VILNIUS UNIVERSITY

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Effects of TMS on EEG in patients with schizophrenia

Master's Thesis

Neurobiology study program

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Thesis completed at

Department of Electrophysiological Research and Treatment Methods, Republican Vilnius Psychiatric Hospital

Vilnius, 2025

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Abbreviations

APA – American Psychiatric Association

AVHs – Auditory verbal hallucinations

CT – Computer tomography

cTBS – Continuous theta burst stimulation

DLPC – Dorsolateral prefrontal cortex

DMN – Default mode network

DSM-5 – Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

DTI – Diffusion tensor imaging

ECT – Electroconvulsive therapy

EEG – Electroencephalography

EPS – Extrapyramidal symptoms

FGAs – First-generation antipsychotics

fMRI – Functional magnetic resonance imaging

GABA – Gamma-aminobutyric acid

ICD-11 – International Classification of Diseases, 11th Edition

iTBS – Intermittent theta burst stimulation

MEG – Magnetoencephalography

MNI – Montreal Neurological Institute

MRI – Magnetic resonance imaging

NMDA – N-methyl-D-aspartate

OCD – Obsessive-compulsive disorder

PANSS – Positive and Negative Syndrome Scale

PTSD – Post-traumatic stress disorder

rTMS – Repetitive transcranial stimulation

SGAs – Second-generation antipsychotics

STG – Superior temporal gyrus

SUDs – Substance abuse disorders

TBS – Theta burst stimulation

TMS – Transcranial magnetic stimulation

TPJ – Temporoparietal junction

WHO – World Health Organisation

Introduction

Schizophrenia is a complex psychiatric disorder characterised by significant alterations in emotion, cognition, and behaviour, which leads to intense functional impairments and reduced quality of life. Despite decades of research, schizophrenia remains one of the most challenging psychiatric disorders, impacting approximately 1% of the global population, as reported by the American Psychiatric Association (2013). The clinical profile of schizophrenia consists of positive symptoms, like auditory verbal hallucinations; negative symptoms, such as emotional withdrawal, and cognitive impairments, which include difficulties in attention and memory (van Os & Kapur, 2009).

The pathophysiological profile of schizophrenia is multifaceted, including structural brain abnormalities, neurotransmitter dysregulation, and disrupted neural connectivity. Neuroimaging studies consistently demonstrate structural alterations, such as cortical thinning and enlargement of the ventricles (Fusar-Poli *et al.*, 2013). Furthermore, functional connectivity disruptions, including hypo- and hyper-connectivity, particularly within cortico-subcortical networks, appear to be implicated in symptom generation (Friston & Frith, 1995). Electrophysiological studies further underline these disruptions, revealing frequency band abnormalities, especially increased theta and beta activity associated with cognitive and perceptual disturbances (Uhlhaas & Singer, 2010).

Antipsychotic medication remains the first-line treatment for schizophrenia. However, approximately 20-30% of patients are treatment-resistant, particularly for persistent positive symptoms such as auditory hallucinations (Kane *et al.*, 1988). The limited efficacy and substantial side effects of pharmacological treatment emphasise the need for effective supporting therapies. Therefore, a non-invasive neuromodulatory technique, namely repetitive transcranial magnetic stimulation, has emerged as a promising alternative, especially for the treatment-resistant portion of the patients. Repetitive stimulation has demonstrated the potential to reduce auditory hallucinations and improve overall clinical outcomes by targeting hyperactive cortical regions, such as the left temporoparietal junction (Yuanjun *et al.*, 2024).

The combination of electroencephalography with repetitive transcranial magnetic stimulation offers a powerful approach. Electroencephalographic-based biomarkers provide a much-needed understanding of the neural mechanisms which form therapeutic responses, enabling more individualised treatment strategies. Despite promising results, the relationship between specific oscillatory patterns and clinical symptom improvements following the alternative treatment remains only partially understood.

This study aims to address this gap by evaluating the impact of repetitive stimulation on electrophysiological spectral changes and clinical symptomatology, focusing on the positive symptoms of schizophrenia in particular. The tasks include:

1. Create an algorithm for automated EEG recording artefact filtration and analysis.
2. Evaluate EEG spectral power changes in theta, alpha, beta and gamma frequency bands pre- and post- TMS.
3. Compare EEG spectral power differences between schizophrenia patients and healthy controls.
4. Evaluate the dynamics of clinical positive symptom improvement after TMS therapy using PANSS test.
5. Explore the correlation EEG spectral power and clinical symptom changes.

1. Literature review

1.1. Introduction to schizophrenia

Schizophrenia is a complex, severe psychiatric disorder that affects approximately 1% of the total population and is characterised by a constellation of cognitive, emotional, and behavioural alterations (American Psychiatric Association [APA], 2013). Its clinical profile is heterogeneous and is usually categorised into three groups of symptoms: positive (e.g., hallucinations, delusions), negative (e.g., anhedonia, alogia, flat affect), and disorganised symptoms (e.g., disorganised thinking and behaviour).

The illness typically emerges in late adolescence or early adulthood and tends to follow a chronic course with varying degrees of relapse and remission (Bakewell, 2023). Regardless of decades of research, schizophrenia remains one of the most debilitating psychiatric disorders, with a significant impact on functioning, relationships, employment, and overall quality of life (van Os & Kapur, 2009).

1.1.2. Historical and diagnostic context

The perception of schizophrenia has evolved substantially since its primary description as "dementia praecox" by Emil Kraepelin in the late 19th century. Kraeplin underlined the early onset and deteriorating course, which he opposed with manic-depressive disorder. Later, Eugen Bleuler introduced the term used today, "schizophrenia", in 1911 to capture the so-called "splitting" of mental functions, and his framework laid the basis for the understanding of core cognitive disintegration in the illness.

Nowadays, the diagnosis of schizophrenia is standardised by modern protocol manuals, such as DSM-5 (APA, 2013) and ICD-11 (World Health Organisation [WHO], 2019). For the diagnosis to be received, both manuals emphasise the required presence of two or more of the following symptoms from the positive group: delusions, hallucinations, disorganised speech, grossly disorganised or catatonic behaviour, and, additionally, negative symptoms, including functional impairment and symptom duration over six months.

Over the recent years, there have been efforts to reclassify schizophrenia based on symptom clusters or dimensions (van Os & Tamminga, 2007), for example, Crow's Type I (positive symptom-dominant, hyperdopaminergic) and Type II (negative symptom-dominant, structural degeneration) subtypes, which should reflect partially distinct pathophysiological processes.

1.1.3. Epidemiology and global burden

Schizophrenia affects roughly 23 million individuals worldwide (WHO, 2022), with an incidence of about 15 per 100,000 people per year. It is slightly more prevalent in males, with a male-to-female ratio of 1.4:1, who often exhibit earlier onset and more severe negative symptoms (Abel *et al.*, 2010). The disease burden is tremendous, ranked among the top 20 causes of disability globally. In addition to cognitive and functional deficiencies, individuals with schizophrenia face a reduced life expectancy of 15-20 years, mainly due to cardiovascular disease, metabolic disorders, and suicide (Laursen *et al.*, 2014).

When it comes to the origin of schizophrenia, family and twin studies demonstrate a strong hereditary component, specifically heritability estimation being around 80%. However, the disorder is not purely genetic. Environmental and developmental factors, including prenatal infections, early-life stress, social adversity, and cannabis use, have all been implicated in increasing the risk (Murray *et al.*, 2017).

1.1.4. Pathophysiological overview

Even though no single pathophysiological model is capable of comprehensively explaining schizophrenia, the disorder is widely recognised as a neurodevelopmental condition involving disturbed brain maturation, atypical synaptic pruning, and dysconnectivity across cortico-subcortical networks.

From a structural perspective, MRI and CT studies have consistently shown ventricular enlargement, cortical thinning, and hippocampal volume loss, particularly in chronic cases (Fusar-Poli *et al.*, 2013). Functional imaging studies also reveal hypofrontality during executive tasks and hyperactivation in temporal regions during hallucinations, especially in the left superior temporal gyrus (STG) and Heschl's gyrus (Allen *et al.*, 2008; Mwansisya *et al.*, 2017; Gornerova *et al.*, 2023).

From a cellular and system perspective, neurotransmitter dysfunction is central to current models. The dopamine hypothesis, the oldest and most tested theory, suggests that excessive dopamine transmission in mesolimbic pathways contributes to positive symptoms. Meanwhile, mesocortical hypodopaminergia may be responsible for negative and cognitive alterations (Howes & Kapur, 2009). More recent evidence implicates glutamatergic dysfunction, particularly NMDA receptor hypofunction, in the causation of both positive and negative symptoms (Moghaddam & Javitt, 2012). Furthermore, GABAergic interneuron deficits and disrupted oscillatory activity propose that schizophrenia may also be a disorder of impaired cortical inhibition and timing (Lisman *et al.*, 2008).

1.1.5. Functional connectivity and dysrhythmia

Beyond steady structural changes, schizophrenia is increasingly described as a disorder of neural dysconnectivity, both hyper- and hypo-connected, depending on the network and symptom dimension (Friston & Frith, 1995). Resting-state EEG and fMRI studies have revealed abnormal synchronisation patterns, with excessive low-frequency activity (delta, theta) and unstable higher-frequency power (beta, gamma), reflecting impaired integration across brain networks (Arora *et al.*, 2020).

These functional alterations appear to be tracked with specific symptom clusters. For instance, alpha desynchronisation and increased left temporal beta activity have been linked to hallucinations and delusions, while frontal theta has been associated with cognitive control deficits (Newson & Thiagarajan, 2019; Karson *et al.*, 1988).

1.1.6. Treatment gaps and neuromodulation rationale

While antipsychotics remain the first-line treatment, a significant portion of patients, which amounts to approximately 20-30%, are treatment-resistant, notably for positive symptoms such as auditory hallucinations (Kane *et al.*, 1988). The limited efficacy and substantial side effects of antipsychotic medications together underscore the need for adjunctive or alternative therapies.

This situation has given rise to the investigation of neuromodulation techniques, such as repetitive transcranial magnetic stimulation (rTMS), which has the ability to target hyperactive cortical regions implicated in hallucinations and delusions. This alternative treatment is especially promising for patients with resistant auditory hallucinations, where 1 Hz protocols applied to the left temporoparietal junction (TPJ) have shown efficacy (Yuanjun *et al.*, 2024). These modulations are thought to act via modulation of cortical flexibility, entrainment of neural oscillations, and reconfiguration of network connectivity.

1.2. Neurobiological and neurochemical basis of schizophrenia

More and more, schizophrenia is being recognised as a disorder of disrupted brain connectivity, altered neurotransmission, and atypical synaptic plasticity. Developments in neuroimaging techniques, electrophysiology, and molecular genetics have helped to improve the understanding of the illness toward a systems-categorised neurodevelopmental disorder.

1.2.1. Structural brain abnormalities

Neuroimaging studies consistently reveal structural brain abnormalities in individuals with schizophrenia. The changes include enlarged ventricles, reduced grey matter volume, and cortical thinning, especially in the prefrontal and parietal cerebral cortices, temporal lobes, and hippocampus

(Kandel, 2013; Fusar-Poli *et al.*, 2013; Wright *et al.*, 2000). The prefrontal area alteration is observed in the dorsolateral prefrontal cortex (DLPC) region, which is hypothetically caused by the reduction in axonal, dendritic and synaptic processes. Specifically, the loss of cell bodies in the thalamus (mediodorsal nucleus) reduces its size, which affects the DLPC since the thalamus sends its axons to this area. Meanwhile, temporal region changes are spotted in the temporal gyrus, pole, hippocampus, and amygdala (mostly in males). As a result, the mentioned modifications increase ventricular volume, negatively impacting working memory and cognitive control (Kandel, 2013). More than that, these alterations often predate the onset of clinical symptoms and may reflect potential neurodevelopmental trajectories (Pantelis *et al.*, 2003).

One of the core positive symptoms, specifically auditory hallucinations, has been linked to alterations in the STG, especially in the left hemisphere. Reduced volume in this area correlates with the level of hallucination severity and can be accompanied by altered auditory processing in EEG and fMRI studies (Arora *et al.*, 2020; Allen *et al.*, 2008; Gornerova *et al.*, 2023).

1.2.2. Functional connectivity and cortical dysrhythmia

As previously mentioned, schizophrenia is characterised by both hypo- and hyper-connectivity within and across brain networks (Friston, 1998). Functional MRI and EEG studies reveal dysregulated resting-state activity and abnormal default mode network (DMN) behaviour. Cortical communication becomes inefficient, leading to a breakdown in the integration of perception, cognition, and emotion (Whitfield-Gabrieli & Ford, 2012).

EEG spectral abnormalities are thought to reflect disconnection patterns and could serve as physiological markers of disrupted network dynamics (Newson & Thiagarajan, 2019; Grin-Yatsenko *et al.*, 2017).

1.2.3. Neurochemical profile: classic and contemporary models

The central hypothesis for understanding schizophrenia is the dopamine theory. The original model stated that mesolimbic hyperdopaminergia is a driver of positive symptoms, delusions, and hallucinations in particular (Carlsson & Lindqvist, 1963). However, the subsequent, more recent versions suggest a dual dysfunction. Specifically, transmission in subcortical regions (especially the striatum) and dopaminergic hypofunction in the prefrontal cortex contribute to positive and negative symptoms (Howes & Kapur, 2009).

Elevated dopamine synthesis capacity, shown in PET studies, is found in individuals who are at ultra-high risk for psychosis and also those who are experiencing their first episode of schizophrenia

(Howes *et al.*, 2012). Most antipsychotic medications exert their effect by blocking D2 receptors, particularly in the mesolimbic system.

However, dopamine dysfunction alone cannot account for the full spectrum of symptoms, particularly cognitive impairments and treatment-resistant negative symptoms.

1.2.4. Glutamatergic and GABAergic contributions

Another neurochemical theory of schizophrenia pathophysiology is based on glutamate dysfunction. The glutamate hypothesis suggests that NMDA receptor hypofunction is a core point of the illness profile. This model is supported by findings that NMDA antagonists (e.g., ketamine, phencyclidine) induce schizophrenia-like symptoms in healthy individuals (Javitt & Zukin, 1991; Moghaddam & Javitt, 2012).

Glutamatergic abnormalities are thought to disrupt cortical excitation/inhibition balance, specifically in circuits that involve GABAergic interneurons. Consequently, deficits in gamma-band oscillations and working memory are observed (Lisman *et al.*, 2008; Uhlhaas & Singer, 2010). These alterations could explain cognitive impairments, the sensory gating deficits and abnormal salience attribution, which, all together, in turn, characterise psychotic states.

Supporting evidence consists of post-mortem studies that show reduced parvalbumin-expressing interneurons and altered NMDA receptor expression in the prefrontal cortex and hippocampus of patients with schizophrenia (Benes *et al.*, 2001; Chang *et al.*, 2018).

1.2.5. Serotonin, acetylcholine, and other systems

Despite being less popular, other neurotransmitter systems are being implicated with increasing interest. The first theory is based on serotonin (5-HT), specifically the 5-HT2A receptor. Since this receptor is involved in mood and perceptual mechanisms, its dysfunction could be linked with schizophrenic symptoms. Additionally, atypical antipsychotics often have 5-HT2A antagonism as a part of their profile. The next theory includes acetylcholine. Since nicotinic receptor dysfunction is common in schizophrenia, it can relate to cognitive deficits and high smoking prevalence (Freedman *et al.*, 2000). Last but not least the inflammation and oxidative stress hypothesis. The involvement of the immune system is suggested by elevated cytokine levels, microglial activation, and impaired antioxidant defence.

1.2.6. Developmental and genetic risk models

Nowadays, schizophrenia is viewed as a neurodevelopmental disorder caused by both genetic and environmental factors. Genome-wide association studies have identified over 100 loci associated with

schizophrenia risk, many involving synaptic, glutamatergic, and calcium signalling pathways (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014).

Environmental factors include obstetric complications, early trauma, cannabis use, and urban upbringing. Those elements interact with the mentioned genetic risks and, consequently, influence developmental trajectories of brain connectivity and neurotransmission (Murray *et al.*, 2017).

1.3. Clinical features and diagnostic criteria

Schizophrenia's diagnosis is based not on definitive tests or biomarkers. It is based on clusters of symptoms and clinical observations. Hence, it is a syndromic disorder. It is characterised by psychosis, functional decline, and disorganisation, which are, in turn, manifested in varying intensities across individuals over time. Recognising the core symptom domains and their diagnostic criteria is crucial for understanding how different biological systems, such as oscillatory brain dynamics, correlate with psychiatric expression.

1.3.1. Symptom dimensions

As previously mentioned, clinically, schizophrenic symptoms are divided into three main groups: positive, negative, and cognitive symptoms. Positive category includes hallucinations, delusions and disorganised thought and speech. Negative cluster includes affective flattening, poverty of speech, or alogia, lack of motivation, or avolition, and reduced pleasure, or anhedonia. Cognitive symptoms include attention deficits, working memory, and executive functioning (APA, 2013; WHO, 2019).

This thesis is focused on the positive symptom dimension in particular. Additionally, it aligns with hyperactivity in specific cortical networks, temporal lobe in hallucinations, for instance, and is often a target of neuromodulatory interventions such as rTMS.

1.3.2. Positive symptoms: core features

Auditory hallucinations, which are usually experienced as voices perceived without any external stimuli, are the most common type of hallucinations in schizophrenia. These are often vivid and distressing, experienced as distinct from one's inner speech. Functional neuroimaging studies have linked these symptoms to increased activation in the left STG, Heschl's gyrus, and Broca's area — all brain regions associated with speech production and recognition (Allen *et al.*, 2008; Mwansisya *et al.*, 2017; Gornerova *et al.*, 2023).

Delusions, on the other hand, are fixed false beliefs not shared by cultural coevals. Delusions regarding control, reference, persecution, and magnificence are frequent. They are thought to be

contributed to by dysfunctional salience and attribution, partially mediated by dopaminergic and DMN dysregulation (Kapur, 2003).

A breakdown in the normal standard and structure of thought observed in schizophrenia is reflected by disorganised speech and behaviour. Tangentiality, derailment, and incoherence are indicative signs which are thought to arise from disconnection in the prefrontal cortex and reduction in executive control (Andreasen *et al.*, 1998).

1.3.3. Diagnostic criteria: DSM-5 and ICD-11

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (APA, 2013) defines schizophrenia diagnosis based on the presence of at least two or more main symptoms, each of which should be present for a significant part of one month. At least one of them must be delusions, hallucinations, or disorganised speech. Other criteria include marked social or occupational dysfunction, continuous signs of disturbance for at least six months, exclusion of mood disorders and substance-induced psychosis.

The International Classification of Diseases, 11th Edition (ICD-11) (WHO, 2019) follows similar criteria. The main difference between those two diagnostic protocols lies in ICD-11, which places a greater emphasis on symptom course and functional impact. Nevertheless, both systems highlight the disorder's heterogeneity, which has led to the appearance of dimensional models that better reflect clinical reality.

1.3.4. The role of PANSS in symptom quantification

Clinicians typically use a thirty-item structured rating scale, the Positive and Negative Syndrome Scale (PANSS), to capture the severity of symptoms. The units are divided into seven positive symptom items (e.g., delusions, hallucinations, conceptual disorganisation), seven negative symptom items (e.g., emotional withdrawal, blunted affect), and 16 general psychopathology items (e.g., anxiety, tension, poor impulse control).

Each unit is rated from one, or absent, to seven, or extreme, creating a detailed clinical profile. The PANSS is widely applied in research and clinical settings, including this thesis's area of focus, namely, rTMS. The aim is to track symptom fluctuations over time and correlate them with biological markers (Kay *et al.*, 1987).

1.3.5. Subtypes of schizophrenia

Despite being a single diagnosis, schizophrenia has subtype variability:

- Paranoid schizophrenia. It is characterised by dominating persistent delusions, typically paranoid, alongside frequent auditory hallucinations. Affect, motor abnormalities, and speech disturbances are minimal or absent. Individuals suffering from this subtype often demonstrate relatively preserved cognitive functioning compared to other subtypes (WHO, 2016).
- Hebephrenic, or disorganised, schizophrenia. It is expressed in significant emotional instability, incoherent speech, fragmented hallucinations and delusions, and unpredictable, irresponsible behaviour. Negative symptoms, which include emotional flattening and social withdrawal, often appear rapidly, contributing to a generally poor prognosis. This subtype is predominantly diagnosed in adolescents or young adults. Additionally, affected individuals usually require significant support for daily functioning (WHO, 2016).
- Catatonic schizophrenia. It is characterised by substantial psychomotor disturbances, ranging from extreme agitation to stupor, accompanied by repetitive or sustained postures, automatic obedience, or severe resistance to movement. Episodes can include vivid hallucinatory states. The severity of motor symptoms can significantly impact physical health, requiring careful observation and intervention to avoid complications such as malnutrition, dehydration, or injuries, which could appear due to prolonged immobility (WHO, 2016).
- Undifferentiated schizophrenia. Its conditions meet the general criteria for schizophrenia; however, it does not fit a specific subtype due to the absence of clear dominance of symptoms. These manifestations often include mixed features, consequently complicating diagnosis and treatment strategies. Clinical management usually requires an individualised and flexible therapeutic approach (WHO, 2016).
- Post-schizophrenic depression. It is expressed in the appearance of a depressive episode post-period of schizophrenic psychosis. The depressive symptoms, which occur alongside a decreased intensity of residual schizophrenic symptoms, contribute to the increased chance of suicide. This interplay of mental health issues complicates patient management significantly, underscoring the crucial need for ongoing psychiatric support and vigilant monitoring of ideation and behaviour (WHO, 2016).
- Residual schizophrenia. It is being described as chronic schizophrenia since persistent negative symptoms primarily characterise it after the lessening of active psychosis. These symptoms include social withdrawal, lack of emotional response, diminished speech, impaired self-care, and social and occupational dysfunction. Long-term management and psychological interventions are crucial in addressing functional impairments in this group (WHO, 2016).

- Simple schizophrenia. It is characterised by the gradual development of pronounced negative symptoms without apparent psychotic episodes. Symptoms include progressive functional decline and substantial deterioration in societal interactions, responsibilities, self-care, and vocational capabilities. Early detection and intervention strategies are essential due to the subtle and progressive nature of symptom development in this subtype (WHO, 2016).
- Other schizophrenia and schizophrenia unspecified. These categories signify unusual instances without sufficient details to align with other subtypes. These classifications highlight the complex variability seen in patients with schizophrenia, underscoring the importance of ongoing assessment and personalised treatment strategies (WHO, 2016).

This dimensional perspective is of particular importance for EEG and rTMS research since, as previously mentioned, different symptom clusters are associated with distinct oscillatory and connectivity patterns.

Targeting the positive symptom cluster, especially hallucinations, aligns with neuromodulatory approaches such as 1 Hz or theta-burst rTMS. Those protocols aim to reduce cortical hyperexcitability in auditory regions.

1.3.6. Comorbidity

Schizophrenia frequently co-occurs or can be mistaken for other psychiatric disorders, complicating diagnosis, treatment, and prognosis. These comorbidities include mood and anxiety disorders, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and substance use disorders (SUDs).

Mood disorders are a significant concern for people dealing with schizophrenia, with depression being a common issue among them. This combination can make everyday functioning much harder and increase the risk of suicidal thoughts. A systematic review by McGinty and Upthegrove (2020) shows that if someone experiences depressive symptoms during their first psychotic episode, they are likely to face much worse functional outcomes later. Additionally, bipolar disorder shares many traits with schizophrenia, which adds to the challenges in getting an accurate diagnosis. Laursen *et al.* (2009) documented a notable comorbidity index between schizophrenia and bipolar disorder, thereby indicating a continuum of symptoms rather than a strict delineation between the two disorders.

Another group that is quite common in schizophrenia patients is the anxiety cluster, including generalised anxiety disorder and panic disorder. Their presence has the potential to worsen psychotic symptoms and slow down treatment adherence. A study conducted by Braga *et al.* (2004) showed that

comorbid anxiety disorders in schizophrenia are linked to increased severity of psychotic symptoms and functional impairment.

OCD co-occurs with schizophrenia more often than expected by chance. Patients with both conditions tend to experience more severe neuropsychological impairments. Whitney *et al.* (2004) reported that schizophrenic individuals with comorbid OCD exhibited greater deficits in executive functioning compared to those without OCD.

Another significant comorbidity is PTSD. According to research, individuals with schizophrenia have higher rates of PTSD, which is associated with more severe psychotic symptoms and poorer outcomes (Seow *et al.*, 2016)

Substance use disorders (SUDs) are common in individuals with schizophrenia, affecting more than 70% of this population (Regier *et al.*, 1990). Substance use often exacerbates psychotic episodes, decreases adherence to medication, and raises hospitalisation rates. A detailed theory proposed by Khokhar *et al.* (2018) connects the neurobiology of schizophrenia with substance use disorders (SUDs), highlighting the necessity for integrated treatment strategies.

The existence of comorbid psychiatric disorders in schizophrenia requires a comprehensive multidisciplinary approach to treatment. Based on the previously mentioned information, models that address both psychotic and comorbid conditions have the potential to lead to better outcomes. Furthermore, early identification and targeted interventions are essential for improving quality of life and decreasing the burden created by illness.

1.4. Pharmacological treatment of schizophrenia

Antipsychotic medication remains the primary and most effective treatment for positive symptoms of schizophrenia. Antipsychotics were introduced in the middle of the 20th century and have transformed the trajectory of illness flow. Their appearance has allowed many patients to avoid long-term hospitalisation and achieve partial functional recovery. However, as with any drug, outcomes vary widely, also posing a major clinical challenge of treatment resistance. Moreover, even in positive response to the treatment, adverse side effects and partial symptomatic control often require tailored regulations involving drug combinations, dosage adjustments, and further integration of neuromodulation techniques such as rTMS.

1.4.1. Pharmacological principles and mechanisms of action

Most antipsychotics express their action through dopaminergic antagonism, influencing the D2 receptor in particular. This receptor is overactive in the mesolimbic pathway in individuals with schizophrenia, as previously mentioned. By blocking the said receptors, antipsychotics help decrease abnormal dopaminergic firing, reducing hallucinations and delusions (Kapur & Seeman, 2001). However, dopaminergic blockade in other pathways, including the nigrostriatal, tuberoinfundibular, and mesocortical ones, tends to produce a range of unwanted effects. Those include motor disturbances, endocrine dysregulation, and cognitive blunting (Muench & Hamer, 2010).

The second generation of atypical antipsychotics was introduced in the 1990s. These drugs widened the pharmacological scope by targeting serotonin 5-HT2A and dopamine D2 receptors. This dual mechanism and affinities for histaminergic, adrenergic, and muscarinic receptors provide atypicals with a generally improved side effect profile regarding extrapyramidal symptoms (EPS). Nevertheless, it also increases risks regarding weight gain, glucose dysregulation, and metabolic syndrome (Newcomer, 2005; De Hert *et al.*, 2011).

1.4.2. First-generation antipsychotics (FGAs)

FGAs, such as haloperidol and chlorpromazine, are potent dopamine D2 antagonists with strong efficacy in controlling acute psychosis. However, they are associated with significant EPS due to their high D2 receptor occupancy. The symptoms include drug-induced parkinsonism, akathisia, and tardive dyskinesia (Miyamoto *et al.*, 2005). Haloperidol, primarily, is often used in emergency settings for rapid symptom control but is less recommended for long-term use because of its burden of motor side effects.

Despite their disadvantages, FGAs remain useful in the application in cases of short-term psychosis, resource-limited settings, or in combination with newer agents in treatment-resistant cases.

1.4.3. Second-generation antipsychotics (SGAs)

In the modern pharmacological field, SGAs are more commonly used for schizophrenia treatment than their predecessors. They are generally known for lower EPS risk due to faster dissociation from D2 receptors and higher 5-HT2A antagonism (Kapur & Seeman, 2001). Nevertheless, although they have broader receptor profiles, SGAs still have multiple side effects, including weight gain, sedation, and insulin resistance.

Commonly prescribed second-generation antipsychotics (SGAs) include risperidone, olanzapine, quetiapine, aripiprazole, and clozapine. Risperidone is a potent D2 and 5-HT2A antagonist, which is

widely used as a primary drug because of its robust antipsychotic effect; however, it is also known for prolactin elevation and dose-dependent extrapyramidal symptoms (EPS) (Miyamoto *et al.*, 2005; Stahl, 2013). Olanzapine has high efficacy but is also associated with marked metabolic side effects and sedative action due to strong H1 receptor binding (De Hert *et al.*, 2011; Stahl, 2013). Quetiapine demonstrates relatively weak D2 blockade, resulting in minimal EPS; it is also applied in cases of bipolar depression and anxiety symptoms, though it carries side effects of significant sedation and weight gain (Miyamoto *et al.*, 2005; Stahl, 2013). Aripiprazole is a partial D2 agonist that potentially stabilizes dopaminergic tone instead of blocking it completely, which, in turn, reduces the risks of EPS and prolactin-related side effects (Kapur & Seeman, 2001; Miyamoto *et al.*, 2005; Stahl, 2013). Finally, clozapine is used for treatment-resistant cases of schizophrenia and has a unique receptor profile, which includes D4, 5-HT2A, and muscarinic receptor activity; it is exceptionally effective but carries serious risks such as agranulocytosis, seizures, myocarditis, and extensive metabolic complications (Freudenreich & Goff, 2002; Miyamoto *et al.*, 2005; De Hert *et al.*, 2011).

1.4.4. Treatment resistance and clozapine's role

An estimated 20-30% of individuals with schizophrenia are categorised as treatment-resistant. This group of cases is defined by failure to respond to at least two adequate trials of antipsychotics from different classes (Kane *et al.*, 1988; Howes *et al.*, 2017). In these situations, clozapine remains the most evidence-based option since it has shown superiority in multiple head-to-head trials. Having said that, clozapine is underprescribed because of the need for weekly or biweekly blood monitoring and its serious adverse side effects (Wheeler *et al.*, 2009).

1.4.5. Polypharmacy and combination strategies

Despite clinical guidelines often recommending monotherapy, polypharmacy is a frequent practice in real-world psychiatry, especially in complex or refractory cases. Combinations are used to diminish side effects (e.g., aripiprazole is applied to reduce risperidone-induced prolactin elevation), enhance efficacy in partial responders (e.g., the combination of clozapine and risperidone), or manage comorbid mood or anxiety symptoms (e.g., quetiapine used as a sedation supplement). On the other hand, risks of polypharmacy include increased medication burden, drug-drug interactions, side effects on cognition, and non-adherence (Tiihonen *et al.*, 2011; Gallego *et al.*, 2012). Hence, careful monitoring and individualised clinical decision-making are required.

1.5. Non-pharmacological interventions: transcranial magnetic stimulation in psychiatry

Pharmacological treatment remains the primary strategy of schizophrenia treatment, especially for the management of positive symptoms. Nonetheless, as previously mentioned, a significant portion of patients do not achieve adequate symptom control with antipsychotics alone. Consequently, the increasing interest in non-pharmacological interventions has developed. Among all, transcranial magnetic stimulation (TMS) has emerged as a promising complementary treatment, particularly for treatment-resistant schizophrenia. TMS is a non-invasive method of modulating cortical excitability and altering dysfunctional brain circuits implicated in psychosis. It is especially advantageous for disorders like schizophrenia, which are characterised by network-level dysfunction, impaired inhibition, and abnormal neural oscillations (Uhlhaas & Singer, 2010; Friston, 1998).

The mechanism of TMS is based on the principle of electromagnetic induction, first described by Faraday in the 19th century. A rapidly changing magnetic field is generated by a coil placed against the scalp, inducing an electric current in the underlying cortical neurons. In case of the sufficient current magnitude, neurons depolarise and induce action potentials. Unlike other brain stimulation techniques, such as electroconvulsive therapy (ECT), TMS does not require anaesthesia and is focal, painless, and well-tolerated (Lefaucheur, 2019; Hallett, 2007).

There are multiple protocols and forms of TMS, each with different physiological effects. Single-pulse TMS is primarily used for diagnostic and research purposes, such as measuring cortical excitability. Repetitive TMS is based on recurring TMS pulses at a specific frequency directed toward a specific brain region. It can induce longer-lasting changes in cortical activity with a very low risk of side effects, including seizures. Low-frequency rTMS (typically 1 Hz) is associated with inhibitory effects, whereas high-frequency stimulation (e.g., 10 Hz or 20 Hz) is excitatory. These effects are believed to mimic long-term depression and long-term potentiation, the synaptic plasticity mechanisms that underlie learning and memory (Lefaucheur *et al.*, 2020).

Recently, patterned forms of stimulation, such as theta burst stimulation (TBS), have been developed. The TBS mechanism delivers high-frequency pulses (50 Hz) in a pattern that mimics endogenous theta rhythms (5 Hz). Continuous TBS (cTBS) aims to suppress cortical activity, while intermittent TBS (iTBS) enhances it. These approaches require less treatment time and could offer comparable or, in some conditions, even superior efficacy to conventional rTMS (Huang *et al.*, 2005).

TMS is thought to impact neuronal oscillatory activity, synaptic transmission, and cortico-cortical connectivity. Studies have shown that rTMS can alter the expression of neurotransmitters such as

dopamine, GABA, and glutamate, depending on the stimulation site and protocol. These neuromodulatory effects are highly relevant to schizophrenia, where imbalances in these systems underlie core symptoms (Howes & Kapur, 2009; Moghaddam & Javitt, 2012).

Clinically, TMS has primarily been studied and approved for application in major depressive disorder. In this context, high-frequency stimulation of the left dorsolateral prefrontal cortex (DLPC) is associated with antidepressant effects. In schizophrenia, however, the emphasis is more on low-frequency rTMS, which is applied to the left TPJ. This area consistently shows hyperactivity in patients who experience auditory hallucinations, particularly the superior temporal gyrus, which forms the anterior-inferior boundary with the junction (Allen *et al.*, 2008; Gornerova *et al.*, 2023; Yuanjun *et al.*, 2024). By decreasing the excitability of this region, rTMS can relieve hallucinations and partially normalise associated functional connectivity patterns, as revealed by both EEG and fMRI studies.

The efficacy of rTMS for positive symptoms, particularly hallucinations, has been explored in numerous clinical trials. Meta-analyses generally suggest moderate effect sizes for reducing hallucinations with 1Hz rTMS over the TPJ, especially when delivered over multiple sessions (Aleman *et al.*, 2007; Slotema *et al.*, 2010). Continuous TBS has demonstrated similar promise, often achieving comparable effects with fewer sessions, making it more practical for inpatient settings (Oberman *et al.*, 2011). Studies using neuronavigated TMS, where stimulation targets are guided by individual anatomical scans or standard MNI templates, report enhanced response rates due to increased precision and reproducibility (Klirova *et al.*, 2013; Gornerova *et al.*, 2023).

Having that said, the response to TMS in schizophrenia is heterogeneous, and not all patients benefit equally. Factors like age, illness duration, baseline oscillatory profiles, and medication use may influence treatment outcomes. Moreover, maintenance protocols and combination strategies with pharmacotherapy or cognitive remediation remain active areas of research (Woods *et al.*, 2020).

It is important to mention that TMS is generally safe and well-tolerated, although it has few adverse effects. The most common side effects include mild headaches, scalp discomfort, and facial twitching during stimulation. Serious risks such as seizures are exceedingly rare when safety guidelines are followed (Rossi *et al.*, 2009). TMS does not require sedation or hospitalisation, making it an appealing option for outpatient and accessory treatment plans.

Overall, TMS is a valuable neuromodulatory approach that aligns mechanically and clinically with the pathophysiology of schizophrenia. TMS offers a complementary strategy to pharmacological treatment by targeting atypical cortical excitation, dysfunctional oscillations, and connectivity

imbalances. Especially in this case, for patients with persistent positive symptoms who have not responded to antipsychotic medication alone.

1.6. Repetitive transcranial magnetic stimulation for positive symptoms in schizophrenia

While antipsychotics remain the first-line treatment option for people with schizophrenia, a significant percentage of patients do not experience meaningful improvement in positive symptoms, as previously mentioned. In those cases, alternative interventions like repetitive TMS have attracted increasing attention.

1.6.1. Symptom mechanisms and cortical targets

Positive symptoms, particularly auditory verbal hallucinations (AVHs), have been linked to abnormal neural activity in the left temporoparietal junction. This area encompasses the superior temporal gyrus, Wernicke's area, and parts of the posterior inferior parietal lobe. Functional neuroimaging studies consistently reveal hyperactivation of the junction region during episodes of hallucinations (Allen *et al.*, 2008). EEG and MEG studies similarly indicate atypical oscillatory activity, including increased beta and gamma band activity in the temporal regions. This may indicate intrusive, internally generated speech mismatched to external sources (Arora *et al.*, 2020).

Considering this neurobiological profile, the left TPJ has been made the most common target for rTMS in schizophrenia. This conclusion was based on the premise that inhibitory stimulation to the hyperactive region has the potential to reduce the severity or frequency of hallucinations.

1.6.2. Repetitive TMS protocols and efficacy

There are two main protocols that are used for targeting AVHs: low-frequency (1 Hz) rTMS and continuous TBS. Low-frequency rTMS is typically delivered at 100% of the resting motor threshold for 20 minutes per session across 10-20 sessions. It has demonstrated moderate size effects in decreasing hallucination severity in multiple randomised control trials (Slotema *et al.*, 2010; Lefaucheur *et al.*, 2020). In the meantime, as noted earlier, cTBS operates by mimicking the brain's natural rhythms and needs less time. It has also demonstrated encouraging outcomes, possibly reaching similar efficacy (Oberman *et al.*, 2011).

A 2014 meta-analysis of 17 studies concluded that 1 Hz rTMS targeting the TPJ has reduced AVHs with an average standardised mean difference (SMD) of -0.42, which is considered a moderate effect (Slotema *et al.*, 2010). Other studies have applied neuronavigation techniques to improve spatial precision and reproducibility using anatomical MRI or standard MNI templates (Klirova *et al.*, 2013).

Neuronavigated rTMS could enhance treatment efficacy by ensuring accurate coil placement over the intended cortical area, especially in a structurally heterogeneous disorder such as schizophrenia.

1.6.3. Impact on EEG oscillations and network connectivity

In addition to symptomatic improvement, rTMS produces measurable changes in neural activity, specifically in EEG-recorded oscillatory dynamics. Repeated 1 Hz stimulation has been associated with reduced beta and gamma power in the stimulated temporal lobe. These results suggest a downregulation of hyperactive local networks (Jin *et al.*, 2006).

On top of the power changes, TMS has been demonstrated to modulate connectivity patterns across brain regions. For instance, resting-state EEG studies suggest that rTMS can enhance frontotemporal coherence. This tendency potentially reflects improved top-down regulation over sensory processing regions implicated in hallucinations (Hoffman *et al.*, 2003).

1.6.4. Clinical relevance and limitations

Despite promising results, the clinical implementation of rTMS in schizophrenia remains heterogeneous. Not all patients respond, and the duration of symptom improvement varies. Factors influencing rTMS results include symptom chronicity, anatomical variability in TPJ morphology, medication status and interactions, and EEG baseline profiles and responsiveness.

Moreover, rTMS has limited effects on negative and cognitive symptoms, which require different neuromodulation strategies or targets, such as DLPC stimulation. While sham-TMS (TMS that provides no actual stimulation, hence provides the placebo effect) studies support the efficacy of rTMS for AVHs, success levels tend to be modest, and maintenance protocols are often necessary to sustain improvements (Lefaucheur *et al.*, 2020).

Nevertheless, rTMS remains a valuable addition, especially for patients with persistent AVHs who do not achieve complete remission with antipsychotic medication alone. The non-invasive nature of the procedure, with a relatively minor side effect profile and network-level action, make rTMS a perfect candidate for integrated, multimodal treatment approaches in modern schizophrenia care.

1.7. EEG in neuropsychiatric research

Electroencephalography (EEG) has played a critical role in advancing our understanding of brain function, especially in psychiatric disorders. It is a non-invasive technique with millisecond-level temporal resolution. That being said, EEG is exclusively shaped to capture the fast-paced dynamics of neuronal oscillations. This tool is crucial for studying conditions characterised by dysregulated brain

rhythms, like schizophrenia. Unlike structural imaging methods, EEG directly detects neural activity, allowing researchers to monitor real-time variations in cortical excitability, network connectivity, and transitions between functional states.

The EEG signal reflects the summation of postsynaptic potentials from large populations of pyramidal neurons oriented perpendicular to the scalp. These synchronised oscillations arise from complex interactions between excitatory and inhibitory neurons. Additionally, they are organised into distinct frequency bands, each associated with specific cognitive and behavioural states (Buzsáki & Draguhn, 2004). In psychiatric neuroscience, abnormalities within the mentioned bands have been extensively documented and are progressively recognised as biomarkers of neuropathology, particularly in schizophrenia (Uhlhaas & Singer, 2010).

1.7.1. Functional roles of EEG frequency bands

EEG signals are traditionally divided into five key frequency bands: delta, theta, alpha, beta, and gamma. Delta band (0.5-3 Hz) is predominant during deep sleep. In pathological conditions, it is observed to be elevated quite often. Increases in delta during wakefulness may show cortical deactivation or white matter pathology. Theta band (4-7 Hz) is linked to internal attention, emotional processing, and working memory. In schizophrenia, frontal theta increases are associated with cognitive inefficiency and disorganised thought (Schmiedt *et al.*, 2005).

The alpha band (8-12 Hz) is standard during restful wakefulness with closed eyes. A decrease in alpha, especially in parieto-occipital regions, is a well-reproduced finding in schizophrenia, which suggests deficient cortical inhibition (Boutros *et al.*, 2008). The beta band (13-30 Hz) is involved in active cognitive processes and sensory integration. Excess beta activity in schizophrenia has been connected to perceptual instability and overprocessing of irrelevant stimuli (Winterer & Weinberger, 2004). The gamma band (30+ Hz) is associated with cognitive binding, executive function, and consciousness. Gamma dysregulation is considered an indicator of schizophrenic neural disintegration. Studies report both elevated and fragmented gamma responses during hallucinations and thought disorders (Uhlhaas & Singer, 2015).

Oscillatory coherence and synchrony within and across these bands facilitate neural communication and functional integration. Disruptions in this balance, whether through excessive synchrony, incoherence, or spectral amplitude changes, have been strongly linked to the disconnection hypothesis of schizophrenia. This theory assumes that long-range communication between the brain regions is impaired (Friston, 1998).

1.7.2. EEG biomarkers in schizophrenia research

EEG abnormalities are among the most consistent findings in schizophrenia research. Those discoveries have been observed across various stages of illness, including preliminary, first episode, and chronic phases. Resting state EEG, in particular, provides a look into the brain's innate dynamics, offering stable, reproducible measures of neurophysiological vulnerability (Hirano *et al.*, 2015).

Significant findings include:

- Increased frontal theta activity has been correlated with negative symptoms and executive dysfunction (Chen *et al.*, 2016).
- Reduced posterior alpha activity indicated impairment in thalamocortical regulation and attentional disengagement (Boutros *et al.*, 2008).
- Elevated beta and gamma oscillations, particularly in temporal and frontotemporal regions, during psychotic episodes. These findings reflect possible neural overactivation and sensory misattribution (Homan *et al.*, 2012).

Importantly, EEG abnormalities are not just byproducts. Longitudinal studies suggest that they could predict clinical deterioration, response to treatment, and even functional outcomes, offering the advantage of both state and trait biomarkers (Pascual-Marqui *et al.*, 2014).

1.7.3. Neural synchrony, connectivity, and oscillopathies

Schizophrenia is progressively conceptualised as a disorder of neural synchrony and timing rather than localised structural deficits. EEG studies have detected consistent disruptions in coherence, phase-locking, and cross-frequency coupling, especially between frontal and temporal regions (Brockhaus-Dumke *et al.*, 2008). This evidence supports the hypothesis of psychotic symptoms emerging from a failure to coordinate disturbed neural assemblies, particularly during high-order cognitive tasks.

For instance, reduced alpha and theta coherence between frontal and parietal lobes may underlie working memory deficits. Meanwhile, excessive gamma bursts in the temporal lobe have been linked to auditory verbal hallucinations (Uhlhaas & Singer, 2015). Hence, EEG provides a functional correlate to anatomical and diffusion tensor imaging findings of reduced white matter integrity and connectivity disruptions.

1.7.4. EEG and neuromodulatory interventions

Adding EEG to neuromodulatory techniques like rTMS has substantially improved our ability to assess treatment effects at the systems level. EEG has the ability to detect changes in oscillatory power, spectral entropy, and functional connectivity following TMS sessions.

The integration of EEG with neuromodulatory techniques like repetitive transcranial magnetic stimulation (rTMS) has significantly enhanced our ability to assess treatment effects at a systems level. EEG can detect changes in oscillatory power, spectral entropy, and functional connectivity following TMS sessions, shedding light on both the local and network-wide consequences of stimulation.

Studies show that rTMS applied to regions implicated in positive symptoms, such as the left TPJ, can result in decreased temporal beta and gamma activity. Consequently, it creates a tendency that potentially reflects reduced hallucination severity (Homan *et al.*, 2012). Coincidentally, increases in alpha coherence may demonstrate restored cortical inhibition, which is often deficient in schizophrenia.

Additionally, baseline EEG markers such as temporal gamma power or fronto-temporal theta coherence have been proposed as predictors of rTMS treatment response, emphasising the potential of EEG to guide individualised therapeutic strategies (Jardri *et al.*, 2011).

1.7.5. EEG findings in schizophrenia

Schizophrenia is widely recognised as a disorder of disrupted neural communication, with core symptoms such as hallucinations, disorganised thought, and cognitive deficits. All of the listed indicators are consequences of failures in cortical processing and long-range connectivity (Friston & Frith, 1995; Uhlhaas & Singer, 2010). As a direct measure of neural oscillatory activity, EEG has revealed the temporal and spectral disorganisation underlying these symptoms. Over the last several decades, a large body of research has consistently demonstrated that individuals with schizophrenia exhibit abnormal EEG signals across all major frequency bands, with alterations present during both resting-state and task-based recordings (Boutros *et al.*, 2008; Uhlhaas & Singer, 2010). These variations provide important insights into the disorder's pathophysiology. They also hold considerable significance for diagnosis, symptom monitoring, and treatment response assesment (Uhlhaas & Singer, 2015).

One of the most confirmed findings in resting-state EEG studies is a global decrease in alpha power, particularly over posterior parietal and occipital regions (Boutros *et al.*, 2008). Alpha oscillations are assumed to play a part in sensory inhibition and attentional disengagement. Therefore, their suppression in schizophrenia suggests a fundamental deficit in the ability to filter out irrelevant sensory input (Uhlhaas & Singer, 2010). This diminished alpha activity has been interpreted as an indicator of deficient

thalamocortical modulation, which is thought to be essential for the production of coherent sensory experiences and stable cognition (Winterer & Weinberger, 2004). Multiple studies have also identified reduced alpha coherence between cortical regions, further suggesting widespread dysregulation in top-down mechanisms (Boutros *et al.*, 2008).

Apart from alpha deficits, patients who have schizophrenia frequently display increased theta activity, especially over midline frontal electrodes (Koshiyama *et al.*, 2021). Theta rhythms are usually associated with working memory and cognitive control processes. Hence, their elevation may reflect compensatory mechanisms for fundamental cognitive inefficiencies (Hirano *et al.*, 2015). Increased frontal theta power has been observed in chronic patients, as well as in unmedicated individuals and those in the early stages of the illness. These findings suggest this power band's utility as a potential trait marker (Uhlhaas & Singer, 2015). Furthermore, frontal theta has been linked to the severity of negative symptoms and deficits in executive functioning, which supports its role in the core cognitive impairments that characterise schizophrenia (Chen *et al.*, 2016).

Higher frequency oscillations, such as beta and gamma, also exhibit atypical patterns in schizophrenia, although the findings are more heterogeneous (Hirano *et al.*, 2015). Beta activity, which is typically associated with sensorimotor integration and attentional focus, is often elevated in frontal and temporal regions (Moran & Senkowski, 2025). In multiple cases, this heightened beta power correlates with positive symptom severity, including delusional thinking and perceptual distortions (Uhlhaas & Singer, 2010). Critical for cognitive binding and conscious awareness, gamma oscillations have received particular attention as they reflect the integrity of fast-spiking interneuron networks (Uhlhaas & Singer, 2015). Increased gamma power in temporal and temporoparietal regions has been consistently linked to auditory verbal hallucinations (Homan *et al.*, 2012; Jardri *et al.*, 2011; Uhlhaas & Singer, 2015). Moreover, studies using source-localised EEG and simultaneous fMRI have identified overlapping regions of abnormal gamma activity and structural dysconnectivity in the superior temporal gyrus, a key intersection in the auditory network (Jardri *et al.*, 2011; Uhlhaas & Singer, 2015).

The topographical distribution of these oscillatory abnormalities provides further evidence for a model of schizophrenia that centres on cortical disintegration (Friston & Frith, 1995). Frontal regions, especially the DLPC, frequently demonstrate a combination of theta elevation and reduced beta synchrony. Those patterns align with deficits in executive control and decision-making (Uhlhaas & Singer, 2010). Meanwhile, temporal regions exhibit excessive gamma bursts that track with hallucinatory episodes. Consequently, it may reflect a failure in distinguishing internally generated speech from external stimuli (Jardri *et al.*, 2011; Uhlhaas & Singer, 2015). On the other hand, though less extensively

studied, parietal and occipital areas often show reductions in alpha and beta power, therefore hinting at potential disruptions in sensory integration and spatial awareness (Boutros *et al.*, 2008).

It is important to mention that EEG markers in schizophrenia have demonstrated correlations not only with the general illness state but also with specific symptom domains. Positive symptoms have been linked to increased gamma and beta activity in perceptual networks (Uhlhaas & Singer, 2010). Meanwhile, negative symptoms and cognitive deficits are more closely associated with low-frequency abnormalities in the theta and alpha ranges (Chen *et al.*, 2016). These interconnections emphasise the possibility of EEG serving as a biomarker detector tool for specific clinical phenotypes and forming individualised intervention strategies (Uhlhaas & Singer, 2015).

In recent years, researchers have further classified EEG abnormalities in schizophrenia into trait, state, and endophenotypic markers (Uhlhaas & Singer, 2015). Trait indicators, such as persistent frontal theta increase, are observed across illness stages and sometimes even in unaffected first-degree relatives (Hirano *et al.*, 2015). State markers, such as temporal gamma spikes, fluctuate with symptom intensity and often become normalised with successful treatment (Homan *et al.*, 2012). Endophenotypes, which narrow the gap between genetic risk and clinical expression, are observed in at-risk populations and serve as possible intermediate phenotypes for genetic and developmental studies (Winterer & Weinberger, 2004).

EEG has also been incorporated into multimodal imaging frameworks, providing an important electrophysiological addition to structural and functional MRI. For example, the mentioned gamma alterations detected via EEG often align with white matter disruptions in the arcuate fasciculus and frontotemporal tracts observed in diffusion tensor imaging studies (Geoffroy *et al.*, 2014). This synthesis supports the idea that schizophrenia is a disorder affecting systems, marked by both temporal and spatial disintegration (Friston & Frith, 1995).

In summary, EEG research has provided a comprehensive understanding of how schizophrenia interferes with the rhythmic coordination of brain activity. This disorder is characterised by widespread oscillatory abnormalities exhibiting distinct spectral features corresponding to positive, negative, and cognitive symptom groups (Uhlhaas & Singer, 2015). These findings both highlight the pathophysiology of schizophrenia and point toward electrophysiological indicators that have the potential to improve diagnosis procedures, guide treatment, and amplify our understanding of how neurobiological dysfunction translates into clinical experience.

1.8. Integration of rTMS and EEG in schizophrenia research

In recent years, the integration of repetitive TMS and EEG has emerged as a potent tool for studying and treating psychiatric disorders, especially schizophrenia. When utilised together, these modalities create a versatile framework for modulating and assessing brain activity. While rTMS provides targeted neuromodulatory stimulation to cortical areas associated with psychopathology, EEG records the resultant variations in neural oscillations and network synchrony. This combination has not only deepened the mechanistic understanding of schizophrenia but has also paved the way for more personalised, biomarker-driven interventions.

The foundation for combining rTMS and EEG is based on the pathophysiological characteristics of schizophrenia. These features include disrupted cortical excitability, abnormal oscillatory patterns, and impaired long-range communication between brain regions. These dysfunctions are particularly prominent in patients with treatment-resistant positive symptoms, such as auditory verbal hallucinations. As previously mentioned, neuroimaging and electrophysiological studies have consistently shown that these symptoms are linked to hyperactivity in the left temporoparietal cortex, specifically the STG, which is involved in auditory perception and language processing. Repetitive TMS, especially when delivered at low frequencies (e.g., 1 Hz) or in continuous TBS, has been demonstrated to inhibit cortical excitability in this region, therefore decreasing the severity of AVHs in a significant subgroup of patients (Slotema *et al.*, 2010; Yuanjun *et al.*, 2024).

EEG acts as an additional technique for tracking the neural effects of rTMS. Multiple studies have reported that successful rTMS interventions lead to modulation of frequency-specific oscillations. For instance, reductions in beta and gamma powers in the temporal lobe after rTMS have been interpreted as a normalisation of the hyperactive sensory circuits implicated in hallucinations (Homan *et al.*, 2012; Jin *et al.*, 2006; Moran & Senkowski, 2025). Moreover, rTMS has been shown to enhance alpha synchrony and theta coherence, potentially reflecting improved top-down control and network stability. These changes align with clinical improvements and, sometimes, have come before observable symptom reductions, supporting their potential role as early indicators of treatment response (Fitzgerald, 2011).

EEG usage in this context extends beyond outcome measurement; it becomes increasingly important for predicting treatment responses. Baseline oscillatory patterns, such as heightened gamma activity in the STG and increased frontal theta power, have been linked to enhanced responsiveness to TMS interventions. These results support a precision medicine approach in which neurophysiological biomarkers guide target selection, stimulation settings, and clinical decisions. (Jardri *et al.*, 2011). Some

research even suggests implementing EEG-based neuronavigation, allowing for stimulation site adjustments based on individual oscillatory maps instead of solely on anatomical references.

Beyond its clinical advantages, integrating rTMS and EEG has expanded the theoretical understanding of schizophrenia. TMS-EEG studies have revealed that the brains of individuals with schizophrenia are less responsive to external perturbation, which is sustained by the evidence of diminished evoked potentials and altered phase-locking in both frontal and temporal cortices. These results strongly support the hypothesis that schizophrenia is characterised by a widespread disruption in cortical synchrony. rTMS may serve as a potential method to externally entrain and resynchronize dysregulated networks (Uhlhaas & Singer, 2015).

However, despite this optimistic perspective, the combination of rTMS and EEG also introduces methodological challenges. EEG is highly sensitive to TMS-induced artifacts, such as magnetic coil discharge or muscle activation, requiring specialised equipment and signal processing techniques to extract clean post-stimulation data. Therefore, in this study, the EEG recordings were made before the start of the stimulation procedure and later on after it, reflecting the overall improvement results.

Furthermore, interindividual variability in skull thickness, brain anatomy, and neurochemical state can influence both the efficacy of rTMS and the interpretability of EEG outcomes. These challenges, however, have urged technological advancements, including real-time EEG-triggered TMS, closed-loop systems, and machine-learning approaches that improve noise rejection and signal categorising.

In summary, the combination of rTMS and EEG creates a unified approach for both influencing brain activity and monitoring its neurophysiological effects, particularly in schizophrenia, where abnormal oscillations play a key role in symptom manifestation. This combined approach allows researchers and clinicians to intervene at the level of dysfunctional circuits and to monitor and improve those interventions in an individualised, data-driven manner. The growing body of literature in this field offers compelling evidence that rTMS-EEG integration presents a promising frontline in neuroscience and schizophrenia treatment. This approach holds potential for symptom management and revealing the fundamental mechanisms of this complex disorder.

2. Methods and materials

2.1. Research design

This study incorporated a within-subject, pre-post experimental design to assess the effects of suppressive repetitive TMS on electroencephalographic oscillatory activity in patients with schizophrenia showing predominantly positive symptoms. The within-subject approach was chosen to minimise inter-individual variability and to detect neurophysiological changes induced by the intervention sensitivity. The study used limited resting state EEG recordings.

2.2. Participants

Nineteen patients (11 female, 7 male) aged 19-68 (M=36, SD=14.27) with a confirmed diagnosis of schizophrenia according to ICD-11 criteria. Seventeen participants exhibited dominant positive symptoms (9 female, 7 male) aged 19-68 (M=36, SD=14.37); therefore, the other two were excluded from further analysis. The prior consent was collected from all the participants. The symptoms were confirmed through clinical interviews and PANSS assessment. Exclusion criteria included comorbid neurological disorders, substance dependence, or any contraindications to rTMS (e.g., history of seizures, metallic implants).

Participants maintained stable antipsychotic medication regimens throughout the study period. The patients were prescribed a mix of antipsychotics, reflecting both monotherapy and polypharmacy (Table 3.1.1). Common agents included clozapine, risperidone, olanzapine, haloperidol, aripiprazole, and quetiapine. The selection of the drugs was carried out by professionals of the Republican Vilnius Psychiatric Hospital and was based on individual symptom profiles, previous treatment history, and tolerability.

Notably, several patients received aripiprazole in combination with a primary antipsychotic (e.g., clozapine or risperidone) to either improve tolerability or counteract metabolic and hormonal side effects. One participant was prescribed olanzapine and haloperidol, reflecting a strategy to combine strong symptom control with sedation and dopaminergic blockade, although at increased risk for EPS and metabolic complications.

The pharmacological diversity of this particular case demonstrates real-world treatment challenges and sheds more light on the clinical complexity of managing schizophrenia beyond the limits of standardised protocols.

Table 3.1.1. Summary of the drugs taken by patients in this study.

Drug	Class	Mechanism of Action	Primary Effects	Common Side Effects	Clinical Notes
Clozapine	SGA	D4, D2, 5-HT2A, M1, H1, alpha-1 blockade	Broad-spectrum, TRS efficacy	Agranulocytosis, sedation, weight gain, seizures	Gold standard for TRS; requires blood monitoring
Risperidone	SGA	D2 and 5-HT2A antagonist	Strong antipsychotic, reduces agitation	EPS, hyperprolactinemia, anxiety	Effective in acute and chronic phases
Olanzapine	SGA	5-HT2A > D2, also H1, M1, alpha-1 antagonism	Potent symptom control, mood stabilization	Weight gain, sedation, metabolic syndrome	High risk of obesity and insulin resistance
Quetiapine	SGA	Weak D2, strong H1 and alpha-1 antagonism	Sedation, anxiolysis, mood support	Drowsiness, hypotension, weight gain	Often used off-label for sleep or mood symptoms
Haloperidol	FGA	High-affinity D2 antagonist	Rapid control of agitation and psychosis	EPS, akathisia, dystonia, QT prolongation	Preferred in acute psychosis; high EPS risk
Aripiprazole	SGA	Partial D2 agonist, 5-HT1A agonist, 5-HT2A antagonist	Stabilizes dopamine, mood lift	Akathisia, insomnia, GI complications	Used as adjunct to reduce prolactin or counter sedation

Additionally 18 healthy control subjects (9 female) aged 24-69 (M=38.83, SD=13.71) participated in the study for a single EEG recording.

2.3. rTMS procedure

TMS procedures were applied using MagVenture Magpro X100 TMS stimulator with MagVenture Cool Coil B65 liquid-cooled figure-eight coil. During the stimulation, 280 μs biphasic impulses were used in 1 Hz or cTBS protocol. The stimulation target was set over the left temporoparietal junction either by a midpoint between P3/T3 electrode location in the 10-20 system or MNI coordinates: -63; -33; 6. A localite TMS Navigator MR-less system was used for neuronavigated coil placement. This neuronavigation system utilises a standard MNI (MNI ICBM152 non-linear symmetric T1 Average Brain) brain map.

The intensity of TMS was set to 100% of the resting motor threshold for 1 Hz rTMS and 80% for cTBS rTMS. 1 Hz rTMS consisted of 1 Hz stimulation in a single train lasting 20 min (1200 impulses overall). cTBS consisted of three 50 Hz pulse bursts, presented at 5 Hz frequency, applied in a single train, lasting 40 sec (600 impulses overall). Stimulation protocols of 1 Hz/cTBS were selected at random. Patients have undergone 15-30 procedures.

2.4. EEG data acquisition

For EEG recording EBNeuro Galileo Mizar apparatus was used. EEG was recorded before rTMS course and 20-30 minutes after the last procedure in the electrically shielded booth. Over the head of the patient, 20 round bridge type Ag/AgCL electrodes were placed according to international 10-20 system and secured with the special cap. Fpz electrode was used as a ground, and ear electrodes acted as a reference.

Electrode impedance was maintained lower than 5 kΩ. Resting state EEG was recorded for 10 minutes with the patient sitting with eyes closed. The sample rate of the recordings was set at 256 Hz.

2.5. EEG preprocessing

The initial steps included converting the files from EDF to SET format, reassignment of channel locations to standard BESA (standard-10-5-cap385) of MATLAB protocols, and re-referencing to the Cz electrode, which were executed using MATLAB 2022a and the EEGlab plugin 2025.0.0. Further preprocessing was conducted using Python 3.9.18 with MNE-Python for the remainder of the pipeline. The initial effects of preprocessing are reflected in Figure 1.

Preprocessing included:

- Band-pass filtering set between 0.5 and 70 Hz.
- Application of a 50 Hz notch filter to remove line noise.
- Algorithmic inspection, denoising, and rejection of artefactual segments.
- Selection of clean, 300-second segments for each pre- and post-TMS condition and healthy controls.

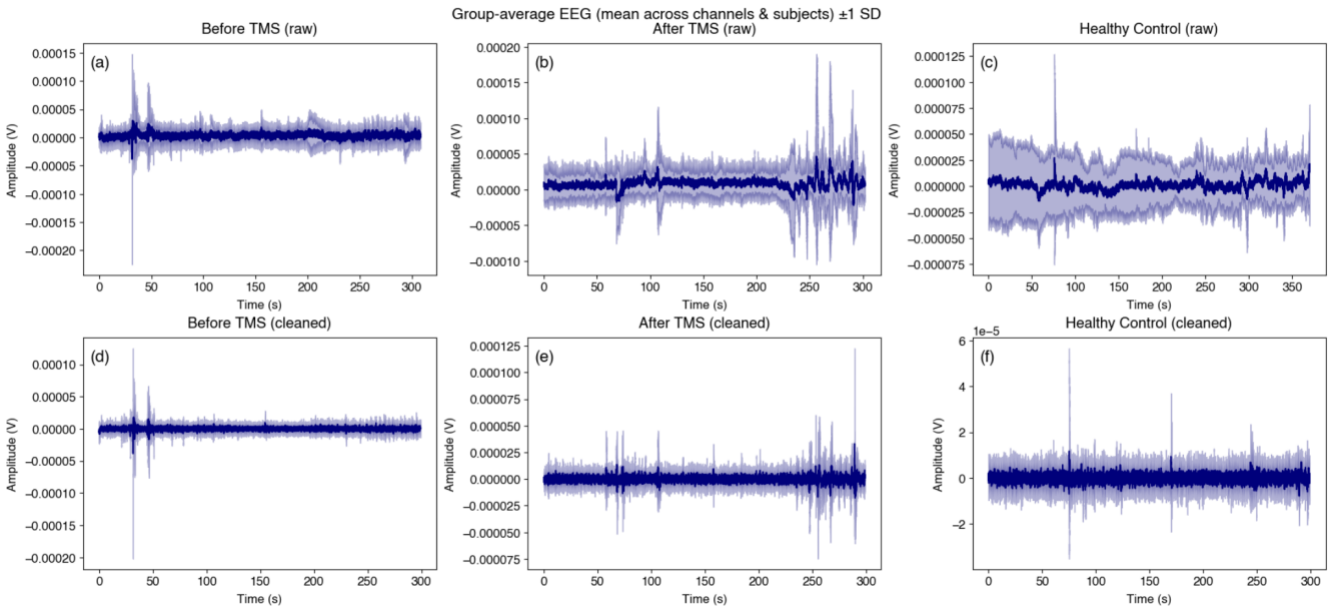

Figure 2.1. Group-averaged EEG signals before and after TMS intervention and in healthy controls (raw and cleaned data). (a) Raw EEG before TMS. (b) Raw EEG after TMS. (c) Raw EEG in healthy controls. (d) Cleaned EEG before TMS. (e) Cleaned EEG after TMS. (f) Cleaned EEG in healthy controls. Shaded areas represent ±1 standard deviation from the mean amplitude across all channels and participants.

2.6. EEG analysis

The spectral analysis focused on four canonical EEG bands: theta (4-8 Hz), alpha (8-12 Hz), beta (13-30 Hz), and gamma (30-70 Hz). Power spectral density (PSD) was computed using Welch's method with Hanning windowing and 50% overlap. Mean band power was extracted for each frequency band 1st and 2nd highest peaks and normalised for statistical comparison. For the in-depth theta and beta power bands analysis, the channel-wise PSD was computed via Welch's method over the band to obtain the mean PSD.

All the analysis was conducted in Python 3.9.18 using the following libraries:

- MNE 1.8.0: signal handling, filtering, and PSD calculation
- numpy 1.26.4: data handling and statistical tests
- scipy 1.13.1: data handling and statistical tests
- matplolib 3.9.2: visualization
- pandas 2.2.3: data structurisation
- pywt 1.6.0: wavelet-based analysis

2.7. Clinical assessment

Psychopathological symptoms were assessed two times: at the baseline – before the first TMS session and after the last TMS session. A standardised Positive and Negative Syndrome Scale (PANSS) was used to evaluate patients' negative and positive symptoms, including auditory hallucinations.

2.8. Statistical analysis

EEG band power differences before and after rTMS were assessed using one-way repeated measures ANOVA for each frequency band. ANOVA statisctical analysis was conducted in Python using scipy.stats package.

Beyond group-level comparisons, individual-level changes in EEG power were calculated by subtracting pre- and post-TMS values for each patient (Δ Power). These Δ values were used to investigate within-subject changes and to assess whether specific power shifts corresponded to PANSS score changes, mainly in the positive symptom subscale.

Therefore, the following analytical strategies were applied:

- Descriptive analysis of EEG power trends across the mentioned frequency bands.
- Statistical testing (ANOVA + post hoc) to identify significant band power differences between groups.
- Correlation analysis between EEG power changes and PANSS score reductions to explore predictive relationships between neurophysiological and clinical outcomes.
- Bar and box plots to illustrate PANSS score trends across the intervention period.

Furthermore, an F-test for equality of variances was applied to EEG power values in the beta and theta bands before and after rTMS. This test determines whether the distribution of oscillatory power became more or less variable following treatment. Due to its sensitivity to dispersion, the F-test is particularly relevant in schizophrenia research, where heightened neural variability is often pathognomonic. The test was conducted in Excel using the XLMiner Analysis ToolPak add-in (version 2025.0.0).

To explore the relationship between changes in EEG band power and improvements in clinical symptoms, specifically PANSS positive scores, both Pearson and Spearman correlation coefficients were calculated. Pearson's correlation was used to assess the linear association between continuous variables, assuming normally distributed data and homoscedasticity. However, due to the relatively small sample size and the presence of potential outliers or non-linear trends, Spearman's rank-order correlation was

also employed. Spearman's method is a non-parametric alternative that measures monotonic relationships, providing a more robust analysis in cases where data may violate the assumptions of parametric testing. Using both methods allowed for a comprehensive and conservative assessment of possible associations between neurophysiological and clinical changes following TMS treatment. The process was conducted the same way as ANOVA analysis, in Python using scipy.stats package.

3. Results

3.1. EEG spectral power trends and statistical differences across frequency bands.

The EEG data were analysed to assess the impact of rTMS on oscillatory brain activity in schizophrenia patients. Power spectral density was calculated for four frequency bands, including theta, alpha, beta and gamma, across three groups, namely before TMS, after TMS and healthy controls (Figure 3.1). The results were visualised using line plots of frequency versus power and supported by ANOVA-based statistical analysis.

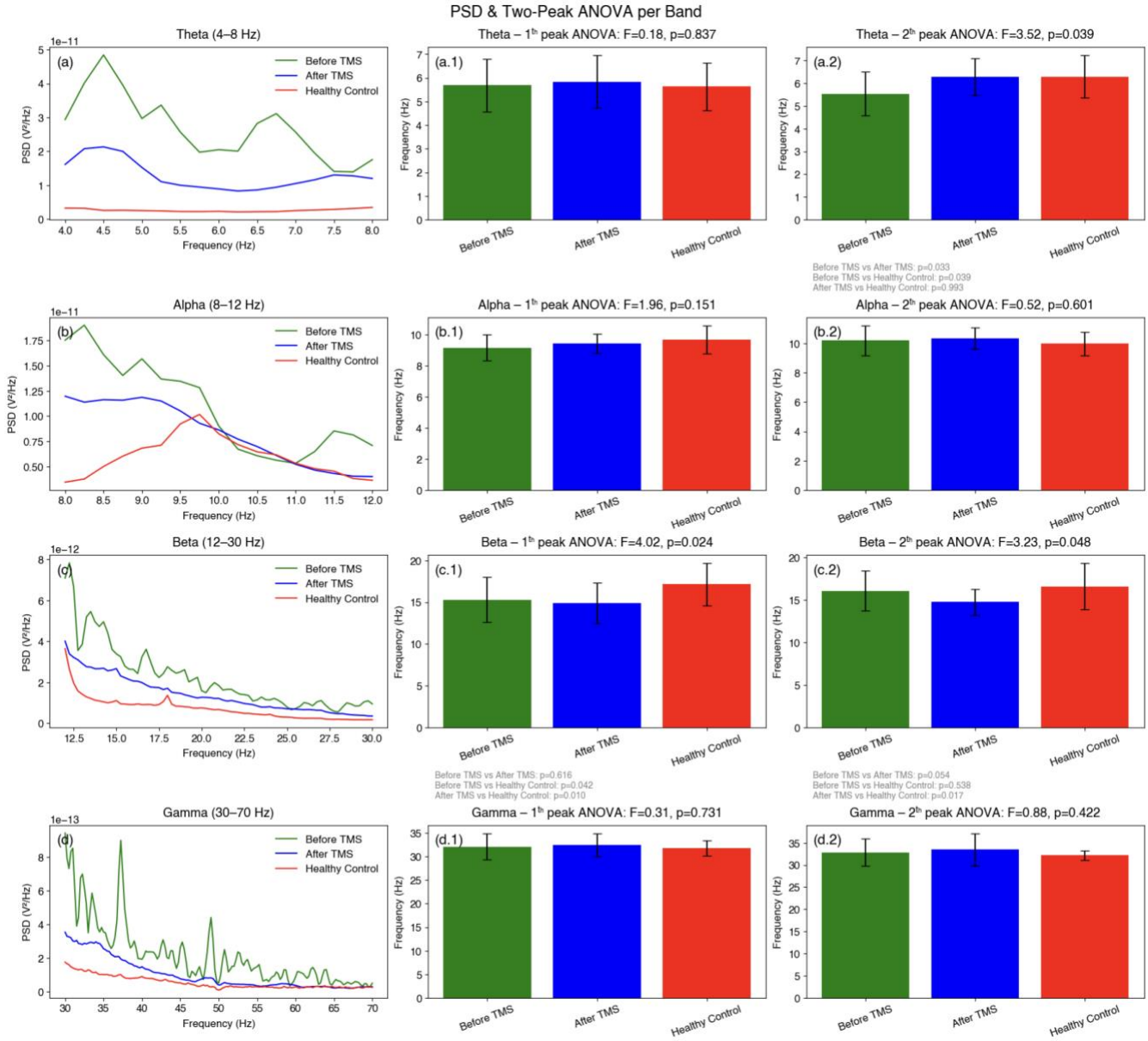

Figure 3.1. PSD curves (left column: panels a, b, c, d) and two-peak frequency comparisons (right columns: panels a.1–d.2) across theta, alpha, beta, and gamma bands. Two highest peaks were marked as high1 and high2 respectively. Statistically significant group differences were found in theta (panel a.2) and beta (panels c.1, c.2), with post-TMS peak frequencies shifting toward the healthy control group. No significant effects were found in alpha or gamma bands. Error bars represent the standard error of the mean.

3.1.1. Frequency trend analysis

As demonstrated by the graphs in Figure 3.1, there are multiple fluctuations in the frequencies across the tested groups. Theta band: The pre-TMS group showed elevated theta power, with a prominent peak at approximately 4.5 Hz. After TMS, theta power decreased noticeably and altered closer to healthy control levels, suggesting a partial normalisation of cortical slowing, which, in turn, is associated with cognitive and executive deficits.

Alpha band: Across all groups, alpha power peaked at around 8.25-9.75 Hz. The schizophrenia groups showed reduced alpha power in comparison to healthy controls. However, the change between pre- and post-TMS conditions was minimal, therefore indicating that suppressive TMS might not significantly impact alpha-band activity.

Beta band: A pronounced reduction in beta activity was observed post-TMS, especially at approximately 12.25 Hz. Before TMS, patients showed increased beta activity. After treatment, beta power dropped substantially, approaching the values recorded in healthy participants.

Gamma band: Despite gamma activity remaining elevated in patients in comparison to controls, minor decreases were detected after TMS around 30 Hz. However, gamma band changes were not statistically significant, and variability remained high.

3.1.2. Statistical analysis (ANOVA)

One-way ANOVA was conducted for each frequency band and sub-band, comparing the three groups (Figure 3.1):

Table 3.1. Summary of ANOVA post hoc analysis across analysed frequency bands.

Band	**Sub-band**	**F-value**	**p-value (overall ANOVA)**	**Post hoc comparisons**
Beta	Beta-high1	4.020	0.0239	Before vs Healthy: p = 0.042 After vs Healthy: p=0.0096 Before vs After: p=0.616
	Beta-high2	3.227	0.0479	After vs Healthy: p=0.0166
Theta	Theta-high2	3.518	0.0394	Before vs Healthy: p=0.042 After vs Healthy: p=0.0096 Before vs After: p=0.616
	Others	-	NS	Not significant
Alpha	All	-	NS	Minor numerical changes in alpha-high1
Gamma	All	-	NS	Minor numerical changes in gamma-high1

As per Table 3.1, statistically significant effects were observed in the beta and theta bands. Specifically, in the beta-high1 sub-band, a substantial group difference was found ($F = 4.020$, $p = 0.0239$). Post hoc analysis revealed that beta-high1 power was significantly higher in the pre-TMS group compared to healthy controls ($p = 0.042$), and in the post-TMS group compared to healthy controls ($p = 0.0096$). Still, no difference was found between pre- and post-TMS conditions ($p = 0.616$). Similarly, the beta-high2 sub-band showed a significant overall difference ($F = 3.227$, $p = 0.0479$), with a notable increase in the post-TMS group relative to controls ($p = 0.0166$).

According to the results of the analysis, summarised in Table 3.2.1, in the theta band, theta-high2 demonstrated significant group effects ($F = 3.518$, $p = 0.0394$). Here, both the pre-TMS and post-TMS groups exhibited significantly higher theta power than healthy controls ($p = 0.042$ and $p = 0.0096$, respectively). However, there was no significant change between pre- and post-TMS conditions ($p = 0.616$). Furthermore, No significant group differences were observed in alpha or gamma sub-bands ($p > 0.05$), although minor numerical trends were detected in alpha-high1 and gamma-high1.

3.2. Analysis of beta and theta power changes

An F-test was conducted to assess whether the variances in EEG power within the beta and theta bands differed significantly before and after rTMS treatment. The results are displayed in Table 3.2.

Table 3.2. Summary of the results of F-tests conducted to compare the variances of EEG power in the beta and theta bands before and after rTMS treatment

Band	Condition Compared	F-value	p-value	F-critical ($\alpha = 0.05$)	Result
Beta	Before TMS vs After TMS	16.88	4.31E-07	2.33	Significant ↓ variance
Theta		67.37	1.23E-11	2.33	Significant ↓ variance

As summarised in Table 3.2, both frequency bands demonstrated statistically significant reductions in variance following stimulation. Specifically, the beta band yielded an F-value of 16.88 with a p-value of 4.31×10^{-7}, exceeding the critical F-value threshold of 2.33. Similarly, the theta band showed a robust effect, with an F-value of 67.37 and a p-value of 1.23×10^{-11}.

3.3. Changes in PANSS positive symptom scores

Beyond neurophysiological data, the clinical impact of rTMS was assessed using the Positive and Negative Syndrome Scale, or PANSS, a widely validated tool for quantifying symptom severity in schizophrenia. This section focuses on the positive symptom subscale, which captures key features such as hallucinations, delusions, conceptual disorganisation, and suspiciousness.

3.3.1. Overview of PANSS Evaluation

Each patient underwent the PANSS assessment twice, before the rTMS treatment and after completing the full stimulation protocol. The comparison of those two points in time provides a clinically grounded measure of rTMS treatment efficacy. On top of that, patients were selected for this study based on the presence of positive symptoms, making this subsample particularly well suited for evaluating symptom-related outcomes.

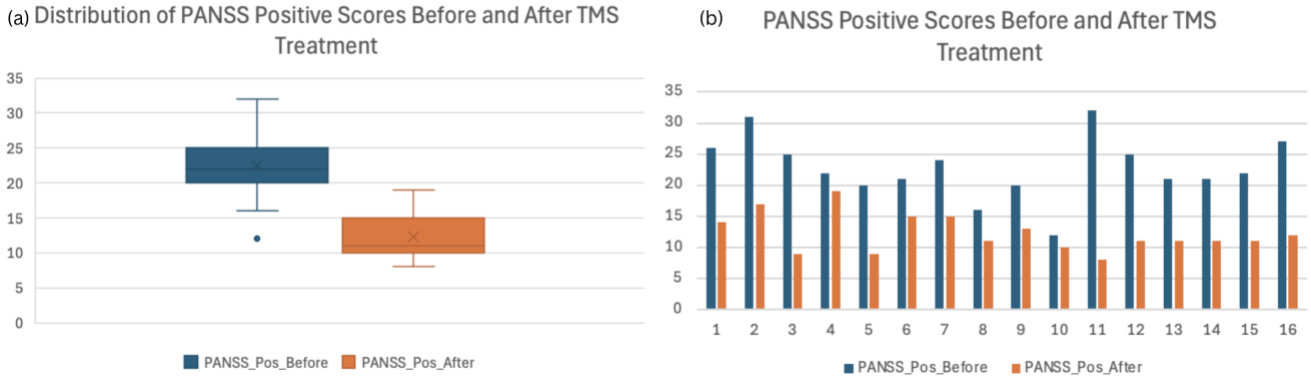

Figure 3.2. Summary of changes in PANNS positive scores before and after TMS treatment across patients. (a) Boxplot of PANSS positive scores before and after TMS treatment, showing a consistent reduction across patients. Median and interquartile ranges suggest a downward shift in symptom severity. (b) Bar chart comparing individual PANSS positive scores before and after TMS, further illustrating symptom improvement in nearly all patients following intervention. These visualisations highlight the overall clinical effect of rTMS on psychotic symptoms.

3.3.2. PANSS positive score reduction

A boxplot comparing PANSS positive scores before and after rTMS in Figure 3a showed a marked reduction in symptom severity post-treatment. The median score decreased, and the interquartile range narrowed, suggesting general improvement and reduced variability in clinical response.

Patients with higher pre-treatment PANSS scores, as demonstrated by the bar plot in Figure 3b, namely PANSS Positive Scores Before and After TMS Treatment, tended to show larger reductions. However, a few individuals exhibited more modest change, highlighting interindividual variability in response. Nevertheless, the overall downward trend is consistent and compelling.

Before TMS, PANSS positive scores ranged broadly, with several patients scoring above 20, indicating moderate to severe psychotic symptoms. While after TMS, most patients demonstrated clear reductions in score, with several dropping below the clinical threshold of moderate severity. The spread of scores decreased, suggesting that rTMS produced more uniform effects in this sample.

3.4. Correlation between EEG power changes and PANSS symptom improvement

Following the demonstration that rTMS induced substantial changes in both oscillatory brain dynamics and positive symptom severity, the next step was to assess whether these two domains were functionally related. Therefore, this section describes whether reductions in EEG beta and theta band power following rTMS correlate with reductions in PANSS positive symptom scores. That relationship, if confirmed, would provide further support for the use of electrophysiological biomarkers in predicting and tracking clinical response in schizophrenia.

Table 3.3. Correlation coefficients between changes in EEG band power (beta and theta) and improvement in positive PANSS scores

EEG band	Pearson r	p-value	Spearman ρ	p-value
Beta	0.193	0.4734	0.205	0.4469
Theta	0.233	0.3842	0.485	0.0572

The relationships between EEG power reductions and improvements in positive symptoms were assessed using both Pearson and Spearman correlation coefficients (Table 3.2, Figure 3.3). In the theta band, the Pearson correlation between changes in theta power and Δ PANSS positive scores was $r = 0.233$ ($p = 0.3842$), while the corresponding Spearman coefficient was $\rho = 0.485$ ($p = 0.0572$). Although the Pearson result was not statistically significant, the stronger Spearman correlation

approached significance, suggesting a potentially meaningful monotonic relationship between reductions in theta power and positive symptom improvement.

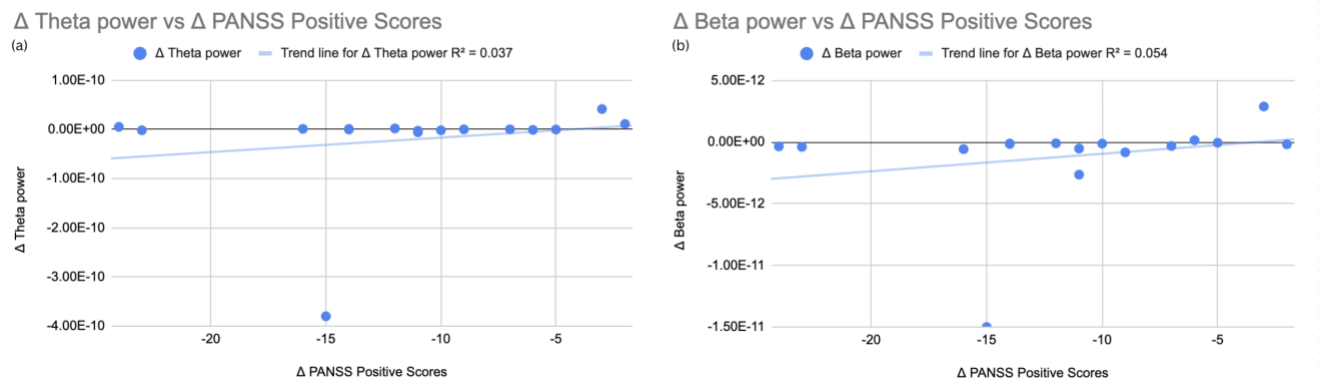

Figure 3.3. Scatter plots displaying the relationships between changes in EEG power (Δ Beta and Δ Theta) and changes in PANSS Positive scores following rTMS treatment. Panel (**a**) shows Δ Theta power vs ΔPANSS Positive scores, with a weak positive linear trend (Pearson r = 0.233, R^2 = 0.037). Panel (**b**) shows Δ Beta power vs ΔPANSS Positive scores, which demonstrated a slightly stronger trend (Pearson r = 0.193, R^2 = 0.054)

The relationships between EEG power reductions and improvements in positive symptoms were assessed using both Pearson and Spearman correlation coefficients (Table 3.2, Figure 3.3). In the theta band, the Pearson correlation between changes in theta power and Δ PANSS positive scores was r = 0.233 (p = 0.3842), while the corresponding Spearman coefficient was ρ = 0.485 (p = 0.0572). Although the Pearson result was not statistically significant, the stronger Spearman correlation approached significance, suggesting a potentially meaningful monotonic relationship between reductions in theta power and positive symptom improvement.

For the beta band, both Pearson (r = 0.193, p = 0.4734) and Spearman (ρ = 0.205, p = 0.4469) correlations were low in magnitude and not significant. This indicates a weaker association between beta power changes and clinical improvement in positive symptoms.

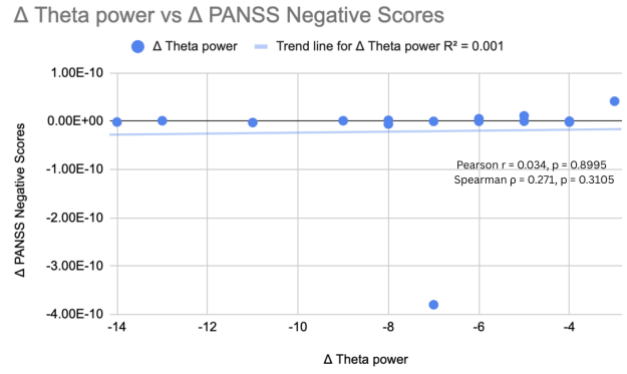

Figure 3.4. Scatter plot displaying the relationship between changes in theta band power (Δ Theta) and PANSS negative scores following rTMS treatment.

The relationship between theta band reductions and improvements in PANSS negative symptoms was evaluated using Pearson and Spearman correlation coefficients (Figure 3.4). The Pearson correlation between changes in theta power and Δ PANSS negative scores was $r = 0.034$ ($p = 0.8995$), while the corresponding Spearman coefficient was $\rho = 0.271$ ($p = 0.3105$). Both results were not statistically significant.

4. Discussion

This study explored the impact of suppressive repetitive TMS on electrophysiological patterns and symptom severity in schizophrenia, particularly focusing on the positive cluster. The analysis combined electroencephalographic power spectra and changes in clinical scores on the PANSS to evaluate the effects of rTMS on oscillatory brain activity and its potential to reduce positive psychotic symptoms.

The EEG analyses revealed a decrease in power band frequency post-TMS (Figure 3.1), approaching the level of brain activity observed in healthy controls. Furthermore, it demonstrated that beta and theta frequency bands had the highest responsiveness rate to rTMS treatment (Figure 3.1, Table 3.1, Table 3.2). Post-intervention recordings revealed a significant reduction in power within the mentioned bands. Post-TMS decreases in beta band power towards levels observed in healthy controls support the notion of normalising neural hyperexcitability in sensory processing networks (Jin *et al.*, 2006). Similarly, theta power also showed post-TMS reduction, indicating potential improvements in cognitive regulation and attentional control. These trends were supported by ANOVA results, which provided statistically significant differences in the second-highest theta peak and first and second beta peaks across pre-TMS, post-TMS, and healthy control conditions. Moreover, these observations align with theoretical models suggesting that excessive beta oscillations are linked to sensory misattribution, delusional thinking, and other positive symptoms in schizophrenia (Uhlhaas & Singer, 2010; Homan *et al.*, 2012).

The observed EEG spectral power notions support the main characteristics of schizophrenia, specifically abnormal oscillatory dynamics, reflecting disrupted cortical connectivity and neurotransmitter imbalances, which are extensively discussed in the literature (Friston & Frith, 1995; Uhlhaas & Singer, 2010). More than that, the reported changes in theta and beta bands potentially correspond to rTMS-induced modulation of hyperactive neural circuits, which are thought to underlie psychotic episodes and cognitive dysfunction (Uhlhaas & Singer, 2015). The mentioned reduction of beta power post-treatment reinforces the band's relevance as a neurophysiological biomarker of clinical improvement. Moreover, the more detailed analysis of beta and theta power revealed statistically significant reductions in variance after the treatment (Table 3.2). These findings suggest that rTMS reduces mean power in the mentioned bands, therefore stabilising their activity. The observations are supported by the existing research that provides evidence of beta activity reduction post-rTMS (Jin *et al.*, 2006; Hoffman *et al.*, 2003).

Additionally, the statistically significant differences in theta and beta-high frequency bands between patient groups and healthy controls, as well as the pronounced reductions in variance post-treatment (Table 3.1) underline the modulatory efficacy of rTMS. These electrophysiological outcomes substantiate the claim that suppressive rTMS can effectively attenuate cortical hyperactivity, particularly within the left temporoparietal junction (TPJ), an area consistently implicated in auditory hallucinations and other positive symptoms (Allen *et al.*, 2008; Slotema *et al.*, 2010).

On the other hand, alpha and gamma band activities did not respond to the treatment at the same rates as beta and theta bands, suggesting that these frequencies were less sensitive to the stimulation parameters in this study. Besides potential explanations for the appearance of minimal changes, such as the complexity of oscillatory dysconnectivity, the targeted area of rTMS remained the left TPJ, which has been mainly linked to beta abnormalities (Homan *et al.*, 2012).

When it comes to the clinical profile, the significant improvements observed in PANSS positive scores (Figure 3.2) further support the therapeutic potential of rTMS. Changes in the mentioned scores demonstrate a decline across the sample following treatment. This reduction suggests that positive symptoms became less pronounced, hence less severe. The distribution of PANSS scores became more stable post-treatment, indicating a more uniform clinical response among participants. The decrease in symptom severity aligns with existing literature, which highlights the role of targeted neuromodulation in alleviating resistant psychotic symptoms (Yuanjun *et al.*, 2024). However, the variability in patient responses underscores a continuing challenge in schizophrenia treatment, suggesting that personalised approaches based on individual neurophysiological profiles could enhance outcomes.

Even though the observed improvements in PANSS positive scores correlated weakly with EEG power changes in the reviewed bands (Table 3.2, Figure 3.3), the stronger Spearman correlation observed with theta activity indicates a potential meaningful and complex relationship. This trend is supported by the previous findings suggesting that theta synchronisation plays a significant role in cognitive deficits and psychotic symptom manifestation in schizophrenia (Schmiedt *et al.*, 2005). On the other hand, the typical association of theta band power decrease and negative symptoms improvement (Chen *et al.*, 2016) was not supported by the findings (Figure 3.4). The potential cause of the lack of observations of this relationship can be the focus of the study on the positive cluster, with patients exhibiting auditory verbal hallucinations. Further research into baseline EEG characteristics could offer predictive markers of individual response to rTMS therapy, contributing to more tailored treatment strategies.

4.1. Limitations

The study had several limitations, including a lack of complete clinical profiles for some patients, a small sample size, varying periods of illness duration (minimum 2 years, maximum 33 years), age differences, and both mono- and polypharmacotherapy. Additionally, the study used limited resting state EEG recordings before and after the treatment, which might have not been sufficient to capture such events as alpha and gamma activity. Further research is required to confirm existing findings, especially longitudinal studies, as well as the incorporation of various neuroimaging techniques, such as DTI and fMRI.

Conclusions

The main objective of this thesis was to evaluate the effects of the stimulation on electrophysiological patterns and positive clinical symptoms in schizophrenic patients. Specifically, the study aimed to analyse EEG spectral power changes across various frequency bands, namely theta, alpha, beta and gamma, and assess their correlation with symptom severity, which the Positive and Negative Syndrome Scale measured. EEG recordings and PANSS evaluations were performed at two time points, specifically before and after rTMS intervention, which targeted the left temporoparietal junction.

The findings imply that rTMS effectively modulates EEG oscillatory patterns, particularly reducing cortical hyperactivity, which is associated with positive symptoms of schizophrenia. This study emphasises the potential of EEG-informed rTMS as a targeted therapeutic approach. Also, it suggests directions for future research, including larger sample sizes, multimodal imaging integration, and longitudinal studies to improve treatment strategies. The set tasks were accomplished:

1. The developed algorithm for automated EEG artefact filtration and analysis significantly improves data processing accuracy and reliability.
2. Theta and beta EEG spectral power significantly decreased following TMS therapy, indicating effective neuromodulatory effects.
3. Schizophrenia patients exhibit higher theta and beta EEG spectral power compared to healthy controls, with post-TMS patient values shifting towards normal ranges.
4. Positive symptoms, as measured by PANSS, markedly improved post-TMS, highlighting the clinical efficacy of the treatment.
5. Reduction in EEG theta power correlates with positive symptom improvement, suggesting theta band changes as potential biomarkers for clinical response to TMS therapy.

The summary of this thesis highlights several contributions to the existing body of schizophrenia research. First and foremost, it provides robust evidence of rTMS significantly influencing cortical activity, particularly within the theta and beta frequency bands, therefore suggesting effective modulation of neural hyperactivity, which is associated with positive symptoms. Specifically, a substantial decrease in theta and beta power following rTMS treatment, as confirmed by the results of the F-test (Table 3.2). Secondly, it confirms the clinical efficacy of rTMS by demonstrating measurable improvements in PANSS positive symptom scores (Figure 3), supporting its potential as an additional therapy in treatment-resistant schizophrenia.

Moreover, this research stresses the value of integrating EEG biomarkers into clinical practice, creating a potential predictive framework for treatment responsiveness. The recognition of specific electrophysiological changes post-TMS improves the precision of neuromodulatory interventions, leading to more individualised and effective treatment approaches.

Despite the promising findings, this study also acknowledges certain limitations, including the modest sample size and lack of long-term follow-up. Expanding future research and incorporating multimodal imaging techniques will further improve comprehension and clinical relevance.

Finally, the findings of this research greatly enrich the development of personalised, evidence-based interventions for schizophrenia, highlighting the substantial impact of neuromodulatory methods such as rTMS in improving patient outcomes and overall quality of life.

Acknowledgements

Thanks to my supervisor, Dr. Vladas Valiulis for his diligent support and guidance.

Thanks to Dr. Evaldas Pipinis for his help with MATLAB functions.

Thanks to Dr. Giedrė Valiulienė for her help and support.

Thanks to the Department of Neurobiology and Biophysics of the Life Sciences Center for the knowledge and skills, it takes a village to raise a scholar.

Thanks to my friends and family for their support and for listening to me discuss my research for hours.

Thanks to my therapist for keeping me sane.

Thanks to me, my mind and body for not shutting down and making it possible to finish this thesis.

Special thanks to the Ukrainian Armed Forces for giving me the opportunity to be a free Ukrainian and pursue my dreams.

Two AI tools were used in this work. OpenAI (2025) *ChatGPT* [Large Language Model] for structurisation, sorting and summary of several papers. https://chat.openai.com/chat

Grammarly (2025) for grammar correction and text improvement. https://app.grammarly.com/

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Abstract (in Lithuanian)

VILNIAUS UNIVERSITETAS
GYVYBĖS MOKSLŲ CENTRAS

Anastasiia Tesliuk

Magistro darbas

TMS poveikis šizofrenija sergančių pacientų EEG

Šizofrenija yra sunki psichinė liga, pasireiškianti reikšmingais mąstymo, emocijų bei elgesio sutrikimais. Įparstiniam gydymui atsparių simptomų, ypač klausos haliucinacijų, terapijoje, dideliu potencialu pasižymi alternatyvios neuromoduliacinės metodikos, tokios kaip transkranijinė magnetinė stimuliacija.

Pagrindinis šio darbo tikslas buvo ištirti TMS elektrofiziologinį poveikį šizofrenijos pacientams ir jo ryšį su su klinikinių simptomų pagerėjimu. Konkretūs uždaviniai apėmė EEG spektro galios pokyčių teta, alfa, beta ir gama dažnių intervaluose įvertinimą prieš TMS terapij1 ir po jos, klinikinių simptomų įverinimą naudojant pozityvių ir negatyvių simptomų skalę, bei sąryšio tarp EEG pokyčių ir klinikinių pokyčių nustatymą.

Tyrime dalyvavo septyniolika šizofrenijos pacientų, kuriems buvo užrašoma EEG prieš ir po TMS, nutaikytos į kariojo smegenų pusrutulio temporoparietalinę jungtį. EEG analizė atskleidė reikšmingą teta ir beta dažnių galios sumažėjimą po gydymo. Taip pat klinikiniu aspektu buvo nustatytas žymus PANSS pozityvių simptomų skalės įverčio sumažėjimas, koreliuojantis su elektrofiziologiniais pokyčiais.

Tyrimas parodė, kad EEG spektro galia, ypač teta ir beta dažnių diapazonuose, gali būti naudojami kaip kaip patikimas terapinio atsako indiakatorius alternatyviems gydymo būdams. Rezultatai pagrindžia, jog tikslinga neuromoduliacija efektyviai normalizuoja padidėjusį smegenų žievės aktyvumą, susijusį su pozityviais šizofrenijos simptomais, ir suteikia pagrindą tolimesniems EEG pagrindu sukurtiems TMS įverčiams sukurti.

Abstract (in English)

VILNIUS UNIVERSITY
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Anastasiia Tesliuk

Master's thesis

Effects of TMS on EEG in patients with schizophrenia

Schizophrenia is a severe psychiatric disorder associated with significant cognitive, emotional and behavioural disturbances. Neuromodulation techniques, such as repetitive transcranial magnetic stimulation, demonstrate potential in managing treatment-resistant symptoms, particularly auditory verbal hallucinations.

The main objective of this thesis was to investigate the electrophysiological effects of the mentioned stimulation and their association with clinical symptom improvement in schizophrenia patients. Specific goals included evaluating EEG spectral power changes in theta, alpha, beta and gamma frequency bands pre- and post-rTMS, evaluating symptom severity using the Positive and Negative Syndrome Scale, and exploring correlations between EEG changes and clinical outcomes.

Seventeen schizophrenia patients were included in the study, with EEG data collected before and after targeted rTMS treatment of the left temporoparietal junction. EEG analysis revealed significant reductions in theta and beta band power following treatment. Additionally, in a clinical context, a notable improvement in PANSS positive scores was observed, correlating with electrophysiological findings.

The study demonstrates that EEG spectral power, especially within theta and beta bands, is a reliable indicator of therapeutic response to the alternative treatment. Results imply that targeted neuromodulation effectively normalises cortical hyperactivity associated with positive symptoms in schizophrenia, providing a foundation for further development of EEG-informed rTMS interventions.