R., ... & Lehmann, D. (2003). Chronic schizophrenics with positive symptomatology have shortened EEG microstate durations. *Clinical Neurophysiology*, *114*(11), 2043-2051.

Sun, Q., Zhao, L., & Tan, L. (2022). Abnormalities of electroencephalography microstates in drug-naïve, first-episode schizophrenia. *Frontiers in Psychiatry*, *13*, 853602.

Tait, L., & Zhang, J. (2022). MEG cortical microstates: spatiotemporal characteristics, dynamic functional connectivity and stimulus-evoked responses. *NeuroImage*, *251*, 119006.

Thakkar, K. N., & Rolfs, M. (2019). Disrupted corollary discharge in schizophrenia: Evidence from the oculomotor system. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *4*(9), 773-781.

van Tol, M. J., van der Meer, L., Bruggeman, R., Modinos, G., Knegtering, H., & Aleman, A. (2014). Voxel-based gray and white matter morphometry correlates of hallucinations in schizophrenia: the superior temporal gyrus does not stand alone. *NeuroImage: Clinical*, *4*, 249-257.

Tomescu, M. I., Rihs, T. A., Roinishvili, M., Karahanoglu, F. I., Schneider, M., Menghetti, S., ... & Cappe, C. (2015). Schizophrenia patients and 22q11. 2 deletion syndrome adolescents at risk express the same deviant patterns of resting state EEG microstates: a candidate endophenotype of schizophrenia. *Schizophrenia Research: Cognition*, *2*(3), 159-165.

Tomescu, M. I., Rihs, T. A., Rochas, V., Hardmeier, M., Britz, J., Allali, G., ... & Michel, C. M. (2018). From swing to cane: sex differences of EEG resting-state temporal patterns during maturation and aging. *Developmental cognitive neuroscience*, *31*, 58-66.

Tso, I. F., Taylor, S. F., Grove, T. B., Niendam, T., Adelsheim, S., Auther, A., ... & McFarlane, W. R. (2017). Factor analysis of the Scale of Prodromal Symptoms: data from the Early Detection and Intervention for the Prevention of Psychosis Program. *Early intervention in psychiatry*, *11*(1), 14-22.

Turner S, Harvey C, Hayes L, et al. Childhood adversity and clinical and psychosocial outcomes in psychosis. *Epidemiology and Psychiatric Sciences*. 2020;29:e78. doi:10.1017/S2045796019000684

Utevsky, A. V., Smith, D. V., & Huettel, S. A. (2014). Precuneus is a functional core of the default-mode network. *Journal of Neuroscience*, *34*(3), 932-940.

Vollema, M. G., & van den Bosch, R. J. (1995). The multidimensionality of schizotypy. *Schizophrenia bulletin*, *21*(1), 19-31.

Walker, E. F., & Diforio, D. (1997). Schizophrenia: a neural diathesis-stress model. *Psychological review*, *104*(4), 667.

Whitfield-Gabrieli, S., & Ford, J. M. (2012). Default mode network activity and connectivity in psychopathology. *Annual review of clinical psychology*, *8*, 49-76.

Whitford, T. J., Mitchell, A. M., & Mannion, D. J. (2017). The ability to tickle oneself is associated with level of psychometric schizotypy in non-clinical individuals. *Consciousness and cognition*, *52*, 93-103.

Woodward, T. S., Jung, K., Hwang, H., Yin, J., Taylor, L., Menon, M., ... & Erickson, D. (2014). Symptom dimensions of the psychotic symptom rating scales in psychosis: a multisite study. *Schizophrenia bulletin*, *40*(Suppl_4), S265-S274.

Wu, G., Palaniyappan, L., Zhang, M., Yang, J., Xi, C., Liu, Z., ... & Pu, W. (2022). Imbalance between prefronto-thalamic and sensorimotor-thalamic circuitries associated with working memory deficit in schizophrenia. *Schizophrenia Bulletin*, *48*(1), 251-261.

Yao, R., Xue, J., Yang, P., Deng, H., Tan, S., & Li, H. (2021). Dynamic changes of brain networks during working memory tasks in schizophrenia. *Brain Research, 453*, 187–205. https://doi.org/10.1016/j.brainres.2020.11.001

Yan, T., Wang, G., Liu, T., Li, G., Wang, C., Funahashi, S., ... & Pei, G. (2023). Effects of Microstate Dynamic Brain Network Disruption in Different Stages of Schizophrenia. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*.

Yoshimura, M., Koenig, T., Irisawa, S., Isotani, T., Yamada, K., Kikuchi, M., ... & Dierks, T. (2007). A pharmaco-EEG study on antipsychotic drugs in healthy volunteers. *Psychopharmacology*, *191*, 995-1004.

Yuan, H., Zotev, V., Phillips, R., Drevets, W. C., & Bodurka, J. (2012). Spatiotemporal dynamics of the brain at rest—exploring EEG microstates as electrophysiological signatures of BOLD resting state networks. Neuroimage, 60(4), 2062-2072.

Yung, A. R., Nelson, B., Thompson, A., & Wood, S. J. (2010). The psychosis threshold in Ultra High Risk (prodromal) research: is it valid? *Schizophrenia research*, *120*(1-3), 1-6.

Zhang, W., Li, S., Wang, X., Gong, Y., Yao, L., Xiao, Y., ... & Lui, S. (2018). Abnormal dynamic functional connectivity between speech and auditory areas in schizophrenia patients with auditory hallucinations. *NeuroImage: Clinical*, *19*, 918-924.

Zmigrod, L., Garrison, J. R., Carr, J., & Simons, J. S. (2016). The neural mechanisms of hallucinations: a quantitative meta-analysis of neuroimaging studies. *Neuroscience & Biobehavioral Reviews*, *69*, 113-123.