MISMATCH NEGATIVITY TO DIFFERENT DEVIANTS AND LINKS WITH AUDITORY HALLUCINATIONS IN SCHIZOPHRENIA

BRONWEN SCHRYVER

BSc, Mount Saint Vincent University, 2018

Thesis submitted to the University of Ottawa

in partial fulfillment of the requirements for the Degree of

Master of Arts in Experimental Psychology

School of Psychology, Faculty of Social Sciences

University of Ottawa

ABSTRACT

Schizophrenia (SZ) is a complex and chronic psychotic disorder that affects approximately 1% of the world's population and is associated with positive, negative, and cognitive symptoms. Auditory verbal hallucinations (AVHs) are a key symptom of SZ that cause functional impairments and distress. Despite antipsychotic medication treatments, 25% of patients experience medication resistant AVHs. Additional research into the underlying neuronal mechanisms of AVHs is needed to develop alternative treatments. The mismatch negativity (MMN) is an auditory event-related potential that represents pre-attentive detection of stimulus deviance. MMN deficits are prominent in SZ and are associated with greater AVH frequency. MMN deficits may also be related to qualitative features of AVHs, which have yet to be extensively assessed.

The primary aim of this work was to assess differences in MMN features (amplitude and latency) between SZ patients and healthy controls (HCs) using two different versions of the MMN five deviant multi-feature task (pure tone and speech-based sounds). The second aim was to examine relationships between MMN features, clinical ratings of AVH severity (The Psychotic Symptom Rating Scale [PSYRATS] total score, Positive and Negative Syndrome Scale [PANSS] item 3 ["hallucinatory behaviour"]) and self-report measures of AVH features in SZ patients (i.e., the Beliefs About Voices Questionnaire-Revised [BAVQ-R], Voice Acceptance and Action Scale [VAAS] and the Voice Power Differential Scale [VPDS]), the latter has yet to be assessed. The secondary aim was to directly compare differences in the MMN responses between SZ and HC groups across the two tasks. Finally, exploratory aims included examining differences in MMN responses to low and high frequency and intensity deviants in the tone task and assessing differences in the MMN response between groups at the mastoid sites (TP_9/TP_{10}),

where the polarity reversal of the MMN occurs. These more methodological aims have not been previously assessed, to our knowledge.

The SZ group (n = 16) had significantly smaller MMN amplitudes to the frequency, gap and intensity deviants compared to the HC group (n = 17) in the MMN tone task. In the MMN speech task, the SZ group had significantly smaller MMN amplitudes to the frequency, intensity, vowel duration and consonant deviants compared to the HC group. The correlation analysis revealed that the most pronounced relation was a positive association between MMN amplitudes to the intensity deviant (tone task) and total scores on the VPDS (i.e., smaller/less negative MMN amplitudes were associated with higher VPDS scores). For the secondary analyses, the SZ group had smaller MMN amplitudes to the frequency deviant in both the tone and speech MMN tasks. Finally, the exploratory mastoid analysis in the tone task revealed that the SZ group had smaller MMN amplitudes to the frequency deviant at both mastoid sites. In the speech task, MMN amplitudes were larger at the left mastoid site (TP_9) compared to the right mastoid site (TP_{10}) across all deviant types. The HC group also had larger MMN amplitudes at the left mastoid site (TP_9) compared to the SZ group.

This study revealed MMN deficits in SZ patients across a variety of deviant types, including both pure tone deviants and speech-based deviants. MMN deficits were most pronounced for the frequency and intensity deviants across both tasks, suggesting that SZ patients with persistent AVHs may have more generalized deficits in the automatic processing of basic units of speech and pure tones, rather than impaired processing of specific acoustic features. Associations between MMN features and subjective measures of AVHs revealed that impaired processing of pure tone intensity deviants is related with a greater perceived “power” of the voice, impaired processing of speech-based frequency deviants is related to greater clinical

AVH severity, and that impaired and less efficient processing of both vowel and pure tone deviants are related to a higher perceived hostility of the voice. This study adds valuable information to the literature regarding relationships between MMN features and subjective aspects of the AVH experience in SZ patients. Importantly, this work is novel as it is the first to directly compare MMN responses across two tasks (speech and sound) in SZ patients with persistent AVHs. This thesis emphasizes the importance of examining subjective aspects of the AVH experience in the context of the MMN to gather a more complete understanding of how AVHs are impacting brain responses.

ACKNOWLEDGEMENTS

I would like to give a huge thank you to my supervisor, Dr. Natalia Jaworska, for her immense amount of support both personally and academically throughout my journey of completing this degree. This thesis is greatly different from what I expected it to be when I began this degree, and I faced many challenges along the way, but thanks to the support and guidance from Natalia it is something that I am ultimately very proud of. I would also like to thank the members of my thesis committee, Dr. Verner Knott, Dr. Patrick Davidson and Dr. Kenneth Campbell for their support, encouragement, and feedback on my work over the years. I am also deeply grateful for the support and help from various lab members over the years, including Molly and Courtney for helping with getting the project off the ground and setting up the various tasks, as well as Tola, Corrine, Marie, Emma, Sara, Jency, and Sara L. for their assistance with testing and recruitment.

From my personal life, I would like to thank my amazing boyfriend Nick, who I met in the latter half of my degree, but who has supported me unconditionally from the beginning. Your words of encouragement, positive attitude, and endless support gave me the strength to push through to the finish line which I am forever grateful for. Thank you to my family members, including my mom, my dad, my brother Nigel, my grandparents (Nannie & Poppie) and my stepfamily for their ongoing love and support, being a listening ear, and for giving me advice to help me navigate this path of my life. Thank you to my friend Jordan, who is one of my biggest supporters and always gave me words of validation and encouragement whenever I needed it, and who I could always count on to rave about our favourite music group together. Finally, thank you to my best friend from the program, Megan, who has been there for me through the good and the bad times, who understands the struggles of life during grad school and who I can always

count on for some much-needed self-care activities like plant shopping or paint night. Without this support from my friends, family, and colleagues, I would not have been able to make it to where I am today.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LEGEND

AVHs	Auditory Verbal Hallucinations
BAI	Beck Anxiety Inventory
BAVQ-R	Beliefs About Voices Questionnaire-Revised
BDI-II	Beck Depression Inventory
CBTp	Cognitive behavioural therapy for psychosis
DLPFC	Dorsolateral prefrontal cortex
EEG	Electroencephalography
ERP	Event-related potential
FF	Fundamental frequency
FGAs	First-generation antipsychotics
FMRI	Functional magnetic resonance imaging
HC	Healthy control
ICA	Independent component analysis
ITG	Inferior temporal gyrus
LTD	Long-term depression
LTP	Long-term potentiation
MMN	Mismatch negativity
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MTG	Middle temporal gyrus
nAChRs	Nicotinic acetylcholine receptors
NART	National Adult Reading Test

NMDA	N-methyl-D-aspartate
PAC	Primary auditory cortex
PANSS	Positive and Negative Symptom Scale
PSYRATS	Psychotic Symptoms Rating Scale
Q-LES-Q-SF	Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form
RCT	Randomized control trial
rTMS	Repetitive transcranial magnetic stimulation
SD	Standard Deviation
SGAs	Second-generation antipsychotics
STG	Superior temporal gyrus
SZ	Schizophrenia
tDCS	Transcranial direct current stimulation
TPJ	Temporo-parietal junction
VPDS	Voice Power Differential Scale
VAAS	Voices Acceptance and Action Scale

1. INTRODUCTION

1.1 Schizophrenia – Overview

Schizophrenia (SZ) is a complex and chronic psychotic disorder that affects approximately 1% of the world's population and typically emerges in late adolescence and early adulthood (Gogtay et al., 2011; Kahn et al., 2015). SZ carries significant personal, social, and economic burdens, as many patients are unable to maintain social relationships, hold employment and struggle with homelessness (Stępnicki et al., 2018). Age of onset appears to play a role in severity, as it has been found that those with an earlier age of onset tend to experience greater symptom severity and an overall worse prognosis compared to those with a later age of onset (DeLisi, 1992; Luoma et al., 2008). The disorder is characterized by a combination of positive (e.g., delusions and hallucinations) and negative symptoms (e.g., flattened affect, anhedonia, avolition, alogia) coupled with widespread cognitive impairments (Andreasen & Olsen, 1982), resulting in considerable functional impairment, including difficulty with carrying out daily tasks, engaging in social interactions and maintaining employment (Świtaj et al., 2012). Cognitive functions that are commonly impaired in SZ include executive functioning (e.g., planning, decision making), memory (working memory, short-term and long-term), sustained attention, emotional processing, and social cognition (Heinrichs & Zakzanis, 1998). The core criteria for a diagnosis of SZ according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) includes the presence of two or more of the main psychotic symptoms (i.e., delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behaviour and negative symptoms) for at least 6 months (including 1 month of active psychotic symptoms; at least one symptom must be either delusions, hallucinations or disorganized speech) and major impairment of functioning in one or more major life areas (e.g. work, interpersonal

relationships, self-care, academic achievements; Arciniegas, 2015; Tandon et al., 2013). Schizoaffective disorder is a variant of SZ which, from a diagnostic perspective, requires an uninterrupted period of illness during which there is a major mood episode (either major depressive or manic) for the majority of the total duration of the illness, in addition to the presence of two or more of the characteristic SZ symptoms (Malaspina et al., 2013). There are also relatively high rates of comorbid psychiatric disorders in SZ, including depression, anxiety, and substance use disorders (Buckley et al., 2009).

1.2 Auditory Verbal Hallucinations (AVHs)

Auditory verbal hallucinations (AVHs), which can be defined as perceptions of speech or sounds in the absence of external corresponding auditory stimuli, occur in 60-80% of SZ patients (Andreasen & Flaum, 1991), making them the most prevalent type of hallucination in SZ. Generally, AVHs reflect a diverse auditory experience involving words, sentences or conversations spoken by familiar or unfamiliar voices, as well as by single or multiple voices that may give commands, comments, insults, or encouragement. The clinical presentation of AVHs are heterogenous, and do not manifest in the same way across patients. Individual experiences of AVHs can range from very mild, quiet, and infrequent sounds or voices that do not cause much disruption to daily functioning, to constant, loud, and intrusive voices which cause significant difficulty in maintaining a normal life (Larøi et al., 2012). AVHs also often contain derogatory and threatening content, thereby increasing patient anxiety, and possibly encouraging social withdrawal (Delespaul et al., 2002). AVHs play a key role in the functional outcomes of SZ patients, with chronic presence of hallucinations significantly impairing quality of life (Shergill, Murray & McGuire, 1998) and cognitive functioning (Brekke, Hoe, Long & Green, 2007). Importantly, about 25% of SZ patients experience AVHs that are medication-

resistant and chronic (Shergill et al., 1998), highlighting the need for further research into the underlying neuronal mechanisms of AVHs, and the need for improved treatment options.

1.2.1 Assessment of AVHs

Common symptom scales for assessing AVHs include the clinician-rated Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987), Brief Psychiatric Rating Scale (BPRS; Ventura et al., 1993) and Scale for the Assessment of Negative and Positive Symptoms (SANS/SAPS; Andreasen, 1990). These scales contain statements regarding the patients' experience with specific symptoms of SZ, and each item is assessed based on the frequency and intensity of the symptom. While these scales are limited to measures of AVH frequency and intensity, other scales, such as The Psychotic Symptoms Rating Scale (PSYRATS; Haddock et al., 1999) and the revised Beliefs About Voices Questionnaire (BAVQ-R; Chadwick et al., 2000) include additional items that attempt to assess themes or contents of AVHs, and the amount of distress experienced by the patient due to their AVHs. The use of self-report questionnaires for assessing SZ symptoms, particularly positive symptoms and AVHs, remains somewhat controversial, given that insight might be impaired, and denial can be central to the disorder (Selten et al., 2000). However, many SZ patients can distinguish between hallucinatory experiences from common perceptual experiences, except perhaps during the acute stages of their illness (Delespaul, Devries & van Os, 2002). The integration of self-report questionnaires in both clinical practice and research studies (in addition to clinician-rated questionnaires) can elucidate more subjective aspects of AVHs, such as negative effects on emotions (Kim et al., 2019), thus contributing to increased understanding of the impact of AVHs on the lives of SZ patients.

1.2.2 Major Theories of AVHs

There are several models and theories attempting to explain the origins of AVHs. For instance, the unstable memories theory of AVHs is based on the idea that AVHs arise from the spontaneous activation of memories or other auditory mental representations (Ćurčić-Blake et al., 2017b; Waters et al., 2006). This theory posits that AVHs occur as a combination of deficits in intentional inhibition, or unsuccessful suppression of unwanted or irrelevant auditory memories, along with a deficient ability to bind contextual cues, resulting in incomplete representations of the origins of mental events (Waters et al., 2006). In support of the theory that AVHs may arise partially due to deficits in inhibitory processes, Michie et al. (2005) found that SZ patients with AVHs made more inhibition errors (false alarms) on a continuous recognition task compared to both SZ patients without AVHs and healthy controls. Additionally, Waters et al. (2003) found that greater AVH severity was associated with more inhibitory errors on two tasks assessing the intentional suppression of cognitive events. It has also been found that SZ patients exhibit impaired contextual memory, as measured by a task testing the ability to recognize and bind together contextual cues, and that SZ patients with AVHs showed greater deficits compared to those without AVHs (Waters et al., 2004). The source monitoring theory suggests that deficits in self-monitoring and reality discrimination lead to AVHs, whereby inner speech is not recognized as self-generated and is misattributed to external sources (Allen, Aleman & Mcguire, 2007; Ćurčić-Blake et al., 2017b). The interhemispheric miscommunication theory proposes that altered connectivity between the bilateral auditory cortices via the corpus callosum may underlie AVHs (Ćurčić-Blake et al., 2017b; Steinmann, Leicht, & Mulert, 2014), as this interhemispheric auditory pathway is responsible for the integration of prosodic (patterns of stress and intonation in a language) and syntactic (arrangement of words that create sentences in a language) information necessary for speech comprehension. Hubl et al. (2004) found that SZ

patients with AVHs showed increased white matter connectivity in the part of the corpus callosum where interhemispheric auditory fibres cross compared to SZ patients without AVHs. Furthermore, Mulert et al. (2011) found reduced gamma-phase synchronization (i.e., synchronous neural oscillations in the gamma band [>30 Hz]) between the bilateral primary auditory cortices in SZ patients, as well as a positive correlation between interhemispheric gamma-phase synchronization and auditory hallucination symptom scores. Thus, it has been suggested that both altered (perhaps heightened) integrity of interhemispheric auditory pathways as well as disturbed gamma-phase synchronization between the left and right auditory cortices could contribute to abnormal auditory processing and the occurrence of AVHs. Finally, the top-down and bottom-up theory of AVHs (discussed further in section 1.2.4) is based on the idea that AVHs may be due to imbalances in the mechanisms underlying both bottom-up sensory processing and top-down inhibitory cognitive control. Specifically, this theory suggests that increased activity in left hemispheric speech regions leads to the perceptual experience of AVHs coupled with a failure of top-down inhibitory control processes; this framework thus underlies the misrepresentation of auditory information to an internal, rather than an external source.

1.2.3 Putative Neurochemical Underpinnings of AVHs

Dopamine is a neurotransmitter produced in the substantia nigra and ventral tegmental regions of the brain. The longstanding 'dopamine hypothesis of SZ' posited that SZ symptoms arise due to hyperactive dopamine transmission. This was originally supported by early studies showing that administration of compounds that increase extracellular dopamine (i.e., amphetamine) can induce psychotic symptoms, followed by other research which showed that administration of drugs that reduce dopamine levels reduced psychotic symptoms (Carlsson et al., 1973; Walinder et al., 1976). Post-mortem studies showed that SZ patients have increased

striatal dopamine levels as well as increased density of D2 receptors (Owen et al., 1978; Seeman et al., 1987). Positron emission topography (PET) studies have shown that SZ patients have increased stimulation of D2 receptors (Abi-Dargham et al., 2000), as well as abnormally high dopamine release following amphetamine administration (Abi-Dargham et al., 1998), an effect which has also been associated with worsening of positive symptoms (Laruelle & Abi-Dargham, 1999). Further evidence of the involvement of the D2 receptor in SZ also came from genetic findings which showed an association between the DRD2 gene and SZ (Ripke et al., 2014). Bloemen et al. (2013) also found that compared to HCs, an ultra-high risk (UHR) for psychosis group showed higher synaptic dopamine concentrations, which was also associated with greater severity of positive symptoms. Further, dopamine depletion led to significant reduction of positive symptoms in the UHR group.

More recently, the dopamine hypothesis has been refined to include potentially decreased dopaminergic activity in other brain regions, such as the prefrontal cortex, to account for the negative and cognitive symptoms of SZ (Davis et al., 1991). Evidence for the involvement of dopaminergic abnormalities in the frontal cortex comes from early studies showing reduced frontal cerebral blood flow in SZ patients while completing the Wisconsin Card Sorting Test (Weinberger, Berman & Zec, 1986). Further, blood flow in the prefrontal cortex has been shown to increase in SZ patients following administration of dopamine agonists (i.e., amphetamine) and this increase in blood flow was correlated with improved performance on the Wisconsin Card Sorting Test (Daniel et al., 1991). Therefore, it is possible that hyperdopaminergic characteristics in striatal areas coupled with hypodopaminergic characteristics in frontal areas of the cortex could explain the pathophysiology of SZ. Granted, other neurotransmitter systems may play a more central role in the prefrontal hypoactivation noted in SZ patients. Although the dopamine

hypothesis has been the dominant theory, it is likely too simplistic to fully understand and explain the many heterogenous symptoms of SZ, especially given that neurotransmitter systems interact with each other. Recently, other neurotransmitters such as glutamate have also been investigated in the context of SZ.

Glutamate is the major excitatory neurotransmitter in the brain and is also the most widespread neurotransmitter in prefrontal and temporal regions, which are also two major brain regions implicated in AVHs (Hugdahl et al., 2009). Glutamatergic abnormalities may play a role in the psychotic symptoms of SZ, including AVHs (Merritt et al., 2016). In line with this idea, research has shown that the administration of N-methyl-D-aspartate (NMDA) receptor (a type of glutamate receptor) antagonists, such as ketamine (as subanesthetic doses), induces a psychotic-like state in healthy volunteers, including the emergence of AVHs, and exacerbates pre-existing psychotic symptoms in SZ patients (Merritt et al., 2016; Javitt & Zukin, 1991). Furthermore, several genes that code for proteins involved in glutamatergic transmission have been associated with SZ (Ripke et al., 2014). Using magnetic resonance spectroscopy (MRS), which allows for the quantification of various brain metabolites *in vivo*, several studies have examined glutamate levels in SZ patients. However, the reports have been conflicting, ranging from SZ patients showing increased (Chang et al., 2007), unaltered (Ohrmann et al., 2007), and lower frontal glutamate levels (Choe et al., 1996). To examine the potential role of glutamate in AVH severity in SZ patients, Hugdahl et al. (2015) used MRS to measure glutamate+glutamine (Glx) levels in frontal and temporal brain regions. When using magnetic fields strengths below 7.0T, it is difficult to precisely estimate individual glutamate and glutamine concentrations, therefore, many MRS studies report the combined Glx estimate (Snyder & Wilman, 2010). Compared to HCs, SZ patients had reduced Glx levels in both regions. However, once the SZ group was

divided based on AVH severity (low vs. high), SZ patients with high vs. low AVH severity exhibited increased Glx levels in both regions (Hugdahl et al., 2015). Greater AVH severity was also associated with higher Glx levels (no associations between Glx levels and negative symptoms existed). Finally, Ćurčić-Blake et al. (2017a) found that SZ patients with a lifetime history of AVHs had higher glutamate levels in left prefrontal regions compared to SZ patients without lifetime AVHs. Overall, these studies indicate that the glutamate system may be altered in SZ, and particularly among patients with severe and chronic AVHs, though, the exact nature of this is unclear. As such, some drugs targeting the glutamate system have been under investigation as a potential add-on treatment for SZ. N-acetyl cysteine (NAC), a compound which increases extracellular glutamate, has been shown to significantly reduce positive symptoms (Sepehrmanesh et al., 2018), negative symptoms (Berk et al., 2008; Farokhnia et al., 2013), improve cognitive deficits including processing speed, working memory and attention (Sepehrmanesh et al., 2018), and improve patients' ability to engage in social interactions (Berk et al., 2011). However, some side effects were noted, including drowsiness, constipation, dizziness, vomiting, increased appetite, nausea, headache, dry mouth (Farokhnia et al., 2013) and abdominal cramping and discomfort (Sepehrmanesh et al., 2018). Thus, further study of glutamate-targeting drugs with more favourable side-effect profiles is likely warranted.

1.2.4 Putative Neural Correlates of AVHs

While the specific neuronal mechanisms of AVHs remain unclear, considerable advances in clarifying their underlying neural circuits have been made with the increasing use of neuroimaging work (as outlined in some of the above sections). Structural neuroimaging studies have shown that AVHs are associated with volume reductions in brain areas involved in auditory processing and speech generation, including the primary auditory cortex (PAC), superior

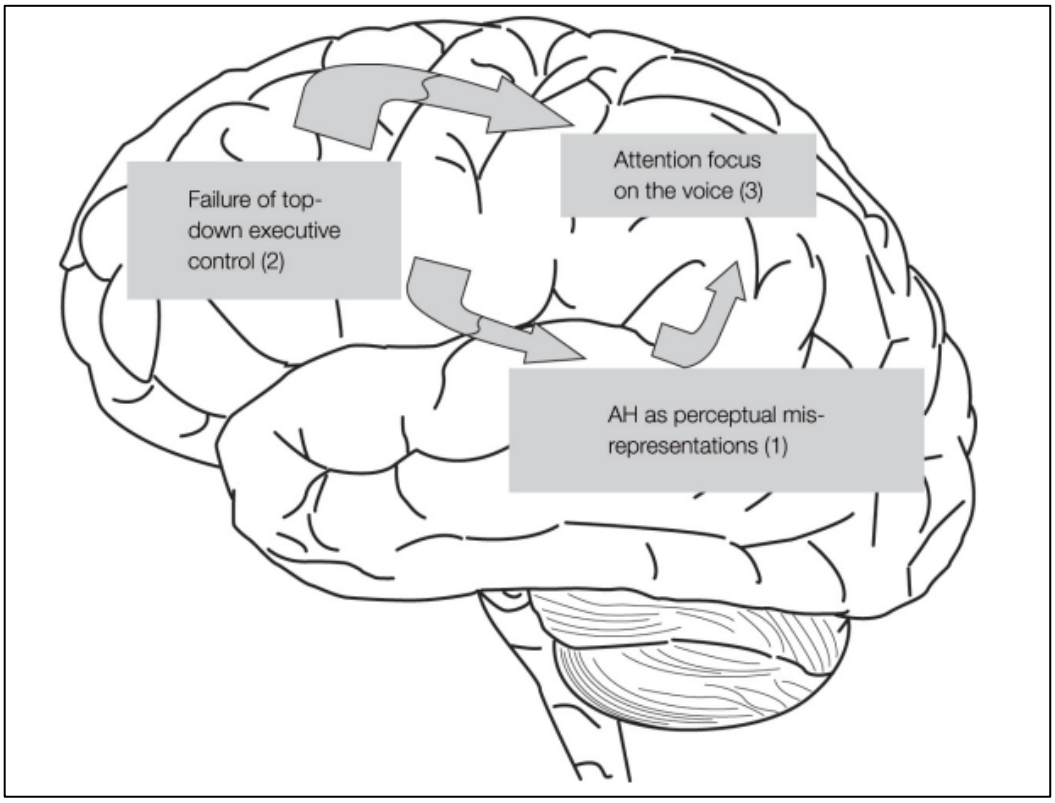
temporal gyrus (STG) and middle temporal gyrus (MTG; Allen et al., 2008; Allen et al., 2012). Additionally, a meta-analysis revealed that grey matter volume reductions in the bilateral STG (particularly the left STG, including the Heschl's gyri) were associated with greater AVH severity (Modinos et al., 2013). Cortical thickness studies have also revealed significant reductions in the left Heschl's gyrus, STG (Mørch-Johnsen et al., 2017; van Swam et al., 2012), MTG (Cui et al., 2018) and the inferior temporal gyrus (ITG; Oertel-Knöchel, et al., 2013; van Lutterveld et al., 2014). Greater cortical thickness reductions in the MTG were also found to be associated with greater AVH severity (Cui et al., 2018).

Functional neuroimaging studies have shown greater activation in the left auditory cortex during the occurrence of AVHs (Dierks et al., 1999; Shergill et al., 2000; van de Ven et al., 2005). This finding was initially interpreted as the auditory cortex being hyperactive, suggesting that increased spontaneous auditory activity may be associated with the occurrence of AVHs. However, when presented with external auditory stimuli, SZ patients with AVHs showed reduced activation of the left auditory cortex compared to HCs (Ford et al., 2009; Hubl et al., 2007; Kompus et al., 2011; Woodruff et al., 1997). As such, it appears that the auditory cortex of SZ patients who are prone to experiencing AVHs is tuned to favour internally generated auditory information processing, thus, leaving less neural resources available for the processing of incoming external auditory information (Ford et al., 2009; Kompus et al., 2011). Another brain area that has been implicated in AVHs is the prefrontal cortex due to its involvement in inhibitory executive control, which is known to be affected in SZ (Heinrichs & Zakzanis, 1998). Hugdahl et al. (2009) presented a model of AVHs based on the top-down and bottom-up theory (**Figure 1**), which, from a neural perspective, implicates the involvement of three main brain areas in AVHs. This model suggests that AVHs arise due to bottom-up perceptual

misrepresentations originating in the left auditory cortex (i.e., MTG/STG), failure of/insufficient top-down inhibitory control from the prefrontal cortex, as well as an attentional shift towards the voices via the involvement of the parietal cortex. Further, reduced fronto-temporal functional connectivity has also been noted in SZ patients and has been associated with AVH severity (Lawrie et al., 2002). As such, this represents putative dysconnectivity between these regions as putative neural substrates of AVHs.

Figure 1.

Outline of a Model for Auditory Verbal Hallucinations (AVHs) as Perceptual Misrepresentations, Parietal Lobe Attention Enhancement and Failure of Prefrontal Executive Suppression Control.



Note. Figure adapted from Hugdahl et al., (2009) Front Neurosci; 3(1):34-45. The model emphasizes the involvement of the middle and superior temporal gyri (1) for the generation of

AVHs, prefrontal cortex (2) for top-down executive control and parietal cortex (3) for attention focus.

1.2.5 Pharmacological Treatments for AVHs

Antipsychotic medications are the primary line of treatment for SZ and are also used to treat other psychotic disorders such as schizoaffective disorder, delusional disorder, and bipolar disorder. They are typically categorized into first-generation antipsychotics (FGAs; formerly known as 'typical') and second-generation antipsychotics (SGAs; formerly 'atypical'). The major pharmacological property that is shared by antipsychotic medications is the blockade of the dopamine D2 receptor (Kapur & Remington, 2001). While both FGAs and SGAs block dopamine receptors, SGAs also inhibit serotonin receptors (most involved is the 5-HT_{2A} receptor; Chokhawala & Stevens, 2019). FGAs include medications such as chlorpromazine, haloperidol and loxapine, while SGAs include medications such as aripiprazole, clozapine, olanzapine, quetiapine, and risperidone. While FGAs are effective in reducing positive symptoms, they are not particularly effective at treating negative symptoms or cognitive impairments (Tandon et al., 2009). FGAs are also associated with extrapyramidal side effects (i.e., tardive dyskinesia). SGAs have a lower risk of inducing extrapyramidal side effects; however, they carry a higher risk of metabolic side effects, including weight gain, high blood sugar and high cholesterol, which could lead to the development of other health issues, such as cardiovascular disease and diabetes (Tandon, 2011). Further, their efficacy for treating negative symptoms (e.g., blunted affect; depression) is not as high as originally expected, with only modest benefits (Hasan et al., 2012; Möller & Czobor, 2015). While antipsychotics are generally effective at reducing the acute symptoms of psychosis and risk of psychotic episode relapse, responsiveness to pharmacotherapies varies greatly, as does response based on stage of illness,

with first-episode patients typically responding better than patients with chronic SZ (Chakos et al., 2001).

1.2.6 Psychological Treatments for AVHs

Non-pharmacological treatment interventions also exist for SZ and managing AVHs, including cognitive behavioural therapy for psychosis (CBTp). CBTp is a form of psychotherapy that encourages the patient to examine and challenge their psychotic experiences and facilitates developing effective coping strategies to manage symptoms. CBTp aims to reduce the severity of distress and amount of interference symptoms such as AVHs cause to overall functioning and quality of life (e.g., by redefining the relationship to "voices"; Health Quality Ontario, 2018). CBTp is often used in conjunction with antipsychotic medications; however, as CBTp is a relatively novel intervention, the overall effectiveness of CBTp for reducing symptoms and improving patient functioning is still unclear. A meta-analysis found that CBTp showed a small benefit on overall functioning at the end of the intervention period (recommended 16 sessions, at minimum (Norman et al., 2017), however, improvements were non-significant at follow-up (at 3-18 months). With respect to distress, there was a small but significant reduction following CBTp, while quality of life was unaffected (Laws et al., 2018). Another meta-analysis focusing on the effects of CBTp on clinical symptoms found that 44.5% of patients who received CBT showed a ~20% reduction in overall symptoms (PANSS total score; minimal improvement), while 13.2% of patients exhibited a ~50% reduction in symptoms compared to baseline (Bighelli et al., 2018). This meta-analysis also found that characteristics such as patients' treatment resistance status, baseline symptom severity, and clinician expertise with CBTp could play a role in patients' response (Bighelli et al., 2018). van der Gaag et al. (2014) conducted yet another meta-analysis focusing on evaluating CBTp specifically targeting hallucinations and delusions and found that

CBTp was an effective treatment for both features, with small-to-medium effect sizes. Further, all studies included in this meta-analysis reported significant improvements in hallucinations in the CBTp arm. Taken together, CBTp does seem to be small-to-moderately effective in treating symptoms of SZ and reducing patient distress/increasing overall functioning, though there are fewer data on its impacts on specific symptoms.

1.2.7 Stimulation-Based Treatments for AVHs

Other non-pharmacological treatment interventions for AVHs include neurostimulation techniques such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). rTMS is believed to modulate neural communication and induce changes in neuronal plasticity (Valero-Cabré, Pascual-Leone & Coubard, 2011), however, the therapeutic effects (in various psychiatric disorders, including SZ; Li et al., 2020) are dependent on the strength of the applied frequency. Specifically, low frequency rTMS (e.g., 1 Hz) is thought to inhibit cortical excitability and high frequency rTMS (e.g., 5-10 Hz) is thought to increase it (Lefaucheur et al., 2014). In one of the seminal studies assessed rTMS in the context of SZ, low frequency (1 Hz) rTMS applied over the left temporoparietal cortex significantly reduced AVH severity in 3 SZ patients (Hoffman et al., 1999). Other studies have attempted to replicate these findings, with conflicting results. Poulet et al. (2005) found a robust improvement in AVH severity (assessed using the Auditory Hallucinations Rating Scale [AHRS]) following 5 days of 1 Hz rTMS over the left temporoparietal cortex (sham-controlled), and these effects persisted for up to 2 months. Brunelin et al. (2006) also reported similar reductions in AVH severity (AHRS-assessed) using the same rTMS parameters (1 Hz over the temporoparietal cortex). However, there have been several other studies reporting no significant improvements in AVHs following 1 Hz rTMS vs. sham rTMS applied over the left temporoparietal cortex,

including Saba et al. (2006), Rosa et al. (2007), Slotema et al. (2011) and de Jesus et al. (2011). Despite these mixed results, meta-analyses indicate that 1 Hz rTMS over the left temporoparietal cortex reduces AVH severity with moderate effect sizes (Li et al., 2020; He et al., 2017; Otani et al., 2015; Slotema et al., 2014). Overall, although further replication is required, and stimulation parameters would benefit from further optimization and standardization, non-invasive brain stimulation techniques such as rTMS appear to have the potential in improving AVH severity in SZ patients.

tDCS is yet another relatively non-invasive brain stimulation technique that delivers a weak electrical current (1-2 mA) to the scalp to target underlying brain areas through two or more electrodes (anode and cathode; Nitsche & Paulus, 2000; Priori et al., 1998; Woods et al., 2016). tDCS modulates neuronal membrane potentials by influencing the likelihood of neuronal firing, with anodal stimulation increasing cortical excitability (depolarizing neuronal membranes) of underlying neurons and cathodal stimulation decreasing it (via hyperpolarization of neural membranes; Nitsche et al., 2003; Woods et al., 2016; Stagg, Antal & Nitsche, 2018). Long-term after-effects of tDCS involve the strengthening and weakening of synaptic connections by modulating molecular mechanisms related to synaptic plasticity, including long-term potentiation (LTP), which enhances synaptic efficiency, and long-term depression (LTD), which reduces it. The depolarizing effects of anodal tDCS are thought to result in eventual LTP, while the hyperpolarizing effects of cathodal tDCS leads to LTD (Malenka & Bear, 2004; Stagg, Antal & Nitsche, 2018). Given its ability to modulate cortical excitability and influence synaptic plasticity mechanisms such as LTP and LTD, tDCS holds promise as a potential treatment for people experiencing AVHs. tDCS protocols that simultaneously deliver cathodal stimulation to the left temporo-parietal junction (TPJ; an area of hyperactivity in the absence of external cues in

SZ patients) and anodal stimulation to the left DLPFC (an area of purported hypoactivity in SZ patients; Hugdahl et al., 2009) have been shown to effectively reduce AVH frequency and severity in SZ patients in a handful of studies. In a randomized controlled trial (RCT), Brunelin et al. (2012) administered twice daily tDCS sessions (2 mA current for 20 minutes; anode over left DLPFC, cathode over left TPJ) for 5 consecutive days in 30 SZ patients (N=15 active tDCS, N=15 sham tDCS [40 seconds of 2 mA stimulation, then series of short current pulses of 110 microamps for 15 ms every 550 ms]) with treatment resistant AVHs. The authors found that active tDCS significantly reduced AVHs (assessed using the AHRS) in SZ patients compared to sham, an effect which lasted up to 3 months. Reductions in AVHs following the same protocol as in Brunelin et al. (2012, 2x/day, 5 days; frontal: anode, TPJ: cathode) were also reported in follow-up studies by various groups (Mondino et al. (2015), Brunelin et al. (2015), Shivakumar et al. (2015) and Bose et al. (2014)), though not all included sham control arms. Kantrowitz et al. (2019) replicated the results of Brunelin et al. (2012) and divided their sample based on severity of cognitive symptoms (PANSS-assessed) and found that the greatest reductions in AHRS scores occurred among SZ patients with lower cognitive symptom severity. Despite the above-outlined promising advances in non-pharmacological treatments for treating AVHs in SZ patients, this is an area of research that requires further study and optimization, such as refining stimulation parameters, assessing placebo/sham related effects, and incorporating brain imaging techniques to allow for the assessment of potential stimulation-induced changes in the brain and relationships between brain-based changes and symptom improvements.

1.3 Event-Related Potentials (ERPs)

The electroencephalogram (EEG) represents brain electrical activity measured by electrodes applied over various regions of the scalp (i.e., frontal, temporal, parietal, and occipital

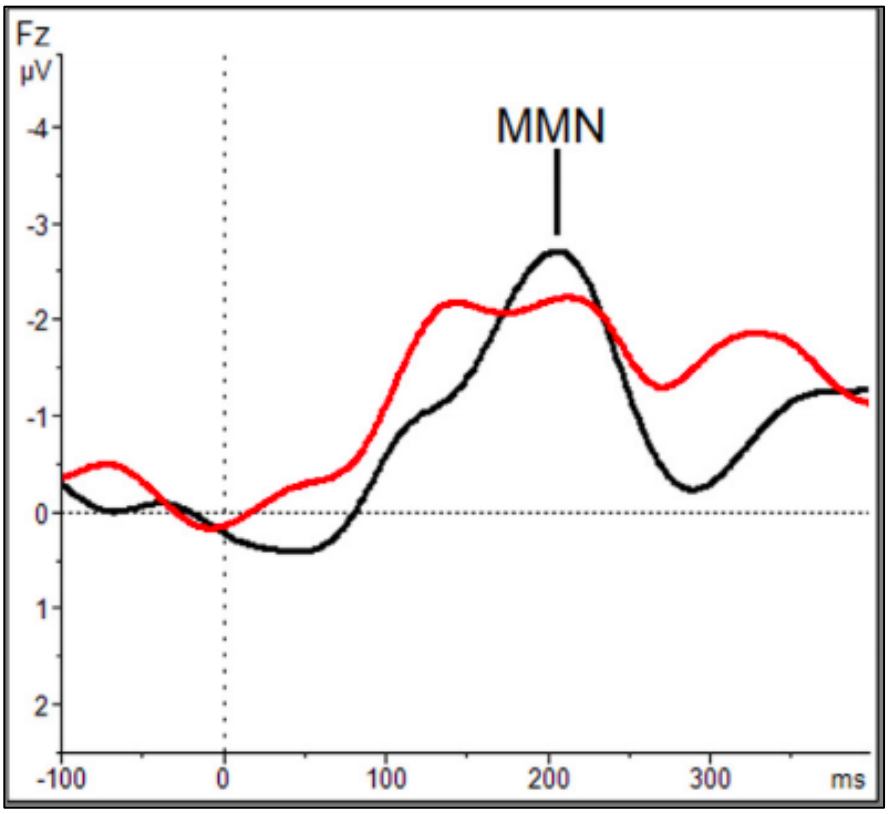
regions). EEG recorded from the scalp reflects the summed electrical activity from apical dendrites of large pyramidal neurons in the cerebral cortex (Shibasaki, 2008). Event-related potentials (ERPs) are derived from EEG and represent the summation of the neural responses to the presentation of a stimulus, which can include tones, visual stimuli, or cognitive events (Luck, 2014). ERPs are superior in temporal resolution compared to other neuroimaging techniques, enabling ms-by-ms assessment of neural activity and the detection of near instantaneous changes in cognitive processing (Luck, 2014).

1.3.1 Mismatch Negativity (MMN)

The mismatch negativity (MMN) is an ERP thought to represent the automatic detection of discriminable changes in auditory stimuli and serves as an index of pre-attentive detection of stimulus deviance (Näätänen, 1995). The MMN, which is typically assessed as the difference between standard/frequent and deviant auditory stimuli, has a negative peak, a fronto-central maximum amplitude, and a latency of ~100-250 ms (Näätänen, 2003; Näätänen et al., 2014; **Figure 2**). The MMN is typically generated by deviant auditory stimuli embedded within a string of repetitive standard sounds; deviant stimuli may differ from the standard in various ways, including in frequency, duration, intensity, and location (Näätänen & Alho, 1997).

Figure 2.

Grand Averaged Mismatch Negativity (MMN) Difference Waveform for Schizophrenia Patients During the Early Course of their Disorder (Red) and Healthy Controls (Black) at the Frontal Fz Site.



Note. Figure adapted from Fisher et al., (2019) Psychiatry Res. Neuroimaging; 287:1-9.

The MMN is generated primarily by neural generators in the bilateral auditory cortices, but also receives contributions from the frontal regions due to the involuntary attentional switching that occurs with changes in auditory stimuli (Näätänen and Alho, 1997; Näätänen et al., 2007). The contribution of supratemporal generators to the MMN response is consistent with observations that MMN inverts polarity at mastoid electrode sites when the nose is used as the reference (Alho et al., 1986; Sams et al., 1985). Distinct patterns of activation in the auditory cortex may occur depending on the type of deviant. For instance, using functional magnetic resonance imaging (fMRI), Molholm et al. (2005) found activation in the transverse temporal gyrus for duration deviants while frequency deviants were associated with activation in the posterior STG. The MMN can be elicited using pure tones or speech-based sounds, which can elicit slight differences in the resultant MMN. For example, Iino et al., 2018 found that MMN

amplitudes to vowel-based sounds were larger than MMN amplitudes to pure tones in healthy participants, a finding which has been reported by several other groups (Fisher et al., 2008a; Sorokin et al., 2010; Takei et al., 2009). Additionally, Iino et al., 2018 reported that MMN latencies to vowel-based sounds were shorter compared to MMN latencies to pure tones in HCs, a finding which has also been documented Kasai et al. (2002) in both HCs and SZ patients. The responsiveness of the MMN increases as the physical differences between the standard and deviants increase (Inouchi et al., 2004; Naatanen et al., 2007), therefore, the larger MMN amplitude to speech-based sounds has been attributed to the fact that they have a broader range of acoustic information compared to pure tones (Iino et al., 2018). Additionally, the MMN has been shown to be larger in response to familiar sounds of one's native language versus unfamiliar sounds; additionally, words elicit a larger MMN than meaningless pseudowords (Pulvermuller & Shtyrov, 2006), thus, larger MMN amplitudes to speech-based sounds relative to pure tones could be explained by increased familiarity with these stimuli.

The MMN has been thought to reflect a predictive coding mechanism, meaning that the brain continuously generates and updates its predictions of the physical world by integrating incoming sensory information (Friston, 2005; Fong et al., 2020). Specifically, sensory prediction relies on the incorporation of information from the past (memory) which allows the generation of a regularity signal that is tuned to irregularity violations (Fong et al., 2020). MMN generation is thought to result due to a comparison of the incoming deviant stimulus to a stored neural representation of the standard (i.e., frequently occurring or 'regular' stimulus), and thus can provide an index of sensory memory updating. According to this model, neural responses to stimuli that match predictions are suppressed, whereas stimuli that are unexpected, violating these predictions, trigger a mismatch "prediction error" signal (Friston, 2005). The MMN is thus

thought to be a neural substrate of prediction errors, since it is elicited when there is a discrepancy between the input and the prediction (i.e., when an unexpected deviant sound is encountered; Fong et al., 2020). In SZ patients who are prone to hallucinations, it has been hypothesized that abnormal perceptual processing abilities interact with inaccurate predictions about the environment, resulting in diminished prediction error signalling (McCleery et al., 2018).

MMN generation has been linked to NMDA receptor functioning, as evidenced by studies showing reductions in MMN amplitudes following pharmacological NMDA receptor blockage (Kreitschmann-Andermahr et al., 2001; Umbricht et al., 2000; Umbricht et al., 2002). The involvement of NMDA receptors in the generation of the MMN is particularly relevant to SZ, given that the administration of subanesthetic doses of ketamine (an NMDA receptor antagonist) both induces psychotic symptoms in healthy volunteers and exacerbates pre-existing psychotic symptoms in SZ patients (Merritt et al., 2016; Javitt & Zukin, 1991). Decreased MMN amplitudes have been robustly observed in patients with SZ, especially to duration deviants (Javitt et al., 1993; Javitt et al., 1995; Salisbury et al., 2002; Shelley et al., 1991; Wynn et al., 2010). As such, the MMN has been proposed as a potential biomarker for SZ, although studies have reported mixed findings regarding MMN reductions in early-phase, first episode, and high-risk populations. While some studies have found MMN amplitude reductions in the early stages of SZ and first-episode groups (Randau et al., 2019; Solís-Vivanco et al., 2014), others have not (Salisbury et al., 2002). However, MMN amplitude reductions have also been found in first-degree relatives of SZ patients (Michie et al., 2002).

MMN deficits have also been associated with specific SZ symptoms, including AVHs. Fisher, Labelle & Knott (2008) found that hallucinating patients had smaller MMNs to duration

deviants compared to non-hallucinating patients and HCs. The same group also found, in a later study (Fisher et al., 2012) that SZ patients had reduced MMN amplitudes to duration, gap, intensity, and location deviants compared to HCs, and that gap MMN amplitudes were correlated with hallucinatory state and frequency measures of AVHs. This also supports the idea that the integration of multiple deviants within a task may be more informative than the use of only a single deviant. Finally, MMN amplitudes have also been associated with functional outcomes in SZ patients. For example, Wynn et al. (2010) reported that larger MMN amplitudes were correlated with improved functioning at work and independent living, as well as better social perception. Despite the large body of literature investigating MMN deficits in SZ, the work examining the MMN in the context of AVHs still requires further study. Specifically, it remains to be clarified which deviant types elicit the strongest group differences between HCs and SZ patients, as well as which deficits are the most prominent in SZ patients with persistent AVHs. Further, differences in MMN deficits to pure tones and speech-based stimuli need to be assessed directly, as this has yet to be done in the context of SZ and AVHs. Finally, the MMN to certain deviant types has been associated with clinical measures of AVHs (Fisher et al., 2012), however, research studies have yet to assess how MMN deficits may relate to other more subjective aspects of the AVH experience, which could provide some unique information about the neural correlates of AVHs.

1.4 Objectives & Hypotheses

This study was part of a larger randomized control trial (RCT) that examined the effects of a repetitive (2x daily for 5 consecutive days) fronto-temporal tDCS intervention on clinical and self-reported ratings of AVH severity and brain-based measures of auditory processing. The effects of tDCS on clinical or brain-based measures were not assessed as part of this thesis.

1.4.1 Primary Aims

The first primary aim of this thesis was to assess baseline differences in MMN features (focus on amplitude and latency) to pure tones and speech-based sounds using two different versions of the MMN five deviant multi-feature task (tasks tested separately for the primary aims; Näätänen et al., 2004; Pakarinen et al., 2009; De La Salle et al., 2019) between SZ patients and HCs. The second aim was to examine relations between baseline MMN features (amplitudes and latencies), clinical ratings of AVH severity (PSYRATS total score, PANSS item 3 ["hallucinatory behaviour"]) and self-report measures of AVH features (i.e., the Beliefs About Voices Questionnaire-Revised [BAVQ-R], Voice Acceptance and Action Scale [VAAS] and the Voice Power Differential Scale [VPDS]). Importantly, to the best of our knowledge, this is the first study to assess MMN features in relation to these subjective measures of the AVH experience.

1.4.2 Secondary Aims

Secondary aims of this thesis included comparing baseline differences in MMN features (amplitude and latency) between the HC and SZ groups on the two MMN tasks directly (tasks were tested separately in the primary aims). This was explored because there has been other work that has shown that speech indexed MMNs are larger than tone based MMNs in HCs (Iino et al., 2018; Fisher et al., 2008a; Sorokin et al., 2010; Takei et al., 2009); direct comparisons in SZ patients are lacking.

1.4.3 Exploratory Aims

The first exploratory aim of this thesis were to examine MMN features between the HC and SZ groups on deviants that contained two sound files (i.e., low/high frequency deviant, low/high intensity deviant) to examine whether any differences existed in the MMN response to

low/high frequency and intensity stimuli, as this has yet to be assessed in the context of SZ and AVHs and could provide interesting insights into deviant processing in SZ. The second exploratory aim was to examine MMN amplitudes between groups on each deviant at the mastoid sites (TP_9/TP_{10}), which may be of interest given the polarity reversal of the MMN at mastoid sites (Schröger, 1998) as well as the left-lateralization of speech processes (Shtyrov et al., 2000; Desai et al., 2008; Tervaniemi & Hugdahl, 2003).

1.4.4 Hypotheses

For the primary aims, it was expected that SZ patients would show reduced MMN amplitudes to all five deviant types compared to HCs across both the tone and speech MMN tasks, with the greatest reductions emerging for the duration and frequency deviants. It was also expected that SZ patients would have longer MMN latencies to all five deviant types compared to HCs across both MMN tasks. For the secondary aims, it was expected that MMN amplitudes would be larger in the speech task compared to the tone task across both HC and SZ groups, but that MMN amplitudes would be smaller in the SZ group compared to the HC group across both tasks. There were no specific hypotheses set for the first exploratory aim. For the second exploratory aim, it was expected that MMN amplitudes would be larger in the left-hemisphere, especially in the speech task, given the left-lateralization of speech processes (Shtyrov et al., 2000; Desai et al., 2008; Tervaniemi & Hugdahl, 2003).

2. METHODS

2.1 Study Overview

As outlined, this study was part of a larger, ongoing, double blind, sham-controlled randomized control trial that aims to assess the effects of repetitive tDCS on AVH frequency and

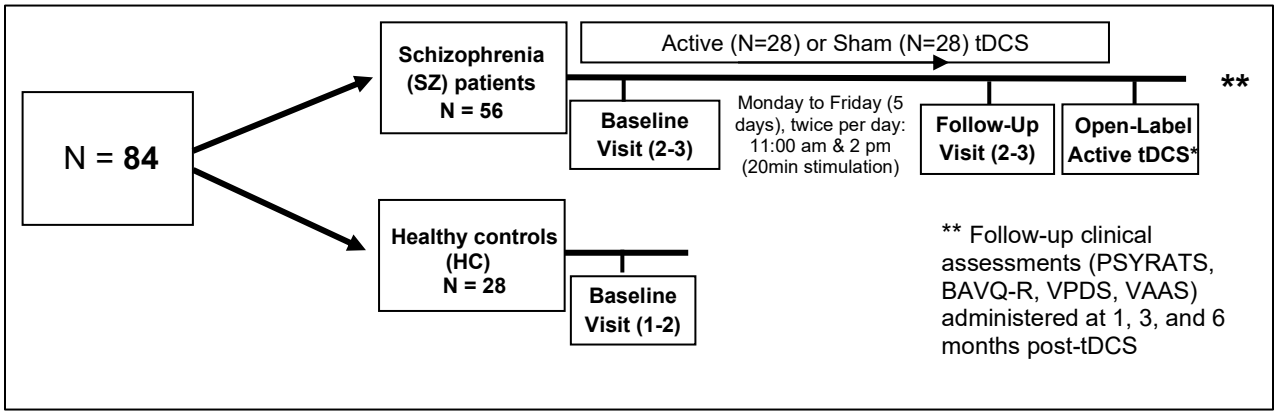
severity, EEG-indexed neural profiles, neuroimaging data (MRI), cognitive functioning and quality of life. Patients with a primary diagnosis of SZ (males and females, aged 18-65 years) and age and sex-matched HCs were recruited. SZ patients were randomly assigned to one of two conditions: active or sham tDCS. SZ patients completed the study procedures over a three-week period (**Figure 3**). At baseline, they completed a series of self-report questionnaires, underwent an EEG recording, an MRI scan, and cognitive assessments. Subsequently, SZ patients received tDCS (either active or sham) twice daily for five consecutive days (Monday-Friday). Finally, during the post-intervention period (week three), SZ patients repeated all baseline measures. SZ patients also completed clinical follow-up assessments at 1, 3 and 6 months post-tDCS to assess any potential long-term effects of tDCS on AVHs. HC participants did not undergo tDCS and completed the baseline sessions only (without completing any SZ or AVH specific questionnaires). After completing the study, SZ patients who were randomized to the sham tDCS condition were offered the opportunity to receive open-label active tDCS to ensure that they had equal access to this potential treatment.

All participants were required to understand written and spoken English. All potential participants (HC and SZ) completed a thorough in-person or telephone screening, which assessed their medical, personal, and familial psychiatric histories as well as their current and past substance use via Structured Clinical Interview for DSM-5 Disorders (SCID) adapted questions (First et al., 2016; **Appendix I & II**). Participants who were deemed eligible for the study were booked for their in-person laboratory sessions. All in-person sessions took place at the Clinical EEG & Neuroimaging Research Laboratory at the Royal Ottawa Mental Health Centre (ROMHC). Upon arrival, participants were provided with an informed consent form, which contained a full description of the study procedures. Once pertinent questions regarding the study

were addressed, and once the consent form was signed, a copy was provided to participants and originals were kept in the laboratory. This study was evaluated and approved by ROMHC Research Ethics Board (REB #2017020 & REB #2017034; **Appendix III**) and the University of Ottawa Research Ethics Board (REB #H-01-19-2833; **Appendix IV**). This thesis is focused on the aims outlined in section 1.4.

Figure 3.

Complete Study Design and Testing Procedures for Schizophrenia Patients (SZ) and Healthy Controls (HC).



Note. BAVQ-R: Beliefs About Voices Questionnaire-Revised; PSYRATS: Psychotic Symptom Rating Scale; tDCS: transcranial direct current stimulation; VAAS: Voices Acceptance and Action Scale; VPDS: Voice Power Differential Scale.

*Open-label active tDCS is optional for patients who received sham stimulation.

2.1.1 SZ Patient Inclusion Criteria

SZ patients were recruited from both the Outpatient and Inpatient Schizophrenia Programs at the ROMHC. Psychiatrists at the ROMHC informed suitable SZ patients (details below) about the study, and interested patients signed a 'consent to be contacted' form, thus

providing permission to be contacted by research personnel. Psychiatrists also completed a brief clinical assessment with interested patients to determine whether they met inclusion criteria (**Appendix V**). SZ patients were required to have a primary diagnosis of SZ or schizoaffective disorder and be clinically stable at the discretion of their psychiatrist (i.e., not suffering an acute psychotic episode or presenting with symptom severity that would impede adherence with the study protocol). SZ patients with comorbid mood disorders were eligible if SZ or schizoaffective disorder was their primary diagnosis (comorbidities are noted). Multiple adjunct treatments were permitted; however, primary medications were limited to one of the atypical antipsychotics (i.e., first-generation, or typical antipsychotic usage is exclusionary, e.g., haloperidol) in attempt to control for differences in medication class effects on neural features. SZ patients were required to have had no terminations or initiations of their primary medication (i.e., atypical antipsychotic) in the 4 weeks prior to screening/study enrollment and during the study.

Participants were also excluded if they had a history of drug or alcohol dependence or abuse within the last 6 months (confirmed with a toxicology screen [Innovacon Multi-Drug One Step Multi-Line Screen Test Panel]; and based on clinical history), had a significant medical illness or mental retardation/learning disability (to the extent that completing the study protocol would be difficult; self-report), displayed extra-pyramidal symptoms resulting in disordered movements that could impact electrophysiological recordings, had an abnormal audiometric assessment (Lafayette Instrument Inc.; thresholds for pure tones <25 dB [SPL] of 500 Hz, 1000 Hz and 2000 Hz), had a history of seizures, epilepsy or stroke (significant neurological issues) or reported previous head injuries/concussions resulting in the loss of consciousness for ≥5 minutes. These exclusionary measures were included as these confounding variables would hamper the interpretability of the neural measures. Smokers were included but abstinence from nicotine was

required for all participants for 3 hours prior to the testing session. Abstinence from smoking was confirmed using a carbon monoxide (CO) test (piCO+ Smokalyzer®, coVita).

2.1.2 AVH Specific Inclusion Criteria

SZ patients were required to have a history of AVHs over the course of their illness and currently reporting at least three AVHs per week (self-report measures). Clinical assessments of AVH severity at the time of study enrollment was carried out by the treating psychiatrist who completed the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). SZ patients were required to exhibit a score of ≥3 on the "hallucinatory behaviour" item (item #3) of the PANSS, denoting at least mild to severe AVH experiences, for study inclusion (**Appendix V**).

2.1.3 HC Participant Inclusion Criteria

HC participants were recruited from the community using advertisements posted on community websites (e.g., Kijiji, Craigslist), recruitment posters displayed at the University of Ottawa, using the laboratory's 'consent to be contacted for research' database and by word of mouth. Interested participants were scheduled to complete a telephone screening (~30 minutes) conducted by the study coordinator to assess eligibility (**Appendix II**). Eligible HC participants were required to be in good physical health (i.e., no serious medical conditions/illnesses), have no history of mental health issues or psychiatric disorders, have no family history of SZ in first degree relatives (given the high heritability of SZ; Wilson & Stanley, 2006) and have no history of mental health issues in first degree relatives that required extensive treatment or hospitalization (e.g., treatment resistant psychiatric illness). HC participants were also subjected to the same general exclusion criteria as the SZ patients (see section 2.1.1).

2.1.4 Assessments

Both HCs and SZ patients completed the following questionnaires at baseline: Edinburgh Handedness Inventory (Oldfield, 1971; **Appendix VI**), which was administered to assess handedness; the National Adult Reading Test (NART; Bright, Jaldow & Kopelman, 2002; **Appendix VII**) was used as a global metric of intelligence; the Beck Depression Inventory-II (BDI-II; Beck, Steer & Brown, 1996; **Appendix VIII**) and Beck Anxiety Inventory (BAI; Steer et al., 1993; **Appendix IX**) were used to control for depressive and anxiety symptoms; the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF; Endicott, Nee, Harrison & Blumenthal, 1993; **Appendix X**) was used to assess life satisfaction.

SZ patients were also administered the following questionnaires regarding their AVHs: the Beliefs about Voices Questionnaire-Revised (BAVQ-R; Chadwick, Lee & Birchwood, 2000; **Appendix XI**) measures perceptions about and responses to AVHs; the Voice Power Differential Scale (VPDS; Birchwood et al., 2000; **Appendix XII**) examines perceived power differences between the patient and their voice(s); the Voices Acceptance and Action Scale (VAAS; Shawyer et al., 2007; **Appendix XIII**) evaluates patients' acceptance-based attitudes and actions towards their AVHs and command hallucinations. Finally, the Psychotic Symptom Rating Scale (PSYRATS; Haddock, McCarron, Tarrier & Faragher, 1999; **Appendix XIV**) was administered by research personnel to measure AVHs on their frequency, duration, severity, intensity of distress, loudness, location, degree of negative content, controllability, beliefs about the origins of the voices and disruption to the patient's life. A visual hallucinations version of the PSYRATS was also adapted from the original and was administered only to patients who also reported visual hallucinations in addition to AVHs (**Appendix XV)**.

2.2 Electrophysiological Recordings

All participants were asked to adhere to certain abstinence criteria prior to EEG/neuroimaging testing sessions, including abstaining from nicotine for 3 hours prior to the testing session, abstaining from caffeine for 6 hours prior to the testing session, as well as abstaining from alcohol and recreational drugs beginning at midnight the night prior to the testing session (verified by self-report).

EEG activity was recorded from 32 channels using an electrode cap (Ag/AgCl electrodes; EasyCap, Herrsching-Breitbrunn, Germany) positioned according to the international 10-20 system of electrode placement, with amplifier bandpass settings of 0.1–100 Hz, and digital sampling at 500 Hz. Electrical recordings were carried out using a Brain Vision QuickAmp (Brain Products GmbH, Munich, Germany) amplifier and Brain Vision Recorder V1.4.3 (Brain Products GmbH, Munich, Germany) software. The reference electrode was placed on the nose while additional electrodes were placed on the outer eye canthi and above/below the right eye to record horizontal (HEOG) and vertical (VEOG) electrooculographic (EOG) activity, respectively. Additional electrodes were placed on the left and right mastoids (TP_9 and TP_{10}), while an AFz electrode served as the ground. Impendence was maintained at $\leq$5 KΩ. Auditory MMNs to both non-speech and speech deviants were elicited using two variations of the five deviant multi-feature MMN task (details below). During both MMN tasks, participants viewed a silent, minimally arousing neutral nature documentary video (Madagascar: The Land Where Evolution Ran Wild [Gunton, 2011]).

2.2.1 MMN Tone Task

MMNs to pure tone deviants were elicited with the five deviant multi-feature MMN task (Näätänen et al., 2004). The standard stimuli were 75 ms pure tones (70 dB; composed of 500, 1000 and 1500 Hz partials); deviant tones differed from the standard in frequency, duration,

intensity, perceived sound origin location, or contain a gap in the middle of the tone. Partials were used as pitch discrimination is thought to be facilitated by spectrally rich sounds compared to pure sinusoidal tones, resulting in larger MMN amplitudes (Tervaniemi et al., 2000). The task stimuli were presented using E-Prime 3.0 software (Psychology Software Tools, Pittsburgh, PA). Presented through headphones (Sony MDR7506), all stimuli (except intensity deviants) were at a sound pressure level of 70 dB. There were two types of stimuli for each of the frequency, intensity, and location deviants. Half of the frequency deviants were 10% higher (composed of 550, 1100 & 1650 Hz partials) while the other half are 10% lower (450, 900 & 1350 Hz partials). Half of the intensity deviants were 60 dB, while the other half were 80 dB. The perceived difference between the standard tone and location deviant was approximately 90°. A change in the perceived location of sound origin was created by introducing a time difference of 800 μs for half of the location deviants to the right channel (ear) and half of the deviants to the left channel (ear). For these deviants that were composed of two types of stimuli, the stimuli were averaged together during EEG preprocessing. The duration deviant was 25 ms, while the gap deviant was created by removing 7 ms (including 1 ms rise/decay) from the middle of the standard stimulus, leaving a silent gap in the middle of the tone. The stimulus onset asynchrony (SOA: onset to onset) was 500 ms, and all stimuli were presented in 3 blocks of 5 minutes (615 stimuli) for a total of approximately 15 minutes (1845 stimuli). In each block, the first 15 tones were standards to generate the memory trace to the standard, followed by a sequence whereby every second stimulus was a standard (P = 0.5), and every other stimulus was one of the five deviants (P = 0.1 each). The deviants were presented so that in an array of five deviants (alternating with a standard tone), each deviant category was presented once, and two deviants of the same category never followed each other.

2.2.2 MMN Speech Task

MMNs to five speech (syllabic) deviants were elicited using a previously published multi-feature task constructed from phonetic and acoustic changes in speech sounds (Pakarinen et al., 2009; De La Salle et al., 2019). EEG recordings were collected in response to five deviations in Finnish semi-synthetic consonant-vowel (CV) syllables. The presentation of phonemes in the native language have been shown to result in larger MMNs due to activation of long-term memory processes (Dehaene-Lambertz, 1997; Näätänen et al., 1997), therefore, Finnish-language CV syllables were used to minimize the effects of previous language learning/native language. The deviants were changes in syllable fundamental frequency and intensity, changes in vowel duration, and consonant and vowel changes. The stimuli consisted of semi-synthetic Finnish-language CV syllables created using the semisynthetic speech generation method (Alku, Tiitinen & Näätänen, 1999). The standard stimuli was /te:/. The fundamental frequency (FF) was 101 Hz, and the syllable duration was 170 ms. The deviant stimuli differed from the standards either in syllable frequency (FF ±8%; 93/109 Hz), syllable intensity (±6 dB), vowel-duration (-70 ms shorter than standard) consonant (/pe:/) or vowel (/ti:/). The sounds were presented using the same stimulus sequence as used in the above tone task: every second syllable was a standard (P = 0.5), and every other stimulus was one of the 5 deviant syllables (P = 0.1 each). There were three 5-minute blocks including 615 stimuli, of which the first 15 were always standards, for a total of 1845 stimuli. The deviants were presented so that in an array of five deviants (with an alternating standard in between each deviant), each deviant category was presented once, and two deviants of the same category never followed each other.

2.3 Data Processing

EEG preprocessing was completed using Brain Vision Analyzer 2.2 software (Brain Products, Munich, Germany). Offline, EEG data was re-referenced to the nose reference, digitally filtered (0.1–20 Hz; notch = 60 Hz; slope = 24 dB/Oct), ocular-corrected (Gratton et al., 1983) and segmented (−100 to 500 ms relative to the onset of the auditory stimulus). Subsequently, semi-automatic artifact rejection was carried out excluding epochs ±75 μV; this was followed by baseline correction using a 100 ms pre-stimulus window. Participants with < 117 epochs out of a maximum of 180 per deviant type (i.e., 65%) following artifact rejection were flagged for further manual inspection. Manual inspection included topographic interpolation of no more than three channels and/or independent component analysis (ICA) to remove artifacts such as electrocardiogram (ECG) artifacts and residual ocular artifacts. In the MMN tone task, five components were removed for N = 3 participants. For the MMN speech task, four components were removed for N = 1 participant, five components were removed for N = 1 participant, and 7 components were removed for N = 1 participant. For all remaining participants <3 components were removed. The remaining epochs (minimum 117 out of a maximum of 180 per deviant type; 65%) were then averaged based on deviant type and subtraction waveforms were computed (deviant – standard) by digital point-by-point subtraction of the averaged waveform voltage values to the standard stimulus from the voltage values of the waveform associated with each of the auditory deviants. MMNs values were extracted as mean amplitude (±5 ms) values around the peak negative MMN amplitudes within a 100-250 ms time-window. The time-window which was derived from an inspection of the grand-averaged waveforms per condition (groups collapsed) and is consistent with previous literature (as are all the preprocessing steps; De La Salle et al., 2019; Fisher et al., 2019). Mean MMN amplitudes and latencies for each deviant type in both MMN tasks (speech and tone) were extracted from

one frontal electrode site (Fz) as inspection of the data indicated maximum MMNs in the frontal region (data not shown); this is consistent with others' findings (De La Salle et al., 2019; Fisher et al., 2019; Fisher, Labelle & Knott, 2012). Further inspection also revealed the expected MMN polarity inversion at mastoid sites (Schröger, 1998; quality control measure; data not shown). For exploratory purposes, mean MMN amplitudes and latencies for deviants that contained two separate sound files (i.e., low/high frequency deviant, low/high intensity deviant) were extracted from site Fz to examine potential differences in the MMN. These two deviants were explored in more depth as they showed the most robust responses/elicited the most pronounced grand averaged MMNs in the current sample. Finally, MMN amplitudes and latencies were also extracted as the most positive peak at the two mastoid sites (TP_9/TP_{10}) where the MMN is inverted in voltage polarity (when processed with a nose reference) to carry out exploratory analyses between groups and across deviant types.

2.4 Statistical Analyses

For all analyses (primary, secondary, and exploratory), the assumptions for analysis of variance (ANOVA; normality, outliers, homogeneity of variances, homogeneity of covariance, sphericity) were tested. Although several variables violated certain assumptions across the different analyses, we proceeded with the analyses given that there is no suitable non-parametric alternative to the mixed-measures ANOVA (Field, 2009), and given the novel yet somewhat exploratory nature of this work. Data transformations were carried out on the data points that violated normality (i.e., log, ln, and z score transformations), but following the transformations these data points continued to violate normality assumptions, thus, we proceeded with analyses using the raw (i.e., non-transformed) data. To be fully transparent about which assumptions were violated for which analyses, specific and comprehensive information about the assumptions for

each ANOVA test are presented in supplementary tables (see **Tables S1-S11**). If sphericity was violated, Greenhouse-Geisser-adjusted values are always reported. For all analyses, ANOVAs were initially carried out without covariates; however, adjusted *p*-values include handedness and smoking status as covariates. Smoking status and handedness were included as covariates because they are known to influence the MMN (Inami & Kirino, 2019; Schwade, Didoné & Sleifer, 2017), and they differed between the groups (see **Table 2**). Though other factors (e.g., NART and years of education) differed between the groups, they were not included as covariates because they have been previously shown not to influence the MMN, i.e., the primary outcome of interest (Fulham et al., 2014; Kaser et al., 2013). Further, given the small sample, we could not control for all variables as this would substantially reduce our power.

2.4.1 Primary Analyses

Chi-square tests were carried out to determine if there were differences between the HC and SZ groups on demographic variables including sex, handedness, and smoking status. Separate one-way ANOVA tests were carried out to examine potential differences between the groups on age, years of education and NART scores. For the primary analyses, 2 separate mixed-measures ANOVAs for MMN amplitude and latency were carried out for both the tone and speech tasks (4 ANOVAs total) at site Fz, with deviant type as the within-subjects factor (5 levels: frequency, intensity, duration, gap, location [tone task], frequency, intensity, vowel duration, vowel change, consonant [speech task]) and group (HC vs. SZ) as the between-subjects factor. For the primary analyses, significance was set at $p<.05$. Pairwise comparisons were used to follow-up on significant interactions ($p<.05$) or trends ($p<.1$) between groups.

Spearman's correlations (which are less sensitive to outliers and can be used when the data has violated parametric assumptions such as normal distribution; Field, 2009) were used to

assess potential relationships between MMN amplitudes and latencies (site Fz), clinical AVH measures (i.e., PSYRATS total scores, PANSS total scores, PANSS item 3 scores) and self-report AVH measures (i.e., BAVQ-R subscale scores, VPDS scores and VAAS scores) in the SZ group only. Correlations were only carried out on the deviants that elicited robust MMNs (i.e., tone duration, frequency and intensity deviants and speech frequency, intensity, and vowel change deviants). To control for multiple comparisons, significance was set at $p<.005$ (a strict Bonferroni correction was deemed too stringent given the rather modest sample size and exploratory nature of this work). Second, partial correlations were then carried out to control for smoking status and handedness when testing these associations (adjusted p-values), to ensure consistency with the ANOVAs. As with the ANOVA analyses, though other factors (e.g., NART and years of education; see **Table 2**) differed between the groups, they were not included as additional covariates because they have been previously shown not to influence the MMN (Fulham et al., 2014; Kaser et al., 2013), and because control for all variables was not feasible/would substantially reduce power.

2.4.2 Secondary Analyses

Secondary analyses were carried out comparing MMN amplitudes and latencies between groups on deviants that were the most similar (i.e., frequency and intensity deviants) across the two tasks (i.e., speech and tone). 2 separate mixed-measures ANOVAs were carried out for amplitude and latency at site Fz, with task (2 levels: tone, speech) and deviant type (2 levels: frequency, intensity) as within-subjects factors, and group (HC vs. SZ) as the between-subjects factor. Pairwise comparisons were used to follow-up on significant interactions (defined as $p<.01$) or trends (defined as $p<.05$). Again, if sphericity was violated, Greenhouse-Geisser-adjusted values are reported.

2.4.3 Exploratory Analyses

Exploratory analyses were carried out comparing MMN amplitudes and latencies between groups on deviants that contained two sound files (i.e., low/high frequency deviant, low/high intensity deviant). 4 separate mixed-measures ANOVAs were carried out on MMN amplitude and latency for the frequency and intensity deviants in the tone task at site Fz, with deviant type as the within-subjects factor (2 levels: low, high) and group (HC vs. SZ) as the between-subjects factor. Statistics were not carried out for the speech task due to the lack of a distinct peak in the SZ group (see **Figure S1**). Mean MMN amplitudes and latencies per group for the low and high frequency and intensity deviants in the speech task are presented in **Tables S12** and **S13.**

Finally, we compared MMN amplitudes between groups on each deviant at the mastoid sites (TP_9/TP_{10}). 2 separate mixed-measures ANOVAs for MMN amplitudes were carried out for the tone and speech tasks, with deviant type (5 levels: frequency, intensity, duration, gap, location [tone task], frequency, intensity, vowel duration, vowel change, consonant [speech task]) and site (2 levels: TP_9, TP_{10}) as within-subjects factors and group (HC vs. SZ) as the between-subjects factor. Greenhouse-Geisser-adjusted values are reported if sphericity was violated. For all exploratory analyses, significance was set at $p<.01$ and trends were defined as $p<.05$.

3. RESULTS

3.1 Participants

Recruitment began in December 2018 and, for this thesis, ended March 2022 (interruption of ~1.5 years due to the COVID-19 pandemic). A total of 64 individuals were contacted, 44 were screened, 38 met inclusion criteria, 33 were enrolled and 31 completed the entire study (N=14 SZ patients; N=17 HCs). Two SZ patients withdrew after the first baseline EEG testing session due to the relatively large time commitment of the broader study protocol (i.e., tDCS intervention). As such, the baseline data comprising this thesis included N=16 SZ patients and N=17 HCs. **Table 1** contains a breakdown of recruitment progress for SZ patients and HCs.

An *a priori* power analysis was conducted using G*Power 3.1. Power calculations between the HC and SZ groups on MMN amplitudes at baseline (family-wise alpha = 0.05; ability to detect an effect size of 0.31 [age-adjusted effect size of frequency deviant from preliminary analyses in Summer 2020]; 2 groups), yielded a total sample size of N = 40 (N = 20 per group), which should allow sufficient power (95%) to detect differences in MMN amplitudes (specifically using the frequency deviant). As such, this study was slightly underpowered.

Table 1.

Recruitment Summary of Schizophrenia Patients (SZ) and Healthy Controls (HC). Numbers reflect the N.

	SZ	HC	Total
Contacted	22	42	64
Screened	17	27	44
Qualified	16	22	38
Enrolled	16	17	33
Withdrawn	2	0	2
Completed	14	17	31

Note: "Completed" means that the participant has completed *all* aspects of the study (i.e., pre-, and post-tDCS intervention; N = 16 SZ patients included in baseline analyses).

3.2 Demographics

Demographic characteristics of the HC and SZ groups are summarized in **Table 2**. The Chi-square test revealed no difference in sex between groups [X^2 (1) = 2.53, p = .112]. There were group differences on handedness [X^2 (1) = 4.84, p = .028] and smoking status [X^2 (2) = 10.01, p = .007]. Specifically, a greater proportion of the SZ population were left-handers (p = .028) and smokers (p = .007). One-way ANOVAs revealed significant differences between groups on years of education [F(1, 31) = 7.76, p = .009, η_p^2 = .20,] and NART scores [F(1, 31) = 8.59, p = .006], with the SZ group being less educated and having a higher number of errors on the NART. There were no group differences in age [F(1, 31) = 3.27, p = .080, η_p^2 = .10]. Finally, there were significant differences between groups on BDI [F(1, 31) = 31.26, p = <.001, η_p^2 = .50], BAI [F(1, 31) = 24.36, p <.001, η_p^2 = .44] and Q-LES-S-SF total scores [F(1, 31) = 23.47, p = <.001, η_p^2 = .43], with the SZ group reporting higher levels of depression and anxiety symptoms, and a lower quality of life compared to the HC group.

Table 2.

Demographic Characteristics of Healthy Control (HC) and Schizophrenia Patient (SZ) Groups.

Characteristics	HC (N = 17)	SZ (N = 16)	Significance (N = 31)
Age (M ± SD)	36.24 ± 14.07	44.50 ± 12.0	F = 3.27 p = .080
Sex	7 males, 10 females	11 males, 5 females	X^2 = 2.53 p = .112
Education (yr; M ± SD)	17.0 ± 3.4	13.9 ± 2.9	F = 7.76 p = .009*
NART Score (# of errors)	10.0 ± 5.83	17.56 ± 8.79	F = 8.59 p = .006*

Smoking Status, n (%)			
Smoker	0 (0%)	7 (43.8%)	$X^2 = 2.53$
Non-Smoker	17 (100%)	7 (43.8%)	$p = .007$*
Ex-Smoker	0 (0%)	2 (12.5%)	
Handedness, n (%)			
Right	17 (100%)	12 (75%)	$X^2 = 4.48$
Left	0 (0%)	4 (25%)	$p = .028$*
BDI-II (M ± SD)	2.65 ± 2.18	19.0 ± 11.86	$F = 31.26$ $p = <.001$**
BAI (M ± SD)	2.65 ± 2.45	17.94 ± 12.54	$F = 24.36$ $p = <.001$**
Q-LES-Q-SF (M ± SD)	64.71 ± 5.77	51.19 ± 9.85	$F = 23.47$ $p = <.001$**

Note. NART: National Adult Reading Test; BDI-II: Beck Depression Inventory-II; BAI: Beck Anxiety Inventory; Q-LES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form.

*$p < .05$, **$p < .001$.

3.3 Clinical Characteristics

Clinical characteristics of the SZ patients are summarized in **Table 3**. All SZ patients who participated in this study were currently taking medication (i.e., antipsychotic), some were also taking antidepressants, benzodiazepines, or anticholinergics. Medication information for the SZ patients is presented in **Table 4.** Information about current and lifetime alcohol and drug use is presented in **Table 5.**

Table 3.

Clinical Characteristics (Mean ± SD) of the Schizophrenia Patient (SZ) Group at Baseline.

Clinical Characteristics	SZ (N = 16)

Average Duration of Illness (Years)	17.5 ± 8.98
PSYRATS Total Score (/44)	29.56 ± 5.92
PANSS Total Score (/210)	65.88 ± 20.35
PANSS Item 3 Score (/7)	3.94 ± 1.06
BAVQ-R Malevolence Subscale Score (/18)	8.63 ± 5.12
BAVQ-R Omnipotence Subscale Score (/18)	10.25 ± 3.84
BAVQ-R Benevolence Subscale Score (/18)	7.31 ± 5.31
BAVQ-R Resistance Subscale Score (/27)	14.63 ± 5.81
BAVQ-R Engagement Subscale Score (/24)	9.31 ± 7.66
VPDS Total Score (/35)	20.69 ± 5.96
VAAS Section A (General Hallucinations) Score (/60)	42.88 ± 5.98
VAAS Section B (Command Hallucinations) Score (/95)	66.50 ± 9.16

Note. BAVQ: Beliefs About Voices Questionnaire-Revised; PANSS: Positive and Negative Syndrome Scale; PSYRATS: Psychotic Symptom Rating Scale; VAAS: Voice Acceptance and Action Scale; VPDS: Voice Power Differential Scale.

Table 4.

Medication Details for the Schizophrenia Patient (SZ) Group.

Medication Name	N (%)
Antipsychotics	
Clozapine	4 (25%)
Risperidone	2 (12.5%)
Olanzapine	5 (31.3%)
Quetiapine	6 (37.5%)
Apriprazole	4 (25%)
Paliperidone	6 (37.5%)
Lurasidone	2 (12.5%)
Ziprasidone	1 (6.3%)
Flupenthixol	1 (6.3%)
Brexpiprazole	1 (6.3%)
Selective Serotonin Reuptake Inhibitors (SSRIs)	
Escitalopram	1 (6.3%)
Citalopram	1 (6.3%)
Fluoxetine	1 (6.3%)
Serotonin Receptor Antagonist and Reuptake Inhibitor (SARIs)	
Trazodone	1 (6.3%)
Serotonin Modulator and Stimulator (SMS)	
Vortioxetine	1 (6.3%)
Norepinephrine-Dopamine Reuptake Inhibitor (NDRI)	
Bupropion	1 (6.3%)

Selective Serotonin and Norepinephrine Reuptake Inhibitor (SNRI)	
Duloxetine	2 (12.5%)
Venlafaxine	1 (6.3%)
Benzodiazepines	
Lorazepam	5 (31.3%)
Clonazepam	3 (18.8%)
Anticholinergics	
Benztropine	1 (6.3%)
Methylphenidate	2 (12.5%)
Procyclidine	1 (6.3%)

Table 5.

Current Usage of Alcohol and Drugs for the Healthy Control (HC) and Schizophrenia Patient (SZ) Groups.

Substance	HC (N = 15)	SZ (N = 15)
Alcohol, n (%)	10 (66.7%)	5 (33.3%)
Cannabis, n (%)	3 (20%)	1 (6.7%)
Cocaine, n (%)	0 (0%)	0 (0%)
Methylenedioxymethamphetamine (MDMA), n (%)	0 (0%)	0 (0%)
Psilocybin, n (%)	0 (0%)	0 (0%)
Lysergic acid diethylamide (LSD), n (%)	0 (0%)	0 (0%)

Note. "Current usage" refers to current users of that substance of any amount.

Table 6.

Lifetime Occasions (Mean ± SD) of Alcohol and Drug Use for the Healthy Control (HC) and Schizophrenia Patient (SZ) Groups.

Substance	HC (N = 14)	SZ (N = 11)
Alcohol	1416.14 ± 2284.19	20381.18 ± 60490.76
Cannabis	49.36 ± 86.27	906.45 ± 1846.22
Cocaine	0 ± 0	99.27 ± 312.39
Methylenedioxymethamphetamine (MDMA)	0.57 ± 2.14	14.64 ± 46.91
Psilocybin	0.64 ± 1.65	0 ± 0
Lysergic acid diethylamide (LSD)	0 ± 0	10.18 ± 31.16

3.4 Primary Analyses

Grand averaged MMN waveforms for each of the five deviant types in the tone and speech tasks for both SZ and HC groups are presented in **Figures 4** and **Figure 5**, respectively.

Mean MMN amplitudes and latencies per group for each of the five deviant types of the tone and speech tasks are presented in **Tables 7-10**.

3.4.1 MMN Tone Task

For MMN amplitudes in the tone task, there was a main effect of group, $F(1, 31) = 8.64$, $p = .006$, $\eta_p^2 = .22$ (adjusted by handedness & smoking status: [$F(1, 29) = 4.39$, $p = .045$, $\eta_p^2 = .13$]), with the SZ group having smaller MMN amplitudes (M = -1.56 μV, SE = .16) compared to the HC group (M = -2.19 μV, SE = .15). There was also a main effect of deviant type, $F(4, 124) = 10.39$, $p = <.001$, $\eta_p^2 = .25$ (adjusted [$F(4, 116) = .45$, $p = .74$, $\eta_p^2 = .02$]), with the gap deviant (M = -1.38 μV, SE = .12) being associated with a smaller amplitude than the duration ($p = <.001$; M = -2.24 μV, SE = .17), frequency ($p = <.001$; M = -2.09 μV, SE = .15), intensity ($p = <.001$; M = -1.96 μV, SE = .15), and location deviants ($p = .032$; M = -1.70 μV, SE = .11). Finally, there was a significant deviant type x group interaction $F(4, 124) = 4.24$, $p = .006$, $\eta_p^2 = .12$ (adjusted [$F(4, 116) = 3.27$, $p = .020$, $\eta_p^2 = .10$]), with the SZ group having smaller MMN amplitudes to the frequency ($p = <.001$), gap ($p = .026$), and intensity deviants ($p = .046$) compared to the HC group (see **Table 7** and **Figure 4**).

For MMN latencies in the tone task, there was a main effect of deviant type, $F(4, 124) = 5.26$, $p = .002$, $\eta_p^2 = .15$ (adjusted [$F(4, 116) = 1.11$, $p = .35$, $\eta_p^2 = .04$]), with the intensity deviant (M = 180.67 ms, SE = 5.46) having a longer latency than the duration ($p = <.001$; M = 151.76 ms, SE = 5.18), frequency ($p = .025$; M = 166.86 ms, SE = 4.75), gap ($p = .002$; M = 158.09 ms, SE = 4.27), and location deviants ($p = .012$; M = 155.87 ms, SE = 7.02). There were no other statistically significant group effects on MMN latency in the tone task.

Table 7.

Mean Unadjusted (±SD) and Adjusted (±SE) Mismatch Negativity (MMN) Amplitudes Elicited by Each Deviant Type (Tone Task) for Schizophrenia Patients (SZ) and Healthy Controls (HC).

MMN (μV)	HC (N = 17)		SZ (N = 16)		Significance	
	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
Duration	-2.48 (0.97)	-2.50 (0.24)	-2.0 (0.95)	-1.98 (0.25)	$p = .164$	$p = .191$
Frequency	-2.76 (1.03)	-2.72 (0.24)	-1.42 (0.68)	-1.46 (0.25)	$p = <.001$**	$p = .002$*
Gap	-1.66 (0.85)	-1.62 (0.19)	-1.10 (0.48)	-1.14 (0.20)	$p = .026$*	$p = .131$
Intensity	-2.28 (0.87)	-2.25 (0.25)	-1.64 (0.89)	-1.69 (0.26)	$p = .046$*	$p = .162$
Location	-1.78 (0.58)	-1.68 (0.18)	-1.63 (0.72)	-1.73 (0.19)	$p = .502$	$p = .865$

[a] Means adjusted by handedness and smoking status.
*$p < .05$, **$p < .001$.

Table 8.

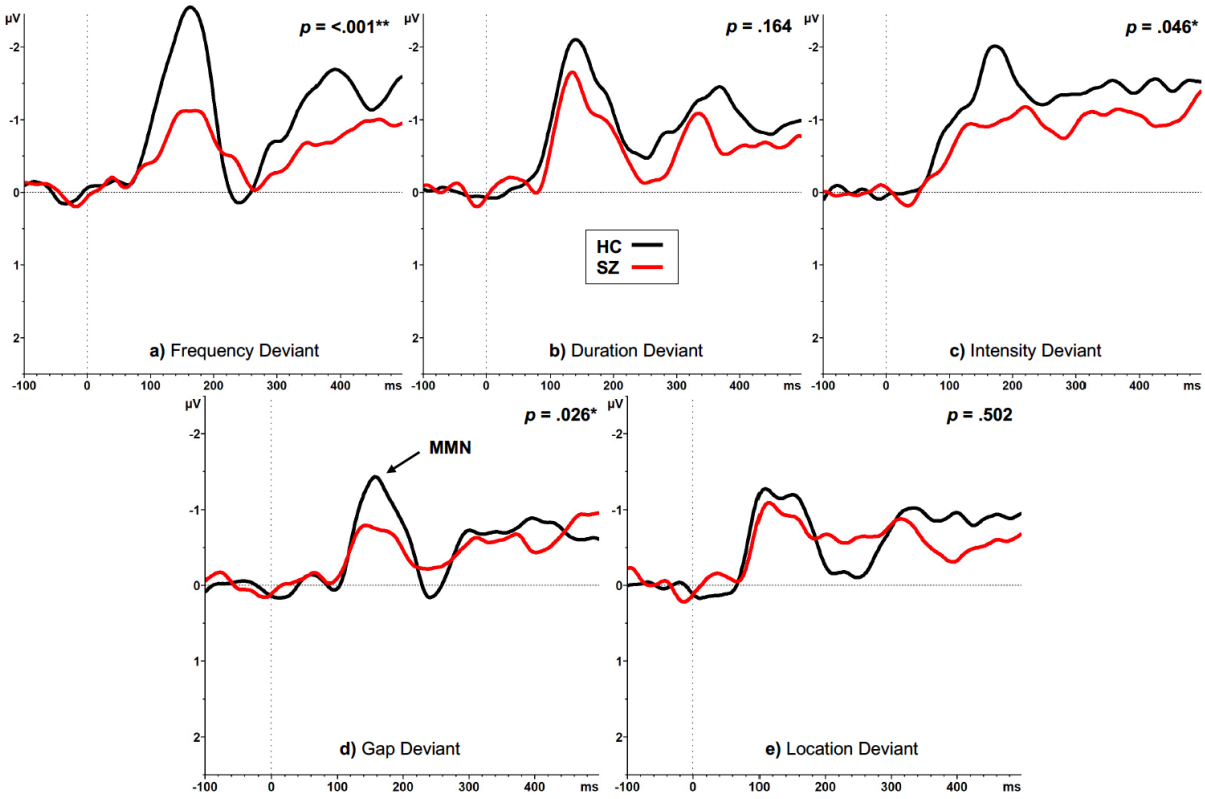
Mean Unadjusted (±SD) and Adjusted (±SE) Mismatch Negativity (MMN) Latencies Elicited by Each Deviant Type (Tone Task) for Schizophrenia Patients (SZ) and Healthy Controls (HC).

MMN (ms)	HC (N = 17)		SZ (N = 16)		Significance	
	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
Duration	155.77 (27.25)	155.78 (8.34)	147.75 (32.23)	147.73 (8.65)	$p = .445$	$p = .547$
Frequency	164.47 (18.47)	158.93 (7.32)	169.25 (34.21)	175.14 (7.59)	$p = .618$	$p = .173$
Gap	157.18 (21.75)	154.25 (6.79)	159.0 (27.14)	162.11 (7.04)	$p = .832$	$p = .471$
Intensity	170.47 (24.16)	164.13 (8.41)	190.88 (37.51)	197.61 (8.73)	$p = .071$	$p = .018$*
Location	150.12 (34.89)	147.10 (10.81)	161.63 (45.38)	164.83 (11.22)	$p = .419$	$p = .309$

[a] Means adjusted by handedness and smoking status.
*$p < .05$, **$p < .001$.

Figure 4.

Grand Averaged Mismatch Negativity (MMN) Waveforms at Site Fz for Each of the Five Deviant Types in the Tone Task for Healthy Controls (HC; Black) and Schizophrenia Patients (SZ; Red).



*$p < .05$, **$p < .001$.

3.4.2 MMN Speech Task

For MMN amplitudes in the speech task, there was a main effect of group, $F(1, 31) = 10.39$, $p = .003$, $\eta_p^2 = .25$ (adjusted [$F(1, 29) = 5.19$, $p = .030$, $\eta_p^2 = .15$]), with the SZ group having smaller MMN amplitudes (M = -.90 μV, SE = .16) compared to the HC group (M = -1.61 μV, SE = .15). There was also a main effect of deviant type, $F(4, 124) = 17.99$, $p = <.001$, $\eta_p^2 = .37$ (adjusted [$F(4, 116) = 2.16$, $p = .10$, $\eta_p^2 = .07$]), with the vowel change deviant (M = -1.90 μV, SE = .20) having a larger amplitude than the frequency ($p = .010$; M = -1.43 μV, SE = .15), intensity ($p = <.001$; M = -1.30 μV, SE = .15), vowel duration ($p = <.001$; M = -.88 μV, SE = .12), and consonant deviants ($p = <.001$; M = -.75 μV, SE = .10). Finally, there was a deviant

type x group interaction $F(4, 124) = 2.72$, $p = .050$, $\eta_p^2 = .08$ (adjusted [$F(4, 116) = 1.26$, $p = .29$, $\eta_p^2 = .04$]), with planned follow-up comparisons showing that the SZ group had smaller MMN amplitudes to the frequency ($p = <.001$), intensity ($p = .027$), vowel duration ($p = .046$), and consonant deviants ($p = .018$) compared to the HC group (see **Table 9** and **Figure 5**).

For MMN latencies in the speech task, there was a main effect of deviant type, $F(4, 124) = 3.67$, $p = .011$, $\eta_p^2 = .11$ (adjusted [$F(4, 116) = 3.62$, $p = .012$, $\eta_p^2 = .11$]), with the vowel change deviant (M = 153.84 ms, SE = 5.55) having a shorter latency than the frequency ($p = <.001$; M = 182.87 ms, SE = 6.04), intensity ($p = <.001$; M = 180.24 ms, SE = 5.75), vowel duration ($p = .011$; M = 177.79 ms, SE = 7.12), and consonant deviants ($p = .017$; M = 173.58 ms, SE = 7.96). There were no other statistically significant effects on MMN latency in the speech task.

Table 9.

Mean Unadjusted (±SD) and Adjusted (±SE) Mismatch Negativity (MMN) Amplitudes Elicited by Each Deviant Type (Speech Task) for Schizophrenia Patients (SZ) and Healthy Controls (HC).

MMN (μV)	HC (N = 17)		SZ (N = 16)		Significance	
	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
Frequency	-2.10 (0.98)	-2.01 (0.24)	-0.76 (0.69)	-0.86 (0.25)	$p = <.001$**	$p = .005$*
Intensity	-1.66 (0.96)	-1.60 (0.25)	-0.95 (0.78)	-1.01 (0.26)	$p = .027$*	$p = .136$
Vowel Duration	-1.12 (0.56)	-1.08 (0.19)	-0.63 (0.77)	-0.67 (0.19)	$p = .046$*	$p = .174$
Vowel Change	-2.18 (1.22)	-2.11 (0.32)	-1.63 (1.07)	-1.70 (0.33)	$p = .175$	$p = .415$
Consonant	-0.99 (0.64)	-1.07 (0.18)	-0.51 (0.45)	-0.43 (0.16)	$p = .018$*	$p = .013$*

[a] Means adjusted by handedness and smoking status.
*$p < .05$, **$p < .001$.

Table 10.

Mean Unadjusted (±SD) and Adjusted (±SE) Mismatch Negativity (MMN) Latencies Elicited by Each Deviant Type (Speech Task) for Schizophrenia Patients (SZ) and Healthy Controls (HC).

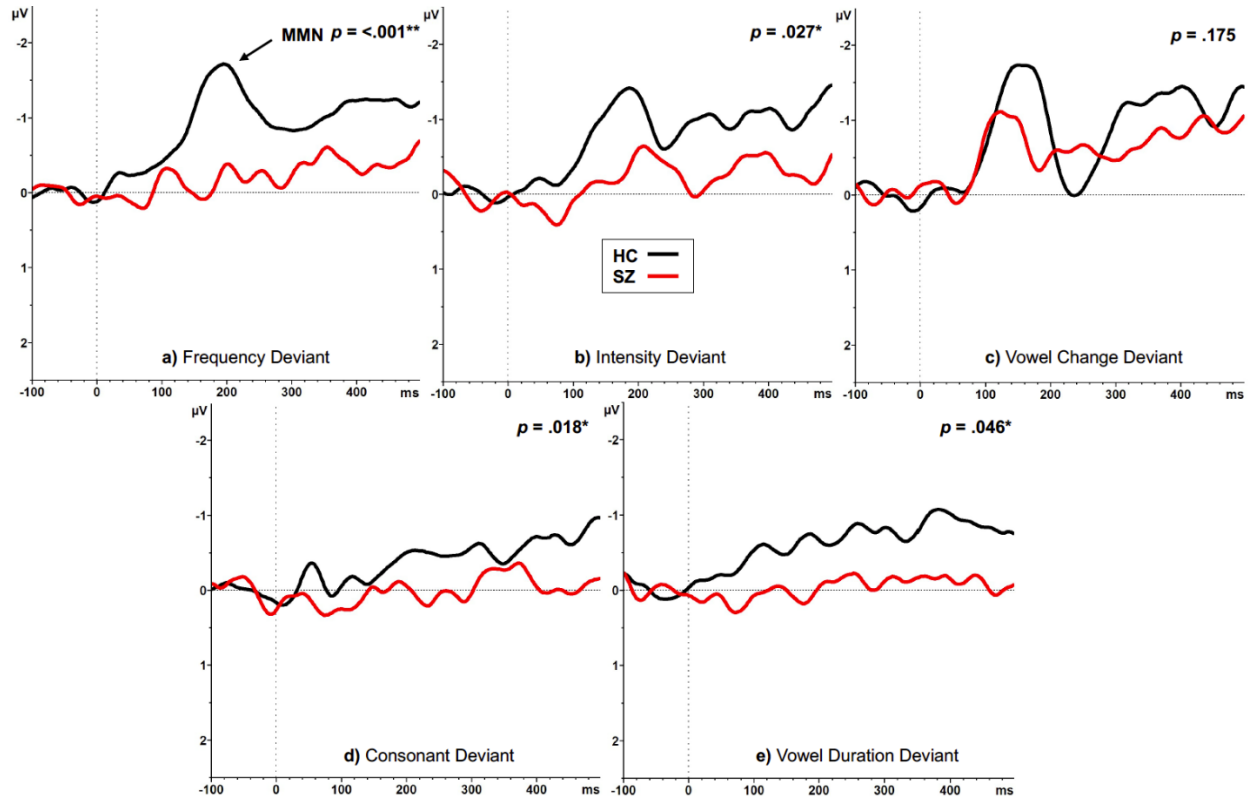
MMN (ms)	HC (N = 17)		SZ (N = 16)		Significance	
	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
Frequency	194.12 (25.52)	190.53 (9.30)	171.63 (42.36)	175.43 (9.64)	$p = .072$	$p = .314$
Intensity	182.47 (25.04)	181.99 (9.28)	178.0 (39.80)	178.51 (9.64)	$p = .700$	$p = .815$
Vowel Duration	176.82 (35.01)	168.48 (9.87)	178.75 (46.34)	187.62 (10.24)	$p = .893$	$p = .231$
Vowel Change	163.18 (25.72)	168.67 (8.62)	144.50 (37.30)	138.66 (8.94)	$p = .102$	$p = .036$*
Consonant	179.41 (52.96)	184.62 (12.33)	167.75 (36.35)	162.22 (12.79)	$p = .469$	$p = .261$

[a] Means adjusted by handedness and smoking status.

*$p < .05$, **$p < .001$.

Figure 5.

Grand Averaged Mismatch Negativity (MMN) Waveforms at Site Fz for Each of the Five Deviant Types in the Speech Task for Healthy Controls (HC; Black) and Schizophrenia Patients (SZ; Red).



*$p < .05$, **$p < .001$.

3.4.3 Correlations

Correlations for the tone and speech tasks are presented in **Table 11** and **Table 12**, respectively. In the SZ group, MMN amplitudes to the intensity deviant in the tone task (site Fz) were positively correlated with total scores on the VPDS ($r_s = .71$, $p = .002$, N=16, adjusted by handedness and smoking status [$r = .54$, $p = .045$, N=16]), see **Figure 6**. No other significant correlations emerged at the corrected $p<.005$ level; however, there were several correlations that were trending towards significance (defined as $p < .05$ for unadjusted correlations).

In the SZ group, there was a trend for MMN amplitudes to the duration deviant in the tone task (site Fz) to positively correlate with BAVQ-R Malevolence subscale scores ($r_s = .50$, $p = .049$, N=16, adjusted [$r = .53$, $p = .049$, N=16]), see **Figure 7**. Finally, there were trends for

MMN latencies to the vowel change deviant in the speech task (site Fz) to be negatively correlated with BAVQ-R Malevolence subscale scores (r_s = -.59, p = .015, N=16, adjusted [r = -.56, p = .037, N=16]), see **Figure 8**, BAVQ-R Resistance subscale scores (r_s = -.53, p = .037, N=16, adjusted [r = -.32, p = .26, N=16]), see **Figure 9**, and VAAS Section A scores (r_s = -.55, p = .028, N=16, adjusted [r = -.36, p = .21, N=16]), see **Figure 10**.

There was one additional relation that emerged in the partial correlations that was not significant without adjusting for handedness and smoking status: MMN amplitudes to the frequency deviant in the speech task (site Fz) were positively correlated with scores on the PANSS Item #3 (hallucinatory behaviour; r_s = .33, p = .22, N=16, adjusted [r = .69, p = .007, N=16]).

Table 11.

Correlations Between Mismatch Negativity (MMN) Event-Related Potential (ERP) Features (Tone Task) and Clinical Characteristics in the Schizophrenia (SZ) Group (N = 16).

	Frequency Deviant Amplitude	Frequency Deviant Latency	Intensity Deviant Amplitude	Intensity Deviant Latency	Duration Deviant Amplitude	Duration Deviant Latency
PSYRATS Total Score	r_s = .33 p = .21	r_s = .00 p = .99	r_s = .23 p = .40	r_s = -.22 p = .41	r_s = .34 p = .19	r_s = -.12 p = .65
PANSS Total Score	r_s = -.03 p = .91	r_s = .42 p = .11	r_s = .04 p = .89	r_s = -.05 p = .87	r_s = -.05 p = .85	r_s = .33 p = .22
PANSS Item #3 Score	r_s = .13 p = .62	r_s = .10 p = .71	r_s = .26 p = .33	r_s = .25 p = .34	r_s = -.05 p = .86	r_s = .23 p = .39
BAVQ-R Malevolence Score	r_s = .11 p = .68	r_s = .15 p = .58	r_s = .32 p = .23	r_s = -.01 p = .97	r_s = .50 p = .05*	r_s = -.36 p = .17
BAVQ-R Omnipotence Score	r_s = .11 p = .68	r_s = .06 p = .83	r_s = .25 p = .35	r_s = .13 p = .63	r_s = .07 p = .80	r_s = .03 p = .90

BAVQ-R Benevolence Score	r_s = .00 p = 1.00	r_s = .28 p = .30	r_s = .23 p = .38	r_s = .30 p = .26	r_s = -.35 p = .19	r_s = .34 p = .19
BAVQ-R Resistance Score	r_s = .44 p = .08	r_s = -.15 p = .59	r_s = .41 p = .11	r_s = .11 p = .68	r_s = .39 p = .14	r_s = -.12 p = .67
BAVQ-R Engagement Score	r_s = .09 p = .75	r_s = -.12 p = .67	r_s = .25 p = .35	r_s = .04 p = .89	r_s = -.16 p = .56	r_s = .22 p = .42
VPDS Total Score	r_s = .50 p = .05*	r_s = -.30 p = .27	r_s = .71 p = .002**	r_s = -.26 p = .33	r_s = .29 p = .27	r_s = -.10 p = .72
VAAS Section A Score	r_s = .13 p = .63	r_s = .19 p = .49	r_s = .15 p = .57	r_s = -.08 p = .77	r_s = .41 p = .11	r_s = -.10 p = .71
VAAS Section B Score	r_s = .08 p = .76	r_s = .12 p = .65	r_s = .04 p = .90	r_s = -.02 p = .96	r_s = .08 p = .77	r_s = -.13 p = .63

Note. BAVQ: Beliefs About Voices Questionnaire-Revised; PANSS: Positive and Negative Syndrome Scale; PSYRATS: Psychotic Symptom Rating Scale; VAAS: Voice Acceptance and Action Scale; VPDS: Voice Power Differential Scale.

*p < .05, **p < .001.

Table 12.

Correlations Between Mismatch Negativity (MMN) Event-Related Potential (ERP) Features (Speech Task) and Clinical Characteristics in the Schizophrenia (SZ) Group (N = 16).

	Frequency Deviant Amplitude	Frequency Deviant Latency	Intensity Deviant Amplitude	Intensity Deviant Latency	Vowel Change Deviant Amplitude	Vowel Change Deviant Latency
PSYRATS Total Score	r_s = .13 p = .64	r_s = -.49 p = .06	r_s = .13 p = .62	r_s = -.21 p = .44	r_s = -.04 p = .88	r_s = -.26 p = .33
PANSS Total Score	r_s = .40 p = .12	r_s = -.01 p = .98	r_s = .13 p = .63	r_s = .07 p = .79	r_s = .22 p = .41	r_s = .18 p = .52

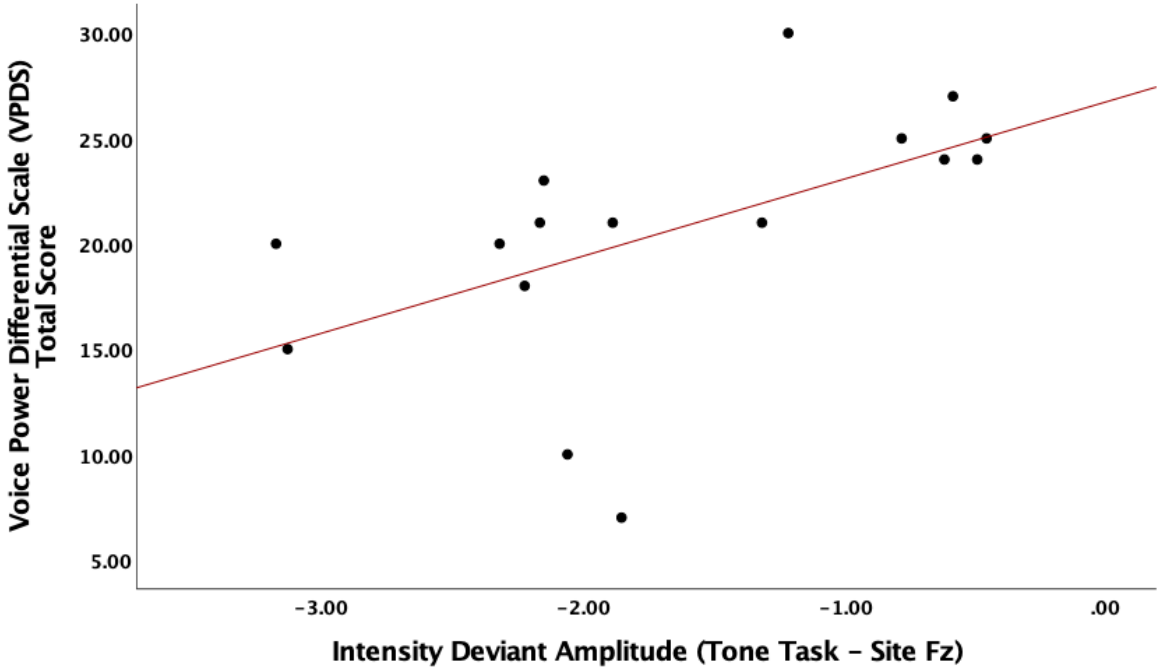
PANSS Item #3 Score	r_s = .33 p = .22	r_s = .10 p = .71	r_s = .27 p = .31	r_s = -.04 p = .89	r_s = .31 p = .25	r_s = -.10 p = .71
BAVQ-R Malevolence Score	r_s = -.24 p = .37	r_s = -.28 p = .30	r_s = -.09 p = .75	r_s = -.28 p = .29	r_s = -.07 p = .80	r_s = -.59 p = .02*
BAVQ-R Omnipotence Score	r_s = .01 p = .97	r_s = -.09 p = .75	r_s = .20 p = .45	r_s = -.26 p = .34	r_s = -.18 p = .50	r_s = -.18 p = .52
BAVQ-R Benevolence Score	r_s = .07 p = .79	r_s = .44 p = .09	r_s = .08 p = .76	r_s = .29 p = .27	r_s = .41 p = .12	r_s = .20 p = .46
BAVQ-R Resistance Score	r_s = -.24 p = .38	r_s = -.01 p = .99	r_s = -.20 p = .47	r_s = -.10 p = .72	r_s = .10 p = .71	r_s = -.53 p = .04*
BAVQ-R Engagement Score	r_s = .01 p = .99	r_s = .24 p = .38	r_s = .18 p = .51	r_s = .28 p = .29	r_s = .21 p = .43	r_s = .18 p = .51
VPDS Total Score	r_s = -.20 p = .45	r_s = .02 p = .94	r_s = .07 p = .81	r_s = .02 p = .94	r_s = .20 p = .47	r_s = -.31 p = .25
VAAS Section A Score	r_s = -.39 p = .13	r_s = -.06 p = .84	r_s = -.32 p = .23	r_s = -.07 p = .79	r_s = -.18 p = .50	r_s = -.55 p = .03*
VAAS Section B Score	r_s = -.18 p = .50	r_s = .08 p = .76	r_s = -.20 p = .46	r_s = .04 p = .89	r_s = .00 p = 1.00	r_s = -.39 p = .14

Note. BAVQ: Beliefs About Voices Questionnaire-Revised; PANSS: Positive and Negative Syndrome Scale; PSYRATS: Psychotic Symptom Rating Scale; VAAS: Voice Acceptance and Action Scale; VPDS: Voice Power Differential Scale.

*p < .05, **p < .001.

Figure 6.

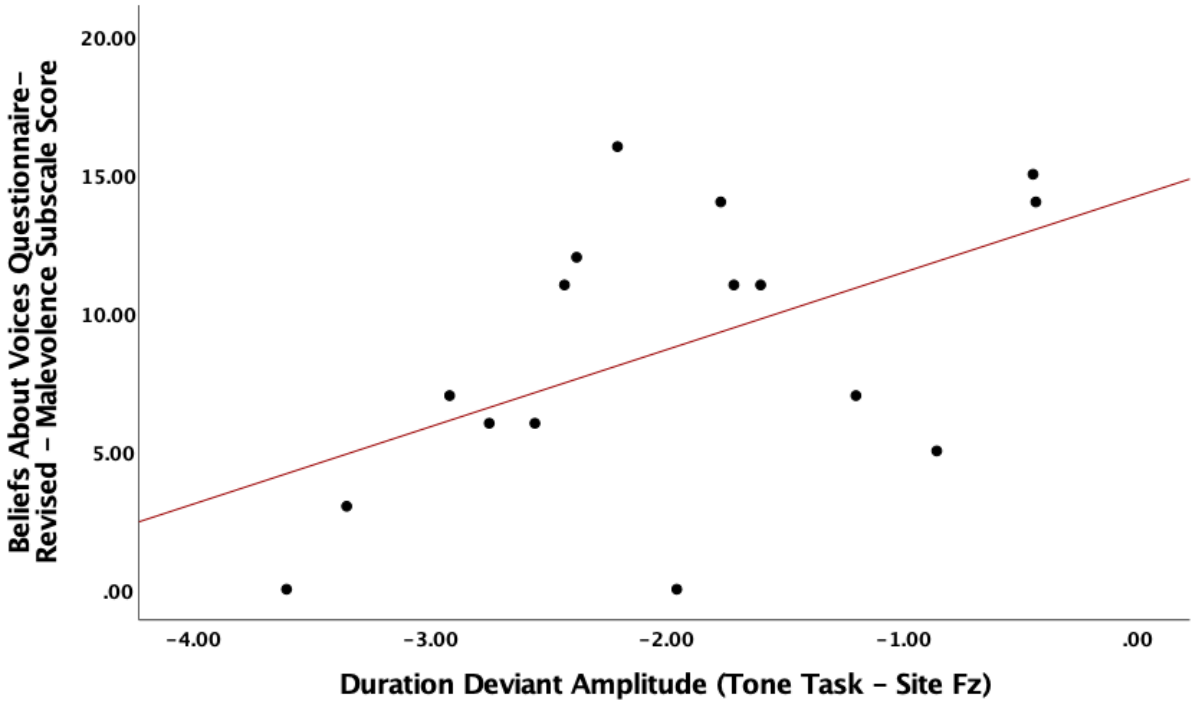
Scatterplot Illustrating the Positive Correlation Between Intensity Deviant Mismatch Negativity (MMN) Amplitudes (Tone Task) and Voice Power Differential Scale (VPDS) Total Scores in the Schizophrenia (SZ) Group.



Note. Figure not adjusted for handedness and smoking status (r_s = .71, p = .002, N=16, adjusted by handedness and smoking status [r = .54, p = .045, N=16]).

Figure 7.

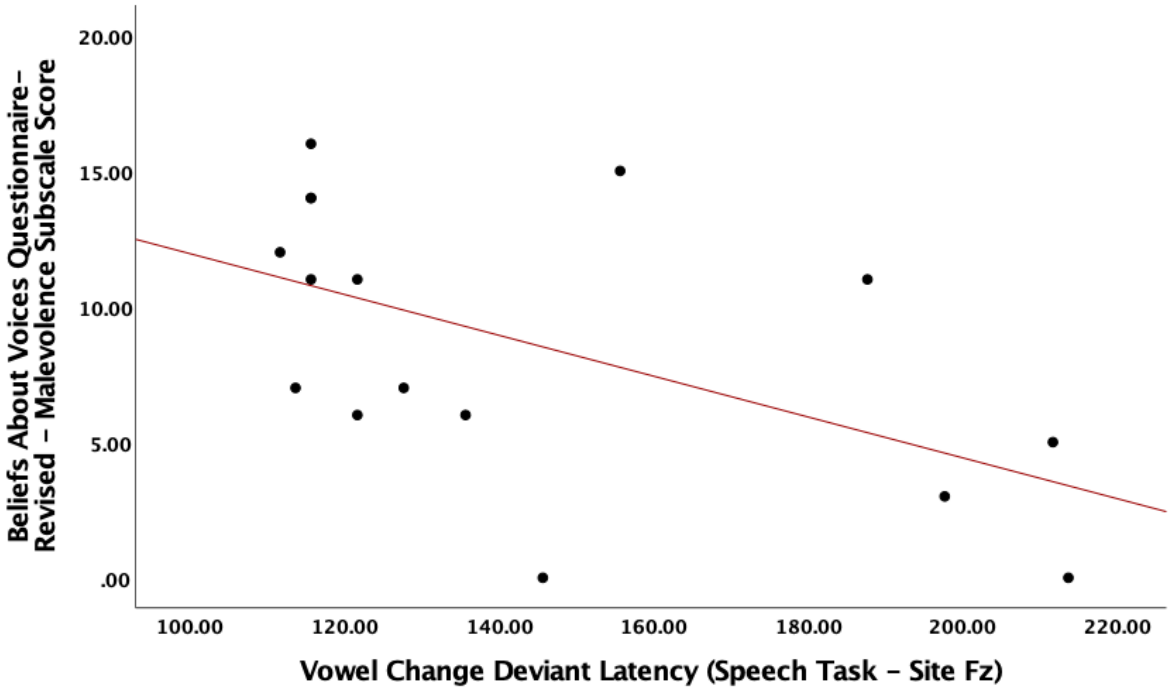
Scatterplot Illustrating the Positive Correlation Between Duration Deviant Mismatch Negativity (MMN) Amplitudes (Tone Task) and Beliefs About Voices Questionnaire-Revised (BAVQ-R) Malevolence Subscale Scores in the Schizophrenia (SZ) Group.



Note. Figure not adjusted for handedness and smoking status (r_s = .50, p = .049, N=16, adjusted by handedness and smoking status [r = .53, p = .049, N=16]).

Figure 8.

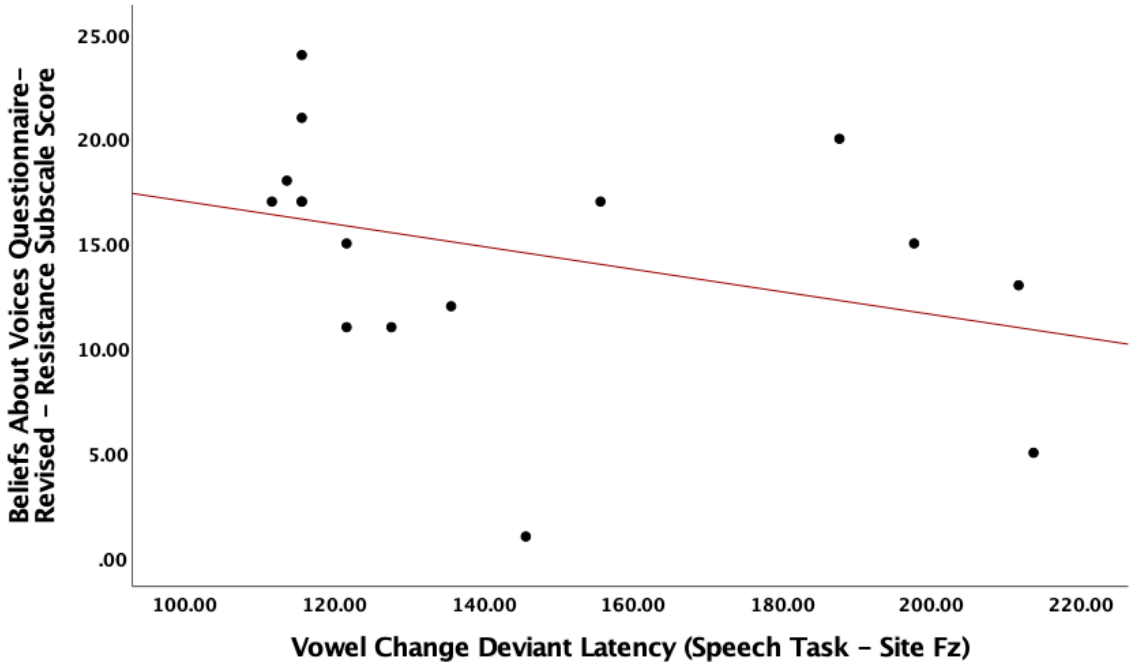
Scatterplot Illustrating the Negative Correlation Between Vowel Change Deviant Mismatch Negativity (MMN) Latencies (Speech Task) and Beliefs About Voices Questionnaire-Revised (BAVQ-R) Malevolence Subscale Scores in the Schizophrenia (SZ) Group.



Note. Figure not adjusted for handedness and smoking status (r_s = -.59, p = .015, N=16, adjusted by handedness and smoking status [r = -.56, p = .037, N=16]).

Figure 9.

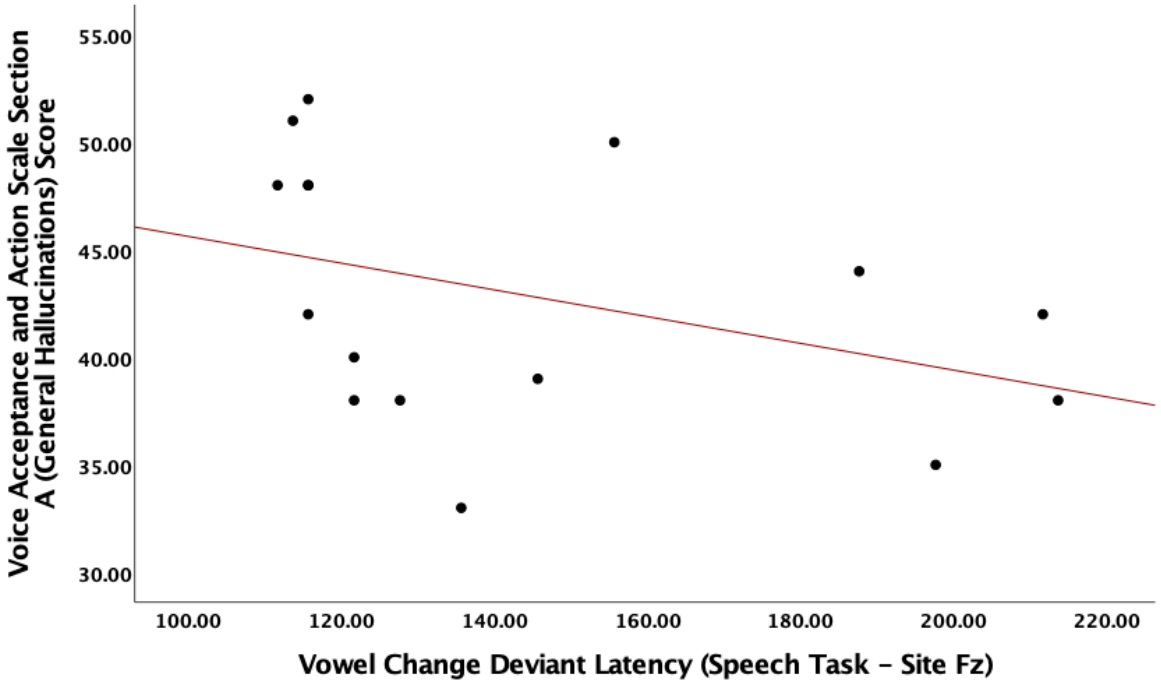
Scatterplot Illustrating the Negative Correlation Between Vowel Change Deviant Mismatch Negativity (MMN) Latencies (Speech Task) and Beliefs About Voices Questionnaire-Revised (BAVQ-R) Resistance Subscale Scores in the Schizophrenia (SZ) Group.



Note. Figure not adjusted for handedness and smoking status (r_s = -.53, p = .037, N=16, adjusted by handedness and smoking status [r = -.32, p = .26, N=16]).

Figure 10.

Scatterplot Illustrating the Negative Correlation Between Vowel Change Deviant Mismatch Negativity (MMN) Latencies (Speech Task) and Voice Acceptance and Action Scale Section A (General Hallucinations) Scores in the Schizophrenia (SZ) Group.



Note. Figure not adjusted for handedness and smoking status (r_s = -.55, p = .028, N=16, adjusted by handedness and smoking status [r = -.36, p = .21, N=16]).

3.5 Secondary Analyses

Mean MMN amplitudes and latencies per group for the frequency and intensity deviants of the tone and speech tasks are presented in **Table 13** and **Table 14,** respectively. Grand average MMN waveforms per group for the frequency and intensity deviants of the tone and speech tasks are presented in **Figure 11**. For MMN amplitudes to the frequency and intensity deviants across both tasks, there was a main effect of group, $F(1, 31) = 16.83$, $p = <.001$, $\eta_p^2 = .35$ (adjusted [$F(1, 29) = 8.27$, $p = .007$, $\eta_p^2 = .22$]), with the SZ group having smaller MMN amplitudes (M = -1.19 µV, SE = .18) than the HC group (M = -2.20 µV, SE = .17). There was also a main effect of task, $F(1, 31) = 24.32$, $p = <.001$, $\eta_p^2 = .44$ (adjusted [$F(1, 29) = .03$, $p = .87$, $\eta_p^2 = .00$]), with MMN amplitudes being larger in the tone task (M = -2.03 µV, SE = .14)

compared to the speech task (M = -1.37 μV, SE = .14). Finally, there was a deviant type x group interaction, $F(1, 31) = 12.51$, $p = .001$, $\eta_p^2 = .29$ (adjusted [$F(1, 29) = 7.03$, $p = .013$, $\eta_p^2 = .20$]), with the frequency deviant being smaller in the SZ group (M = -1.09 μV, SE = .18) compared to the HC group ($p = <.001$; M = -2.43 μV, SE = .18). The MMN to the intensity deviant tended to be smaller in the SZ group (M = -1.30 μV, SE = .19) compared to the HC group ($p = .018$; M = -1.97 μV, SE = .19), but this effect did not reach the $p<.01$ alpha level set for the secondary analyses. No other significant main effects or interactions were found.

Table 13.

Mean Unadjusted (±SD) and Adjusted (±SE) Mismatch Negativity (MMN) Amplitudes Elicited by the Frequency and Intensity Deviants in the Tone and Speech Tasks for Schizophrenia Patients (SZ) and Healthy Controls (HC).

MMN (μV)	HC (N = 17)		SZ (N = 16)		Significance	
	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
Tone Frequency	-2.76 (1.03)	-2.72 (0.24)	-1.42 (0.68)	-1.46 (0.25)	$p = <.001$**	$p = .002$*
Tone Intensity	-2.28 (0.87)	-2.25 (0.25)	-1.64 (0.89)	-1.69 (0.26)	$p = .046$*	$p = .162$
Speech Frequency	-2.10 (0.98)	-2.01 (0.24)	-0.76 (0.69)	-0.86 (0.25)	$p = <.001$**	$p = .005$*
Speech Intensity	-1.66 (0.96)	-1.60 (0.25)	-0.95 (0.78)	-1.01 (0.26)	$p = .027$*	$p = .136$

[a] Means adjusted by handedness and smoking status.
*$p < .05$, **$p < .001$.

Table 14.

Mean Unadjusted (±SD) and Adjusted (±SE) Mismatch Negativity (MMN) Latencies Elicited by the Frequency and Intensity Deviants in the Tone and Speech Tasks for Schizophrenia Patients (SZ) and Healthy Controls (HC).

MMN (ms)	HC (N = 17)		SZ (N = 16)		Significance	
	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]

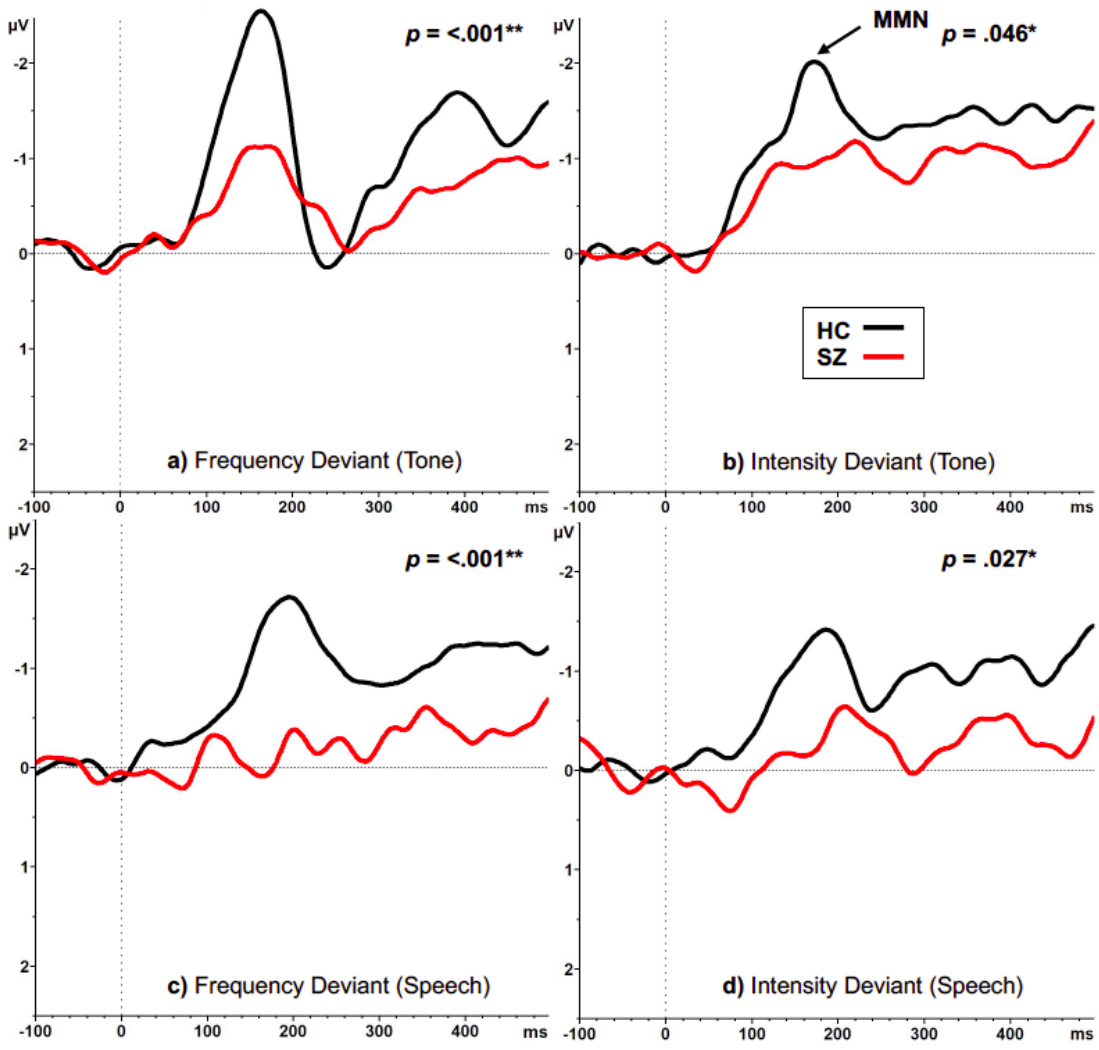
Tone Frequency	164.47 (18.47)	158.93 (7.32)	169.25 (34.20)	175.14 (7.59)	$p = .618$	$p = .173$
Tone Intensity	170.47 (24.16)	164.13 (8.41)	190.88 (37.51)	197.61 (8.73)	$p = .071$	$p = .018$*
Speech Frequency	194.12 (24.52)	190.53 (9.30)	171.63 (42.36)	175.43 (9.64)	$p = .072$	$p = .314$
Speech Intensity	182.47 (25.04)	181.99 (9.28)	178.00 (39.80)	178.51 (9.62)	$p = .700$	$p = .815$

[a] Means adjusted by handedness and smoking status.

*$p < .05$, **$p < .001$.

Figure 11.

Grand Averaged Mismatch Negativity (MMN) Waveforms at Site Fz for the Frequency and Intensity Deviants in the Tone and Speech Tasks for Healthy Controls (HC; Black) and Schizophrenia Patients (SZ; Red).



*p < .05, **p < .001.

3.6 Exploratory Analyses

3.6.1 Low vs. High Frequency & Intensity MMN Analysis

Mean MMN amplitudes and latencies per group for the frequency (low vs. high) and intensity (low vs. high) deviants of the tone task are presented in **Tables 15** and **16.** Grand average MMN waveforms per group for the low and high frequency and intensity deviants of the tone task are presented in **Figure 12**.

For MMN amplitudes to the low and high frequency deviants in the tone task, there was a main effect of group, $F(1, 31) = 15.41$, $p = <.001$, $\eta_p^2 = .33$ (adjusted [$F(1, 29) = 9.49$, $p = .004$, $\eta_p^2 = .25$]), with the SZ group having smaller MMN amplitudes (M = -1.60 μV, SE = .23) compared to the HC group (M = -2.85 μV, SE = .22). There was no main effect of deviant type (low vs. high frequency deviant) or deviant x group interaction. No significant main effects or interactions were found for MMN latencies to the low and high frequency deviants in the tone task.

For MMN amplitudes to the low and high intensity deviants in the tone task, there was a trend for a main effect of group, $F(1, 31) = 5.49$, $p = .026$, $\eta_p^2 = .15$ (adjusted [$F(1, 29) = 5.47$, $p = .10$, $\eta_p^2 = .09$]), with the SZ group having smaller MMN amplitudes (M = -1.78 μV, SE = .24) compared to the HC group (M = -2.55 μV, SE = .23). No other significant effects were noted. For MMN latencies to the low and high intensity deviants in the tone task, there was a deviant type x group interaction, $F(1, 31) = 11.34$, $p = .002$, $\eta_p^2 = .27$ (adjusted [$F(1, 29) = 3.73$, $p = .063$, $\eta_p^2 = .11$]), with the SZ group having a longer MMN latency (M = 191.38 ms, SE = 7.81) for the high intensity deviant compared to the HC group ($p = .009$; M = 161.06 ms, SE = 7.58).

Table 15.

Mean Unadjusted (±SD) and Adjusted (±SE) Mismatch Negativity (MMN) Amplitudes Elicited by the Frequency (Low vs. High) and Intensity (Low vs. High) Deviants (Tone Task) for Schizophrenia Patients (SZ) and Healthy Controls (HC).

MMN (μV)	HC (N = 17)		SZ (N = 16)		Significance	
	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
Low Frequency	-2.90 (1.11)	-2.88 (0.25)	-1.59 (0.71)	-1.62 (0.26)	$p = <.001$**	$p = .004$*
High Frequency	-2.80 (1.29)	-2.79 (0.29)	-1.61 (0.74)	-1.63 (0.30)	$p = .003$*	$p = .018$*

Low Intensity	-2.51 (1.13)	-2.48 (0.30)	-1.77 (1.06)	-1.81 (0.31)	$p = .063$	$p = .174$
High Intensity	-2.59 (1.03)	-2.57 (0.31)	-1.78 (1.15)	-1.81 (0.32)	$p = .042$*	$p = .130$

[a] Means adjusted by handedness and smoking status.
*$p < .05$, **$p < .001$.

Table 16.

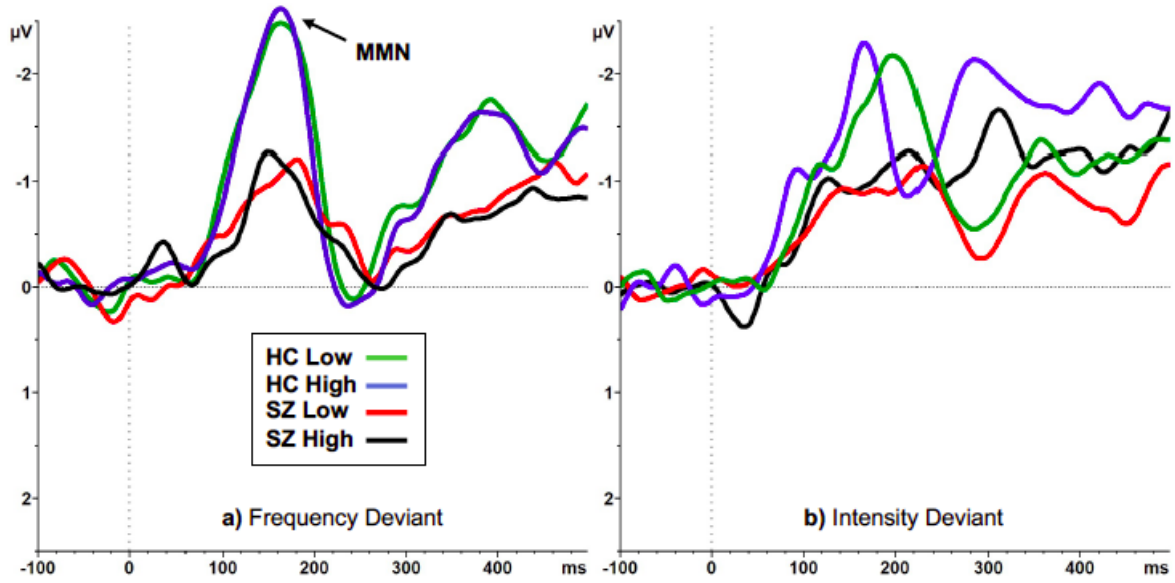
Mean Unadjusted (±SD) and Adjusted (±SE) Mismatch Negativity (MMN) Latencies Elicited by the Frequency (Low vs. High) and Intensity (Low vs. High) Deviants (Tone Task) for Schizophrenia Patients (SZ) and Healthy Controls (HC).

MMN (ms)	HC (N = 17)		SZ (N = 16)		Significance	
	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
Low Frequency	169.18 (20.63)	165.23 (8.20)	186.0 (37.10)	190.20 (8.51)	$p = .115$	$p = .065$
High Frequency	163.18 (19.24)	160.77 (7.71)	176.88 (34.60)	179.43 (8.00)	$p = .166$	$p = .138$
Low Intensity	193.41 (27.68)	185.59 (8.66)	187.63 (37.46)	195.93 (8.98)	$p = .616$	$p = .457$
High Intensity	161.06 (25.15)	158.29 (8.69)	191.38 (36.64)	194.31 (9.01)	$p = .009$*	$p = .014$*

[a] Means adjusted by handedness and smoking status.
*$p < .05$, **$p < .001$.

Figure 12.

Grand Averaged Mismatch Negativity (MMN) Waveforms at Site Fz for the Low and High Frequency Deviant (a) and the Low and High Intensity Deviant (b) in the Tone Task for Healthy Controls (HC) and Schizophrenia Patients (SZ).



3.6.2 Mastoid Analysis

Mean MMN amplitudes per group for each of the five deviants of the tone and speech tasks at the mastoid sites are presented in **Table 17** and **Table 18,** respectively. Grand average waveforms of the MMN polarity reversal at mastoid sites (TP_9/TP_{10}) per group for each of the five deviants of the tone and speech tasks are presented in **Figure 13** and **Figure 14**, respectively.

3.6.2.1 MMN Tone Task. For MMN amplitudes at the mastoid sites in the tone task, there was a trend for a main effect of group, $F(1, 31) = 4.69$, $p = .038$, $\eta_p^2 = .13$ (adjusted [$F(1, 29) = 2.44$, $p = .13$, $\eta_p^2 = .08$]), with the SZ group having smaller MMN amplitudes at the mastoid sites (M = 1.78 μV, SE = .16) compared to the HC group (M = 2.28 μV, SE = .16). There was a main effect of deviant type, $F(1, 31) = 12.72$, $p = <.001$, $\eta_p^2 = .29$ (adjusted [$F(4, 116) = .45$, $p = .74$, $\eta_p^2 = .02$]), with the gap deviant having a smaller amplitude (M = 1.48 μV, SE = .12) than the duration ($p = <.001$; M = 2.43 μV, SE = .17), location ($p = .004$; M = 1.84 μV, SE = .12), intensity ($p = <.001$; M = 2.24 μV, SE = .15), and frequency deviants ($p = <.001$;

M = 2.16 μV, SE = .17). There was also a main effect of site, $F(1, 31) = 11.53$, $p = .002$, $\eta_p^2 = .27$ (adjusted [$F(1, 29) = .43$, $p = .52$, $\eta_p^2 = .02$]), with larger MMN amplitudes at the left mastoid site (TP_9; M = 2.21 μV, SE = .11) compared to the right mastoid site (TP_{10}; M = 1.85 μV, SE = .14). For interactions, there was a deviant type x group interaction, $F(1, 31) = 4.73$, $p = .003$, $\eta_p^2 = .13$ (adjusted [$F(4, 116) = 2.28$, $p = .065$, $\eta_p^2 = .07$]), with the SZ group having a smaller amplitude to the frequency deviant (M = 1.52 μV, SE = .25) compared to the HC group ($p = <.001$; M = 2.80 μV, SE = .24).

Table 17.

Mean Unadjusted (±SD) and Adjusted (±SE) Mismatch Negativity (MMN) Amplitudes Elicited by Each Deviant Type (Tone Task) for Schizophrenia Patients (SZ) and Healthy Controls (HC) at Mastoid Sites (TP_9/TP_{10}).

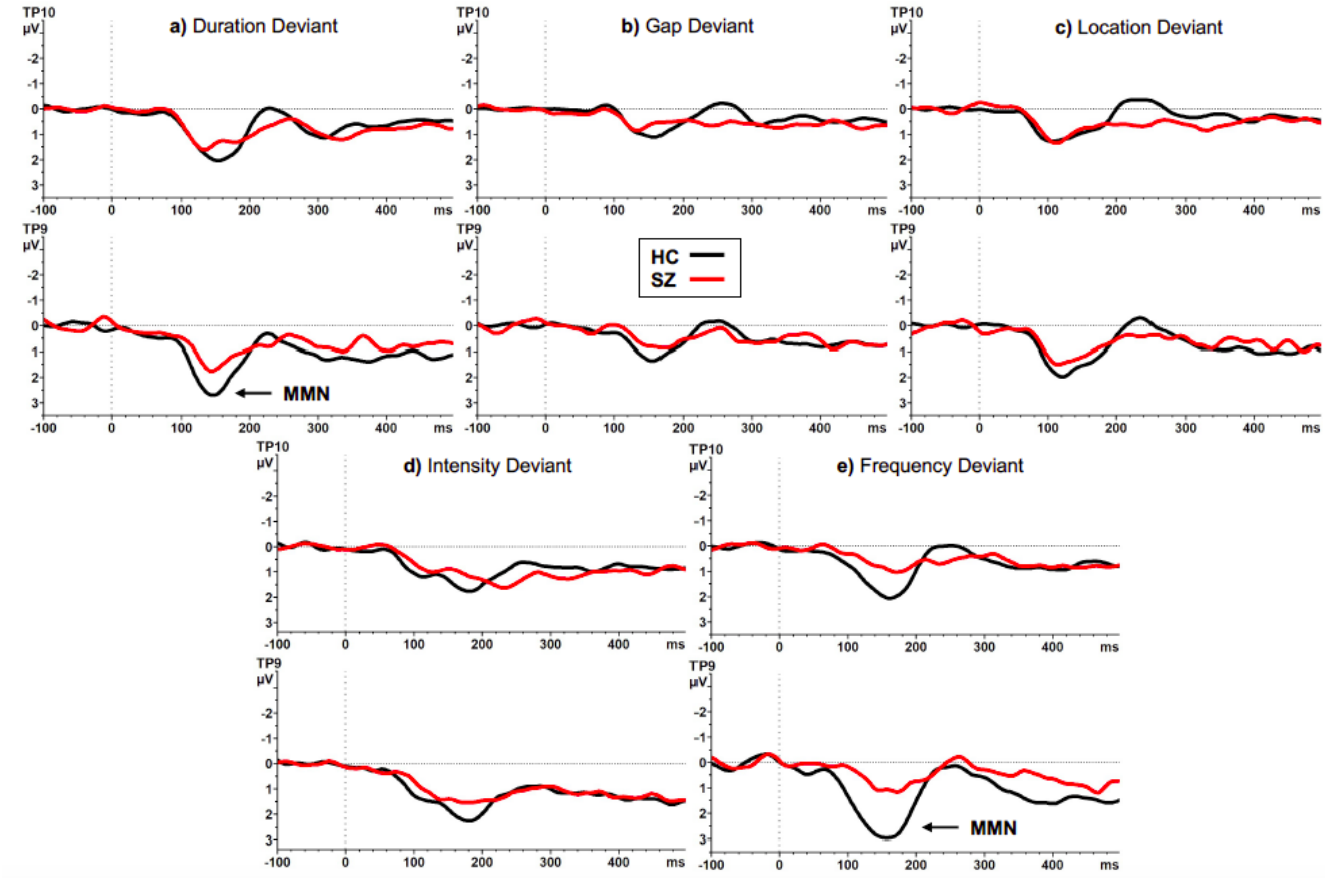
MMN (μV)	Site	HC (N = 17)		SZ (N = 16)		Significance	
		Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
Duration	TP_9	2.92 (1.22)	2.86 (0.29)	2.31 (0.84)	2.37 (0.30)	$p = .103$	$p = .288$
	TP_{10}	2.43 (1.19)	2.35 (0.30)	2.06 (1.02)	2.14 (0.31)	$p = .341$	$p = .667$
Gap	TP_9	1.64 (0.88)	1.69 (0.21)	1.36 (0.65)	1.30 (0.22)	$p = .316$	$p = .252$
	TP_{10}	1.55 (0.87)	1.47 (0.23)	1.37 (0.76)	1.45 (0.24)	$p = .530$	$p = .968$
Location	TP_9	2.26 (0.64)	2.26 (0.18)	1.90 (0.74)	1.91 (0.19)	$p = .144$	$p = .233$
	TP_{10}	1.55 (1.05)	1.58 (0.25)	1.64 (0.72)	1.61 (0.26)	$p = .771$	$p = .942$
Intensity	TP_9	2.65 (0.89)	2.71 (0.28)	2.16 (1.10)	2.09 (0.25)	$p = .166$	$p = .174$
	TP_{10}	2.16 (0.90)	2.20 (0.24)	1.98 (0.83)	1.94 (0.25)	$p = .546$	$p = .503$
Frequency	TP_9	3.22 (1.11)	3.19 (0.28)	1.64 (0.88)	1.68 (0.29)	$p = <.001$**	$p = .002$*
	TP_{10}	2.38 (1.41)	2.26 (0.32)	1.41 (0.85)	1.53 (0.34)	$p = .025$*	$p = .162$

[a] Means adjusted by handedness and smoking status.

*$p < .05$, **$p < .001$.

Figure 13.

Grand Averaged Waveforms of the Mismatch Negativity (MMN) Polarity Reversal at Site TP_{10} and TP_9 for Each of the Five Deviant Types in the Tone Task for Healthy Controls (HC; Black) and Schizophrenia Patients (SZ; Red).



3.6.2.2 MMN Speech Task. For MMN amplitudes at the mastoid sites in the speech task, there was a main effect of group, $F(1, 31) = 10.06$, $p = .003$, $\eta_p^2 = .25$ (adjusted [$F(1, 29) = 5.84$, $p = .022$, $\eta_p^2 = .17$]), with the SZ group having smaller MMN amplitudes (M = 1.08 μV, SE = .16) compared to the HC group (M = 1.77 μV, SE = .15). There was also a main effect of deviant type, $F(1, 31) = 35.30$, $p = <.001$, $\eta_p^2 = .53$ (adjusted [$F(4, 116) = 1.95$, $p = .15$, $\eta_p^2 = .06$), with the vowel change deviant having a larger amplitude (M = 2.27 μV, SE = .20) than the frequency ($p = <.001$; M = 1.61 μV, SE = .15), intensity ($p = <.001$; M = 1.51 μV, SE = .13), vowel duration ($p = <.001$; M = .80 μV, SE = .10), and consonant deviants ($p = <.001$; M = .94

μV, SE = .10). There was also a main effect of site, $F(1, 31) = 14.38$, $p = <.001$, $\eta_p^2 = .32$ (adjusted [$F(1, 29) = .13$, $p = .72$, $\eta_p^2 = .01$]), with larger MMN amplitudes at the left (TP_9; M = 1.61 μV, SE = .13) compared to the right mastoid site (TP_{10}; M = 1.24 μV, SE = .11). For interactions, there was a site x group interaction, $F(1, 31) = 15.26$, $p = <.001$, $\eta_p^2 = .33$ (adjusted [$F(1, 29) = 10.62$, $p = .003$, $\eta_p^2 = .27$]), with the SZ group having smaller MMN amplitudes at the left mastoid site (TP_9; M = 1.08 μV, SE = .18) compared to the HC group (TP_9; M = 2.15 μV, SE = .18). Finally, there was a trend for a deviant type x site x group interaction, $F(1, 31) = 3.78$, $p = .012$, $\eta_p^2 = .11$ (adjusted [$F(4, 116) = 4.11$, $p = .009$, $\eta_p^2 = .12$]), with the SZ group having smaller MMN amplitudes at the left mastoid site for the frequency ($p = <.001$), intensity ($p = .002$), vowel duration ($p = .005$) and vowel change ($p = .001$) deviants compared to the HC group (see **Table 18**).

Table 18.

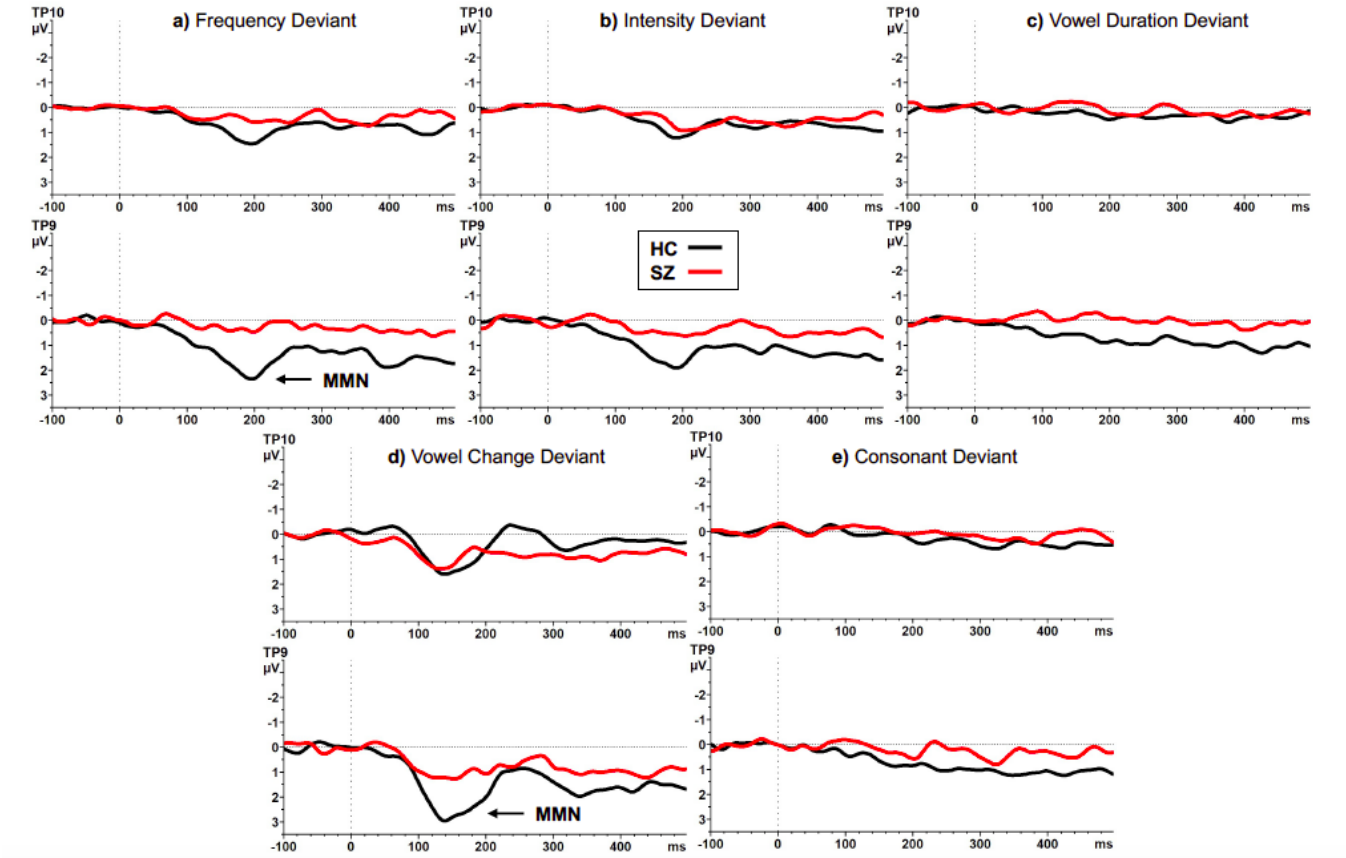
Mean Unadjusted (±SD) and Adjusted (±SE) Mismatch Negativity (MMN) Amplitudes Elicited by Each Deviant Type (Speech Task) for Schizophrenia Patients (SZ) and Healthy Controls (HC) at Mastoid Sites (TP_9/TP_{10}).

MMN (μV)	Site	HC (N = 17)		SZ (N = 16)		Significance	
		Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
Frequency	TP_9	2.67 (1.33)	2.71 (0.30)	0.93 (0.66)	0.87 (0.18)	$p = <.001$**	$p = <.001$**
	TP_{10}	1.78 (0.99)	1.76 (0.22)	1.09 (0.58)	1.10 (0.23)	$p = .021$*	$p = .072$
Intensity	TP_9	2.09 (0.96)	1.98 (0.22)	1.11 (0.62)	1.22 (0.23)	$p = .002$*	$p = .040$*
	TP_{10}	1.54 (0.98)	1.57 (0.24)	1.30 (0.65)	1.28 (0.25)	$p = .417$	$p = .448$
Vowel Duration	TP_9	1.31 (0.70)	1.29 (0.20)	0.56 (0.74)	0.58 (0.21)	$p = .005$*	$p = .033$*
	TP_{10}	0.79 (0.54)	0.70 (0.16)	0.55 (0.61)	0.64 (0.16)	$p = .230$	$p = .802$
Vowel Change	TP_9	3.31 (1.34)	3.34 (0.33)	1.85 (0.93)	1.81 (0.34)	$p = .001$*	$p = .006$*
	TP_{10}	2.01 (1.57)	1.91 (0.38)	1.90 (1.13)	2.01 (0.40)	$p = .830$	$p = .881$
Consonant	TP_9	1.40 (0.69)	1.44 (0.19)	0.93 (0.67)	0.89 (0.20)	$p = .059$	$p = .081$
	TP_{10}	0.82 (0.66)	0.87 (0.18)	0.59 (0.65)	0.54 (0.18)	$p = .329$	$p = .236$

[a] Means adjusted by handedness and smoking status.
*$p < .05$, **$p < .001$.

Figure 14.

Grand Averaged Waveforms of the Mismatch Negativity (MMN) Polarity Reversal at Site TP_{10} and TP_9 for Each of the Five Deviant Types in the Speech Task for Healthy Controls (HC; Black) and Schizophrenia Patients (SZ; Red).



4. DISCUSSION

4.1 Summary

The primary aim of this thesis was to assess differences in MMN features (amplitudes and latencies) to both pure tones and speech-based sounds between SZ patients and HCs, and to

examine relations between MMN features, clinical ratings of AVH severity and self-report measures of AVH features in the SZ group. The secondary aim was to compare differences in MMN features between the groups on the two MMN tasks directly (as tasks were tested separately in the primary aims). Finally, the exploratory analyses included examining differences in MMN features between the HC and SZ groups on two versions of the frequency and intensity deviants (i.e., low/high frequency deviant, low/high intensity deviant) and examining MMN amplitudes between groups on each deviant type of the two tasks at the mastoid sites (TP_9/TP10; MMN polarity reversal sites). This work is novel in that it directly compares MMN responses between the tone and speech five deviant multi-feature MMN tasks. Second, very few previous studies have examined relations between MMN features and subjective AVH measures, specifically measures of the subjective voice hearing experience (i.e., BAVQ-R, VAAS, VPDS). In fact, to the best of our knowledge, this is the first study to assess relations between MMN features and *subjective* measures of AVHs in people with SZ.

In brief, in the primary analyses of the MMN tone task, the SZ group was found to have significantly smaller MMN amplitudes to the frequency, gap and intensity deviants compared to the HC group; the effect on the frequency deviant in particular remained significant even after controlling for handedness and smoking status, suggesting that this group difference was most pronounced to the frequency deviant. In the primary analyses centered on the MMN speech task, the SZ group had significantly smaller MMN amplitudes to the frequency, intensity, vowel duration and consonant deviants compared to the HC group; the effect on the frequency and consonant deviants remained significant even after controlling for handedness and smoking status. There were no main effects of group on MMN latencies in either the tone or speech tasks. Although there were several correlations between MMN features and clinical and self-report

measures of AVHs, the most pronounced relation was a positive association between MMN amplitudes to the intensity deviant (tone task) and total scores on the VPDS (i.e., smaller/less negative MMN amplitudes were associated with higher VPDS scores).

For the secondary analyses, when comparing amplitudes and latencies of the frequency and intensity deviants across the two MMN tasks directly, the SZ group had smaller MMN amplitudes to the frequency deviant in both the tone and speech MMN tasks. Finally, for the exploratory mastoid analyses in the tone task, the SZ group had smaller MMN amplitudes to the frequency deviant at both mastoid sites. In the speech task, MMN amplitudes were larger at the left mastoid site (TP_9) compared to the right mastoid site (TP_{10}) across all deviant types. The HC group also had larger overall MMN amplitudes at the left mastoid site (TP_9) compared to the SZ group. Overall, these results are in line with our hypotheses and previous literature but expand on previous work by comprehensively assessing multiple (i.e., 10) deviant types across two tasks (comparing responses across the two tasks directly) and examining which MMN-indexed deficits were most prominent in a sample of SZ patients with persistent AVHs. Importantly, this work emphasizes the importance of not only focusing on clinical measures of AVH severity, as has been done historically, but shows the relevance of also examining *subjective* aspects of the AVH experience to gather a more complete understanding of how AVHs are impacting the brain/how they related with neural-based features. Thus, despite the modest sample size, some robust results emerged and yielded novel insights into neural features of AVHs.

4.2 Primary Analyses: MMN Tone Task

Our finding that SZ patients had smaller MMN amplitudes to the frequency, intensity and gap deviants in the tone task and the frequency, intensity, vowel duration and consonant deviants in the speech task are somewhat in line with our hypotheses as well as previous

literature. Specifically, for the tone task, it was hypothesized that the SZ group would have smaller MMN amplitudes compared to HCs across all deviant types, especially to the duration deviant, as impairments in duration deviant MMN amplitudes is one of the most robustly reported findings in the MMN-SZ literature (Erickson et al., 2016; Umbricht & Krljes, 2005). However, surprisingly, our results did not yield a significant group difference in duration deviant amplitudes (though, visually, the SZ group had a smaller amplitude, $p = .164$, thus, this may have been an issue of power).

Instead, we found that the SZ group had smaller MMN amplitudes to the frequency, intensity, and gap deviants. These results are mostly in line with the findings of Fisher et al. (2012), who reported that SZ patients with a current history of AVHs (N = 12) had smaller MMN amplitudes compared to HCs on duration, intensity, gap, and location deviants. Given that this study used the exact same equipment/testing conditions (performed in the same laboratory), the current study is a good replication of Fisher et al. (2012). Interestingly, the only deviant type that did not show a group difference from Fisher et al. (2012) was the frequency deviant, for which we found the most robust differences in the current sample. The SZ patients in the Fisher et al. (2012) study were experiencing an acute exacerbation of their illness, while our SZ patient sample were clinically stable; this might account for these differences. Length of illness may also influence MMN deficits to certain deviant types. For instance, Todd et al. (2008) found that SZ patients in the early phase of illness showed largest MMN deficits to duration and intensity deviants compared to HCs, while SZ patients with a chronic illness duration showed largest MMN deficits to frequency deviants, and duration deviants to a lesser degree. Lee et al. (2018) proposed that the current functional status of SZ patients could explain the more pronounced deficits to frequency deviants, as they found that patients with lower levels of functioning

showed deficits in both frequency and duration MMN, whereas those with higher levels of functioning showed more isolated deficits in the duration indexed MMN with a preserved frequency MMN. Xiong et al. (2019) also found similar results, in that frequency MMN deficits were preserved in a first-episode SZ patient group but present in a chronic SZ patient group. Lee et al. (2018) proposed that frequency MMN changes may be particularly relevant to the decline in function that occurs during the early stages of schizophrenia, given that intact frequency MMN has been reported among first episode SZ patients (Haigh et al., 2017), especially among those with higher levels of premorbid functioning (Salisbury et al., 2017). Importantly, declines in MMN amplitude to the frequency deviant still tend to occur over the first few years of illness (Javitt et al., 2000), which is in line with the associated structural changes that occur in auditory cortex (Kasai et al., 2003). The current sample consisted of patients with a more chronic course of SZ (M = 17.5 years) and many individuals had a relatively lower level of functioning (as indexed by lower quality of life scores and higher number of errors on the NART in the SZ group) therefore, this could potentially explain why the strongest deficit was seen for frequency deviants in our sample, as other work appears to support this. Further, Molholm et al. (2005) found that different deviant characteristics activate different networks in the auditory system; specifically, the frequency deviant activates the primary auditory cortex and posterior STG, while the duration deviant activates the secondary auditory cortex. The well documented structural abnormalities in both the primary auditory cortex and the STG in SZ patients (Allen et al., 2008; Allen et al., 2012), as well as the relations between these abnormalities and AVH severity (Modinos et al., 2013), could help to explain why the frequency deviant was the most robust deficit found in the current sample. Finally, these MMN deficits may also reflect a faulty prediction coding system in SZ patients. As outlined, the repetitive standard stimuli form a

"prediction template" for the future incoming stimuli; when the sensory data matches the prediction, the prediction error is minimized (Fong et al., 2020). Since the prediction has been shaped by the standard stimuli, the deviant stimuli, which have distinct sensory input (vs. standard), should therefore produce a prediction error. Previous studies have shown evidence of an impaired prediction coding system in SZ using a roving oddball paradigm (i.e., Baldeweg et al., 2004; McCleery et al., 2019). The roving oddball paradigm is suitable for investigating the association between prediction errors and the MMN, as the stimuli have different conditional probabilities and can thus manipulate prediction and associated prediction errors (Kirihara et al., 2020). As such, future studies should aim to clarify whether this prediction coding hypothesis is relevant to SZ patients with AVHs using the roving oddball paradigm.

4.3 Primary Analyses: MMN Speech Task

Although the speech MMN has not been studied in nearly as much depth as the tone MMN has, we again hypothesized that the SZ group would have smaller MMN amplitudes across all five speech deviant types, with the most pronounced MMN response expected for the vowel duration deviant (in line with the robust tone duration deviant deficits in SZ [Erickson et al., 2016; Umbricht & Krljes, 2005]). Our results are partially in line with our hypotheses, as we found that the SZ group had smaller MMN amplitudes to the frequency, intensity, vowel duration and consonant deviants; however, the strongest effect was again seen in the frequency deviant. Kasai et al. (2002) reported significant deficits in MMN amplitudes in SZ patients (Japanese native speakers) specifically to a vowel change deviant (Japanese vowel /a/ vs. /o/), these findings were corroborated by Fisher et al. (2008a) in an English-speaking sample of SZ patients. Subsequently, Fisher et al. (2019) reported that chronic SZ patients exhibited smaller MMN amplitudes to a vowel change deviant (standard vowel /e/: 400 ms duration, deviant vowel

/ö/: 400 ms duration) compared to HCs, while no such differences were seen for the early-stage SZ patient group. More recently, Mi et al. (2021) found that SZ patients had smaller MMN amplitudes to both consonant and vowel deviants compared to HCs (assessed using a passive two deviant oddball MMN task: standard "da", deviants "ba" and "du"), with the largest difference being to the vowel deviant. Finally, Francis et al. (2020) noted that hallucinating SZ patients had smaller MMN amplitudes at site C4 to a consonant deviant (standard "ba'" and deviant "da", 150ms durations) compared to both HCs and non-hallucinating patients. Interestingly, we found no group differences for our vowel change deviant (although, visually, the SZ group had a smaller amplitude; $p = .175$), but we did find that SZ patients had putative impairments in processing of the consonant deviant as indexed by smaller MMNs compared with HCs. Mi et al. (2021) had hypothesized that SZ patients may show different degrees of MMN impairment between the vowel and consonant deviants, given the differences in processing of the two phoneme categories (i.e., vowels are more sensitive to changes in frequency spectrum, while consonants are more sensitive to temporal change; Perez et al., 2013). Another possible explanation could be the choice of vowels ("ti") and choice of consonant stimuli ("pe") in the present study (standard "te"), which could contribute to the differences in findings across studies and potentially explain why we found impairments in processing of consonants but not vowel deviants. It should be noted that some of the speech MMN responses were not very robust in the SZ group (i.e., consonant and vowel duration deviants), and it is possible that the grand averaging of the individual responses "washed away" the true MMN when combined into one signal due to increased individual variability (discussed further in section 4.5). Overall, the results of the current study show that SZ patients with persistent AVHs may have more

generalized deficits in the automatic processing of basic units of speech and pure tones, beyond the processing of specific acoustic features.

4.4 Primary Analyses: Correlations

For the correlational analysis, the main finding was the positive correlation between intensity deviant MMN amplitudes (tone task) and VPDS total scores (r_s = .71, p = .002). Higher scores on the VPDS indicate a greater power differential between the patient and their voice(s), which was associated with a smaller/less negative MMN amplitude to the intensity deviants in the tone task. Thus, impaired processing of pure tone intensity deviants, as indexed by reduced MMNs, appears to be related with a greater perceived "power" of the voice. While there are no known previous studies that have assessed the relations between MMN deficits and measures of the subjective AVH experience in SZ patients, Fisher et al. (2011) found that smaller intensity deviant amplitudes were associated with higher PSYRATS scores and thus greater AVH severity. Lee et al. (2017) examined the underlying neural mechanisms of MMN deficits in SZ and found that the processing of intensity deviants engaged activity in ventral attention networks that contribute to stimulus salience processing. As such, it is feasible that decreased MMN amplitudes to the intensity deviant might reflect decreased salience network engagement in lieu of increased salience of the voices that have higher perceived power. However, this would best be studied by way of neuroimaging.

A negative correlation was also found between MMN latencies to the vowel change deviant (speech task) and BAVQ-R malevolence subscale scores (r_s = -.59, p = .015), such that a longer MMN latency was associated with higher scores, which is reflective of patients holding greater beliefs about ill intentions of their voices. MMN latency is considered to index the cortical processing duration regarding the nature and difficulty of the standard-deviant

comparison process (Fitzgerald & Todd, 2020). Thus, SZ patients who hold stronger beliefs that their voices have bad intentions may also have greater impairments in this comparison process. There was also a trend for a positive correlation between duration deviant MMN amplitudes (tone task) and BAVQ-R malevolence subscale scores (r_s = .50, p = .049), meaning smaller/less negative MMN amplitudes were related to greater beliefs of the voices having ill intentions. Taken together, these two findings suggest that impaired auditory change detection of both vowel and pure tone deviants are related to the perceived hostility of the voice. Lee et al. (2017) found ventral attention network engagement in response to the duration deviant; as such, it is feasible that decreased duration MMNs reflect decreased attention to the stimuli in favour of enhanced salience attribution (and thus cortical resources) to the perceived hostility of their voice. Importantly, these findings are completely novel, as no known previous studies have investigated relationships between MMN features and some of the subjective aspects of voice hearing, such as power differentials or the different types of beliefs a patient may hold regarding their voice(s). Future research should continue to include these types of measures especially in the context of MMN research, as well as prioritizing the integration of neuroimaging methods such as fMRI, to clarify and further uncover these important and potentially clinically relevant relationships.

In terms of relations between MMN features and clinical measures of AVH severity, we found only one significant association, which was that smaller/less negative MMN amplitudes to the frequency deviant in the speech task were associated with a greater AVH severity (measured with PANSS item #3 'hallucinatory behaviour', r_s = .33, p = .22, N=16, adjusted [r = .69, p = .007, N=16]). In contrast to our findings, Perrin et al. (2018) found the opposite relationship, in that larger/more negative MMN amplitudes to a location deviant were associated with greater

AVH severity (measured with the Schedule for Assessment of Positive Symptoms [SAPS]), while a meta-analysis (Erickson et al., 2017) found no associations between MMN impairments and AVH severity in SZ. It is important to note that the correlation we found was not significant (p = .22) until controlling for handedness and smoking status, after which it was (p = .007). Given the pro-cognitive effects of nicotine, specifically among those with greater cognitive impairments such as in the current sample (Newhouse et al., 2004), as well as the purported dysfunction of nicotinic acetylcholine receptors (nAChRs) in SZ (Knott et al., 2012), it is feasible that SZ patients with more severe AVHs and a greater baseline MMN deficit experience a greater cognitive enhancement effect through nicotine. Thus, this could be a reason why controlling for smoking status allowed for the emergence of this correlation.

Overall, the main findings of the correlational analysis were the associations between smaller intensity deviant MMN amplitudes and a greater perceived power differential between the voice and voice hearer, as well as smaller duration deviant amplitudes and greater perceived hostility of the voice. Both findings could be related to impaired salience processing, which has been suggested to underlie intensity and duration deviant deficits, but this is an area that requires more thorough investigation, especially when it comes to examining aspects of the subjective AVH experience. The integration of neuroimaging techniques such as fMRI could aid in clarifying these relations.

4.5 Secondary Analyses: Tone vs. Speech Task

The main findings of the secondary analysis were that compared the HC group, the SZ group had smaller MMN amplitudes to the frequency deviant in both the tone and speech MMN tasks; the intensity deviant also tended to be smaller in the SZ group across both tasks. These results are in line with previous literature demonstrating MMN deficits to the frequency (Javitt et

al., 1993; Hirayasu et al., 1998; Todd et al., 2008; Perrin et al., 2018) and intensity deviants (Fisher et al., 2008b; Todd et al., 2008) in SZ patients, however, these previous studies did not directly compare MMN features across the two task modalities. In fact, to the best of our knowledge, this is the first study to *directly* compare MMN responses between tone and speech-based tasks in SZ patients and HCs, further underscoring the contribution of the present work. The frequency and the intensity deviants elicited the most pronounced MMNs across both tasks in the current sample, which was the rationale for only including these two deviant types in the secondary analysis. Further, our findings are line with a meta-analysis (Avissar et al., 2018) showing that simple physical deviants (i.e., duration, pitch/frequency, intensity deviants) yield larger MMN deficits in SZ patients than complex deviants (i.e., complex pattern deviants, happily or angrily spoken deviant syllables, frequency modulated tones, missing fourth or sixth stimulus deviant groups). Complex deviants tend to elicit relatively noisy MMN components even in healthy controls (i.e., there is greater variability), which could also help to explain the lack of robust MMN responses to some of the more complex deviants used in our tasks, such as the consonant and vowel duration deviants in the current sample. Again, these results suggest that SZ patients with persistent AVHs appear to have more generalized deficits in the automatic processing of basic units of speech and pure tones, beyond the processing of specific acoustic features. The deficits (i.e., decreased MMNs) do not appear to be modality specific, but instead point towards a more general dysfunction of auditory deviant processing in SZ patients with persistent AVHs.

MMN amplitudes were larger in the tone task compared to the speech task (collapsed across both groups), which is inconsistent with previous literature. Iino et al. (2018) found that MMN amplitudes to vowel-based sounds were larger than to pure tones; however, their sample

was only comprised of healthy participants who were native Japanese speakers, which could explain the findings. Sorokin et al. (2010) also reported finding larger MMN amplitudes to speech-based compared to non-speech sounds, especially to the vowel change and frequency deviants; their sample was comprised of healthy participants who were native Finnish speakers. It has been speculated that the ability to detect changes in speech-based sounds may require more neural resources than detecting changes in pure tones, as speech-based sounds contain a broader scope of acoustic information, thus resulting in a larger MMN amplitude (Iino et al., 2018). Sensory discrimination also requires the ability to detect differences in patterns of neural activity generated by different stimuli (Perez et al., 2013), thus, the MMN response increases when the physical difference between the standard and the deviant stimuli is greater (Näätänen et al., 2007). It is possible that some of the deviants in the speech task did not differ from the standard enough to elicit the expected large MMN response, which can be seen in our grand average waveforms, especially for the consonant and vowel duration deviants. Another possibility is that the speech MMN responses had higher individual variability, and that the semi-automatic peak detection method that was used in the current study was not accurate in picking the true MMN for the speech task. Further, it is possible that the grand averaging of the individual responses "washed away" the true MMN when combined into one signal due to increased variability. For future analyses of this work and for preparation of manuscripts, we plan to use a more individualized peak detection approach (i.e., looking at the average waveforms per individual for each deviant type to see if that reveals the suspected variability/cleaner MMN responses).

4.6 Exploratory Analyses

The mastoid analyses was carried out to explore potential hemispheric differences in MMN responses between the groups. This was especially important to examine especially in the

context of the speech task, given the left-lateralization of speech processes as well as involvement of the left auditory cortex in the generation of AVHs (Hugdahl et al., 2009) and speech processing (Shtyrov et al., 2000; Desai et al., 2008; Tervaniemi & Hugdahl, 2003). The main findings were that the SZ group had smaller MMN amplitudes to the frequency deviant in the tone task compared to the HC group. MMN amplitudes were also expectedly larger at the left (TP_9) compared to the right (TP_{10}) mastoid site in both the tone ($\eta_p^2 = .27$) and speech tasks ($\eta_p^2 = .32$); nevertheless, MMN amplitudes at site TP_9 in the SZ group were still smaller compared to the HC group ($\eta_p^2 = .33$). Finally, the SZ group showed smaller MMN amplitudes than the HCs at the left mastoid site for the frequency, intensity, vowel duration and vowel change deviants.

In terms of hemispheric differences, we found that MMN amplitudes were larger at the left mastoid site across both the tone and speech tasks. This is in line with studies that have previously shown that speech sounds are processed mainly in the left hemisphere (Shtyrov et al., 2000; Desai et al., 2008; Tervaniemi & Hugdahl, 2003). In the context of the MMN there have been some mixed findings, Sorokin et al. (2010) found predominant activation in the left hemisphere for vowel change, vowel duration and frequency deviants in the speech task, however, Iino et al. (2018) found no hemispheric preferences for the processing of speech or pure tone stimuli at the mastoid sites in HCs. In terms of differences between the HC and SZ groups, greater group differences were expected to emerge in the left hemisphere, given the involvement of the left auditory cortex in both speech processing (Shtyrov et al., 2000; Desai et al., 2008; Tervaniemi & Hugdahl, 2003), and the generation of AVHs (Hugdahl et al., 2009). We found that the SZ group had smaller MMN amplitudes compared to HCs at the left mastoid site for the frequency, intensity, vowel duration and vowel change deviants in the speech task, which

is in line with the findings of Hirayasu et al. (1998), who found greater left hemisphere MMN deficits over the temporoparietal junction in SZ patients compared to HCs.

Additionally, some studies have found robust MMN amplitude deficits in SZ patients at site Fz, but MMN amplitudes of normal magnitude at the mastoid sites (Baldeweg et al., 2002; Sato et al., 2003; Todd et al., 2003). This is partially in line with our findings, as we found MMN deficits for the frequency, intensity, and gap deviants at the frontal midline site (tone task), but no deficits at mastoid sites except for the frequency deviant. It has been speculated that the reason for the lack of deficits at the mastoid sites when they are present at frontal sites is that the supratemporal MMN generator may be "intact", while the frontal generator may be more impaired. Indeed, Koshiyama et al. (2020) found that MMN reductions in SZ patients were primarily attributable to decreased contributions from 3 frontal midline sources: orbitofrontal, anterior cingulate, and middle cingulate cortices, while the contributions from the left superior temporal gyrus were abnormally increased. However, the mastoid reversal of the MMN may also be impacted by other variables, such as symptom severity (Shinozaki et al., 2002). Indeed, one study suggests that the reversal of the MMN at mastoid sites may be abnormal only in patients with pronounced cognitive impairments and/or lower levels of functioning (Todd, Michie & Jablensky, 2003). Given that the current sample was comprised of only SZ patients with persistent AVHs and that the STG/auditory regions are known to show structural and functional abnormalities in those with AVHs, a potential explanation for the current results may be that the connections between the frontal and supratemporal MMN generators are impaired in SZ patients who experience AVHs, while this connection may be preserved in SZ patients who do not experience AVHs.

4.7 Limitations and Future Directions

Despite the novelty of some of the findings that we presented, there are some limitations that must be acknowledged. First, the sample size is modest. This study was strongly impacted by the prolonged suspension of recruitment and testing of human participants during the COVID-19 pandemic, thus resulting in an underpowered sample. The *a priori* power analyses indicated that an N=20 per group were needed to allow for sufficient power (95%) to detect differences in baseline MMN amplitudes. However, these numbers were unattainable due to a more than year-long interruption in recruitment and testing. Nevertheless, we did manage to attain a sample size relatively close to our goal (SZ N=16 and HC N=17). This work was also embedded within a larger study involving a week-long intervention and this also made recruitment more challenging; however, the SZ patients that participated in the study were well characterized, clinically stable and experienced regular AVHs. Second, we did not collect data from a non-hallucinating patients' group, mainly due to the nature of the tDCS intervention in this study (i.e., which was geared at modifying auditory hallucinations). The inclusion of such a group would have allowed for the direct comparison on MMN features between these populations (i.e., Francis et al., 2020; Fisher et al., 2008b). Future research should collect these data to better assess the differences in MMN features between HCs and SZ patients with and without AVHs to help clarify what aspects of the MMN are unique to SZ patients with AVHs. Finally, future research should also continue to include the self-reported voices questionnaires (BAVQ-R, VPDS, VAAS) to further investigate the potential relationships between MMN features and the subjective voice hearing experience. The next logical step of this work will be increasing the sample size to ensure sufficient power, and to run additional complementary analyses such as source localization for each of the deviants to better assess the neural generators of each deviant across both tasks, which could aid in revealing key differences in how the

various deviants are processed, as well as trying the individualized peak picking approach for the speech task to see if that helps to better identify the MMN in that task.

4.8 Conclusion

In conclusion, this study revealed MMN deficits in SZ patients across a variety of deviant types, including both pure tone and speech-based deviants. MMN deficits were most pronounced for the frequency and intensity deviants across both tasks, suggesting that SZ patients with persistent AVHs may have more generalized deficits in the automatic processing of basic units of speech and pure tones, rather than impaired processing of specific acoustic features. The deficits (i.e., decreased MMNs) do not appear to be modality specific, but instead point towards a more general dysfunction of auditory deviant processing in SZ patients with persistent AVHs. Correlational analysis revealed that impaired processing of pure tone intensity deviants is related to a greater perceived "power" of the voice, deficits in processing speech-based frequency deviants is related to greater clinical AVH severity, and less efficient processing of both vowel and pure tone deviants are related to a higher perceived hostility of the voice. MMN amplitudes were more defined in the tone task compared to the speech task, however, this could be due to the smaller sample size in the current study and that more complex deviants (i.e., speech vs. tone) tend to elicit relatively noisy MMNs. Finally, a left hemispheric preference was found for the processing of both pure tone and speech-based deviants. Interestingly, the widespread MMN deficits in the SZ group found at the frontal midline site were not apparent at the mastoid sites in the tone task, except for the frequency deviant, while the deficits at mastoid sites remained present in the speech task. This study adds valuable information about relationships between MMN features and subjective aspects of the AVH experience in SZ patients and. Importantly, this work is novel as it is the first to directly compare MMN responses

across the two task modalities in a sample of SZ patients with persistent AVHs. This thesis emphasizes the importance of examining subjective aspects of the AVH experience in the context of the MMN to gather a more complete understanding of how AVHs are impacting the brain.

References

Abi-Dargham, A., Gil, R., Krystal, J., Baldwin, R. M., Seibyl, J. P., Bowers, M., ... & Laruelle, M. (1998). Increased striatal dopamine transmission in schizophrenia: Confirmation in a second cohort. *American Journal of Psychiatry, 155*(6), 761-767.

Abi-Dargham, A., Rodenhiser, J., Printz, D., Zea-Ponce, Y., Gil, R., Kegeles, L. S., ... & Gorman, J. M. (2000). Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. *Proceedings of the National Academy of Sciences, 97*(14), 8104-8109.

Alho, K., Paavilainen, P., Reinikainen, K., Sams, M., & Näätänen, R. (1986). Separability of different negative components of the event-related potential associated with auditory stimulus processing. *Psychophysiology*, *23*(6), 613–623. https://doi.org/10.1111/j.1469-8986.1986.tb00680.x

Alku, P., Tiitinen, H., & Näätänen, R. (1999). A method for generating natural-sounding speech stimuli for cognitive brain research. *Clinical Neurophysiology, 110*(8), 1329-1333.

Allen, P., Aleman, A., & Mcguire, P. K. (2007). Inner speech models of auditory verbal hallucinations: Evidence from behavioural and neuroimaging studies. *International Review of Psychiatry, 19*(4), 407-415.

Allen, P., Larøi, F., McGuire, P. K., & Aleman, A. (2008). The hallucinating brain: A review of structural and functional neuroimaging studies of hallucinations. *Neuroscience & Biobehavioral Reviews, 32*(1), 175-191.

Allen, P., Modinos, G., Hubl, D., Shields, G., Cachia, A., Jardri, R., ... & Hoffman, R. (2012). Neuroimaging auditory hallucinations in schizophrenia: From neuroanatomy to neurochemistry and beyond. *Schizophrenia Bulletin, 38*(4), 695-703.

Andreasen, N. C. (1990). Methods for assessing positive and negative symptoms. *Modern Problems of Pharmacopsychiatry, 24,* 73–88.

Andreasen, N. C., & Flaum, M. (1991). Schizophrenia: The characteristic symptoms. *Schizophrenia Bulletin, 17*(1), 27-49.

Andreasen, N. C., & Olsen, S. (1982). Negative v positive schizophrenia: Definition and validation. *Archives of General Psychiatry, 39*(7), 789-794.

Arciniegas, D. B. (2015). Psychosis. *Continuum: Lifelong Learning in Neurology, 21*(3 Behavioral Neurology and Neuropsychiatry), 715-736.

Avissar, M., Xie, S., Vail, B., Lopez-Calderon, J., Wang, Y., & Javitt, D. C. (2018). Meta-analysis of mismatch negativity to simple versus complex deviants in schizophrenia. *Schizophrenia Research, 191*, 25–34. https://doi.org/10.1016/j.schres.2017.07.009

Baldeweg, T., Klugman, A., Gruzelier, J. H., & Hirsch, S. R. (2002). Impairment in frontal but not temporal components of mismatch negativity in schizophrenia. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology, 43*(2), 111–122. https://doi.org/10.1016/s0167-8760(01)00183-0

Baldeweg, T., Klugman, A., Gruzelier, J., & Hirsch, S. R. (2004). Mismatch negativity potentials and cognitive impairment in schizophrenia. *Schizophrenia Research, 69*(2-3), 203–217. https://doi.org/10.1016/j.schres.2003.09.009

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). Beck depression inventory-II. *San Antonio, 78*(2), 490-498.

Berk, M., Copolov, D., Dean, O., Lu, K., Jeavons, S., Schapkaitz, I., ... & Ording-Jespersen, S. (2008). N-acetyl cysteine as a glutathione precursor for schizophrenia—a double-blind, randomized, placebo-controlled trial. *Biological Psychiatry, 64*(5), 361-368.

Berk, M., Munib, A., Dean, O., Malhi, G. S., Kohlmann, K., Schapkaitz, I., ... & Hanna, B. (2011). Qualitative methods in early-phase drug trials: Broadening the scope of data and methods from an RCT of N-acetylcysteine in schizophrenia. The Journal of Clinical Psychiatry, *72*(7), 909-13.

Bighelli, I., Huhn, M., Schneider-Thoma, J., Krause, M., Reitmeir, C., Wallis, S., ... & Leucht, S. (2018). Response rates in patients with schizophrenia and positive symptoms receiving cognitive behavioural therapy: A systematic review and single-group meta-analysis. *BMC Psychiatry, 18*(1), 1-10.

Birchwood, M., Meaden, A., Trower, P., Gilbert, P. & Plaistow, J. (2000). The power and omnipotence of voices: Subordination and entrapment by voices and significant others. *Psychological Medicine, 30,* 337-344.

Bloemen, O. J., de Koning, M. B., Gleich, T., Meijer, J., de Haan, L., Linszen, D. H., ... & van Amelsvoort, T. A. (2013). Striatal dopamine D2/3 receptor binding following dopamine depletion in subjects at ultra high risk for psychosis. *European Neuropsychopharmacology, 23*(2), 126-132.

Bose, A., Shivakumar, V., Narayanaswamy, J. C., Nawani, H., Subramaniam, A., Agarwal, S. M., ... & Venkatasubramanian, G. (2014). Insight facilitation with add-on tDCS in schizophrenia. *Schizophrenia Research, 156*(1), 63-65.

Bright, P., Jaldow, E. L. I., & Kopelman, M. D. (2002). The National Adult Reading Test as a measure of premorbid intelligence: A comparison with estimates derived from demographic variables. *Journal of the International Neuropsychological Society, 8*(6), 847-854.

Brunelin, J., Hasan, A., Haesebaert, F., Nitsche, M. A., & Poulet, E. (2015). Nicotine smoking prevents the effects of frontotemporal transcranial direct current stimulation (tDCS) in hallucinating patients with schizophrenia. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 8*(6), 1225-1227.

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

Brunelin, J., Poulet, E., Bediou, B., Kallel, L., Dalery, J., D'amato, T., & Saoud, M. (2006). Low frequency repetitive transcranial magnetic stimulation improves source monitoring deficit in hallucinating patients with schizophrenia. *Schizophrenia Research, 81*(1), 41-45.

Buckley, P. F., Miller, B. J., Lehrer, D. S., & Castle, D. J. (2009). Psychiatric comorbidities and schizophrenia. *Schizophrenia Bulletin, 35*(2), 383-402.

Carlsson, A., Roos, B. E., Walinder, J., & Skott, A. (1973). Further studies on the mechanism of antipsychotic action: Potentiation by α-methyltyrosine of thioridazine effects in chronic schizophrenics. *Journal of Neural Transmission, 34*(2), 125-132.

Chadwick, P., Lees, S., and Birchwood, M. (2000). The revised beliefs about voices questionnaire (BAVQ-R). *The British Journal of Psychiatry, 177,* 229–232.

Chakos, M., Lieberman, J., Hoffman, E., Bradford, D., & Sheitman, B. (2001). Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: A review and meta-analysis of randomized trials. *American Journal of Psychiatry, 158*(4), 518-526.

Chang, L., Friedman, J., Ernst, T., Zhong, K., Tsopealas, N.D., & Davis, K. (2007). Brain metabolite abnormalities in the white matter of elderly schizophrenic subjects: Implication for glial dysfunction. *Biological Psychiatry, 62*(12), 1396–1404.

Choe, B.Y., Suh, T.S., Shinn, K.S., Lee, C.W., Lee, C., & Paik, I.H. (1996). Observation of metabolic changes in chronic schizophrenia after neuroleptic treatment by in vivo hydrogen magnetic resonance spectroscopy. *Investigative Radiology, 31*(6), 345–352.

Chokhawala, K., & Stevens, L. (2019). *Antipsychotic medications.* In StatPearls [Internet]. StatPearls Publishing.

Cui, Y., Liu, B., Song, M., Lipnicki, D. M., Li, J., Xie, S., ... & Wang, H. (2018). Auditory verbal hallucinations are related to cortical thinning in the left middle temporal gyrus of patients with schizophrenia. *Psychological Medicine, 48*(1), 115-122.

Ćurčić-Blake, B., Bais, L., Sibeijn-Kuiper, A., Pijnenborg, H. M., Knegtering, H., Liemburg, E., & Aleman, A. (2017a). Glutamate in dorsolateral prefrontal cortex and auditory verbal hallucinations in patients with schizophrenia: A 1H MRS study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 78,* 132-139.

Ćurčić-Blake, B., Ford, J. M., Hubl, D., Orlov, N. D., Sommer, I. E., Waters, F., ... & Mulert, C. (2017b). Interaction of language, auditory and memory brain networks in auditory verbal hallucinations. *Progress in Neurobiology, 148,* 1-20.

Daniel, D. G., Weinberger, D. R., Jones, D. W., Zigun, J. R., Coppola, R., Handel, S., ... & Kleinman, J. E. (1991). The effect of amphetamine on regional cerebral blood flow during cognitive activation in schizophrenia. *Journal of Neuroscience, 11*(7), 1907-1917.

Davis, K. L., Kahn, R. S., Ko, G., & Davidson, M. (1991). Dopamine in schizophrenia: A review and reconceptualization. *The American Journal of Psychiatry, 148*, 1474-1486.

Dehaene-Lambertz G. (1997). Electrophysiological correlates of categorical phoneme perception in adults. *Neuroreport, 8*(4), 919–924. https://doi.org/10.1097/00001756-199703030-00021

De La Salle, S., Shah, D., Choueiry, J., Bowers, H., McIntosh, J., Ilivitsky, V., & Knott, V. (2019). NMDA receptor antagonist effects on speech-related mismatch negativity and its underlying oscillatory and source activity in healthy humans. *Frontiers in Pharmacology, 10*, 455.

Delespaul, P., deVries, M., & van Os, J. (2002). Determinants of occurrence and recovery from hallucinations in daily life. *Social Psychiatry and Psychiatric Epidemiology, 37*(3), 97-104.

DeLisi, L. E. (1992). The significance of age of onset for schizophrenia. *Schizophrenia Bulletin, 18*(2), 209-215.

Desai, R., Liebenthal, E., Waldron, E., & Binder, J. R. (2008). Left posterior temporal regions are sensitive to auditory categorization. *Journal of Cognitive Neuroscience, 20*(7), 1174–1188. https://doi.org/10.1162/jocn.2008.20081

de Jesus, D. R., Gil, A., Barbosa, L., Lobato, M. I., da Silva Magalhães, P. V., de Souza Favalli, G. P., ... & da Silva Belmonte-de-Abreu, P. (2011). A pilot double-blind sham-controlled trial of repetitive transcranial magnetic stimulation for patients with refractory schizophrenia treated with clozapine. *Psychiatry Research, 188*(2), 203-207.

Dierks, T., Linden, D. E., Jandl, M., Formisano, E., Goebel, R., Lanfermann, H., & Singer, W. (1999). Activation of Heschl's gyrus during auditory hallucinations. *Neuron, 22*(3), 615-621.

Endicott, J., Nee, J., Harrison, W., & Blumenthal, R. (1993). Quality of life enjoyment and satisfaction questionnaire: A new measure. *Psychopharmacology Bulletin, 29*(2), 321–326.

Erickson, M. A., Ruffle, A., & Gold, J. M. (2016). A meta-analysis of mismatch negativity in schizophrenia: From clinical risk to disease specificity and progression. *Biological Psychiatry, 79*(12), 980–987. https://doi.org/10.1016/j.biopsych.2015.08.025

Evans, D. E., & Drobes, D. J. (2009). Nicotine self-medication of cognitive-attentional processing. *Addiction Biology*, *14*(1), 32–42. https://doi.org/10.1111/j.1369-1600.2008.00130.x

Farokhnia, M., Azarkolah, A., Adinehfar, F., Khodaie-Ardakani, M. R., Yekehtaz, H., Tabrizi, M., ... & Mirshafiee, O. (2013). N-acetylcysteine as an adjunct to risperidone for treatment of negative symptoms in patients with chronic schizophrenia: A randomized, double-blind, placebo-controlled study. *Clinical Neuropharmacology*, *36*(6), 185-192.

Field, A. (2009). *Discovering statistics using SPSS* (3rd ed.). SAGE Publications.

First, M. B., Williams, J. B., Karg, R. S., & Spitzer, R. L. (2016). *SCID-5-CV: Structured clinical interview for DSM-5 disorders.* American Psychiatric Association Publishing.

Fisher, D. J., Grant, B., Smith, D. M., Borracci, G., Labelle, A., & Knott, V. J. (2011). Effects of auditory hallucinations on the mismatch negativity (MMN) in schizophrenia as measured by a modified 'optimal' multi-feature paradigm. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology, 81*(3), 245–251. https://doi.org/10.1016/j.ijpsycho.2011.06.018

Fisher, D. J., Labelle, A., & Knott, V. J. (2008a). Auditory hallucinations and the mismatch negativity: Processing speech and non-speech sounds in schizophrenia. *International Journal of Psychophysiology, 70*(1), 3-15.

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

Fisher, D. J., Labelle, A., & Knott, V. J. (2012). Alterations of mismatch negativity (MMN) in schizophrenia patients with auditory hallucinations experiencing acute exacerbation of illness. *Schizophrenia Research, 139*(1-3), 237-245.

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

Fitzgerald, K., & Todd, J. (2020). Making sense of mismatch negativity. *Frontiers in Psychiatry, 11,* 468. https://doi.org/10.3389/fpsyt.2020.00468

Fong, C. Y., Law, W., Uka, T., & Koike, S. (2020). Auditory mismatch negativity under predictive coding framework and its role in psychotic disorders. *Frontiers in Psychiatry, 11,* 557932. https://doi.org/10.3389/fpsyt.2020.557932

Ford, J. M., Roach, B. J., Jorgensen, K. W., Turner, J. A., Brown, G. G., Notestine, R., ... & Belger, A. (2009). Tuning in to the voices: A multisite FMRI study of auditory hallucinations. *Schizophrenia Bulletin, 35*(1), 58-66.

Francis, A. M., Knott, V. J., Labelle, A., & Fisher, D. J. (2020). Interaction of background noise and auditory hallucinations on phonemic mismatch negativity (MMN) and p3a

processing in schizophrenia. *Frontiers in Psychiatry, 11,* 540738. https://doi.org/10.3389/fpsyt.2020.540738

Friston K. (2005). A theory of cortical responses. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 360*(1456), 815–836. https://doi.org/10.1098/rstb.2005.1622

Fulham, W. R., Michie, P. T., Ward, P. B., Rasser, P. E., Todd, J., Johnston, P. J., Thompson, P. M., & Schall, U. (2014). Mismatch negativity in recent-onset and chronic schizophrenia: A current source density analysis. *PloS One, 9*(6), e100221. https://doi.org/10.1371/journal.pone.0100221

Gogtay, N., Vyas, N. S., Testa, R., Wood, S. J., & Pantelis, C. (2011). Age of onset of schizophrenia: Perspectives from structural neuroimaging studies. *Schizophrenia Bulletin, 37*(3), 504-513.

Gratton, G., Coles, M., and Donchin, E. (1983). A new method for off-line removal of ocular artifact. *Electroencephalography and Clinical Neurophysiology, 55,* 468–484.

Gunton, M. (Executive Producer). (2011). *Madagascar: The Land Where Evolution Ran Wild.* [Film]. British Broadcasting Corporation Earth.

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

Haigh, S. M., Coffman, B. A., & Salisbury, D. F. (2017). Mismatch negativity in first-episode schizophrenia: A meta-analysis. *Clinical EEG and Neuroscience, 48*(1), 3–10. https://doi.org/10.1177/1550059416645980

Hasan, A., Falkai, P., Wobrock, T., Lieberman, J., Glenthoj, B., Gattaz, W. F., Thibaut, F., Möller, H. J., & World Federation of Societies of Biological Psychiatry (WFSBP) Task Force on Treatment Guidelines for Schizophrenia. (2012). World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 1: Update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. *The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry*, *13*(5), 318–378. https://doi-org.proxy.bib.uottawa.ca/10.3109/15622975.2012.696143

He, H., Lu, J., Yang, L., Zheng, J., Gao, F., Zhai, Y., ... & Ma, X. (2017). Repetitive transcranial magnetic stimulation for treating the symptoms of schizophrenia: A PRISMA compliant meta-analysis. *Clinical Neurophysiology, 128*(5), 716-724.

Health Quality Ontario (2018). Cognitive behavioural therapy for psychosis: A health technology assessment. *Ontario Health Technology Assessment Series, 18*(5), 1–141.

Heinrichs, R. W., & Zakzanis, K. K. (1998). Neurocognitive deficit in schizophrenia: A quantitative review of the evidence. *Neuropsychology, 12*(3), 426.

Hirayasu, Y., Potts, G. F., O" Donnell, B. F., Kwon, J. S., Arakaki, H., Akdag, S. J., ... & McCarley, R. W. (1998). Auditory mismatch negativity in schizophrenia: Topographic evaluation with a high-density recording montage. *American Journal of Psychiatry, 155*(9), 1281-1284.

Hoffman, R. E., Boutros, N. N., Berman, R. M., Roessler, E., Belger, A., Krystal, J. H., & Charney, D. S. (1999). Transcranial magnetic stimulation of left temporoparietal cortex in three patients reporting hallucinated “voices”. *Biological Psychiatry, 46*(1), 130-132.

Hubl, D., Koenig, T., Strik, W., Federspiel, A., Kreis, R., Boesch, C., ... & Dierks, T. (2004). Pathways that make voices: White matter changes in auditory hallucinations. *Archives of General Psychiatry, 61*(7), 658-668.

Hubl, D., Koenig, T., Strik, W. K., Garcia, L. M., & Dierks, T. (2007). Competition for neuronal resources: How hallucinations make themselves heard. *The British Journal of Psychiatry*, 190(1), 57-62.

Hugdahl, K., Craven, A. R., Nygård, M., Løberg, E. M., Berle, J. Ø., Johnsen, E., ... & Ersland, L. (2015). Glutamate as a mediating transmitter for auditory hallucinations in schizophrenia: A 1H MRS study. *Schizophrenia Research, 161*(2-3), 252-260.

Hugdahl, K., Løberg, E. M., & Nygård, M. (2009). Left temporal lobe structural and functional abnormality underlying auditory hallucinations. *Frontiers in Neuroscience, 3*(1), 34-45.

Iino, H., Ohta, K., Hara, K., Miyajima, M., Hara, M., Matsushima, E., & Matsuura, M. (2018). Vowel-speech versus pure-tone processing in healthy subjects. *Neuroscience Research, 137*, 43-48.

Inami, R., & Kirino, E. (2019). Nicotine effect on mismatch negativity in smoking and nonsmoking patients with schizophrenia. *Schizophrenia Research, 208,* 496–497. https://doi.org/10.1016/j.schres.2019.01.002

Inouchi, M., Kubota, M., Ohta, K., Shirahama, Y., Takashima, A., Horiguchi, T., & Matsushima, E. (2004). Human auditory evoked mismatch field amplitudes vary as a function of vowel duration in healthy first-language speakers. *Neuroscience Letters, 366,* 342–346.

Javitt, D. C., Doneshka, P., Grochowski, S., & Ritter, W. (1995). Impaired mismatch negativity generation reflects widespread dysfunction of working memory in schizophrenia. *Archives of General Psychiatry, 52*(7), 550-558.

Javitt, D. C., Doneshka, P., Zylberman, I., Ritter, W., & Vaughan, H. G. (1993). Impairment of early cortical processing in schizophrenia: An event-related potential confirmation study. *Biological Psychiatry, 33*(7), 513-519.

Javitt, D. C., Shelley, A. M., Silipo, G., & Lieberman, J. A. (2000). Deficits in auditory and visual context-dependent processing in schizophrenia: Defining the pattern. *Archives of General Psychiatry*, *57*(12), 1131–1137. https://doi.org/10.1001/archpsyc.57.12.1131

Javitt, D. C., & Zukin, S. R. (1991). Recent advances in the phencyclidine model of schizophrenia. *The American Journal of Psychiatry, 148*(10), 1301–1308.

Kahn, R. S., Sommer, I. E., Murray, R. M., Meyer-Lindenberg, A., Weinberger, D. R., Cannon, T. D., ... & Insel, T. R. (2015). Schizophrenia. *Nature Reviews Disease Primers, 12*(1), 15067.

Kantrowitz, J. T., Sehatpour, P., Avissar, M., Horga, G., Gwak, A., Hoptman, M. J., ... & Carlson, M. (2019). Significant improvement in treatment resistant auditory verbal hallucinations after 5 days of double-blind, randomized, sham controlled, fronto-temporal, transcranial direct current stimulation (tDCS): A replication/extension study. *Brain Stimulation, 12*(4), 981-991.

Kapur, S., & Remington, G. (2001). Dopamine D2 receptors and their role in atypical antipsychotic action: Still necessary and may even be sufficient. *Biological Psychiatry, 50*(11), 873-883.

Kasai, K., Nakagome, K., Itoh, K., Koshida, I., Hata, A., Iwanami, A., ... & Kato, N. (2002). Impaired cortical network for preattentive detection of change in speech sounds in schizophrenia: A high-resolution event-related potential study. *American Journal of Psychiatry, 159*(4), 546-553.

Kasai, K., Shenton, M. E., Salisbury, D. F., Hirayasu, Y., Onitsuka, T., Spencer, M. H., Yurgelun-Todd, D. A., Kikinis, R., Jolesz, F. A., & McCarley, R. W. (2003). Progressive decrease of left Heschl gyrus and planum temporale gray matter volume in first-episode schizophrenia: A longitudinal magnetic resonance imaging study. *Archives of General Psychiatry*, *60*(8), 766–775. https://doi.org/10.1001/archpsyc.60.8.766

Kaser, M., Soltesz, F., Lawrence, P., Miller, S., Dodds, C., Croft, R., Dudas, R. B., Zaman, R., Fernandez-Egea, E., Müller, U., Dean, A., Bullmore, E. T., & Nathan, P. J. (2013). Oscillatory underpinnings of mismatch negativity and their relationship with cognitive function in patients with schizophrenia. *PloS One, 8*(12), e83255. https://doi.org/10.1371/journal.pone.0083255

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin, 13,* 261–276.

Kirihara, K., Tada, M., Koshiyama, D., Fujioka, M., Usui, K., Araki, T., & Kasai, K. (2020). A predictive coding perspective on mismatch negativity impairment in schizophrenia. *Frontiers in Psychiatry*, *11*, 660. https://doi.org/10.3389/fpsyt.2020.00660

Kim, S. H., Hwang, S. S., Jung, H. Y., Kim, Y., Ahn, Y. M., Chung, I. W., & Kim, Y. S. (2019). Differences between self-reported and clinician-rated evaluations of 1-year changes in auditory verbal hallucinations among schizophrenia patients. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 95,* 109671.

Knott, V., Shah, D., Millar, A., McIntosh, J., Fisher, D., Blais, C., & Ilivitsky, V. (2012). Nicotine, auditory sensory memory, and sustained attention in a human ketamine model of schizophrenia: Moderating influence of a hallucinatory trait. *Frontiers in Pharmacology, 3,* 172. https://doi.org/10.3389/fphar.2012.00172

Kompus, K., Westerhausen, R., & Hugdahl, K. (2011). The "paradoxical" engagement of the primary auditory cortex in patients with auditory verbal hallucinations: A meta-analysis of functional neuroimaging studies. *Neuropsychologia, 49*(12), 3361-3369.

Koshiyama, D., Miyakoshi, M., Joshi, Y. B., Molina, J. L., Tanaka-Koshiyama, K., Sprock, J., Braff, D. L., Swerdlow, N. R., & Light, G. A. (2020). Abnormal effective connectivity underlying auditory mismatch negativity impairments in schizophrenia. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 5*(11), 1028–1039. https://doi.org/10.1016/j.bpsc.2020.05.011

Kreitschmann-Andermahr, I., Rosburg, T., Demme, U., Gaser, E., Nowak, H., & Sauer, H. (2001). Effect of ketamine on the neuromagnetic mismatch field in healthy humans. *Cognitive Brain Research, 12*(1), 109-116.

Kumari, V., & Postma, P. (2005). Nicotine use in schizophrenia: The self medication hypotheses. *Neuroscience and Biobehavioral Reviews*, *29*(6), 1021–1034. https://doi.org/10.1016/j.neubiorev.2005.02.006

Laruelle, M., & Abi-Dargham, A. (1999). Dopamine as the wind of the psychotic fire: New evidence from brain imaging studies. *Journal of Psychopharmacology, 13*(4), 358-371.

Larøi, F., Sommer, I. E., Blom, J. D., Fernyhough, C., Ffytche, D. H., Hugdahl, K., ... & Slotema, C. W. (2012). The characteristic features of auditory verbal hallucinations in clinical and nonclinical groups: State-of-the-art overview and future directions. *Schizophrenia Bulletin, 38*(4), 724-733.

Lawrie, S. M., Buechel, C., Whalley, H. C., Frith, C. D., Friston, K. J., & Johnstone, E. C. (2002). Reduced frontotemporal functional connectivity in schizophrenia associated with auditory hallucinations. *Biological Psychiatry, 51*(12), 1008-1011.

Laws, K. R., Darlington, N., Kondel, T. K., McKenna, P. J., & Jauhar, S. (2018). Cognitive Behavioural Therapy for schizophrenia-outcomes for functioning, distress and quality of life: A meta-analysis. *BMC Psychology, 6*(1), 32.

Lee, M., Sehatpour, P., Dias, E. C., Silipo, G. S., Kantrowitz, J. T., Martinez, A. M., & Javitt, D. C. (2018). A tale of two sites: Differential impairment of frequency and duration mismatch negativity across a primarily inpatient versus a primarily outpatient site in schizophrenia. *Schizophrenia Research, 191,* 10–17. https://doi.org/10.1016/j.schres.2017.07.032

Lee, M., Sehatpour, P., Hoptman, M. J., Lakatos, P., Dias, E. C., Kantrowitz, J. T., Martinez, A. M., & Javitt, D. C. (2017). Neural mechanisms of mismatch negativity dysfunction in schizophrenia. *Molecular Psychiatry*, *22*(11), 1585–1593. https://doi.org/10.1038/mp.2017.3

Lefaucheur, J. P., André-Obadia, N., Antal, A., Ayache, S. S., Baeken, C., Benninger, D. H., ... & Devanne, H. (2014). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clinical Neurophysiology, 125*(11), 2150-2206.

Li, J., Cao, X., Liu, S., Li, X., & Xu, Y. (2020). Efficacy of repetitive transcranial magnetic stimulation on auditory hallucinations in schizophrenia: A meta-analysis. *Psychiatry Research,* 113141.

Luck, S. J. (2014). *An Introduction to the Event-Related Potential Technique* (2nd ed.). Cambridge, Masachusetts: Mit Press.

Luoma, S., Hakko, H., Ollinen, T., Järvelin, M. R., & Lindeman, S. (2008). Association between age at onset and clinical features of schizophrenia: The Northern Finland 1966 birth cohort study. *European Psychiatry, 23*(5), 331-335.

Malaspina, D., Owen, M. J., Heckers, S., Tandon, R., Bustillo, J., Schultz, S., ... & Van Os, J. (2013). Schizoaffective disorder in the DSM-5. *Schizophrenia Research, 150*(1), 21-25.

Malenka, R. C., & Bear, M. F. (2004). LTP and LTD: An embarrassment of riches. *Neuron, 44*(1), 5-21.

McCleery, A., Wynn, J. K., Mathalon, D. H., Roach, B. J., & Green, M. F. (2018). Hallucinations, neuroplasticity, and prediction errors in schizophrenia. *Scandinavian Journal of Psychology, 59*(1), 41–48. https://doi.org/10.1111/sjop.12413

Merritt, K., Egerton, A., Kempton, M. J., Taylor, M. J., & McGuire, P. K. (2016). Nature of glutamate alterations in schizophrenia: A meta-analysis of proton magnetic resonance spectroscopy studies. *JAMA Psychiatry, 73*(7), 665-674.

Mi, L., Wang, L., Li, X., She, S., Li, H., Huang, H., Zhang, J., Liu, Y., Zhao, J., Ning, Y., & Zheng, Y. (2021). Reduction of phonetic mismatch negativity may depict illness course and predict functional outcomes in schizophrenia. *Journal of Psychiatric Research, 137,* 290–297. https://doi.org/10.1016/j.jpsychires.2021.02.065

Michie, P. T., Badcock, J. C., Waters, F. A., & Maybery, M. T. (2005). Auditory hallucinations: Failure to inhibit irrelevant memories. *Cognitive Neuropsychiatry, 10*(2), 125-136.

Michie, P. T., Innes-Brown, H., Todd, J., & Jablensky, A. V. (2002). Duration mismatch negativity in biological relatives of patients with schizophrenia spectrum disorders. *Biological Psychiatry, 52*(7), 749-758.

Modinos, G., Costafreda, S. G., van Tol, M. J., McGuire, P. K., Aleman, A., & Allen, P. (2013). Neuroanatomy of auditory verbal hallucinations in schizophrenia: A quantitative meta-analysis of voxel-based morphometry studies. *Cortex, 49*(4), 1046-1055.

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

Möller, H. J., & Czobor, P. (2015). Pharmacological treatment of negative symptoms in schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience*, *265*(7), 567–578. https://doi.org/10.1007/s00406-015-0596-y

Mondino, M., Haesebaert, F., Poulet, E., Suaud-Chagny, M. F., & Brunelin, J. (2015). Fronto-temporal transcranial direct current stimulation (tDCS) reduces source-monitoring deficits and auditory hallucinations in patients with schizophrenia. *Schizophrenia Research, 161*, 515–516.

Mørch-Johnsen, L., Nesvåg, R., Jørgensen, K. N., Lange, E. H., Hartberg, C. B., Haukvik, U. K., ... & Melle, I. (2017). Auditory cortex characteristics in schizophrenia: Associations with auditory hallucinations. *Schizophrenia Bulletin, 43*(1), 75-83.

Mulert, C., Kirsch, V., Pascual-Marqui, R., McCarley, R. W., & Spencer, K. M. (2011). Long-range synchrony of gamma oscillations and auditory hallucination symptoms in schizophrenia. *International Journal of Psychophysiology, 79*(1), 55-63.

Näätänen, R. (1995). The mismatch negativity: A powerful tool for cognitive neuroscience. *Ear and Hearing, 16*(1), 6-18.

Näätänen, R. (2003). Mismatch negativity: Clinical research and possible applications. *International Journal of Psychophysiology, 48*(2), 179-188.

Näätänen, R., & Alho, K. (1997). Mismatch negativity–the measure for central sound representation accuracy. *Audiology and Neurotology, 2*(5), 341-353.

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

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

Näätänen, R., Sussman, E. S., Salisbury, D., & Shafer, V. L. (2014). Mismatch negativity (MMN) as an index of cognitive dysfunction. *Brain Topography, 27*(4), 451-466.

Newhouse, P. A., Potter, A., & Singh, A. (2004). Effects of nicotinic stimulation on cognitive performance. *Current Opinion in Pharmacology, 4*(1), 36–46. https://doi.org/10.1016/j.coph.2003.11.001

Nitsche, M. A., Fricke, K., Henschke, U., Schlitterlau, A., Liebetanz, D., Lang, N., ... & Paulus, W. (2003). Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *The Journal of Physiology, 553*(1), 293-301.

Nitsche, M. A., Nitsche, M. S., Klein, C. C., Tergau, F., Rothwell, J. C., & Paulus, W. (2003). Level of action of cathodal DC polarisation induced inhibition of the human motor cortex. *Clinical Neurophysiology, 114*(4), 600-604.

Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of Physiology, 527*(3), 633-639.

Norman, R., Lecomte, T., Addington, D., & Anderson, E. (2017). Canadian treatment guidelines on psychosocial treatment of schizophrenia in adults. *The Canadian Journal of Psychiatry, 62*(9), 617-623.

Oertel-Knöchel, V., Knöchel, C., Rotarska-Jagiela, A., Reinke, B., Prvulovic, D., Haenschel, C., ... & Linden, D. E. (2013). Association between psychotic symptoms and cortical thickness reduction across the schizophrenia spectrum. *Cerebral Cortex, 23*(1), 61-70.

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia, 9*(1), 97-113.

Ohrmann, P., Siegmund, A., Suslow, T., Pederson, A., Spitzberg, K., Kersting, A., Rothermundt, M., Arolt, V., Heindel, W., & Pfleiderer, B. (2007). Cognitive impairment and in vivo metabolites in first-episode neuroleptic-naïve and chronic medicated schizophrenic patients: A proton magnetic resonance spectroscopy study. *Journal of Psychiatry Research, 41*(8), 625–634.

Otani, V. H. O., Shiozawa, P., Cordeiro, Q., & Uchida, R. R. (2015). A systematic review and meta-analysis of the use of repetitive transcranial magnetic stimulation for auditory hallucinations treatment in refractory schizophrenic patients. *International Journal of Psychiatry in Clinical Practice, 19*(4), 228-232.

Owen, F., Crow, T. J., Poulter, M., Cross, A. J., Longden, A., & Riley, G. J. (1978). Increased dopamine-receptor sensitivity in schizophrenia. *The Lancet, 312*(8083), 223-226.

Pakarinen, S., Lovio, R., Huotilainen, M., Alku, P., Näätänen, R., & Kujala, T. (2009). Fast multi-feature paradigm for recording several mismatch negativities (MMNs) to phonetic and acoustic changes in speech sounds. *Biological Psychology, 82*(3), 219-226.

Perez, C. A., Engineer, C. T., Jakkamsetti, V., Carraway, R. S., Perry, M. S., & Kilgard, M. P. (2013). Different timescales for the neural coding of consonant and vowel sounds. *Cerebral Cortex, 23*(3), 670–683. https://doi.org/10.1093/cercor/bhs045

Perrin, M. A., Kantrowitz, J. T., Silipo, G., Dias, E., Jabado, O., & Javitt, D. C. (2018). Mismatch negativity (MMN) to spatial deviants and behavioral spatial discrimination ability in the etiology of auditory verbal hallucinations and thought disorder in schizophrenia. *Schizophrenia Research, 191*, 140–147. https://doi.org/10.1016/j.schres.2017.05.012

Poulet, E., Brunelin, J., Bediou, B., Bation, R., Forgeard, L., Dalery, J., ... & Saoud, M. (2005). Slow transcranial magnetic stimulation can rapidly reduce resistant auditory hallucinations in schizophrenia. *Biological Psychiatry, 57*(2), 188-191.

Priori, A., Berardelli, A., Rona, S., Accornero, N., & Manfredi, M. (1998). Polarization of the human motor cortex through the scalp. *Neuroreport, 9*(10), 2257-2260.

Psychology Software Tools, Inc. [E-Prime 3.0]. (2016). Retrieved from https://www.pstnet.com.

Pulvermuller, F., & Shtyrov, Y. (2006). Language outside the focus of attention: The mismatch negativity as a tool for studying higher cognitive processes. *Progress in Neurobiology, 79*(1), 49-71.

Randau, M., Oranje, B., Miyakoshi, M., Makeig, S., Fagerlund, B., Glenthøj, B., & Bak, N. (2019). Attenuated mismatch negativity in patients with first-episode antipsychotic-naive schizophrenia using a source-resolved method. *NeuroImage: Clinical, 22,* 101760.

Ripke, S., Neale, B. M., Corvin, A., Walters, J. T., Farh, K. H., Holmans, P. A., ... & Pers, T. H. (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature, 511*(7510), 421-427.

Rosa, M. O., Gattaz, W. F., Rosa, M. A., Rumi, D. O., Tavares, H., Myczkowski, M., ... & Teixeira, M. J. (2007). Effects of repetitive transcranial magnetic stimulation on auditory hallucinations refractory to clozapine. *The Journal of Clinical Psychiatry, 68*(10), 1528-1532.

Saba, G., Verdon, C. M., Kalalou, K., Rocamora, J. F., Dumortier, G., Benadhira, R., ... & Januel, D. (2006). Transcranial magnetic stimulation in the treatment of schizophrenic symptoms: A double-blind sham-controlled study. *Journal of Psychiatric Research, 40*(2), 147-152.

Salisbury, D. F., Polizzotto, N. R., Nestor, P. G., Haigh, S. M., Koehler, J., & McCarley, R. W. (2017). Pitch and duration mismatch negativity and premorbid intellect in the first hospitalized schizophrenia spectrum. *Schizophrenia Bulletin*, *43*(2), 407–416. https://doi.org/10.1093/schbul/sbw074

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

Sams, M., Hämäläinen, M., Antervo, A., Kaukoranta, E., Reinikainen, K., & Hari, R. (1985). Cerebral neuromagnetic responses evoked by short auditory stimuli. *Electroencephalography and Clinical Neurophysiology*, *61*(4), 254–266. https://doi.org/10.1016/0013-4694(85)91092-2

Sato, Y., Yabe, H., Todd, J., Michie, P., Shinozaki, N., Sutoh, T., Hiruma, T., Nashida, T., Matsuoka, T., & Kaneko, S. (2003). Impairment in activation of a frontal attention-switch mechanism in schizophrenic patients. *Biological Psychology, 62*(1), 49–63. https://doi.org/10.1016/s0301-0511(02)00113-8

Schröger, E. (1998). Measurement and interpretation of the mismatch negativity. *Behavior Research Methods, Instruments, & Computers*, *30*(1), 131-145.

Seeman, P., Bzowej, N. H., Guan, H. C., Bergeron, C., Reynolds, G. P., Bird, E. D., ... & Tourtellotte, W. W. (1987). Human brain D1 and D2 dopamine receptors in schizophrenia, Alzheimer's, Parkinson's, and Huntington's diseases. *Neuropsychopharmacology, 1*(1), 5-15.

Selten, J. P., Wiersma, D., & van den Bosch, R. J. (2000). Clinical predictors of discrepancy between self-ratings and examiner ratings for negative symptoms. *Comprehensive Psychiatry, 41*(3), 191-196.

Sepehrmanesh, Z., Heidary, M., Akasheh, N., Akbari, H., & Heidary, M. (2018). Therapeutic effect of adjunctive N-acetyl cysteine (NAC) on symptoms of chronic schizophrenia: A double-blind, randomized clinical trial. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 82*, 289-296.

Schwade, L. F., Didoné, D. D., & Sleifer, P. (2017). Auditory evoked potential mismatch negativity in normal-hearing adults. *International Archives of Otorhinolaryngology, 21*(3), 232–238. https://doi.org/10.1055/s-0036-1586734

Shawyer, F., Ratcliff, K., Mackinnon, A., Farhall, J., Hayes, S. C., & Copolov, D. (2007). The voices acceptance and action scale (VAAS): Pilot data. *Journal of Clinical Psychology, 63*(6), 593-606.

Shelley, A. M., Ward, P. B., Catts, S. V., Michie, P. T., Andrews, S., & McConaghy, N. (1991). Mismatch negativity: An index of a preattentive processing deficit in schizophrenia. *Biological Psychiatry, 30*(10), 1059-1062.

Shergill, S. S., Brammer, M. J., Williams, S. C., Murray, R. M., & McGuire, P. K. (2000). Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. *Archives of General Psychiatry, 57*(11), 1033-1038.

Shergill, S. S., Murray, R. M., & McGuire, P. K. (1998). Auditory hallucinations: A review of psychological treatments. *Schizophrenia Research*, *32*(3), 137–150. https://doi.org/10.1016/s0920-9964(98)00052-8

Shibasaki, H. (2008). Human brain mapping: Hemodynamic response and electrophysiology. *Clinical Neurophysiology, 119*(4), 731-743.

Shinozaki, N., Yabe, H., Sato, Y., Hiruma, T., Sutoh, T., Nashida, T., Matsuoka, T., & Kaneko, S. (2002). The difference in Mismatch negativity between the acute and post-acute phase of schizophrenia. *Biological Psychology, 59*(2), 105–119. https://doi.org/10.1016/s0301-0511(01)00129-6

Shivakumar, V., Chhabra, H., Subbanna, M., Agarwal, S. M., Bose, A., Kalmady, S. V., ... & Venkatasubramanian, G. (2015). Effect of tDCS on auditory hallucinations in schizophrenia: Influence of catechol-O-methyltransferase (COMT) Val158Met polymorphism. *Asian Journal of Psychiatry, 16,* 75.

Shtyrov, Y., Kujala, T., Palva, S., Ilmoniemi, R. J., & Näätänen, R. (2000). Discrimination of speech and of complex nonspeech sounds of different temporal structure in the left and right cerebral hemispheres. *NeuroImage, 12*(6), 657–663. https://doi.org/10.1006/nimg.2000.0646

Slotema, C. W., Blom, J. D., de Weijer, A. D., Diederen, K. M., Goekoop, R., Looijestijn, J., ... & Sommer, I. E. (2011). Can low-frequency repetitive transcranial magnetic stimulation really relieve medication-resistant auditory verbal hallucinations? Negative results from a large randomized controlled trial. *Biological Psychiatry, 69*(5), 450-456.

Slotema, C. W., Blom, J. D., van Lutterveld, R., Hoek, H. W., & Sommer, I. E. (2014). Review of the efficacy of transcranial magnetic stimulation for auditory verbal hallucinations. *Biological Psychiatry, 76*(2), 101-110.

Snyder, J., & Wilman, A. (2010). Field strength dependence of PRESS timings for simultaneous detection of glutamate and glutamine from 1.5 to 7 T. *Journal of Magnetic Resonance, 203*(1), 66-72.

Solís-Vivanco, R., Mondragón-Maya, A., León-Ortiz, P., Rodríguez-Agudelo, Y., Cadenhead, K. S., & de la Fuente-Sandoval, C. (2014). Mismatch Negativity reduction in the left cortical regions in first-episode psychosis and in individuals at ultra-high-risk for psychosis. *Schizophrenia Research, 158*(1-3), 58-63.

Sorokin, A., Alku, P., & Kujala, T. (2010). Change and novelty detection in speech and non-speech sound streams. *Brain Research, 1327,* 77-90.

Stagg, C. J., Antal, A., & Nitsche, M. A. (2018). Physiology of transcranial direct current stimulation. *The Journal of ECT, 34*(3), 144-152.

Steer, R. A., Ranieri, W. F., Beck, A. T., & Clark, D. A. (1993). Further evidence for the validity of the Beck Anxiety Inventory with psychiatric outpatients. *Journal of Anxiety Disorders, 7*(3), 195-205.

Steinmann, S., Leicht, G., & Mulert, C. (2014). Interhemispheric auditory connectivity: Structure and function related to auditory verbal hallucinations. *Frontiers in Human Neuroscience,* 8, 55.

Stępnicki, P., Kondej, M., & Kaczor, A. A. (2018). Current concepts and treatments of schizophrenia. *Molecules, 23*(8), 2087.

Świtaj, P., Anczewska, M., Chrostek, A., Sabariego, C., Cieza, A., Bickenbach, J., & Chatterji, S. (2012). Disability and schizophrenia: A systematic review of experienced psychosocial difficulties. *BMC Psychiatry, 12*(1), 193.

Takei, Y., Kumano, S., Hattori, S., Uehara, T., Kawakubo, Y., Kasai, K., ... & Mikuni, M. (2009). Preattentive dysfunction in major depression: A magnetoencephalography study using auditory mismatch negativity. *Psychophysiology, 46*(1), 52-61.

Tandon, R. (2011). Antipsychotics in the treatment of schizophrenia: An overview. *The Journal of Clinical Psychiatry, 72,* 4-8.

Tandon, R., Gaebel, W., Barch, D. M., Bustillo, J., Gur, R. E., Heckers, S., ... & Van Os, J. (2013). Definition and description of schizophrenia in the DSM-5. *Schizophrenia Research, 150*(1), 3-10.

Tandon, R., Nasrallah, H. A., & Keshavan, M. S. (2009). Schizophrenia,"just the facts" 4. Clinical features and conceptualization. *Schizophrenia Research, 110*(1-3), 1-23.

Tervaniemi, M., Ilvonen, T., Sinkkonen, J., Kujala, A., Alho, K., Huotilainen, M., & Näätänen, R. (2000). Harmonic partials facilitate pitch discrimination in humans: Electrophysiological and behavioral evidence. *Neuroscience Letters*, *279*(1), 29–32. https://doi.org/10.1016/s0304-3940(99)00941-6

Tervaniemi, M., & Hugdahl, K. (2003). Lateralization of auditory-cortex functions. Brain research. *Brain Research Reviews, 43*(3), 231–246. https://doi.org/10.1016/j.brainresrev.2003.08.004

Thönnessen, H., Zvyagintsev, M., Harke, K. C., Boers, F., Dammers, J., Norra, C. h., & Mathiak, K. (2008). Optimized mismatch negativity paradigm reflects deficits in schizophrenia patients. A combined EEG and MEG study. *Biological Psychology, 77*(2), 205–216. https://doi.org/10.1016/j.biopsycho.2007.10.009

Todd, J., Michie, P. T., & Jablensky, A. V. (2003). Association between reduced duration mismatch negativity (MMN) and raised temporal discrimination thresholds in schizophrenia. Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 114(11), 2061–2070. https://doi.org/10.1016/s1388-2457(03)00246-3

Todd, J., Michie, P. T., Schall, U., Karayanidis, F., Yabe, H., & Näätänen, R. (2008). Deviant matters: Duration, frequency, and intensity deviants reveal different patterns of mismatch negativity reduction in early and late schizophrenia. *Biological Psychiatry, 63*(1), 58–64. https://doi.org/10.1016/j.biopsych.2007.02.016

Umbricht, D., Koller, R., Vollenweider, F. X., & Schmid, L. (2002). Mismatch negativity predicts psychotic experiences induced by NMDA receptor antagonist in healthy volunteers. *Biological Psychiatry, 51*(5), 400-406.

Umbricht, D., & Krljes, S. (2005). Mismatch negativity in schizophrenia: A meta-analysis. *Schizophrenia Research, 76*(1), 1–23. https://doi.org/10.1016/j.schres.2004.12.002

Umbricht, D., Schmid, L., Koller, R., Vollenweider, F. X., Hell, D., & Javitt, D. C. (2000). Ketamine-induced deficits in auditory and visual context-dependent processing in

healthy volunteers: Implications for models of cognitive deficits in schizophrenia. *Archives of General Psychiatry, 57*(12), 1139-1147.

Valero-Cabré, A., Pascual-Leone, A., & Coubard, O. A. (2011). Transcranial magnetic stimulation (TMS) in basic and clinical neuroscience research. *Revue Neurologique, 167*(4), 291-316.

van der Gaag, M., Valmaggia, L. R., & Smit, F. (2014). The effects of individually tailored formulation-based cognitive behavioural therapy in auditory hallucinations and delusions: A meta-analysis. *Schizophrenia Research, 156*(1), 30-37.

van de Ven, V. G., Formisano, E., Röder, C. H., Prvulovic, D., Bittner, R. A., Dietz, M. G., ... & Di Salle, F. (2005). The spatiotemporal pattern of auditory cortical responses during verbal hallucinations. *Neuroimage, 27*(3), 644-655.

van Lutterveld, R., van den Heuvel, M. P., Diederen, K. M., de Weijer, A. D., Begemann, M. J., Brouwer, R. M., ... & Sommer, I. E. (2014). Cortical thickness in individuals with non-clinical and clinical psychotic symptoms. *Brain, 137*(10), 2664-2669.

van Swam, C., Federspiel, A., Hubl, D., Wiest, R., Boesch, C., Vermathen, P., ... & Dierks, T. (2012). Possible dysregulation of cortical plasticity in auditory verbal hallucinations–a cortical thickness study in schizophrenia. *Journal of Psychiatric Research, 46*(8), 1015-1023.

Ventura, J., Green, M. F., Shaner, A., & Liberman, R. P. (1993). Training and quality assurance with the Brief Psychiatric Rating Scale: 'The drift buster'. *International Journal of Methods in Psychiatric Research, 3,* 221–244.

Walinder, J., Skott, A., Carlsson, A., & Roos, B. E. (1976). Potentiation by metyrosine of thioridazine effects in chronic schizophrenics: A long-term trial using double-blind crossover technique. *Archives of General Psychiatry, 33*(4), 501-505.

Waters, F. A., Badcock, J. C., Maybery, M. T., & Michie, P. T. (2003). Inhibition in schizophrenia: Association with auditory hallucinations. *Schizophrenia Research, 62*(3), 275-280.

Waters, F., Badcock, J., Michie, P., & Maybery, M. (2006). Auditory hallucinations in schizophrenia: Intrusive thoughts and forgotten memories. *Cognitive Neuropsychiatry, 11*(1), 65-83.

Waters, F. A., Maybery, M. T., Badcock, J. C., & Michie, P. T. (2004). Context memory and binding in schizophrenia. *Schizophrenia Research, 68*(2-3), 119-125.

Weinberger, D. R., Berman, K. F., & Zec, R. F. (1986). Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia: Regional cerebral blood flow evidence. *Archives of General Psychiatry, 43*(2), 114-124.

Wilson, S. T., & Stanley, B. (2006). Ethical concerns in schizophrenia research: Looking back and moving forward. *Schizophrenia Bulletin*, *32*(1), 30–36. https://doi.org/10.1093/schbul/sbj023

Woodruff, P. W., Wright, I. C., Bullmore, E. T., Brammer, M., Howard, R. J., Williams, S. C., ... & Murray, R. M. (1997). Auditory hallucinations and the temporal cortical response to speech in schizophrenia: A functional magnetic resonance imaging study. *American Journal of Psychiatry, 154*(12), 1676-1682.

Woods, A. J., Antal, A., Bikson, M., Boggio, P. S., Brunoni, A. R., Celnik, P., ... & Knotkova, H. (2016). A technical guide to tDCS, and related non-invasive brain stimulation tools. *Clinical Neurophysiology, 127*(2), 1031-1048.

Wynn, J. K., Sugar, C., Horan, W. P., Kern, R., & Green, M. F. (2010). Mismatch negativity, social cognition, and functioning in schizophrenia patients. *Biological Psychiatry, 67*(10), 940-947.

Xiong, Y. B., Bo, Q. J., Wang, C. M., Tian, Q., Liu, Y., & Wang, C. Y. (2019). Differential of frequency and duration mismatch negativity and theta power deficits in first-episode and chronic schizophrenia. *Frontiers in Behavioral Neuroscience*, *13*, 37. https://doi.org/10.3389/fnbeh.2019.00037

APPENDIX I

SCREENING SCRIPT – tDCS-SZ Study
PATIENT VERSION

The following information may have been obtained before the screen (e.g. from e-mail or phone message).

Name: Sex: M or F Age & DOB: (**18-65 yrs**)

Employment: Highest Level of Education:

Smoking status: (smoker vs. non-smoker) First language:

Height: Weight: **Exclude if BMI >40kg/m^2** Handedness: L R

Head measurement (if in person):

Telephone: E-Mail:

Contact information obtained from:

The following is intended as a guide. You do not need to read it word-for-word.

Hi (INSERT INDIVIDUAL'S NAME)
My name is (FIRST NAME) and I am a(n) (POSITION) from the Clinical EEG Lab at the Royal Ottawa Hospital. I am calling about/would like to tell you about our study on the effects of a non-invasive brain stimulation technique on auditory hallucinations, which you had expressed an interest in participating in.

OR

Thank you for calling us to find out more about our research.

Do you have a few minutes so that I can explain the study to you?

The purpose of our study is to examine a non-invasive form of brain stimulation called transcranial direct current stimulation, or tDCS for short, as a potential treatment for auditory hallucinations. This involves delivering a weak current by small electrodes placed on the scalp to target certain brain areas. We will also be using something called EEG in order to measure the brain's electrical activity before and after tDCS sessions. EEG is another non-invasive method that involves placing electrodes on the scalp which record the brain's electrical activity. This will be done while you are listening to sounds, or while you are not doing anything.

There is an additional component of the study that involves measuring your brain's structure and function using a brain imaging technique called magnetic resonance imaging (MRI), as well as another technology called transcranial magnetic stimulation (TMS).

Are you also interested in participating in the MRI/TMS aspect of this study, or just the EEG?

_____

If you choose to participate, you would come into our laboratory for baseline and post-tDCS testing. The baseline and post-tDCS testing sessions will last ~3 hours each, and during these times we will record your EEG and obtain your

MRI scans. These sessions may be broken down, if that works better for you. You would also be asked to come in twice daily for 5 consecutive days of tDCS sessions – with each visit lasting ~20-30 minutes.

During the baseline and post-tDCS visits you will also be required to complete several self-report questionnaires and cognitive tasks. You will be compensated 50$ for both the baseline and post-tDCS testing, with an additional $30/session if you participate in the imaging. For each tDCS sessions, you will be compensated $10/session (or $100 total). All testing will be carried out at the Royal Hospital.

Are you still interested in participating in this study and continuing with the screening?
[IF NO]: Thank you very much for your time.
[IF YES – still interested]:
Is this a good time to go through the screening – it may take ~15-30 minutes?

[IF NO]: Set up a time to call back/*or talk in-person*:

Date: _____ Time: _____

[IF YES]: Before having you visit, we need to ask you some questions to determine if you are a good fit for the study. It is possible that some of these questions may make you feel uncomfortable or distressed. If this happens, let me know, and we can stop this interview or take a break. You can also refuse to answer questions. I also want to assure you that the information collected during this interview is confidential. This information will be destroyed if you do not qualify for the study or choose not to participate. If you qualify, this information will be kept in a safe place. Keeping in mind that some of the questions are quite personal, is it alright if I proceed?

[IF NO]: Thank you very much for your time.

**** Before we begin, are you interested in being contacted for participation in future research studies?**

YES NO

---

1. GENERAL MEDICAL

[IF YES]: I am going to start off by asking you a series of questions about your physical health.

1. Have you been diagnosed with or are you currently being treated for any **major medical** problems or chronic medical conditions?

YES NO

[IF YES]: Which ones?

2. Are you currently taking any medication for any chronic health problems? (e.g. high blood pressure, cholesterol, thyroid, diabetes) - **Any thyroid issues should be stabilized for at least 3 months**

YES NO

[IF YES]: Which ones/how long?

3. Do you have a history of any neurological or neuromuscular problems? (e.g. stroke, epilepsy, brain cysts, migraines, MS).

YES NO

[IF YES]: Which ones?

4. Do you have any major motor impairments? (e.g. cerebral palsy, physical disability, muscular dystrophy)

YES NO

[IF YES]: Which ones?

5. Have you ever had a concussion?

YES NO

[IF YES]: How long were you unconscious? ***Exclude if loss of consciousness lasted >5 minutes**

6. Have you ever been diagnosed with a developmental problem? (e.g. autism)

YES NO

[IF YES]: Which ones?

7. Have you ever been diagnosed with or struggled with major learning disabilities? (e.g. major reading problems, dyslexia; asked about failing school)

YES NO

[IF YES]: Which ones?

8. [FEMALE PARTICIPANTS] Are you currently pregnant and/or breastfeeding? Y / N
[IF YES]: EXCLUDE

9. [FEMALE PARTICIPANTS] Are you currently on any form of hormonal/chemical birth control? Y / N
[IF YES]: Which form? (i.e., pill, patch, IUD, ring, etc.)
How long have you been on this form of birth control?

---

2. FURTHER MEDICAL – STUDY COMPATIBILITY – NEUROIMAGING

1. Do you have any MAJOR issues with back pain?

YES NO

[IF YES]: Would this impede you from sitting up straight or lying still for prolonged periods of time?

YES NO

2. Have you ever had an EEG or have previously participated in an EEG study?

YES NO

[IF YES]: What for/when?

3. Have you ever had an MRI or participated in a MRI study?

YES NO

[IF YES]: What for/when?

4. Are you extremely uncomfortable in closed spaces?

YES NO

[**IF YES]** Would an MRI be problematic for you? (If unsure, ask "are you uncomfortable in elevators/do you specifically avoid enclosed spaces like elevators because they make you uncomfortable or anxious?")

5. Do you have any metal in your body? (e.g. pacemakers, surgical/aneurysm clips, prosthetic valves, metal plates/screws, pins, cochlear implants, braces, etc.?)

YES NO

[IF YES]: What for/when?
6. Do you wear eyeglasses/contacts?

YES NO

Details:

[IF YES]: Inquire about whether they can wear their contact lenses to testing
[IF NO]: Inquire about glasses prescription (we have MR-compatible glasses)

---

3. MENTAL HEALTH SECTION – SZ STUDY SPECIFIC

Exclude if their <u>primary</u> diagnosis is anything but SZ/schizoaffective disorder (mood disorders OK as long as they are secondary to SZ)

I am now going to ask you some questions about your mental health/psychiatric history.

1. Have you ever sought treatment or been treated for emotional or psychiatric problems?

YES NO

[IF YES]: What for? What kind(s) of treatment did you receive?

2. Have you ever been diagnosed with schizophrenia (SZ) or schizoaffective disorder?

YES NO

[IF YES]: Approximately when were you first diagnosed?

NOTES:

3. Have you ever taken medication for treating your schizophrenia/schizoaffective disorder?
NOTE: typical or first-generation antipsychotics are exclusionary – i.e., haloperidol (Haldol), loxapine (loxitane), chlorpromazine (thorazine), etc.* ***Atypicals are ok – i.e., clozapine (clozaril), risperidone (Risperdal), olanzapine (Zyprexa), etc.*

YES NO

[IF YES]: Which medication are you <u>currently</u> taking, as best as you can remember? [this information may be available from the clinician]

4. Approximately how long have you been taking these medication(s)?

[If they have taken medication for SZ, but are not currently]: When did you stop taking this medication?

5. Have you ever taken benzodiazepines (i.e., clonazepam, diazepam/valium, lorazepam, etc.)?

[IF YES]: How long have you been taking these medications? What were you taking them for? Are you currently taking them now?

6. Are you currently taking any medications to help you sleep?

[IF YES]: Which medications are you taking? How long have you been taking these medications?

---

1. Have you ever experienced an auditory hallucination (i.e., hearing voices, noises, whispering, etc)?

YES NO

[IF YES]: How many auditory hallucinations do you typically experience per week?

[IF LESS THAN 3 AVH'S PER WEEK]: **Exclusionary – but use judgement and be flexible**

2. When did you first start experiencing auditory hallucinations?

3. Have you ever experienced visual hallucinations (i.e., seeing objects/people/colours, etc)?

YES NO

[IF YES]: How often would you say that you have these experiences?

4. Have you ever experienced any other kind of hallucinations (i.e., those involving smell, taste or touch)?

YES NO

Details:

MOOD EPISODES

Depressive

1. Has there been a period of time when you were feeling depressed or down most of the day nearly, every day?

YES NO

Details:

2. What about losing interest or pleasure in things you usually enjoy?

YES NO

Details:

3. Have you ever been diagnosed with depression or taken antidepressant medication?

YES NO

(Skip the following if NO)

[IF YES]: How long did this period last?

[IF YES]: Just before this began, were you: Physically ill? Drinking alcohol or using street drugs? Did this begin soon after someone close to you died?

YES NO

Comments:

ANXIETY DISORDERS

Panic

1. Have you ever had a panic attack, when you suddenly felt extremely frightened or suddenly developed a lot of physical symptoms?

YES NO

Details:

(Skip the following if NO)

[IF YES]: Have these attacks ever come on <u>completely out of the blue</u> – in situations where you don't expect to be nervous or uncomfortable?

YES NO

[IF YES]: Just before you began having panic attacks, were you: Taking any drugs, caffeine, diet pills, or any other medications? Physically ill?

YES NO

Agoraphobia

1. Were you ever afraid of going out of the house alone, being in crowds, standing in a line or traveling on buses or trains?

YES NO

(Skip the following if NO)

[IF YES]: What were you afraid would happen?

Does participant mention anxiety about being in places/situations where escape may be difficult or embarrassing or in which help may not be available in the event of panic-like symptoms?

YES NO

Details:

[IF YES]: Just before you began having these fears, were you: Taking any drugs, caffeine, diet pills, or any other medications? Physically ill?

YES NO

Social Phobia

1. Is there anything that you have been afraid to do or felt uncomfortable doing in front of other people, like speaking, eating or writing?

YES NO

Details:

(Skip the following if NO)

[IF YES]: to "Public Speaking": Do you think that you are more uncomfortable than most people who are in a similar situation?

YES NO

[IF YES]: What were you afraid would happen?

Does participant mention that exposure to the feared social situation almost invariably provokes anxiety, which may take the form of a situationally bound or situationally predisposed panic-attack?

YES NO

[IF YES]: Just before you began having these fears, were you: Taking any drugs, caffeine, diet pills, or any other medications? Physically ill?

YES NO

Generalized Anxiety Disorder

1. In the last six months, have you been particularly nervous or anxious?

YES NO

(Skip the following if NO)

[IF YES]: What do you worry about?

2. During the past six months, would you say that you are worrying more often than not?

YES NO

3. When you are worrying, do you find it difficult to stop?

YES NO

4. When you're feeling anxious or nervous, do you feel:

Restless Frequently tired Trouble concentrating/Mind goes blank Irritable Tense muscles Sleep disturbances

5. Have you ever been diagnosed with any other mental health issues that we have not discussed?

YES NO

[IF YES]: What was your diagnosis? When were you diagnosed?

6. Have you taken any medications for this disorder?

YES NO

[IF YES]: Which ones? Are you currently taking these medications?

---

4. DRUG AND ALCOHOL USE

I'm now going to ask you some questions about your substance use. Can you let me know whether you consume the following?

Coffee/tea/energy drinks: **YES NO** _____ times per day/week **(if >4 cups/day regularly remind of abstinence criteria)**

Smoker: **YES NO** Since when? Trying to quit?
Cigarettes per day/week

Do you use vaporizers or e-cigarettes?
IF YES: How long?
IF YES: How frequently throughout the day?

Are you able to go without for a 3 hour period? **YES NO**
IF NO: Have you ever been a smoker? **YES NO**

Alcohol
Currently, how many drinks do you have per day/week?
What age did you start drinking?
What was your drinking pattern like at that time?
When were you using alcohol the most? How many times per week would you drink/how many drinks would you have each time?

Have you ever been treated for alcohol dependence/major alcohol problems? **YES NO**

[IF YES] How long ago?
(Exclude if they currently have a substance abuse problem or have within the past year.)

Drug & Medication Use

Have you ever become dependent on a prescribed medication or taken a lot more than you were supposed to?

YES NO

[IF YES]: Details?

Have you ever used street drugs, including marijuana?

YES NO

[IF NO]: Skip the drug related section below
Have you ever used any of the following?

Guidelines for rating level of drug and medicine use:

Street Drug:

- When were you using (DRUG) the most?_____
- Has there been a time when you used it at least ten times in a one-month period of time?

(1) has ever taken street drug more than 10 times in a one-month period

Prescribed Medicine:

(2) reports becoming dependent on a prescribed drug OR using much more of it than was prescribed

- If drug group never used or used only once, or if prescribed drug used as directed → circle "1"
- If drug used at least twice, but less than level indicated on (1) → circle "2"
- If drug used at level indicated in item (1) or if possibly dependent on prescribed drug (item (2) is true) → circle "3"

Circle the name of each drug ever used	**Period of heaviest use (age or date, & duration) and describe pattern of use**	**Level of use**
Sedatives - hypnotics – anxiolytics: Quaalude, Seconal, Valium, Xanax, Librium, barbiturates, Miltown, Ativan, Dalmane, Halcion, Restoril, or other : _____		1 2 3
Cannabis: marijuana, hashish , THC, or other: _____		1 2 3
Stimulants: amphetamine, "speed", crystal meth, dexadrine, Ritalin, "ice", or other: _____		1 2 3
Opioids: heroin, morphine, opium, Methadone, Darvon, codein, Percodan, Demerol, Dilaudid, unspecified or other: _____		1 2 3
Cocaine: intranasal, IV, freebase, crack, "speedball", unspecified or other: _____		1 2 3

Hallucinogens/PCP: LSD, mescaline, peyote, psilocybin, STP, mushrooms, PCP ("angel dust"), Extasy, MDMA, or other: _____		1 2 3
Other: steroids, "glue", paint, inhalants, nitrous oxide ("laughing gas"), amyl or butyl nitrate ("popers"), nonprescription sleep or diet pills, unknown, or other: _____		1 2 3

***Family Interview for Genetic Studies (*FIGS): Adapted General Screening Questions**

We're almost done. I'm going to ask you a couple of questions regarding your family history, specifically your immediate family – these include your parents, any brothers/sisters you may have, offspring/children and spouses. I'd like you to keep these particular individuals in mind as we go through the questions:

Was anyone in your immediate family adopted?
NO YES:

Does/did anyone in your family have a developmental disability?
NO YES:

Did/does anyone have problems with their nerves or emotions? …to the extent that they take meds e.g. lithium or see a doctor?
NO YES:

Feel very low for a couple of weeks or more, or have a diagnosis of depression?
NO YES:

Attempt or complete suicide?
NO YES:

Seem over-excited (or manic) day and night, or have a diagnosis of mania/bipolar disorder?
NO YES:

Have visions, hear voices, or have beliefs that seem strange or unreal?
NO YES:

Have unusual or bizarre behavior, or have a diagnosis of schizophrenia?
NO YES:

For EEG & brain imaging sessions only (i.e., does not apply to tDCS sessions): You will be required to **abstain from nicotine for 3 hours before your session and caffeine for 6 hours before your session (decaf coffee is fine).** Abstinence from alcohol and over-the-counter drugs (with the exception of prescribed medications) is also required from midnight the night before your visit. We also ask that you abstain from street drugs (including marijuana) from midnight the night before your visit until your session is complete. Do you think this would be a problem?

YES NO

[IF YES]: Ask them if they would like to be contacted for future studies and thank them for their time.

As mentioned, our testing occurs at the Royal Hospital on Carling (1145 Carling Ave) – do you know where it is? Do you foresee any difficulties in getting to/from the test sessions?

Would you require any reimbursement for parking or bus fare? (Tell them to bring receipts)

YES NO

Given that we will need you to commit to 2 tDCS sessions per day for 5 consecutive days during specific times of the day (i.e., first one between 9am-11am, second one 3 hours later from start time of first one), do you think that you will have some scheduling conflicts that might prevent you from being tested at a particular time? (exams, going home, vacations, employment)

If participant seems PERFECT for the study (i.e., no red flags):
Based on this preliminary screen, you seem like a great candidate for the study. Do you have any questions and are you still interested in participating?

[IF YES]: Great! I would like to tentatively schedule you to come in for your first session, although I must first review your file with my supervisor.
Is there a date/time that would work for you (preferably morning/early afternoon):

Alright, I will email or call you to confirm an appointment date as soon as possible.
Thank you.

If participant DOES NOT seem perfect for the study/there are some concerns:

Based on this preliminary screen, you seem like you may qualify for study participation. However, I will need to review this interview with one of the researchers and we will contact you shortly about your participation. Is that alright?

Do you have any further questions?

NOTES:

APPENDIX II

SCREENING SCRIPT – tDCS-SZ Study
HEALTHY CONTROL VERSION

The following information may have been obtained before the screen (e.g. from e-mail or phone message).

Name: _____ Sex: M or F (circle) Age & DOB: _____ (**18-65 yrs**)

Employment: _____ Highest Level of Education: _____

Smoking status: _____ (smoker vs. non-smoker) First language: _____

Height: _____ Weight: _____ **Exclude if BMI >40kg/m^2** Handedness: L R

Telephone: _____ E-Mail:_____

Contact information obtained from: _____

The following is intended as a guide. You do not need to read it word-for-word.

Hi (INSERT INDIVIDUAL'S NAME)
My name is (FIRST NAME) and I am a(n) (POSITION) from the Clinical EEG Lab at the Royal Ottawa Hospital. I am calling about/would like to tell you about our study that will be comparing differences in brain activity and structure/function in people with and without schizophrenia.

OR

Thank you for calling us to find out more about our research.

Do you have a few minutes so that I can explain the study to you?

The purpose of our study is to better understand how the brains of people diagnosed with schizophrenia differ from those without schizophrenia. Specifically, we'd like to see if there are any differences in brain electrical activity patterns that occur while participants perform a few computerized tasks measuring auditory processing. We will be using something called EEG to accomplish this. EEG is a non-invasive method that involves placing electrodes on the scalp, which records the brain's electrical activity while you complete computerized tasks, listen to audio/sounds, or while you are not doing anything in particular.

There is an additional component of the study that involves measuring your brain's structure and function using a brain imaging technique called magnetic resonance imaging (MRI).

If you choose to participate, you would come into our laboratory once for the initial testing session, which includes completing a series of self-report questionnaires, a series of cognitive tasks and EEG recordings – this session will last about 3-4 hours. If you choose to participate in the MRI component, you will come in for an additional session to complete the brain scan which will last about 1.5 hours.

Would you also be interested in participating in the MRI aspect of this study, or just the EEG?

_____

You will be compensated 50$ for the initial EEG testing session, with an additional $30 if you choose to participate in the imaging session. All testing will be carried out at the Royal Ottawa Hospital.

Are you still interested in participating in this study and continuing with the screening?

[IF NO]: Thank you very much for your time.
[IF YES – still interested]:
Is this a good time to go through the screening – it may take ~15-30 minutes?

[IF NO]: Set up a time to call back/*or talk in-person*:

Date: _____ Time: _____

[IF YES]: Before having you visit, we need to ask you some questions to determine if you are a good fit for the study. It is possible that some of these questions may make you feel uncomfortable or distressed. If this happens, let me know, and we can stop this interview, or take a break. You can also refuse to answer questions. I also want to assure you that the information collected during this interview is confidential. The information will be destroyed if you do not qualify for the study or choose not to participate. If you qualify, this information will be kept in a safe place. Keeping in mind that some of the questions I will ask are quite personal, is it alright if I proceed?

[IF NO]: Thank you very much for your time.

**** Before we begin, are you interested in being contacted for participation in future research studies?**

YES NO

---

1. GENERAL MEDICAL

[IF YES]: I am going to start off by asking you a series of questions about your physical health.

1. Have you been diagnosed with or are you currently being treated for any **major medical** problems or chronic medical conditions?

YES NO

[IF YES]: Which ones? _____

2. Are you currently taking any medication for any chronic health problems? (e.g. high blood pressure, cholesterol, thyroid, diabetes) - **Any thyroid issues should be stabilized for at least 3 months**

YES NO

[IF YES]: Which ones/how long? _____

3. Do you have a history of any neurological or neuromuscular problems? (e.g. stroke, epilepsy, brain cysts, migraines, MS).

YES NO

[IF YES]: Which ones? _____

4. Do you have any major motor impairments? (e.g. cerebral palsy, physical disability, muscular dystrophy)

YES NO

[IF YES]: Which ones? _____

5. Have you ever had a concussion?

YES NO

[IF YES]: How long were you unconscious? ***Exclude if loss of consciousness lasted >5 minutes**

_____

6. Have you ever been diagnosed with a developmental problem? (e.g. autism)

YES NO

[IF YES]: Which ones? _____

7. Have you ever been diagnosed with or struggled with major learning disabilities? (e.g. major reading problems, dyslexia)

YES NO

[IF YES]: Which ones? _____

8. [FEMALE PARTICIPANTS] Are you currently pregnant and/or breastfeeding? Y / N
[IF YES]: EXCLUDE

9. [FEMALE PARTICIPANTS] Are you currently on any form of hormonal/chemical birth control? Y / N
[IF YES]: Which form? (i.e., pill, patch, IUD, ring, etc.) _____
How long have you been on this form of birth control? _____

---

2. FURTHER MEDICAL – STUDY COMPATIBILITY – NEUROIMAGING

1. Do you have any MAJOR issues with back pain?

YES NO

[IF YES]: Would this impede you from sitting up straight or lying still for prolonged periods of time?

YES NO

2. Have you ever had an EEG or have previously participated in an EEG study?

YES NO

[IF YES]: What for/when? _____

3. Have you ever had an MRI or participated in a MRI study?

YES NO

[IF YES]: What for/when? _____

4. Are you extremely uncomfortable in enclosed spaces?

YES NO

[**IF YES]** Would an MRI be problematic for you? (If unsure, ask "are you uncomfortable in elevators/do you specifically avoid enclosed spaces like elevators because they make you uncomfortable or anxious?")

_____

5. Do you have any metal in your body? (e.g. pacemakers, surgical/aneurysm clips, prosthetic valves, metal plates/screws, pins, cochlear implants, braces, etc.?)

YES NO

[IF YES]: What for/when? _____

6. Do you wear eyeglasses/contacts?

YES NO

Details: _____

[IF YES]: Inquire about whether they can wear their contact lenses to testing
[IF NO]: Inquire about glasses prescription (we have MR-compatible glasses) _____

---

3. MENTAL HEALTH SECTION

Should have no current/history of serious mental health issues

I am now going to ask you some questions about your mental health/psychiatric history.

1. Have you ever sought treatment or been treated for emotional or psychiatric problems?

YES NO

[IF YES]: What for? What kind(s) of treatment did you receive? _____

2. Have you ever been diagnosed with a mental health condition?

YES NO

[IF YES]: Which condition? When were you diagnosed?

_____

3. Have you ever taken medications of been treated for any mental health conditions?

YES NO

[IF YES]: Which medications? Are you currently taking them?

_____

[IF CURRENTLY TAKING THEM]: How long have you been taking this medication/obtaining the treatment?

_____

[IF NOT CURRENTLY TAKING THEM]: When did you stop taking this medication/treatment?

_____

MOOD EPISODES

Depressive

1. Has there been a period of time when you were feeling depressed or down most of the day nearly, every day?

YES NO

2. What about losing interest or pleasure in things you usually enjoy?

YES NO

(Skip the following if NO)

[IF YES]: How long did this period last? _____

[IF YES]: Just before this began, were you: Physically ill? Drinking alcohol or using street drugs? Did this begin soon after someone close to you died?

YES NO

Comments:_____

3. Have you ever been diagnosed with depression?

YES NO

[IF YES]: When were you diagnosed? Were you prescribed any medications or obtain any treatment for this diagnosis?

Comments:_____

Mania

1. Has there a period in your life when, for at least one week, you were so happy/excited/energized that other people thought you were not your normal self and/or this was highly abnormal for you?

YES NO

Details_____

…You were extremely irritable or angry for most of the time (for at least a week)? Did you fight or argue with people outside of your family?

YES NO

Details_____

[IF YES TO ABOVE] During this time:
Did you feel you had special talents or abilities?

YES NO

[IF YES] What kinds talents/abilities?_____
Became impulsive in a way that was highly unusual for you (e.g. spent a lot of money, had sexual indiscretions)?

YES NO

Needed significantly less sleep but did not feel tired?

YES NO

[IF YES TO ANY OF ABOVE] Are you currently experiencing any of these feelings?

YES NO

[IF YES] to any of above: INELIGIBLE (*please use discretion – ask about context*)

ANXIETY DISORDERS

Panic

1. Have you ever had a panic attack, when you suddenly felt frightened or suddenly developed a lot of physical symptoms?

YES NO

(Skip the following if NO)

[IF YES]: Have these attacks ever come on completely out of the blue – in situations where you don't expect to be nervous or uncomfortable?

YES NO

[IF YES]: Just before you began having panic attacks, were you: Taking any drugs, caffeine, diet pills, or any other medications? Physically ill?

YES NO

Agoraphobia

1. Were you ever afraid of going out of the house alone, being in crowds, standing in a line or traveling on buses or trains?

YES NO

(Skip the following if NO)

[IF YES]: What were you afraid would happen? _____
Does participant mention anxiety about being in places/situations from escape may be difficult or embarrassing or in which help may not be available in the event of panic-like symptoms?

YES NO

[IF YES]: Just before you began having these fears, were you: Taking any drugs, caffeine, diet pills, or any other medications? Physically ill?

YES NO

Social Phobia

1. Is there anything that you have been excessively afraid to do or felt uncomfortable doing in front of other people, like speaking, eating or writing?

YES NO

(Skip the following if NO)
[IF YES]: to "Public Speaking": Do you think that you are much more uncomfortable than most people who are in a similar situation?

YES NO

[IF YES]: What were you afraid would happen?

_____

Does participant mention that exposure to the feared social situation almost invariably provokes anxiety, which may take the form of a situationally bound or situationally predisposed panic-attack?

YES NO

[IF YES]: Just before you began having these fears, were you: Taking any drugs, caffeine, diet pills, or any other medications? Physically ill?

YES NO

Generalized Anxiety Disorder
1. In the last six months, have you been particularly nervous or anxious?

YES NO

(Skip the following if NO)
[IF YES]: What do you worry about? _____

2. During the past six months, would you say that you are worrying more often than not?

YES NO

3. When you are worrying, do you find it difficult to stop?

YES NO

4. When you're feeling anxious or nervous, do you feel:
___Restless ___Frequently tired ___Trouble concentrating/Mind goes blank ___Irritable ___Tense muscles ___Sleep disturbance

_____

5. Have you ever been diagnosed with any other mental health issues that we have not yet discussed?

YES NO

[IF YES]: What was your diagnosis? When were you diagnosed?

_____

6. Have you taken any medications for this disorder?

YES NO

[IF YES]: Which ones? Are you currently taking these medications? _____

---

4. DRUG AND ALCOHOL USE

I'm now going to ask you some questions about your substance use. Can you let me know whether you consume the following?

Coffee/tea/energy drinks: **YES NO** _____ times per day/week **(if more than 4 cups per day, be sure to stress abstinence criteria)**

Smoker: **YES** **NO** Since when?_____ Trying to quit? _____
Cigarettes per day/week_____

Do you use vaporizers or e-cigarettes?
IF YES: How long? _____
IF YES: How frequently throughout the day? _____
Are you able to go without for a 3 hour period? **YES** **NO**

Alcohol
Currently, how many drinks do you have per day/week? _____
What age did you start drinking? _____
What was your drinking pattern like at that time? _____
When were you using alcohol the most? How many times per week would you drink/how many drinks would you have each time? _____

Have you ever been treated for alcohol dependence/major alcohol problems? **YES** **NO**

[IF YES] How long ago? _____
(Exclude if they currently have a substance abuse problem or have within the past year.)

Drug and Medicine Use

Have you ever become dependent on a prescribed medication or taken a lot more than you were supposed to?
YES **NO**
[IF YES]: Details? _____

Have you ever used street drugs, including marijuana?
YES **NO**
[IF NO]: Skip the drug related section below

Guidelines for rating level of drug and medicine use:

Street Drug:
- When were you using (DRUG) the most?_____
- Has there been a time when you used it at least ten times in a one-month period of time?

(1) has ever taken street drug more than 10 times in a one-month period

Prescribed Medicine:
(2) reports becoming dependent on a prescribed drug OR using much more of it than was prescribed

- If drug group never used or used only once, or if prescribed drug used as directed → circle "1"
- If drug used at least twice, but less than level indicated on (1) → circle "2"
- If drug used at level indicated in item (1) or if possibly dependent on prescribed drug (item (2) is true) → circle "3"

Have you ever used any of the following?

Circle the name of each drug ever used (or write in name if other)	**Period of heaviest use (age or date, & duration) and describe pattern of use**	**Level of use**
Sedatives - hypnotics – anxiolytics: Quaalude, Seconal, Valium, Xanax, Librium, barbiturates, Miltown, Ativan, Dalmane, Halcion, Restoril, or other : _____		1 2 3
Cannabis: marijuana, hashish , THC, or other: _____		1 2 3
Stimulants: amphetamine, "speed", crystal meth, dexadrine, Ritalin, "ice", or other: _____		1 2 3
Opioids: heroin, morphine, opium, Methadone, Darvon, codein, Percodan, Demerol, Dilaudid, unspecified or other: _____		1 2 3
Cocaine: intranasal, IV, freebase, crack, "speedball", unspecified or other: _____		1 2 3
Hallucinogens/PCP: LSD, mescaline, peyote, psilocybin, STP, mushrooms, PCP ("angel dust"), Extasy, MDMA, or other: _____		1 2 3
Other: steroids, "glue", paint, inhalants, nitrous oxide ("laughing gas"), amyl or butyl nitrate ("popers"), nonprescription sleep or diet pills, unknown, or other: _____		1 2 3

***Family Interview for Genetic Studies (*FIGS): Adapted General Screening Questions**

We're almost done. I'm going to ask you a couple of questions regarding your family history, specifically your immediate family – these include your parents, and any siblings, offspring/children. I'd like you to keep these particular individuals in mind as we go through the questions:

Was anyone in your immediate family adopted?
NO YES:
_____

Does/did anyone in your family have a developmental disability?

NO YES:

_____

Did/does anyone have problems with their nerves or emotions? …to the extent that they take meds e.g. lithium or see a doctor ?
NO YES:

_____

Feel very low for a couple of weeks or more, or have a diagnosis of depression?
NO YES:

_____

Attempt or complete suicide?
NO YES:

_____

Seem over-excited (or manic) day and night, or have a diagnosis of mania?
NO YES:

_____

Have visions, hear voices, or have beliefs that seem strange or unreal?
NO YES:

_____

Have unusual or bizarre behavior, or have a diagnosis of schizophrenia?
NO YES:

_____

You will be required to **abstain from nicotine for 3 hours before your session and caffeine for 6 hours before your session (decaf coffee is fine).** Abstinence from alcohol and over-the-counter drugs (with the exception of prescribed medications) is also required from midnight the night before your visit until your session is complete. We also ask that you abstain from street drugs (including marijuana) from midnight the night before your visit until your session is complete. Do you think this would be a problem?

YES NO

[IF YES]: Ask them if they would like to be contacted for future studies and thank them for their time.

As mentioned, our testing occurs at the Royal Hospital on Carling (1145 Carling Ave) – do you know where it is? Do you foresee any difficulties in getting to/from the test sessions?

_____

Would you require any reimbursement for bus tickets or parking? (Tell them to bring receipts)

YES NO

Do you think you will have some scheduling conflicts that might prevent you from being tested at a particular time? (exams, going home, vacations, employment)

_____

If participant seems PERFECT for the study (i.e., no red flags):
Based on this preliminary screen, you seem like a great candidate for the study. Do you have any questions and are you still interested in participating?

[IF YES]: Great! I would like to tentatively schedule you to come in for your first session, although I must first review your file with my supervisor.
Is there a date/time that would work for you (preferably morning/early afternoon):
_____

Alright, I will email or call you to confirm an appointment date as soon as possible.
Thank you.

If participant DOES NOT seem perfect for the study/there are some concerns:

Based on this preliminary screen, you seem like you may qualify for study participation. However, I will need to review this interview with one of the researchers and we will contact you shortly about your participation. Is that alright?

Do you have any further questions?
NOTES:

APPENDIX III

The Royal / Le Royal
Mental Health - Care & Research
Santé mentale - Soins et recherche

1145 avenue Carling Avenue
Ottawa ON K1Z 7K4
theroyal.ca / leroyal.ca

Tel. / Tél. 613.722.6521
Toll free / Ligne sans frais 1.800.987.6424

RESEARCH ETHICS BOARD

September 6, 2017

Verner Knott, PhD
Principal Investigator

Re: The Neural, Behavioural and Cognitive Outcome of Transcranial Direct Current Stimulation (tDCS) for Persistent Auditory Verbal Hallucinations in Schizophrenia.

Dear Dr. Knott,

This letter is to acknowledge receipt of your letter (dated August 28, 2017) which included revised copies of the COREB Application Form (version 2, August 2017); Protocol (version 2, August 2017); 2017); Informed Consent Form – Patients (version 2, August 2017); Healthy Volunteers Informed Consent Form (version 2, August 2017); and, Checklist of Resources (version August, 2017) in response to points expressed to you in our letter (dated May 31, 2017) for the above-titled protocol.

The revised material and responses to our questions have been reviewed and **your protocol has now received approval for the period of one (1) year from the date of this letter.**

It should be noted that Dr. Knott, who was also a member of the Research Ethics Board, was not present during the discussion or approval process. This approval is contingent upon maintaining adherence to the normal approval process, namely,

- Reporting to the Board any adverse events of the project in progress,
- Seeking prior approval from the Board of any direct use of public media to recruit research participants

Approval will be reconsidered if Hospital/Institute resources are used beyond those specified on the Checklist of Resources and/or if Grant funding applied for is not received. However, in either case the protocol can be re-submitted with revised Checklist and funding information and will be reconsidered. A signed REB Attestation Form is included with this letter.

Annual progress reports must be submitted to the Board for continuation of Research Ethics approval. Failure to provide annual reports by the due date specified will result in suspension of participant recruitment and ongoing operation of the study. A *termination report* is required at the conclusion of the study.

Sincerely, on behalf of the Board,

Pierre Blier, MD PhD
Chair, Research Ethics Board

The | Le Royal
Mental Health - Care & Research
Santé mentale - Soins et recherche

1145 avenue Carling Avenue
Ottawa ON K1Z 7K4
theroyal.ca / leroyal.ca

Tel. / Tél. 613.722.6521
Toll free / Ligne sans frais 1.800.987.6424

RESEARCH ETHICS BOARD

November 1, 2017

Verner Knott, PhD
Principal Investigator

Re: REB# 2017034
The Neural, Behavioural and Cognitive Outcome of Transcranial Direct Current Stimulation (tDCS) for Persistent Verbal Hallucinations in Schizophrenia – Neuroimaging Arm

Dear Dr. Knott,

This letter is to acknowledge receipt of your letter (dated October 23, 2017) which included revised copies of the COREB Application Form (version 2: October 2017); Protocol (version 2: October 2017); and copies of two recruitment posters for healthy volunteers (version 1: October 2017) and the TCPS2 completion certificate for Dr. Ilivitsky, in response to points expressed to you in our previous letter (dated September 26, 2017) for the above-titled protocol.

The revised material and responses to our questions have been reviewed and **your protocol has now received approval for the period of one (1) year from the date of this letter.**

It should be noted that Dr. Natalia Jaworska, who is a co-investigator and also a member of the Research Ethics Board, was not present for discussion and approval of the protocol. This approval is contingent upon maintaining adherence to the normal approval process, namely,

- Reporting to the Board any adverse events of the project in progress
- Seeking prior approval from the Board of any direct use of public media to recruit research participants

Annual progress reports must be submitted to the Board for continuation of Research Ethics approval. Failure to provide annual reports by the due date specified will result in suspension of participant recruitment and ongoing operation of the study. A *termination report* is required at the conclusion of the study.

APPROVED
Nov. 1/17
Valid After
Oct. 31/18
Royal Ottawa Health Care Group REB

Sincerely, on behalf of the Board,

Pierre Blier, MD PhD
Chair, Research Ethics Board

APPENDIX IV

Université d'Ottawa
Bureau d'éthique et d'intégrité de la recherche

University of Ottawa
Office of Research Ethics and Integrity

H-01-19-2833 - OTH-2833 - Lettre d'approbation administrative / Letter of Administrative Approval

(English message follows)

Cher/Chère Natalia Jaworska,

Veuillez trouver la lettre d'approbation administrative pour le projet intitulé «The Neural, Behavioural, and Cognitive Outcomes of Transcranial Direct Current Stimulation (tDCS) for Persistent Verbal Hallucinations in Schizophrenia ».

L'approbation est valide jusqu'au 29-10-2019 (correspond à la date du CÉR primaire). Afin de garder votre dossier à jour, veuillez nous soumettre une copie de toutes demandes de modification, certificats de renouvellement, et/ou autres documents pertinents soumis à et approuvés par le CÉR primaire, dès qu'ils sont disponibles.

For your information, there is a typo in the Neuroimaging consent form for healthy volunteers (last paragraph of 1st page)

"conducting bring imaging scans"

Recherche financée : Veuillez faire suivre une copie de cette lettre au Service de gestion de la recherche.

Si vous avez des questions, n'hésitez pas à communiquer avec le Bureau d'éthique à ethique@uottawa.ca ou en composant le 613-562-5387.

Vous pouvez voir votre demande en vous connectant à votre compte eReviews.

Cordialement,

Catherine Paquet
Directeur

Ceci est une réponse automatisée, merci de ne pas répondre à ce courriel.

Dear Natalia Jaworska,

Please find attached the letter of administrative approval for your research project titled "The Neural, Behavioural, and Cognitive Outcomes of Transcranial Direct Current Stimulation (tDCS) for Persistent Verbal Hallucinations in Schizophrenia ".

This approval is valid until 29-10-2019 (corresponds to the date of the Primary REB). In order to keep your file up to date, please submit a copy of all modification requests, project renewals, and/or other relevant documents submitted to and approved by the Primary REB, as they become available.

For your information, there is a typo in the Neuroimaging consent form for healthy volunteers (last paragraph of 1st page)

"conducting bring imaging scans"

Funded research: A reminder that you must provide a copy of this letter to Research Management Services.

If you have any questions, please contact the Ethics Office at ethics@uottawa.ca or by telephone at 613-562-5387.

You can view your project at any time by logging into eReviews.

550, rue Cumberland, pièce 154
Ottawa (Ontario) K1N 6N5 Canada

550 Cumberland Street, Room 154
Ottawa, Ontario K1N 6N5 Canada

613-562-5387 · 613-562-5338 · ethique@uOttawa.ca / ethics@uOttawa.ca
www.recherche.uottawa.ca/deontologie I www.recherche.uottawa.ca/ethics

APPENDIX V

Psychiatrist Information Sheet & Clinical Assessment

The Effects of Transcranial Direct Current Stimulation (tDCS) on Hallucinations in Schizophrenia (Short Title: REB #2017034)

Study Summary:

This study will examine the effects of a 5-day (2X/day) course of transcranial direct current stimulation (tDCS) in patients with schizophrenia on clinical features, cognition & brain activity (EEG and optional neuroimaging). These assessments will be carried out before & after tDCS. There will be 2 tDCS conditions: sham/fake tDCS & tDCS that inhibits the auditory cortex and up-regulates frontal cortex activity (20min/session). Patients will be randomly allocated into the sham or active tDCS conditions. The main outcome measure is whether active tDCS can modify auditory hallucinations. Fifty-six (N=28 per tDCS group) adult patients with schizophrenia will be recruited. Healthy controls (N=28) will also be tested once (they will not undergo tDCS).

Inclusion Criteria of Schizophrenia Patients:

- 18-69 years
- Primary diagnosis of schizophrenia or schizoaffective disorder
- Clinically stable to the extent that treating physician feels the patient is able to complete the study → **not** overly agitated/aggressive, actively suicidal or acutely psychotic.
- History of auditory verbal hallucinations (AVHs) over the course of illness >3 AVHs/week
- Positive & Negative Syndrome Scale (PANSS) score of >3 (mild or greater hallucinatory experiences [specifically AVHs]) on “hallucinatory behaviour” symptom (positive scale)
- Primary medication is limited to an atypical antipsychotic (though they are allowed multiple adjunct medications)
- Daily benzodiazepine use is acceptable so long as the participant can hold their morning dose (i.e. to be taken after daily tDCS, in the afternoon)
- No termination or initiation of primary medication (i.e., atypical antipsychotic) in the 4 weeks prior to screening/enrollment

Exclusion Criteria:

- Acute psychotic episode
- Currently taking anticonvulsant medication (due to potential to limit tDCS efficacy)
- Current problems with drug/alcohol dependence (marijuana acceptable)
- Significant medical illness, including major neurological issues (e.g. stroke/epilepsy)
- Severe extra-pyramidal symptoms resulting in highly disordered movements
- Severe hearing impairment
- Actively suicidal

- Mental retardation/major cognitive impairment & reading problems

Script for tentatively suitable participants, who may be interested: *There is a study at the Royal that you may be eligible for, and interested in. This study will examine a potential treatment for auditory hallucinations. This treatment is a non-invasive form of brain stimulation, which delivers a weak current using small electrodes placed on the scalp. This is NOT electroconvulsive therapy. It is non-painful and lasts 20 minutes. You would undergo this treatment 2X per day from Monday to Friday. Brain activity would be measured before and after treatment. You would also have to fill out questionnaires and do some computer tasks. You would be compensated for your time. Would you be interested in having a researcher contact you and tell you more about the study?* **[IF YES], please have participant sign the consent to be contacted form & fill out clinician summary (attached)**

University of Ottawa Institute of Mental Health Research

Services de santé RoyalOttawa Health Care Group

Permission to Be Contacted For Research

The Royals' Institute of Mental Health Research (IMHR) is committed to building a future where we can identify and successfully treat mental illness.

We are asking you for your permission to allow approved research staff to contact you to see if you are interested in participating in a research study being conducted at the IMHR.

Even if you provide permission to be contacted now, you may withdraw your permission at any time. If you prefer not to be contacted for research, your care and treatment will not be affected in any way.

Any personal health information you may give us is protected under the Personal Health Information Protection Act, 2004 (Ontario).

I give my permission to be contacted by research staff from:

The Clinical EEG & Neuroimaging Research Laboratory

Name: _____ Phone #:

E-mail: _____ Date:

Signature: _____

Person seeking permission to: _____
contact subject for research

Signature: _____ Date: _____

The Effects of Transcranial Direct Current Stimulation (tDCS) on Hallucinations in Schizophrenia (Short Title: REB #2017034)

Clinician Study Checklist:

- ☐ 18 – 65 years
- ☐ Primary diagnosis of schizophrenia or schizoaffective disorder
- ☐ Clinically stable (i.e., can participate in study)
- ☐ Currently reporting at least 3 AVHs per week

Date Rated: _____ (m/d/y) Time Rated: _____ (24 hr clock) Rater's Initials:___/___/___

POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS)

Directions: Check (√) the term for each symptom which best describes the patient's condition over the past 72 hours and not relative to any other time.

POSITIVE SCALE

	Symptom	Description						
		Absent	Very Mild	Mild	Moderate	Mod. Severe	Severe	Extreme
1	Delusions	1☐	2☐	3☐	4☐	5☐	6☐	7☐
2	Conceptual Disorganization	1☐	2☐	3☐	4☐	5☐	6☐	7☐
3	Hallucinatory Behaviour	1☐	2☐	3☐	4☐	5☐	6☐	7☐
4	Excitement	1☐	2☐	3☐	4☐	5☐	6☐	7☐
5	Grandiosity	1☐	2☐	3☐	4☐	5☐	6☐	7☐
6	Suspiciousness/ Persecution	1☐	2☐	3☐	4☐	5☐	6☐	7☐
7	Hostility	1☐	2☐	3☐	4☐	5☐	6☐	7☐

NEGATIVE SCALE

	Symptom	Description						
		Absent	Very Mild	Mild	Moderate	Mod. Severe	Severe	Extreme
1	Blunted Affect	1☐	2☐	3☐	4☐	5☐	6☐	7☐
2	Emotional Withdrawal	1☐	2☐	3☐	4☐	5☐	6☐	7☐
3	Poor Rapport	1☐	2☐	3☐	4☐	5☐	6☐	7☐
4	Passive/ apathetic social withdrawal	1☐	2☐	3☐	4☐	5☐	6☐	7☐
5	Difficulty in abstract thinking	1☐	2☐	3☐	4☐	5☐	6☐	7☐
6	Lack of spontaneity and flow of conversation	1☐	2☐	3☐	4☐	5☐	6☐	7☐
7	Stereotyped Thinking	1☐	2☐	3☐	4☐	5☐	6☐	7☐

- ☐ Exhibit a Positive and Negative Syndrome Scale (PANSS) score of >3 on item 3 *(PLEASE ADMINISTER **ENTIRE** PANSS)*

POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS) – Continued*
GENERAL PSYCHOPATHOLOGY SCALE

	Symptom	Description						
		Absent	Very Mild	Mild	Moderate	Mod. Severe	Severe	Extreme
1	Somatic Concern	1☐	2☐	3☐	4☐	5☐	6☐	7☐
2	Anxiety	1☐	2☐	3☐	4☐	5☐	6☐	7☐
3	Guilt Feelings	1☐	2☐	3☐	4☐	5☐	6☐	7☐
4	Tension	1☐	2☐	3☐	4☐	5☐	6☐	7☐
5	Mannerisms and Posturing	1☐	2☐	3☐	4☐	5☐	6☐	7☐
6	Depression	1☐	2☐	3☐	4☐	5☐	6☐	7☐
7	Motor Retardation	1☐	2☐	3☐	4☐	5☐	6☐	7☐
8	Uncooperativeness	1☐	2☐	3☐	4☐	5☐	6☐	7☐
9	Unusual Thought Content	1☐	2☐	3☐	4☐	5☐	6☐	7☐
10	Disorientation	1☐	2☐	3☐	4☐	5☐	6☐	7☐
11	Poor Attention	1☐	2☐	3☐	4☐	5☐	6☐	7☐
12	Lack of Judgement and Insight	1☐	2☐	3☐	4☐	5☐	6☐	7☐
13	Disturbance of Volition	1☐	2☐	3☐	4☐	5☐	6☐	7☐
14	Poor Impulse Control	1☐	2☐	3☐	4☐	5☐	6☐	7☐
15	Preoccupation	1☐	2☐	3☐	4☐	5☐	6☐	7☐
16	Active Social Avoidance	1☐	2☐	3☐	4☐	5☐	6☐	7☐

*Refer to symptom definitions in the Rating Scales Procedures Manual.

☐ No acute psychotic episode

☐ Primary medication is an atypical antipsychotic. List CURRENT medications:

_____

☐ No current major problems with drug/alcohol dependence (marijuana acceptable)

☐ No severe extra-pyramidal symptoms resulting in highly disordered movements or severe medical illness

☐ No history of seizure, epilepsy or stroke (significant neurological issues)

☐ No major cognitive impairments/mental retardation & no major reading issues

APPENDIX VI

Date_____ ID#_____

Handedness Inventory

Please indicate your preferences in the use of hands in the following activities by putting + in the appropriate column. Where the preference is so strong that you would never try to use the other hand unless absolutely forced to, put ++. If any case you are really indifferent put + in both columns.

Some of the activities require both hands. In these cases the part of the task or object for which hand preference is wanted is indicated in brackets.

Please try to answer all the questions and only leave a blank if you have no experience at all of the object or task.

Task	Left	Right
Writing		
Drawing		
Throwing		
Scissors		
Toothbrush		
Knife (without fork)		
Spoon		
Broom (upper hand)		
Striking match (match)		
Opening box (lid)		
Which foot do you prefer to kick with?		
Which eye do you use when using only one? (E.g. taking picture with a camera.)		

L.Q. _____ (Leave this space blank)

APPENDIX VII

North American Adult Reading Test (NAART)

Subject ID:_____ Date:_____

I want you to read slowly down this list of words starting here [Indicate DEBT].
I must warn you that there are many words that you probably won't recognise, in fact most people don't know them, so just have a guess at these, O.K.? Go ahead.

____DEBT
____DEBRIS
____AISLE
____REIGN
____DEPOT
____SIMILE
____LINGERIE
____RECIPE
____GOUGE
____HEIR
____SUBTLE
____CATACOMB
____BOUQUET
____GAUGE
____COLONEL

____CELLIST
____INDICT
____DENTE
____IMPUGN
____CAPON
____RADIX
____AEON
____EPITOME
____EQUIVOCAL
____REIFY
____INDICES
____ASSIGNATE
____TOPIARY
____CAVEAT
____SUPERFLUOUS

____SUBPOENA
____PLACEBO
____PROCREATE
____PSALM
____BANAL
____RAREFY
____GIST
____CORPS
____HORS D'OEUVRE
____SIEVE
____HIATUS
____GAUCHE
____ZEALOT
____PARADIGM

____FACADE
____LEVIATHAN
____PRELATE
____QUADRUPED
____SIDEREAL
____ABSTEMIOUS
____BEATIFY
____GAOLED
____DEMESNE
____SYNCOPE
____ENNUI
____DRACHM
____CIDEVANT
____EPERGNE
____VIVACE
____TALIPES
____SYNECDOCHE

VLQ = 128.7 - .89(errors) =_____
PIQ = 119.4 - .42(errors) =_____
FSIQ = 127.8 - .78(errors) =_____

APPENDIX VIII

Roche

V 0477

Beck Depression Inventory

CRTN: _____ CRF number: _____

Page 14

Baseline

patient inits: _____

BDI-II

Date:

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness

0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2. Pessimism

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3. Past Failure

0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4. Loss of Pleasure

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6. Punishment Feelings

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7. Self-Dislike

0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self-Criticalness

0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying

0 I don't cry anymore than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

THE PSYCHOLOGICAL CORPORATION®
Harcourt Brace & Company
SAN ANTONIO
Orlando • Boston • New York • Chicago • San Francisco • Atlanta • Dallas
San Diego • Philadelphia • Austin • Fort Worth • Toronto • London • Sydney

_____ Subtotal Page 1

Continued on Back

0154018392
NR15645

11. Agitation

0 I am no more restless or wound up than usual.

1 I feel more restless or wound up than usual.

2 I am so restless or agitated that it's hard to stay still.

3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.

1 I am less interested in other people or things than before.

2 I have lost most of my interest in other people or things.

3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.

1 I find it more difficult to make decisions than usual.

2 I have much greater difficulty in making decisions than I used to.

3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.

1 I don't consider myself as worthwhile and useful as I used to.

2 I feel more worthless as compared to other people.

3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.

1 I have less energy than I used to have.

2 I don't have enough energy to do very much.

3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.

1a I sleep somewhat more than usual.

1b I sleep somewhat less than usual.

2a I sleep a lot more than usual.

2b I sleep a lot less than usual.

3a I sleep most of the day.

3b I wake up 1–2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.

1 I am more irritable than usual.

2 I am much more irritable than usual.

3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.

1a My appetite is somewhat less than usual.

1b My appetite is somewhat greater than usual.

2a My appetite is much less than before.

2b My appetite is much greater than usual.

3a I have no appetite at all.

3b I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.

1 I can't concentrate as well as usual.

2 It's hard to keep my mind on anything for very long.

3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.

1 I get more tired or fatigued more easily than usual.

2 I am too tired or fatigued to do a lot of the things I used to do.

3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.

1 I am less interested in sex than I used to be.

2 I am much less interested in sex now.

3 I have lost interest in sex completely.

3 4 5 6 7 8 9 10 11 12 A B C D E

_____ Subtotal Page 2

_____ Subtotal Page 1

_____ Total Score

APPENDIX IX

Beck Anxiety Inventory (BAI)

Below is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by that symptom during the past month, including today, by circling the number in the corresponding space in the column next to each symptom.

	Not At All	Mildly but it didn't bother me much	Moderately - it wasn't pleasant at times	Severely – it bothered me a lot
Numbness or tingling	☐	☐	☐	☐
Feeling hot	☐	☐	☐	☐
Wobbliness in legs	☐	☐	☐	☐
Unable to relax	☐	☐	☐	☐
Fear of worst happening	☐	☐	☐	☐
Dizzy or lightheaded	☐	☐	☐	☐
Heart pounding/racing	☐	☐	☐	☐
Unsteady	☐	☐	☐	☐
Terrified or afraid	☐	☐	☐	☐
Nervous	☐	☐	☐	☐
Feeling of choking	☐	☐	☐	☐
Hands trembling	☐	☐	☐	☐
Shaky / unsteady	☐	☐	☐	☐
Fear of losing control	☐	☐	☐	☐
Difficulty in breathing	☐	☐	☐	☐
Fear of dying	☐	☐	☐	☐
Scared	☐	☐	☐	☐
Indigestion	☐	☐	☐	☐
Faint / lightheaded	☐	☐	☐	☐
Face flushed	☐	☐	☐	☐
Hot/cold sweats	☐	☐	☐	☐

APPENDIX X

Name:_____ Date:_____

Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF)

Taking everything into consideration, during the past week how satisfied have you been with your.....

	Very Poor	Poor	Fair	Good	Very Good
.....physical health?	1	2	3	4	5
.....mood?	1	2	3	4	5
.....work?	1	2	3	4	5
.....household activities?	1	2	3	4	5
.....social relationships?	1	2	3	4	5
.....family relationships?	1	2	3	4	5
.....leisure time activities?	1	2	3	4	5
.....ability to function in daily life?	1	2	3	4	5
.....sexual drive, interest and/or performance?*	1	2	3	4	5
.....economic status?	1	2	3	4	5
.....living/housing situation?*	1	2	3	4	5
.....ability to get around physically without feeling dizzy or unsteady or falling?*	1	2	3	4	5
.....your vision in terms of ability to do work or hobbies?*	1	2	3	4	5
.....overall sense of well being?	1	2	3	4	5
.....medication? (If not taking any, check here _____ and leave item blank.)	1	2	3	4	5
.....How would you rate your overall life satisfaction and contentment during the past week?	1	2	3	4	5

*If satisfaction is very poor, poor or fair on these items, please UNDERLINE the factor(s) associated with a lack of satisfaction.

APPENDIX XI

BAVQ - R

CHADWICK, PAUL, LEES, SUSAN, BIRCHWOOD, MAX

The revised Beliefs About Voices Questionnaire (BAVQ-R)

(from The British Journal of Psychiatry 2000 177: 229-232)

There are many people who hear voices. It would help us to find out how you are feeling about your voices by completing this questionnaire. Please read each statement and tick the box which best describes the way you have been feeling in the *past week*.

If you hear more than one voice, please complete the form for the voice which is dominant.

Thank you for your help.

Name: .....

Age: .....

		Disagree	Unsure	Slightly Agree	Strongly Agree
1	My voice is punishing me for something I have done				
2	My voice wants to help me				
3	My voice is very powerful				
4	My voice is persecuting me for no good reason				
5	My voice wants to protect me				
6	My voice seems to know everything about me				
7	My voice is evil				
8	My voice is helping to keep me sane				
9	My voice makes me do things I really don't want to do				
10	My voice wants to harm me				
11	My voice is helping me to develop my special powers or abilities				
12	I cannot control my voices				
13	My voice wants me to do bad things				
14	My voice is helping me to achieve my goal in life				

15	My voice will harm or kill me if I disobey or resist it				
		Disagree	Unsure	Slightly Agree	Strongly Agree
16	My voice is trying to corrupt or destroy me				
17	I am grateful for my voice				
18	My voice rules my life				
19	My voice reassures me				
20	My voice frightens me				
21	My voice makes me happy				
22	My voice makes me feel down				
23	My voice makes me feel angry				
24	My voice makes me feel calm				
25	My voice makes me feel anxious				
26	My voice makes me feel confident				

When I hear my voice, usually ...

		Disagree	Unsure	Slightly Agree	Strongly Agree
27	I tell it to leave me alone				
28	I try and take my mind off it				
29	I try and stop it				
30	I do things to prevent it talking				
31	I am reluctant to obey it				
32	I listen to it because I want to				
33	I willingly follow what my voice tells me to do				
34	I have done things to start to get in contact with my voice				
35	I seek the advice of my voice				

APPENDIX XII

Voice Power Differential Scale

(Birchwood et al., 2000)

Client's name:.....
Date assessed:.....

Please circle the number which best describes how you feel in relation to your voice.
Name or description of voice:.....

1	2	3	4	5
I am much more Powerful than my voice	I am more powerful than my voice	We have about the same amount of power as each Other	My voice is more powerful than me	My voice is much more powerful than me
1	2	3	4	5
I am much stronger than My voice	I am stronger than my voice	We are as strong as each other	My voice is stronger than me	My voice is much stronger than me
1	2	3	4	5
I am much more Confident than My voice	I am more confident than my voice	We are as confident as each other	My voice is more confident than me	My voice is much more confident than me
1	2	3	4	5
I respect my voice much More than it respects me	I respect my voice more than it respects me	We respect each other about the same	My voice respects me more than I respect it	My voice respects me much more than I respect it
1	2	3	4	5
I am much more able to Harm my voice than it is Able to harm me	I am able to harm my voice than it is able to harm me	We are equally able to harm each other	My voice is more able to harm me than I am able to harm it	My voice is much more able to harm me than I can harm it
1	2	3	4	5
I am greatly superior to My voice	I am superior to my voice	We are equal to each other	My voice is superior to me	My voice is greatly superior to me
1	2	3	4	5
I am much more Knowledgeable than My voice	I am more knowledgeable than my voice	We have about the same amount of knowledge as Each other	My voice is more knowledgeable than me	My voice is much more knowledgeable than me

APPENDIX XIII

ID: _____ **SZ_tDCS Study Session: _____**

Voices Acceptance and Action Scale

Please read the following sentences and rate how they apply to you on a scale of 1 (strongly disagree to 5 (strongly agree).

Question	Strongly disagree	Disagree	Unsure/ neutral	Agree	Strongly Agree
Section A					
I accept the fact that I hear voices	1	2	3	4	5
There are worse things in life than hearing voices	1	2	3	4	5
There is no point getting on with my life while I hear voices	1	2	3	4	5
My voices are just one part of my life	1	2	3	4	5
I can't have a good life while I hear voices	1	2	3	4	5
Hearing voices has taken over my life	1	2	3	4	5
I have learned to live with my voices	1	2	3	4	5
I struggle with my voices	1	2	3	4	5
There is more to me than just my voices	1	2	3	4	5
Action					
When I disagree with a voice, I simply notice it and move on	1	2	3	4	5
My voices stop me doing the things that I want to do	1	2	3	4	5
When my voices say things, I accept what is helpful and reject what is not	1	2	3	4	5
Section B1 (all action)					
I decide what I do, not my voices	1	2	3	4	5
Hearing a command from a voice can cause me to do what it says	1	2	3	4	5
I have to do what my voices say, even if I don't agree with it	1	2	3	4	5
Just because a voice tells me to do something, it doesn't mean I have to do it	1	2	3	4	5
My voices should take the blame when I obey them, not me	1	2	3	4	5
Hearing my voices tell me to do something is as bad as doing it	1	2	3	4	5
My voices are not responsible for my actions, I am	1	2	3	4	5
It is not what my voices say, but what I do, that matters	1	2	3	4	5

Question	Strongly disagree	Disagree	Unsure/ neutral	Agree	Strongly Agree
Section B2					
When I hear a voice telling me to do something that could result in problems or cause trouble, usually ...					
Acceptance					
I feel overwhelmed by it	1	2	3	4	5
I notice it, but I don't react to it	1	2	3	4	5
I just accept that the voice is speaking	1	2	3	4	5
I try hard to avoid feeling upset	1	2	3	4	5
I put up with it	1	2	3	4	5
I argue with the voice	1	2	3	4	5
I think what the voice says doesn't matter	1	2	3	4	5
Action					
I have to stop what I'm doing and focus on the voice	1	2	3	4	5
I worry about what I might do	1	2	3	4	5
I listen to the voice but make my own decisions	1	2	3	4	5
I keep focused on what I want to do	1	2	3	4	5

APPENDIX XIV

Name: _____ Date: _____

PSYRATS

Psychotic Symptom Rating Scales

AUDITORY HALLUCINATIONS

Haddock, G., McCarron, J., Tarrier, N., & Faragher, E. B. (1999). Scales to measure dimensions of hallucinations and delusions: the psychotic symptom rating scales (PSYRATS). *Psychological medicine*, *29*(04), 879-889.

GENERAL INSTRUCTIONS

The following structured interview is designed to elicit specific details regarding different dimensions of auditory hallucinations. When asking questions, the interview is designed to rate the patient's experiences over the last week for the majority of items. There are two exceptions to this e.g. when asking about beliefs regarding cause of voices, rate the patient's response based on what they believe at the time of the interview. Also loudness of voices should be rated according to the loudness of voices at the time of interview or the last time the patient experienced them.

Name: .....

Age: .....

Sex: M / F

Diagnosis (if relevant): .....

Length of time experiencing voices (years): .....

Hallucinations in other modalities: visual / olfactory / gustatory / tactile

AUDITORY HALLUCINATIONS: SCORING CRITERIA

1. FREQUENCY

How often do you experience voices? e.g. every day, all day long etc.

0. Voices not present or present less than once a week (specify frequency if present)
1. Voices occur for at least once a week
2. Voices occur at least once a day
3. Voices occur at least once an hour
4. Voices occur continuously or almost continuously i.e., stop for only a few seconds or minutes

2. DURATION

When you hear your voices, how long do they last, e.g. for a few seconds, minutes, hours, all day long?

0. Voices not present
1. Voices last for a few seconds, fleeting voices
2. Voices last for several minutes
3. Voices last for at least one hour
4. Voices last for hours at a time

3. LOCATION

When you hear your voices, where do they sound like they're coming from?
-inside your head and/or outside your head?
-if voices sound like they are outside your head, whereabouts do they sound like they are coming from?

0. No voices present

1. Voices sound like they are inside head only

2. Voices outside the head, but close to ears or head. Voices inside the head may also be present.

3 Voices sound like they are inside or close to ears and outside head away from ears

4. Voices sound like they are from outside the head only

4. LOUDNESS

How loud are your voices?
Are they louder than your voice, about the same loudness, quieter or just a whisper?

0. Voices not present

1. Quieter than own voice, whispers.

2. About same loudness as own voice

3 Louder than own voice

4. Extremely loud, shouting

5. BELIEFS RE-ORIGIN OF VOICES

What do you think has caused your voices?
-Are the voices caused by factors related to yourself or solely due to other peoples or factors?
If patient expresses an external origin:
- How much do you believe that your voices are caused by ..... (add patient's contribution) on a scale from 0-100 with 100 being that you are totally convinced, have no doubts and 0 being that it is completely untrue?

0. Voices not present

1. Believes voices to be solely internally generated and related to self

2. Holds a less than 50% conviction that voices originate from external causes

3 Holds 50% or more conviction (but less than 100%) that voices originate from external causes

4. Believes voices are solely due to external causes (100% conviction)

6. AMOUNT OF NEGATIVE CONTENT OF VOICES

Do your voices say unpleasant things or negative things?
- Can you give me some examples of what the voices say? (record these examples)
- How much of the time do the voices say these types of unpleasant or negative items?

0. No unpleasant content

1. Occasional unpleasant content

2. Minority of voice content is unpleasant or negative (less than 50%)

3 Majority of voice content is unpleasant or negative (50% or more)

4. All of voice content is unpleasant or negative

7. DEGREE OF NEGATIVE CONTENT

(Rate using criteria on scale, asking patient for more detail if necessary)

0. Not unpleasant or negative

1. Some degree of negative content, but not personal comments relating to self or family e.g. swear words or comments not directed to self, e.g. "the milkman's ugly"

2. Personal verbal abuse, comments on behaviour e.g. "shouldn't do that or say that"

3 Personal verbal abuse relating to self-concept e.g. "you're lazy, ugly, mad, perverted"

4. Personal threats to self e.g. threats to harm self or family, extreme instructions or commands to harm self or others and personal verbal abuse as in (3)

8. AMOUNT OF DISTRESS

Are your voices distressing?
- How much of the time?

0. Voices not distressing at all
1. Voices occasionally distressing, majority not distressing (<10%)
2. Minority of voices distressing (<50%)
3 Majority of voices distressing, minority not distressing (≥ 50%)
4. Voices always distressing

9. INTENSITY OF DISTRESS

When voices are distressing, how distressing are they?
-Do they cause you minimal, moderate, severe distress?
-Are they the most distressing they have ever been?

0. Voices not distressing at all
1. Voices slightly distressing
2. Voices are distressing to a moderate degree
3 Voices are very distressing, although subject could feel worse
4. Voices are extremely distressing, feel the worst he/she could possibly feel

10. DISRUPTION TO LIFE CAUSED BY VOICES

How much disruption do the voices cause to your life?
-Do the voices stop you from working or other daytime activity?
-Do they interfere with your relationships with friends and/or family?
- Do they prevent you from looking after yourself, e.g. bathing, changing clothes, etc?

0. No disruption to life, able to maintain social and family relationships (if present)

1. Voices cause minimal amount of disruption to life e.g. interferes with concentration although able to maintain daytime activity and social and family relationships and be able to maintain independent living without support.

2. Voices cause moderate amount of disruption to life causing some disturbance to daytime activity and/or family or social activities. The patient is not in hospital although may live in supported accommodation or receive additional help with daily living skills.

3 Voices cause severe disruption to life so that hospitalisation is usually necessary. The patient is able to maintain some daily activities, self-care and relationships whilst in hospital. The patient may also be in supported accommodation but experiencing severe disruption of life in terms of activities, daily living skills and/or relationships.

4. Voices cause complete disruption of daily life requiring hospitalisation. The patient is unable to maintain any daily activities and social relationships. Self-care is also severely disrupted.

11. CONTROLLABILITY OF VOICES

-Do you think you have any control over when your voices happen?
-Can you dismiss or bring on your voices?

0. Subject believes they can have control over the voices and can always bring on or dismiss them at will

1. Subject believes they can have some control over the voices on the majority of occasions

2. Subject believes they can have some control over their voices approximately half of the time

3 Subject believes they can have some control over their voices but only occasionally. The majority of the time the subject experiences voices which are uncontrollable

4. Subject has no control over when the voices occur and cannot dismiss or bring them on at all.

APPENDIX XV

Assessment of Visual Hallucinations (PSYRATS-V)

Adapted from: https://www.dualdiagnosis.ie/wp-content/uploads/2011/05/Health-board-assessment-tool-portfolio-10.02.20091.pdf

ID: _____ Date: _____

Initial assessment (to determine if the patient experiences **true visual hallucinations**)

Have you ever seen things that other people cannot see? **Yes** **No**
Details:_____
_____
_____

Formless visual hallucinations: Have you seen shadows or flashes of light? **Yes** **No**
Details:_____
_____
_____

True or pseudo visual hallucinations: True visual hallucinations have all or most of the qualities of a real object. They appear solid, three dimensional, coloured, and may move around in space. Pseudo visual hallucinations do not appear convincingly real and lack most of the qualities of a real object. They may appear translucent, flat and colourless.

Did you see these things with your eyes, or in your mind? _____
How real did they look? _____
Were they solid or could you see through them? _____
Were they three dimensional or flat, like a photograph? _____
Were they coloured or black & white? _____
How long did the image last for? _____
Were you half asleep at the time, or has it occurred when you were fully awake?
_____
Did the image seem to arise out of a pattern on wallpaper or shadows in the room?
_____

How do you explain the images?
_____
_____
_____

Patient appears to experience _____ visual hallucinations (true or pseudo)

- If they experience true visual hallucinations, continue with the PSYRATS-V

PSYRATS-V

Adapted from: Haddock G, McCarron J, Tarrier M, Faragher E (1999). Scales to measure dimensions of hallucinations and delusions: The psychiatric symptom rating scales (PSYRATS). Psychol Med 29, 879-888.

1. When did you first start experiencing your visions? _____

2. <u>Frequency:</u> How often do you experience your visions? (e.g., every day, all day long, etc.)
0 – Visions not present or present less than once a week.
1 – Visions occur for at least once a week.
2 – Visions occur at least once a day.
3 – Visions occur at least once an hour.
4 – Visions occur continuously or almost continuously (i.e., stop for only a few seconds or minutes).

3. <u>Duration:</u> When you have these visions, how long do they last? (e.g., few secs, mins, hrs, all day)
0 – Visions not present.
1 – Visions last for a few seconds, flashing images.
2 – Visions last for several minutes.
3 – Visions last for at least one hour.
4 – Visions last for hours at a time.

3. <u>Location:</u> When you have these visions, where do you see them?
0 – Visions not present.
1 – Visions perceived as coming from within the person only and are not anchored in external space (i.e. the mind).
2 – Visions perceived as coming from within the person (i.e. the mind), may be anchored in external space but in close proximity to the individual.
3 – Visions are perceived through the eyes of the individual (external), may be anchored in external space but in close proximity to the individual.
4 – Visions are perceived through the eyes of the individual (external) and are anchored in external space, just beyond the reach of the individual (or further away).

4. <u>Detail:</u> When you have these visions, how much detail is present?
0 – Visions not present.
1 – Visions are mainly limited to brief flashes of light or images, not much detail present.
2 – Visions are usually indiscrete objects, shapes or outlines of faces/people (not lifelike or three-dimensional, may or may not be coloured, lacks movement, may be translucent)
3 – Visions are present with moderate detail, may be a solid outline of a face/animal/object, may or may not be three-dimensional, may lack some qualities of a real object (i.e. movement, colour, size, etc.)
4 – Visions are clear, lifelike, three-dimensional images of scenes, objects, people, faces, animals, etc., may or may not include movement and/or changes in shape, colour, size, etc.

5. <u>Beliefs on origin of visions:</u> What do you believe has caused you to experience these visions?
0 – Visions not present
1 – Believes visions to be solely internally generated and related to self
2 – Holds <50% conviction that visions originate from external causes
3 – Holds >50% (but <100%) conviction that visions originate from external causes
4 – Believes visions are solely due to external causes

6. <u>Amount of negative content of visions:</u> Do your visions ever do or act out/portray any unpleasant/negative things or scenes?
0 – No unpleasant content
1 – Occasional unpleasant content (<10%)
2 – Minority of vision content is unpleasant or negative (<50%)
3 – Majority of vision content is unpleasant or negative (>50%)
4 – All of the vision content is unpleasant or negative
Details:
_____
_____

7. <u>Amount of distress:</u> Are your visions distressing? How much of the time do you find them distressing?
0 – Visions not distressing at all
1 – Visions occasionally distressing, majority not distressing (<10%)
2 – Minority of visions distressing (<50%)
3 – Majority of visions distressing, minority not distressing (>50%)
4 – Visions always distressing

8. <u>Intensity of distress:</u> When your visions are distressing, how distressing are they? Do you they cause you minimal, moderate or severe distress? Are they the most distressing they have ever been?
0 – Visions not distressing at all
1 – Visions slightly distressing
2 – Visions are distressing to a moderate degree
3 – Visions are very distressing, although subject could feel worse
4 – Visions are extremely distressing; subject feels the worst he/she could possibly feel

9. <u>Disruption to life caused by visions:</u> How much disruption do your visions cause to your life? Do the visions stop you from working or other daily activities? Do they interfere with your relationships with friends or family? Do they prevent you from looking after yourself (i.e. bathing, changing clothes, etc.)?
0 – No disruption to life, able to maintain social/family relationships (if present)
1 – Visions cause minimal amount of disruption to life
2 – Visions cause moderate amount of disruption to life causing some disturbance to daytime activity and/or family and social activities.
3 – Visions cause severe disruption to life so that hospitalization is usually necessary.
4 – Visions cause complete disruption of daily life requiring hospitalization.

10. <u>Controllability of visions:</u> Do you think that you have any control over when your visions happen? Can you dismiss or bring on your visions?
0 – Subject believes they can have control over visions and can always bring on or dismiss visions at will.
1 – Subject believes they can have some control over the visions on the majority of occasions
2 – Subject believes they can have some control over the visions approximately half the time
3 – Subject believes they can have some control over the visions, but only occasionally. The majority of the time the subject experiences visions that are uncontrollable.
4 – Subject has no control over when the visions occur and cannot dismiss or bring them on at all.

APPENDIX XVI

Supplementary Data

Table S1.

Results of Shapiro-Wilk Tests of Normality for Mismatch Negativity (MMN) Amplitudes and Latencies Across Healthy Control (HC) and Schizophrenia (SZ) Groups in the Tone Task.

	Group					
	HC (N = 17)			SZ (N = 16)		
Variable	Statistic	df	Significance	Statistic	df	Significance
Duration Deviant Amplitude	.90	17	$p = .065$	.97	16	$p = .831$
Duration Deviant Latency	.85	17	$p = .012$*	.75	16	$p = <.001$**
Frequency Deviant Amplitude	.95	17	$p = .525$	.93	16	$p = .274$
Frequency Deviant Latency	.97	17	$p = .863$	.94	16	$p = .396$
Gap Deviant Amplitude	.91	17	$p = .116$	.90	16	$p = .072$
Gap Deviant Latency	.93	17	$p = .198$	.94	16	$p = .372$
Intensity Deviant Amplitude	.97	17	$p = .729$	.92	16	$p = .151$
Intensity Deviant Latency	.93	17	$p = .209$	.90	16	$p = .094$
Location Deviant Amplitude	.90	17	$p = .057$	.93	16	$p = .206$
Location Deviant Latency	.92	17	$p = .529$	.92	16	$p = .169$

*$p < .05$, **$p < .001$.

Table S2.

Results of Shapiro-Wilk Tests of Normality for Mismatch Negativity (MMN) Amplitudes and Latencies Across Healthy Control (HC) and Schizophrenia (SZ) Groups in the Speech Task.

	Group					
	HC (N = 17)			SZ (N = 16)		
Variable	Statistic	df	Significance	Statistic	df	Significance
Frequency Deviant Amplitude	.93	17	$p = .216$	.91	16	$p = .128$
Frequency Deviant Latency	.93	17	$p = .230$	.92	16	$p = .154$
Intensity Deviant Amplitude	.95	17	$p = .471$	.97	16	$p = .819$
Intensity Deviant Latency	.97	17	$p = .828$	.90	16	$p = .090$
Vowel Duration Deviant Amplitude	.96	17	$p = .601$	.94	16	$p = .299$
Vowel Duration Deviant Latency	.94	17	$p = .282$	.88	16	$p = .053$
Vowel Change Deviant Amplitude	.95	17	$p = .458$	.94	16	$p = .382$
Vowel Change Deviant Latency	.94	17	$p = .352$	.79	16	$p = .002$*
Consonant Deviant Amplitude	.96	17	$p = .666$	.94	16	$p = .350$
Consonant Deviant Latency	.92	17	$p = .132$	.95	16	$p = .558$

*$p < .05$, **$p < .001$.

Table S3.

Results of Levene's Test of Equality of Error Variances for Mismatch Negativity (MMN) Amplitudes and Latencies in the Tone Task.

Variable	Statistic	df	Significance
Duration Deviant Amplitude	.07	1, 31	$p = .796$
Duration Deviant Latency	.16	1, 31	$p = .689$
Frequency Deviant Amplitude	4.61	1, 31	$p = .040$*
Frequency Deviant Latency	3.15	1, 31	$p = .086$
Gap Deviant Amplitude	10.04	1, 31	$p = .003$*
Gap Deviant Latency	2.58	1, 31	$p = .119$
Intensity Deviant Amplitude	.14	1, 31	$p = .716$
Intensity Deviant Latency	3.11	1, 31	$p = .087$
Location Deviant Amplitude	.25	1, 31	$p = .707$
Location Deviant Latency	1.33	1, 31	$p = .257$

*$p < .05$, **$p < .001$.

Table S4.

Results of Levene's Test of Equality of Error Variances for Mismatch Negativity (MMN) Amplitudes and Latencies in the Speech Task.

Variable	Statistic	df	Significance
Frequency Deviant Amplitude	1.93	1, 31	$p = .175$
Frequency Deviant Latency	4.01	1, 31	$p = .054$
Intensity Deviant Amplitude	.46	1, 31	$p = .505$
Intensity Deviant Latency	9.21	1, 31	$p = .005$*
Vowel Duration Deviant Amplitude	.77	1, 31	$p = .387$
Vowel Duration Deviant Latency	4.76	1, 31	$p = .037$*
Vowel Change Deviant Amplitude	.27	1, 31	$p = .605$
Vowel Change Deviant Latency	2.43	1, 31	$p = .129$

Consonant Deviant Amplitude	2.00	1, 31	$p = .167$
Consonant Deviant Latency	2.57	1, 31	$p = .119$

*$p < .05$, **$p < .001$.

Table S5.

Results of Box's Test of Equality of Covariance Matrices for Mismatch Negativity (MMN) Amplitudes and Latencies in the Tone and Speech Tasks.

Variable	Statistic	F	df	Significance
Tone Task Amplitudes	32.58	1.79	15, 3835.06	$p = .030$*
Tone Task Latencies	18.18	1.00	15, 3835.06	$p = .454$
Speech Task Amplitudes	23.64	1.30	15, 3835.06	$p = .194$
Speech Task Latencies	25.77	1.42	15, 3835.06	$p = .130$

*$p < .05$, **$p < .001$.

Table S6.

Results of Shapiro-Wilk Tests of Normality for Mismatch Negativity (MMN) Amplitudes and Latencies to the Low and High Frequency and Intensity Deviants Across Healthy Control (HC) and Schizophrenia (SZ) Groups in the Tone and Speech Tasks.

	Group					
	HC (N = 17)			SZ (N = 16)		
Variable	Statistic	df	Significance	Statistic	df	Significance
Tone Low Frequency Amplitude	.92	17	$p = .158$	.95	16	$p = .559$
Tone High Frequency Amplitude	.96	17	$p = .699$	.98	16	$p = .906$
Tone Low Frequency Latency	.96	17	$p = .705$	.94	16	$p = .333$
Tone High Frequency Latency	.95	17	$p = .404$	.97	16	$p = .868$

Tone Low Intensity Amplitude	.95	17	$p = .475$	.93	16	$p = .259$
Tone High Intensity Amplitude	.97	17	$p = .753$	.90	16	$p = .090$
Tone Low Intensity Latency	.99	17	$p = .987$	.95	16	$p = .534$
Tone High Intensity Latency	.83	17	$p = .005$*	.86	16	$p = .022$*
Speech Low Frequency Amplitude	.96	17	$p = .573$	.94	16	$p = .366$
Speech High Frequency Amplitude	.94	17	$p = .399$	.94	16	$p = .404$
Speech Low Frequency Latency	.99	17	$p = .999$	.93	16	$p = .236$
Speech High Frequency Latency	.95	17	$p = .510$	.92	16	$p = .179$
Speech Low Intensity Amplitude	.94	17	$p = .355$	.96	16	$p = .706$
Speech High Intensity Amplitude	.94	17	$p = .288$	.94	16	$p = .390$
Speech Low Intensity Latency	.89	17	$p = .052$	.91	16	$p = .104$
Speech High Intensity Latency	.98	17	$p = .915$	.81	16	$p = .004$*

*$p < .05$, **$p < .001$.

Table S7.

Results of Levene's Test of Equality of Error Variances for Mismatch Negativity (MMN) Amplitudes and Latencies to the Low and High Frequency and Intensity Deviants in the Tone and Speech Tasks.

Variable	Statistic	df	Significance
Tone Low Frequency Amplitude	6.43	1, 31	$p = .016$*

Tone High Frequency Amplitude	4.12	1, 31	$p = .051$
Tone Low Frequency Latency	2.51	1, 31	$p = .123$
Tone High Frequency Latency	4.11	1, 31	$p = .051$
Tone Low Intensity Amplitude	.02	1, 31	$p = .883$
Tone High Intensity Amplitude	1.26	1, 31	$p = .270$
Tone Low Intensity Latency	2.37	1, 31	$p = .134$
Tone High Intensity Latency	3.21	1, 31	$p = .083$
Speech Low Frequency Amplitude	1.12	1, 31	$p = .300$
Speech High Frequency Amplitude	5.59	1, 31	$p = .025$*
Speech Low Frequency Latency	4.95	1, 31	$p = .033$*
Speech High Frequency Latency	.85	1, 31	$p = .363$
Speech Low Intensity Amplitude	4.33	1, 31	$p = .046$*
Speech High Intensity Amplitude	3.25	1, 31	$p = .081$
Speech Low Intensity Latency	.31	1, 31	$p = .581$
Speech High Intensity Latency	9.75	1, 31	$p = .004$*

*$p < .05$, **$p < .001$.

Table S8.

Results of Box's Test of Equality of Covariance Matrices for Mismatch Negativity (MMN) Amplitudes and Latencies to the Low and High Frequency and Intensity Deviants in the Tone and Speech Tasks.

Variable	Statistic	F	df	Significance
Tone Low vs. High Frequency Amplitude	5.86	1.82	3, 198975.38	$p = .141$
Tone Low vs. High Frequency Latency	12.67	3.93	3, 198975.38	$p = .008$*

Tone Low vs. High Intensity Amplitude	.77	.24	3, 198975.38	$p = .870$
Tone Low vs. High Intensity Latency	3.62	1.12	3, 198975.38	$p = .339$
Speech Low vs. High Frequency Amplitude	7.09	2.20	3, 198975.38	$p = .086$
Speech Low vs. High Frequency Latency	5.20	1.61	3, 198975.38	$p = .185$
Speech Low vs. High Intensity Amplitude	10.44	3.24	3, 198975.38	$p = .021$*
Speech Low vs. High Intensity Latency	6.74	2.09	3, 198975.38	$p = .099$

*$p < .05$, **$p < .001$.

Table S9.

Results of Shapiro-Wilk Tests of Normality for Mismatch Negativity (MMN) Amplitudes Elicited by Each Deviant Type Across Healthy Control (HC) and Schizophrenia (SZ) Groups in the Tone and Speech Tasks at Mastoid Sites (TP_9/TP_{10}).

	Group					
	HC (N = 17)			SZ (N = 16)		
Variable	Statistic	df	Significance	Statistic	df	Significance
Tone Duration TP_9 Amplitude	.96	17	$p = .605$	.98	16	$p = .975$
Tone Duration TP_{10} Amplitude	.97	17	$p = .763$	.93	16	$p = .248$
Tone Gap TP_9 Amplitude	.93	17	$p = .253$	.98	16	$p = .971$
Tone Gap TP_{10} Amplitude	.91	17	$p = .114$	.97	16	$p = .855$
Tone Location TP_9 Amplitude	.96	17	$p = .559$	.94	16	$p = .376$

Tone Location TP_{10} Amplitude	.88	17	$p = .035$*	.96	16	$p = .687$
Tone Intensity TP_9 Amplitude	.97	17	$p = .818$	.92	16	$p = .161$
Tone Intensity TP_{10} Amplitude	.92	17	$p = .161$	.96	16	$p = .674$
Tone Frequency TP_9 Amplitude	.95	17	$p = .439$	.94	16	$p = .387$
Tone Frequency TP_{10} Amplitude	.94	17	$p = .349$	.92	16	$p = .142$
Speech Frequency TP_9 Amplitude	.95	17	$p = .491$	.96	16	$p = .619$
Speech Frequency TP_{10} Amplitude	.98	17	$p = .967$	.96	16	$p = .572$
Speech Intensity TP_9 Amplitude	.95	17	$p = .517$	.95	16	$p = .409$
Speech Intensity TP_{10} Amplitude	.91	17	$p = .105$	.96	16	$p = .714$
Speech Vowel Duration TP_9 Amplitude	.93	17	$p = .217$	.94	16	$p = .344$
Speech Vowel Duration TP_{10} Amplitude	.95	17	$p = .462$	.93	16	$p = .283$
Speech Vowel Change TP_9 Amplitude	.93	17	$p = .202$	.93	16	$p = .282$
Speech Vowel Change TP_{10} Amplitude	.92	17	$p = .122$	.97	16	$p = .778$
Speech Consonant TP_9 Amplitude	.99	17	$p = .1000$	.98	16	$p = .958$
Speech Consonant TP_{10} Amplitude	.96	17	$p = .669$	.96	16	$p = .627$

*$p < .05$, **$p < .001$.

Table S10.

Results of Levene's Test of Equality of Error Variances for Mismatch Negativity (MMN) Amplitudes Elicited by Each Deviant Type in the Tone and Speech Tasks at Mastoid Sites (TP_9/TP_{10}).

Variable	Statistic	df	Significance
Tone Duration TP_9 Amplitude	2.28	1, 31	$p = .141$
Tone Duration TP_{10} Amplitude	.54	1, 31	$p = .469$
Tone Gap TP_9 Amplitude	.75	1, 31	$p = .394$
Tone Gap TP_{10} Amplitude	.56	1, 31	$p = .466$
Tone Location TP_9 Amplitude	.03	1, 31	$p = .872$
Tone Location TP_{10} Amplitude	.54	1, 31	$p = .469$
Tone Intensity TP_9 Amplitude	.062	1, 31	$p = .805$
Tone Intensity TP_{10} Amplitude	.44	1, 31	$p = .513$
Tone Frequency TP_9 Amplitude	.93	1, 31	$p = .342$
Tone Frequency TP_{10} Amplitude	.4.20	1, 31	$p = .049$*
Speech Frequency TP_9 Amplitude	9.52	1, 31	$p = .004$*
Speech Frequency TP_{10} Amplitude	3.86	1, 31	$p = .059$
Speech Intensity TP_9 Amplitude	3.09	1, 31	$p = .089$
Speech Intensity TP_{10} Amplitude	.39	1, 31	$p = .535$
Speech Vowel Duration TP_9 Amplitude	.25	1, 31	$p = .621$
Speech Vowel Duration TP_{10} Amplitude	.06	1, 31	$p = .801$
Speech Vowel Change TP_9 Amplitude	1.48	1, 31	$p = .233$
Speech Vowel Change TP_{10} Amplitude	.50	1, 31	$p = .486$
Speech Consonant TP_9 Amplitude	.00	1, 31	$p = .998$

Speech Consonant TP_{10} Amplitude	.29	1, 31	$p = .593$

*$p < .05$, **$p < .001$.

Table S11.

Results of Box's Test of Equality of Covariance Matrices for Mismatch Negativity (MMN) Amplitudes in the Tone and Speech Tasks at Mastoid Sites (TP_9/TP_{10}).

Variable	Statistic	F	df	Significance
Tone Mastoid Amplitudes	126.87	1.49	55, 3077.37	$p = .012$*
Speech Mastoid Amplitudes	102.50	1.20	55, 3077.37	$p = .146$

*$p < .05$, **$p < .001$.

Table S12.

Mean Unadjusted (±SD) and Adjusted (±SE) Mismatch Negativity (MMN) Amplitudes Elicited by the Frequency (Low vs. High) and Intensity (Low vs. High) Deviants (Speech Task) for Schizophrenia Patients (SZ) and Healthy Controls (HC).

MMN (μV)	HC (N = 17)		SZ (N = 16)		Significance	
	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
Low Frequency	-2.08 (0.82)	-2.06 (0.23)	-0.81 (0.95)	-0.83 (0.24)	$p = <.001$**	$p = .002$*
High Frequency	-2.39 (1.28)	-2.33 (0.29)	-1.20 (0.67)	-1.26 (0.30)	$p = .002$*	$p = .025$*
Low Intensity	-1.61 (0.44)	-1.54 (0.18)	-0.92 (0.81)	-0.99 (0.19)	$p = .005$*	$p = .064$
High Intensity	-2.15 (1.55)	-2.14 (0.37)	-1.37 (0.95)	-1.39 (0.38)	$p = .092$	$p = .204$

[a] Means adjusted by handedness and smoking status.

*$p < .05$, **$p < .001$.

Table S13.

Mean Unadjusted (±SD) and Adjusted (±SE) Mismatch Negativity (MMN) Latencies Elicited by the Frequency (Low vs. High) and Intensity (Low vs. High) Deviants (Speech Task) for Schizophrenia Patients (SZ) and Healthy Controls (HC).

MMN (ms)	HC (N = 17)		SZ (N = 16)		Significance	
	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
Low Frequency	192.59 (27.69)	192.66 (9.44)	165.13 (40.07)	165.05 (9.79)	$p = .028$*	$p = .075$
High Frequency	194.94 (37.43)	191.17 (11.09)	173.75 (42.49)	177.75 (11.51)	$p = .138$	$p = .452$
Low Intensity	189.06 (34.17)	185.48 (9.85)	182.50 (36.72)	186.31 (10.22)	$p = .599$	$p = .958$
High Intensity	183.65 (21.03)	183.50 (8.66)	187.50 (40.16)	187.66 (8.98)	$p = .730$	$p = .764$

[a] Means adjusted by handedness and smoking status.

*$p < .05$, **$p < .001$.

Figure S1.

Grand Averaged Mismatch Negativity (MMN) Waveforms at Site Fz for the Low and High Frequency Deviant (a) and the Low and High Intensity Deviant (b) in the Speech Task for Healthy Controls (HC) and Schizophrenia Patients (SZ).