

**THE PROCESSING OF AUDITORY DEVIANCE AND AUDITORY  
HALLUCINATIONS IN SCHIZOPHRENIA DURING STABLE  
SYMPTOMATOLOGY AND ACUTE SYMPTOM EXACERBATION**

by

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**ABSTRACT**

As more emphasis is placed on investigating individual symptoms within schizophrenia, the study of auditory hallucinations (AH) is becoming a larger field within research into this devastating illness. This series of studies examined the functional neural correlates of AHs in schizophrenia and their impact on pre-attentive acoustic change detection, as indexed by the mismatch negativity (MMN). Specifically, these studies had an overarching objective of comparing patients with shared symptomatology (i.e. auditory hallucinations), but different current presentations of their illness (e.g. stable vs. acutely ill).

This series of studies examined the electroencephalograph (EEG)-derived MMN, recorded across 32 sites, in schizophrenia patients with current and persistent AHs (HPs). MMNs were recorded in response to two different multi-feature MMN paradigms: the ‘optimal’ 5-deviant paradigm (Näätänen et al, 2004), which presents frequency, duration, intensity, location and gap deviants, and the modified ‘Optimal-3’ paradigm, which only presents frequency, duration, and intensity deviants.

Consistent with the majority of related studies, reduced duration MMN amplitudes were observed compared to healthy controls in all studies. Specifically, smaller duration MMNs were seen in HPs who were community dwelling outpatients, as well as acutely ill inpatients (vs. healthy controls). Additionally, in a comparison of schizophrenia outpatients with stable symptomatology, HPs exhibited reduced duration MMN amplitudes compared to patients with no AHs. Intensity MMN amplitudes were also found to be significantly different in both inpatient and outpatient HPs (vs. healthy controls), while deficits in frequency MMN were observed in outpatient HPs, but not

with inpatients. Conversely, gap and location MMN deficits (vs. healthy controls) were only seen in HPs requiring current hospitalization (vs. outpatients).

Overall, in both HPs with currently stable symptomatology and those with acute exacerbation of illness, there appear to be deficits in MMN amplitude across several deviant types. This suggests that the presence of auditory hallucinations interferes with cognitive processing of incoming auditory stimuli, particularly as it relates to auditory change detection.

## PREFACE

This dissertation is based on the following four original publications.

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

II Fisher, D.J., Grant, B., Smith, D.M., & Knott, V.J. (2011). Effects of deviant probability on the 'optimal' multi-feature mismatch negativity (MMN) paradigm. *International Journal of Psychophysiology*, 79, 311-315. doi: 10.1016/j.ijpsycho.2010.11.006

III Fisher, D.J., Grant, B., Smith, D.M., Borracci, G., Labelle, A., & Knott, V.J. (2011). Effects of deviant probability on the 'optimal' multi-feature mismatch negativity (MMN) paradigm. *International Journal of Psychophysiology*, 79, 311-315. doi: 10.1016/j.ijpsycho.2010.11.006

IV. Fisher, D.J., Labelle, A., Knott, V. Alterations of mismatch negativity (MMN) in schizophrenia patients with auditory hallucinations experiencing acute exacerbation of illness (Manuscript in preparation).

In addition, some unpublished data have been added to this dissertation.

Please note, the text of the original manuscripts comprising this thesis has been modified to avoid repetition.

Derek Fisher was involved in the conceptualization of the research comprising this thesis. He carried out all of the experiments pertaining to Manuscript I and IV and did patient interviews, coordinated testing and supervised/aided in data collection for Manuscripts II and III. He carried out all of the data analysis and prepared all of the manuscripts.

Alain Labelle (M.D.) is clinical director of the schizophrenia program at the Royal Ottawa Mental Health Centre. He aided recruitment of schizophrenia patients, provided clinical ratings and contributed to the conceptualization of the projects, particularly as it related to the practical aspects of recruiting and testing schizophrenia patients.

Bryan Grant (B.A.) was an honours student within the Clinical Neuroelectrophysiology and Cognitive Neuroscience Research Laboratory at the Royal Ottawa Mental Health Centre. He collected electrophysiological data used in Manuscripts II and III.

Dylan Smith (B.Sc.) is a graduate student within the within the Clinical Neuroelectrophysiology and Cognitive Neuroscience Research Laboratory at the Royal Ottawa Mental Health Centre. He collected electrophysiological data used in Manuscripts II and III.

Giuseppe (Joe) Borracci (R.N.) is a psychiatric nurse within the schizophrenia program at the Royal Ottawa Mental Health Centre. He aided in recruitment of patients and provided clinical (PANSS) ratings for Manuscripts II and III.

Verner Knott (D.Phil., C.Psych) was the graduate supervisor of the candidate and research unit director for all of these projects. He was involved in the conceptualization of the projects, supervised statistics and writing and assisted in editing all of the manuscripts.

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Halifax, March 2012.

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## CHAPTER 1: GENERAL INTRODUCTION

### 1.1 Schizophrenia: A clinical overview

Schizophrenia is a uniquely devastating disease, typically emerging during young adulthood with a lifetime prevalence rate of 4.0% across the globe (Saha et al., 2005). As yet, there is no cure for schizophrenia and its affliction lasts across the lifespan. Not only does schizophrenia place a heavy burden on the individuals affected, as 50% of patients will not be able to maintain even part-time employment after first hospitalization (Racenstein et al., 2002), but on society as a whole. In the year 2002, the overall cost of schizophrenia in the United States was \$62.7 billion, including \$22.7 billion in direct health care costs (Wu et al., 2005). It is with this in mind that a massive worldwide research endeavour has attempted to elucidate the causes and mechanisms underlying schizophrenia.

Within the realm of mental illness, schizophrenia is unique in the sheer heterogeneity of the symptoms and syndromes it encompasses. Patients may be assigned this diagnosis based on a wide range of symptoms associated with the disorder, not least of which include disturbances of thought, behaviour, emotion and perception. These perceptual disturbances within schizophrenia individuals may include, but are certainly not limited to, distorted beliefs about themselves, others or the world in general (i.e. delusions) or the perception of phenomena that do not exist (i.e. hallucinations), often resulting in a marked impairment in the individual's cognitive ability to function within society if left untreated. The associated symptoms manifested within each affected person are so individual that the resulting cluster may be seen as a psychiatric fingerprint, unique to each patient.

The heterogeneous nature of schizophrenia, noted in both the clinical and research realms (Carpenter and Kirkpatrick, 1988), has been an integral part of the disease since its first mention in literature; both Kraepelin (1919) and Bleuler (1950) asserted that the heterogeneity of schizophrenia was a fundamental part of its nature. It is with this heterogeneity in mind that efforts have been made to establish sub-patterns, sub-types or syndromes (defined by the presence of a particular cluster of symptoms and clinical characteristics) in an attempt to bring diagnostic order to the chaos of the associated symptoms. One of the more recent, successful and frequently used sub-type systems within the umbrella diagnosis of schizophrenia is that of the positive (Type I) and negative (Type II) syndromes (Crow, 1980; Andreasen and Olsen, 1982), which has since been incorporated into the American Psychiatric Association's (APA) Diagnostic and Statistical Manual (DSM) of Mental Disorders (DSM-IV TR; 2000).

The positive syndrome of schizophrenia consists of florid symptoms, such as delusions, hallucinations, disordered thinking and disordered behaviour (ranging from inappropriate agitation and aggression to catatonic stupor), which actively interfere with mental functioning, and may be seen as an amplification or excess of normal functions. The negative syndrome, in contrast, may be seen as a poverty or diminished capacity of normal cognitive, affective and social functions, including blunted or flat affect, poverty of speech, and loss of drive (avolition). Neuropharmacological research has pointed to dopamine as the main neurotransmitter involved in each of these syndromes. The original dopamine hypothesis states that it is an excess of sub-cortical dopamine acting on the D2 receptor that is responsible for the positive symptoms of schizophrenia. A later update (Davis et al., 1991) expanded this theory, adding that it is a deficit of dopamine in the

pre-frontal cortex that contributes to the negative symptoms and that a sub-cortical excess of dopamine can co-exist with a cortical deficit.

Certainly, within each grouping of syndromes there have been attempts to further sub-classify patients with schizophrenia. The DSM (APA, 2000) lists five clinical subtypes of schizophrenia; paranoid type, disorganized type, catatonic type, undifferentiated type, and residual type. The paranoid type of schizophrenia is marked by prominent delusions or auditory hallucinations, with relative preservation of cognitive functioning and affect. Patients diagnosed with the disorganized type display disorganized speech, disorganized behaviour, flat or inappropriate affect, and neurocognitive deficits, but in the absence of catatonia. The catatonic type is applied to patients exhibiting motor immobility, excessive motor activity, pathological parrot-like repetition of a word or phrase just spoken by another person (echolalia), repetitive imitation of another person's movements (echopraxia), and maintenance of a rigid posture despite attempts to be moved or resistance to instructions (extreme negativism). The essential feature of undifferentiated type is a diagnosis of schizophrenia, but without meeting criteria for catatonic, disorganized or paranoid type. Finally, patients diagnosed as residual type are those who have had at least one episode of schizophrenia, but do not currently exhibit positive psychotic symptoms, yet still show some negative symptoms (e.g. flat affect, poverty of speech) or attenuated positive symptoms such as eccentric behaviour or odd beliefs. Within these sub-categories, the paranoid type tends to be the least severe while disorganized type is the most severe. There has been considerable research interest in establishing even more homogeneous symptom clusters in the hope

that these will lead to better treatments of afflicted patients (Blanchard, Horan, and Collins, 2005; Weiser, Van Os, and Davidson, 2005).

## 1.2 Auditory Hallucinations in Schizophrenia

Although a great deal of clinical and research efforts in schizophrenia have chosen to focus on global syndromes, this approach has been considered by some to be too broad, and it has been suggested that a more focused attempt to characterize the individual symptoms of schizophrenia will help reveal important insights into the disease as a whole (Shapleske et al, 2002) and its underlying psychological processes (Persons, 1986; Bentall et al, 1988). One of the most prevalent symptoms of schizophrenia is the presence of hallucinations, which, like schizophrenia itself, can be extremely heterogeneous in nature. With that in mind, it is important to have a solid construct of hallucinations to work from; this investigation takes the view of a hallucination as “a sensory experience which occurs in the absence of corresponding external stimulation of the relevant sensory organ, has a sufficient sense of reality to resemble a veridical perception, over which the subject does not feel s/he has direct and voluntary control, and which occurs in the awake state” (David, 2004, p. 110). Hallucinations can occur in any of the five senses; auditory, visual, tactile, olfactory, and gustatory hallucinations have all been reported in schizophrenia patients (Weiss & Heckers, 1999), however the most commonly occurring hallucination is that of hearing ‘voices’. Auditory hallucinations (AHs) are one of the hallmark symptoms of patients with schizophrenia (David, 1999); within schizophrenia patients, auditory hallucinations have a reported prevalence of 50-80% (Andreasen & Flaum, 1991). These hallucinations tend to occur in patients

diagnosed with the paranoid sub-type, which, according to the DSM (APA, 2000), tends to be associated with the least neurocognitive decline. It is thought that these hallucinations are the result of a dysfunction of the metacognitive processes that discriminate between self-generated and external sources of information (Bentall & Slade, 1985; Morrison & Haddock, 1997), in addition to other deficits of information processing (Hoffman, 1986). There are a number of good structured instruments designed to quantify the different dimensions of the AH experience, such as the Psychotic Symptom Rating Scales (PSYRATS; Haddock et al., 1999), the Structured Interview for Assessing Perceptual Anomalies (SIAPA; Bunney et al, 1999), and the Mental Health Research Institute Unusual Perceptions Schedule (MUPS; Carter et al, 1995), as well as the auditory hallucination scale within the Positive and Negative Syndrome Scale (PANSS; Kay, Opler & Lindenmayer, 1989). The PSYRATS is a particularly promising scale for quantifying hallucinations as it is relatively brief, rates AHs over a number of domains, and has shown excellent psychometric properties.

### 1.3 Phenomenology of Auditory Hallucinations

Auditory hallucinations, much like schizophrenia itself, show considerable heterogeneity in their presentation and form, a fact that has simultaneously interested and frustrated researchers who have attempted to categorize AHs. One of the earliest attempts to categorize abnormal experiences used the groupings of 'hallucinations' and 'hallucinoses', whereby the latter implied insight into the bizarreness of the experience (Claude & Ey, 1932). This idea was updated by Sedman (1966), who used the terms 'imagery', 'pseudo-hallucinations' and 'true hallucinations' to describe experiences that

were lacking in perceptual reality, mimicked perceptual reality but with insight into the abnormal experience, and clear perceptions without insight, respectively.

Much of this early research did not focus on hallucinations within schizophrenia exclusively, as hallucinations are known to occur in other psychiatric conditions, such as post-traumatic stress disorder (Asaad, 1990), in response to certain drugs, such as psilocybin (Hyde et al, 1978), and even among those in the general population with no psychiatric diagnosis nor under the influence of psychedelic drugs (van Os et al, 2000).

More recent work has focused on hallucinations within schizophrenia, especially AHs, and with that has come better attempts to characterize and describe the hallucinatory experience. Lowe (1973) began this trend by examining several variables of AHs in greater detail, detailing that these characteristics can be used as “discriminatory indicators for differential diagnosis among psychotics.” The characteristics this research focused on included frequency, location (internal or external), similarity to external speech, loudness, constancy, effect on behaviour, source attribution, affective response, and content of AHs. This work was expanded to include personification (accent, gender, familiarity of voice), coping mechanisms and degree of control, number of voices, linguistic complexity, and insight into the experience (Nayani and David, 1996). It is along these lines that research has moved, despite the idiosyncratic nature of individual AHs.

There have been many reported features of the AH experience. Some recent work has used statistical methods such as hierarchical cluster (HC) and multidimensional scaling analysis (MDS) to investigate relationships between phenomenological variables of AHs (Stephane et al, 2003). This approach started by identifying twenty variables of

AH (e.g. location, time course, linguistic complexity) based on the relevant literature and clinical experience of the investigators, and then used the above statistical methods to determine the statistical significance of these within a patient population. The hierarchical cluster analysis revealed two main clusters of AHs. The first included AHs with low linguistic complexity (single word), repetitive content, self-attribution, located in outer space (i.e. 'outside the head'), and association with many different control strategies. The second cluster encompassed AHs with high linguistic complexity (conversations), systematized content (non-repetitive), multiple voices, attributed to others, and located in inner space (i.e. 'inside the head'). These clusters make intuitive sense on many levels; AHs of a single word will often result in repetition of that word, while linguistically complex AHs will have systematized content, and may include multiple voices. In addition, when multiple voices are present, it seems logical that they will be attributed to others. These findings (Stephane et al., 2003) are echoed in the MDS analysis, which identified three prominent dimensions of AHs; linguistic complexity, attribution, and location. Identification of linguistic complexity as a dimension indicates that hallucinating patients experience AHs as either having low complexity (single words), medium complexity (single sentences) or high complexity (conversation), and rarely hear combinations of the three. Stephane and colleagues (2003) suggest that this could represent different levels of language abnormalities in patients. The second identified dimension of AHs, attribution, is also of importance as it lends empirical support to the idea that some patients experience AHs as being their own voice (self-attribution), while others experience them as the voice of another (other attribution). Finally, a third dimension showed that AHs will occur either in inner space (perceived as being inside

the head) or in outer space (outside the head), but rarely a combination of the two. This dimension is supported by a functional magnetic resonance (fMRI) study showing different neural substrates for auditory stimuli perceived outside the head versus those perceived inside the head (Hunter et al, 2003).

One of the most complete surveys of AH phenomenology in schizophrenia was performed by Nayani and David (1996), who described several key characteristics of AHs. Most participants (73%) described voices as being at normal conversational volume, as opposed to whispers (14%) or shouting (13%), and nearly all noted that angry voices were experienced as being louder. The members of their sample mostly experienced hallucinations from several times a day to most of the day; only a small percentage experienced continual, non-stop hallucinations throughout the day. Almost half the participants (42%) experienced their AHs for more than an hour at a time, and those who experienced AHs more often heard a greater variety of hallucinated words. With regards to location, nearly half the sample (49%) heard the voices as external stimuli, as though through their ears, while 38% experienced the voices as being internal and 12% experienced AHs as both internal and external AH percepts. Interestingly, over time AHs were more likely to move to internal space and become more complex. The study participants experienced a range of one to fourteen voices (mean ~ 3), which were sometimes described as arguing or conversing about the patient. All participants, regardless of gender, were more likely to hear a male hallucinated voice. Overall, patients were more likely to hear a middle-aged voice, except for those under 30, who most commonly heard a young voice. Nearly three-quarters of the sample described the accent of the voice to be different from their own, either by region or by class; the most common

description was of an upper-class radio-announcer 'BBC voice'. Most patients admitted to knowing the identity of one or more of their voices, commonly thought to be one of: God, the Devil, a relative, a neighbour or a doctor. Patients experienced an average of 5 different types of voices, with the most common being a command, criticism, verbal abuse, frightening content, and third-person/neutral commentary.

Despite the fact that these results (Nayani & David, 1996) reflect some degree of cultural specificity (e.g.. that of a 'BBC voice'), most of the findings can be applied to AHs within schizophrenia regardless of cultural background. To demonstrate this, the findings were followed up by an American study (Miller, 1996), which replicated many of Nayani and David's findings, while adding the observation that most patients believe that they are the only ones who can perceive the hallucinatory experience.

While there is evidence of prevalent experience of abusive/critical AHs, this is not always the case. There is significant evidence that many patients do experience some positive or pleasant voices (Nayani & David, 1996), while in one study, nearly 10% of patients experienced pleasurable AHs as the norm, with one patient stating: "If I did not have them, what a boring old age I would have! Some day they will give me a mission," (Sanjuan et al, 2004, p. 275). While there does not appear to be any association between pleasurable auditory hallucinations and age or sex, research has shown a correlation between pleasurable AHs and chronicity of hallucinations (Sanjuan et al, 2004). Despite this select population who experience pleasurable AHs, the majority of those afflicted simply wish that the voices would go away, with 98% of patients in one study noting adverse effects of AHs and 68% wishing their AHs would stop (Miller, O'Connor, & DiPasquale, 1993). In this same study, one patient stated that "...sometimes the voices

say they're going to kill me or I'll die tonight; I feel threatened," while another said "I've never been able to have a job because of this," (p. 587). It has yet to be established why AHs are so frequently abusive/critical. However, research into thought suppression has shown that attempts to suppress critical thoughts will often result in the opposite effect (Wegner & Erber, 1992), thus an agitated patient may actually increase the number of abusive AHs by attempting to quell them.

Many patients with AHs must use coping techniques to function in society (Nayani & David, 1996), including separating the voices from other thoughts and actions, using a portable music device for distraction, and simply ignoring the voices. As one sufferer explains, "For me, the voices are externalized and real... Far better is to accept that the voices will be there and try to deal with them." (Cockshutt, 2004).

#### 1.4 Variables Affecting Auditory Hallucinations

The occurrence of AHs appears to be influenced by several factors, including emotion and stress (Bentall, 1990b). Many authors have noted stress-induced arousal to have a significant role in psychosis, a point emphasized by Birley and Brown (1970) in their work showing stressful life events to be significantly associated with schizophrenia episodes. Subsequent research has linked hallucinatory experiences with stressful events such as losing a spouse (Alroe & McIntyre, 1983; Wells, 1983), and terrorist attacks (Siegel, 1984). Clinical data also indicates that AHs are more likely to follow periods of stress (Slade, 1972) or anxiety (Delespaul, de Vries, & van Os, 2002). This is mirrored by work showing a direct relation between AH onset and increases in skin conductance level, an index of autonomic nervous system arousal, in schizophrenia (Cooklin, Sturgeon

& Leff, 1983). In addition, sadness may also be a precipitant of AHs, with half the participants of one study reporting the experience of sadness encouraging hallucinations (Nayani & David, 1996).

It has also been suggested that AH occurrence may be in part determined by predisposing factors, such as genes. Much of the genetic research into this question, however, has been undermined by questions of validity due to their anecdotal nature or poor control of extraneous variables (Bentall, 1990b). Some of the more convincing evidence pointing to a role for predisposing factors in AH occurrence comes from studies examining the cognitive processes of hallucinators and non-hallucinators. This work examined the position that AHs reflect misattribution of sensory information and postulated that those with AHs should be poorer at recognizing their own thoughts compared to non-hallucinators (Heilbrun, 1980). Indeed, hallucinating patients did perform more poorly when asked to identify their own verbatim statements of opinion from a selection of similar statements. A subsequent study also identified hallucinating patients as being particularly poor at detecting the spatial location of sounds (Heilbrun, Blum & Haas, 1983), further implicating predisposing factors as being important in influencing the occurrence of AHs.

While environmental conditions (i.e. being in a specific room or place) do not control the occurrence, intensity, or nature of AHs, social context can influence the course of an episode, especially when combined with other variables, like arousal level. There appears to be an interaction between environment and arousal, as relative isolation combined with stress appears to precipitate hallucinations (Comer, Madow, & Dixon, 1967; Siegel, 1984). Even isolation on its own has been shown to worsen hallucinations

(Nayani & David, 1996). It also appears that passive leisure activities (e.g. watching television) and doing nothing increase the intensity of hallucinations, AH intensity is negatively correlated with activity level in a pseudo-linear fashion. (Delespaul, de Vries, & van Os, 2002). Comparatively, engaging in work activities (e.g. job-related or domestic tasks) has been found to decrease hallucinatory intensity over time (Delespaul, de Vries, & van Os, 2002), as has attention to meaningful stimuli. A study of patients with AHs exposed to various levels of auditory stimulation found that as the attended stimuli became more meaningful, the rate of AHs significantly decreased and that during periods of non-meaningful stimulation (i.e. white noise) or during sensory deprivation, AHs increased (Margo, Helmsley, & Slade, 1981).

These diverse findings relating to variables affecting AHs appear to support, at least in part, Slade's four-factor model of hallucinations (1976). In this working model, Slade proposes that: (1) 'stress events' produce an internal arousal that results in mood state disturbances; (2) these mood state disturbances raise hallucinatory tendency above a critical threshold whereby AHs may be triggered; (3) whether or not an AH occurs is dependent on whether there are sufficient attentional resources for the production and processing of such an event; (4) the result of a hallucinatory experience is a resolution of the mood state disturbances, thereby reinforcing the occurrence of AHs, and lowering the threshold needed to be obtained for future occurrence. Particular emphasis has been placed on the third factor of this model; the conceptualization of attention as a limited-capacity resource means that increasing processing demands reduce the amount of attention available for the hallucinatory experience. Or, as Slade himself puts it: 'sources of external stimulation can only be consciously responded to at the expense of those

emanating from within, and vice-versa' (1976, pp.416). This model is based on three intensive case-studies of AHs in schizophrenia (Slade, 1972, 1973, 1975), as well as two studies investigating the effects of manipulating external stimulation (Slade, 1974) and the psychological factors contributing to AHs (Slade, 1976) in schizophrenia patients.

Slade's four-factor model of AHs is supported by the fact that work activities and passive leisure activities have attenuating and enhancing effects on AH intensity, respectively (Delespaul, de Vries, & van Os, 2002). This corroboration, when combined with Slade's own research, seems to support the theory of a limited-capacity attention system having a modulating effect on the appearance, frequency and intensity of AHs in schizophrenia. However, while illustrating the factors that can exert an influence on the form and occurrence of hallucinations, this work does not satisfactorily illuminate the mechanisms behind AH.

### 1.5. Neurocognitive Models of Auditory Hallucinations

Despite being recognized as a characteristic symptom of schizophrenia, researchers have yet to come to a firm conclusion regarding the neural mechanisms that mediate auditory hallucinations. While it is clear that there are some cognitive biases (maladaptive sets of thinking), it is important to consider several neurocognitive models in attempting to understand exactly what these cognitive deficits are and how they generate AHs (Seal, Aleman, & McGuire, 2004). Among the many theories, there are three that stand out for their coherence and empirical support; these three theories attribute AHs to abnormal auditory verbal imagery, dysfunction in verbal self-monitoring, and dysfunction of episodic memory processes.

Some of the earliest attempts to explain AHs used a model of abnormal auditory verbal imagery, beginning with Galton's (1943) assertion that those who experience particularly vivid and realistic mental imagery are more prone to hallucinations. This was then applied to the idea that hallucinating schizophrenia patients experience particularly vivid imagery, resulting in AHs. Over the years, however, this explanation received little in the way of experimental support. Many studies found either no difference between schizophrenia patients and normal controls with regards to experience of auditory imagery (Brett & Starker, 1977; Chandiramani & Varma, 1987; Bocker et al, 2000; Evans et al, 2000). In fact, there is only one study that shows a relationship between auditory imagery vividness and propensity to hallucinate auditorily (Mintz & Alpert, 1972). In this oft-cited study, dubbed the "White Christmas" investigation, participants were asked to close their eyes and listen to a recording of the song "White Christmas", despite the fact that the record was not actually playing. The results of this study showed that participants with a predisposition to hallucination were more likely to hear the song, and more likely to believe that a record had indeed been playing. While this study displays some evidence of imagery vividness in schizophrenia patients who experience AHs, it can also be interpreted as showing the influence of 'top-down' processing in schizophrenia, an idea that requires further empirical support before one can properly surmise the role of expectation in these patients (Frith & Dolan, 1997). What one can be reasonably sure of, however, is that, as Seal and colleagues (2004) pointed out in their review of cognition and auditory hallucinations, there is no compelling evidence that abnormal auditory imagery is related to AHs in schizophrenia. This conclusion is consistent with a body of research that predisposition to hallucinations has no relationship

to aberrant auditory imagery in the general population (Merckelbach & van de Ven, 2001; Aleman, Bocker & de Haan, 2000).

The most common explanation of AHs is that they are a type of inner speech that is mistakenly attributed to an external or alien source; that is to say there is some dysfunction in verbal self-monitoring. This idea is supported by the finding that manipulations which block subvocalization (e.g. speaking out loud, keeping the mouth open), also attenuate the presence of AHs (Gallagher et al, 1994). Further evidence of misattribution of inner speech can be elucidated from a study of corollary discharge. It has been suggested that motor actions are accompanied by a corollary discharge to the sensory cortex, which signals that the incoming sensory input is self-generated (Sperry, 1950). In healthy controls there is a corollary discharge, indicating communication between the frontal lobes where speech is generated and temporal lobes where it is heard, during talking and during inner speech. It has been suggested that this mechanism is behind our ability to distinguish between our own and others' speech by aiding in the monitoring of our own speech, thoughts and behaviours (Ford et al, 2002). Schizophrenia patients, especially those with prominent hallucinations, showed significant corollary discharge dysfunction (Ford et al, 2001; Ford et al, 2002; Ford and Mathalon, 2004). One notable study has demonstrated this dysfunction using a model of EEG coherence (Ford et al, 2002); if there is communication between two cortical regions, there should be coherence (i.e. frequency dependent matching of EEG) between these regions seen in the EEG. In patients with schizophrenia, there is reduced coherence, especially in the delta and theta bands, between frontal and temporal areas of the brain, indicating a disconnection of these regions and corollary discharge dysfunction. Furthermore,

impaired coherence of the theta band is even more marked in hallucinating schizophrenias, and it is thought that the failure of this mechanism could lead to the misattribution of self-generated thoughts to external sources. This work has since been replicated, lending further support to the idea of corollary discharge dysfunction in schizophrenia, particularly in the presence of AHs (Ford & Mathalon, 2004). It is unknown whether this is the result of pathway or receptor deficits, however these results do suggest that there is a failure to alert the brain that incoming auditory input is self-generated, and this lack of signaled intention leads to the mistaken attribution of inner speech to alien sources, producing the experience of auditory hallucinations (Ford and Mathalon, 2004).

One study that attempted to objectively measure this dysfunction in self-monitoring had participants make judgements about the origin of perceived speech while talking, with another person's speech and their own distorted speech mixed in with the subject's responses (Johns et al, 2001). In this case, speech was to be attributed to 'self', 'other' or 'unsure'. While schizophrenia patients as a group made more errors than healthy volunteers, hallucinating participants, in particular, were more likely to misattribute their own distorted speech to an external speaker. This result has since been replicated in a functional neuroimaging study of verbal self-monitoring (Fu et al, 2001), where acutely psychotic schizophrenia patients were unable to identify their own distorted voice, identifying it as originating from an 'other'. Online scanning using fMRI showed this was associated with dysfunction of the neural areas implicated in verbal self-monitoring.

However, despite the compelling evidence that defective self-monitoring may contribute to the experience of AHs, there is further evidence that this theory alone cannot completely explain this phenomenon. In one study, hallucinating and non-hallucinating schizophrenia patients and healthy controls had their voices recorded and, after a delay, were asked to identify the source (self vs. other) of the pre-recorded speech that was either distorted or undistorted (Allen et al, 2003). While this study did not measure immediate verbal self-monitoring, as participants were not generating speech during the task, hallucinators were still more likely to identify their own speech as originating from another. These results suggest that abnormal verbal self-monitoring is not the only component involved in auditory hallucinations.

A third influential neurocognitive theory of AHs revolves around dysfunctional episodic memory processes. Episodic memories are those that include sensory and semantic/conceptual features of an event, as well as concurrent affective response, motor action and cognitive processes. Given this, it has been hypothesized that hallucinations result from deficient memory encoding, resulting in altered memories that may include improper attribution of speech. This is thought to be due to some verbal information being stored in long-term memory in a pathological way, resulting in an interference of language production processes, and sometimes overtaking these processes by creating inner speech that is experienced as unintended, external auditory input (Hoffman & Rapaport, 1999). Investigations into the dysfunction of episodic memory have attempted to manipulate the conditions under which sensory information is encoded. This approach allows memory to be parsed into item memory (content of memory), source memory (context of memory) and response bias (Murnane & Bayen, 1998). Research into item

memory found that when tasks are difficult, schizophrenia patients perform more poorly than healthy controls (Brebion et al, 1997; Seal et al, 1997; Franck et al, 2000), indicating poor memory encoding under these conditions. It is of note, however, that under relatively easy task conditions the difference between schizophrenia and control groups disappears (Vinogradov et al, 1997). For the most part, investigations of source memory, have found that schizophrenia patients with hallucinations show marked deficiencies in discriminating between memories of their own speech and that of another (Brebion et al, 2000; Keefe et al, 2002). Studies in this area, however, have been far from conclusive as deficits in source memory were seen in conjunction with deficits in item memory, indicating that perhaps hallucinating participants are unable to correctly identify speech source as they are unable to remember the event properly in the first place. Curiously, given this context, schizophrenia patients with AHs are still more likely to attribute self-generated speech to an external source. This suggests that there is a general response bias, a tendency to misattribute words they have said or thought to another speaker, associated with those who experience AHs.

Bentall (1990a, b) argues that the tendency to misattribute event source reflects a bias in the sensory attribution system. This bias is thought to be influenced by 'top-down' processes (the patient's expectations about the kinds of events likely to occur); any sudden intrusive thoughts falling outside of these expectations are attributed to an external source. It has been demonstrated that auditory hallucinators have a bias towards attributing internal experiences to external sources under conditions of uncertainty (Bentall & Slade, 1985). Furthermore, hallucinating schizophrenias have been shown to be more likely to misattribute self-generated words to an external source (e.g. an

experimenter) compared to deluded participants (Bentall et al, 1991). This is consistent with Keefe's (1998) suggestion that the positive symptoms of schizophrenia are associated with 'autonoetic agnosia', a deficit in identification of self-generated events.

Bentall's model also argues that the misattribution of internal speech may be subject to reinforcement processes through the reduction of anxiety; it has been suggested that AHs act to reduce cognitive dissonance created by increased anxiety (Delespaul, DeVries, & Van Os, 2002). Similar findings have shown that when intrusive thoughts are inconsistent with global beliefs and values, this leads to the misattribution of these intrusive thoughts as AHs, a mechanism that also serves to reinforce the subject through the reduction of cognitive dissonance (Morrison, Haddock & Tarrier, 1995). This reinforcement may also be obtained for some patients through the experience of 'pleasurable' AHs, a phenomenon found to occur in 26% of patients in one sample (Sanjuan et al, 2004). This same study found pleasurable AHs to be positively associated with chronicity of hallucinations, also suggesting there is some type of reinforcement mechanism at work.

Thus, it appears that there is more than one type of cognitive mechanism driving the phenomenon of AHs; certainly, deficits of verbal self-monitoring, impaired episodic memory, abnormal top-down processing, and a response bias of attributing speech to another during forgetfulness or lack of certainty all play a role. As Seal and colleagues (2004) point out, this conclusion makes intuitive sense as it is "unlikely that any unidimensional model of cognitive dysfunction could account for the diverse and striking experiences reported by hallucinating individuals." (p. 60)

## 1.6 Structural and Functional Anatomy of Auditory Hallucinations

Nearly 170 years ago, psychiatrist Jean-Etienne-Dominique Esquirol (1838) put forward the view that hallucinations are brain-based, instead of due to outside forces such as demonic possession, and that they arise from aberrant brain functioning. Although it is obvious that Esquirol was right in his prediction that hallucinations originate from the brain, the specific brain regions and mechanisms regulating the appearance and intensity of AHs are still unknown.

It has been suggested that the diversity with AH phenomenology could reflect the diversity of responsible neural mechanisms (Stephane et al, 2003). It is not unreasonable to assume that a phenomenon such as auditory hallucinations would be associated with neuroanatomical abnormalities, and while this appears to be true, there is certainly no definitive consensus as to which specific brain structures are implicated in AH. Structural neuroimaging techniques such as computerized axial tomography (CT) and magnetic resonance imaging (MRI), as well as post-mortem analysis of afflicted patients, have shown regional abnormalities associated with hallucinations. Several studies of schizophrenia patients have shown increased ventricular volume, and reduced volume of temporal lobe structures, particularly in the left hemisphere (McLure et al, 1998; Andreasen et al, 1990). A further study specifically examining the correlation between structural abnormalities and AHs showed a significant inverse relationship between hallucination severity and volume of the left superior temporal gyrus (incorporating the auditory association cortex), this in conjunction with the overall smaller superior temporal gyri (bilaterally), left amygdala, and larger third ventricle volume found across schizophrenia patients (hallucinators and non-hallucinators) in general (Barta et al, 1990).

More recent studies using similar techniques have demonstrated a bilateral reduction of auditory association cortex volume in hallucinating patients (Weiss and Heckers, 1999). This finding is paralleled in part by the observation that the severity of AHs appears to be negatively correlated with the volume of the left anterior portion of the superior temporal gyrus (Rajarethinam et al, 2000). Reductions of cerebral volume have also been reported in schizophrenia with respect to hallucinators vs non-hallucinators, where a deficit of the left hemisphere grey matter, including the insula (which is critical in speech production; Dronkers, 1996) extending to the uncus and medial part of the superior temporal gyrus, has been seen (Shapleske et al, 2002). In addition, this study showed a combination of grey-matter deficit with white matter excess. This suggests that excessive connection, due to a failure of neuronal pruning, to aberrant grey-matter may lead to hallucinatory symptoms due to 'cross-talk' between the inner speech and auditory processing modules.

Where the static neuroimaging of these so called 'structural trait' studies comparing hallucinators and non-hallucinators have lacked for volume of research and regional specificity in AHs, functional neuroimaging studies have improved on both of these points. Characterized as 'functional trait' studies when comparing regional cerebral functioning in schizophrenia hallucinators and non-hallucinators, or 'functional state' studies when recording cerebral activity captured during hallucinations, this research has done much to expand our knowledge of brain functioning underlying AHs, as well as their particular neural signature.

Early functional trait studies employing fMRI or cerebral blood flow methodologies pointed to a number of different areas of activation in hallucinators.

Among the most consistent results were decreased activity of the temporal lobes in schizophrenia patients experiencing AHs as compared to controls (Musalek et al, 1989; Cleghorn et al, 1992), however there have also been, in AH patients compared to controls, reports of increased hippocampal activity (Musalek et al, 1988; Musalek et al, 1989), decreased frontal lobe activity (Musalek et al, 1988; Walter et al, 1990), and decreased striatal activity (Walter et al, 1990; Cleghorn et al, 1990). The results of these studies must be interpreted cautiously due to the low resolution of the imaging equipment used, as well as a lack of experimental control in the patients' neuroleptic use. It is also important to consider the intrinsic nature of these studies when reviewing their results; namely that these studies looked at the global cortical functioning of schizophrenia patients who do, at some times, experience AHs, but who were almost certainly not experiencing hallucinations the entire time they were being scanned, and may not have experienced them at all during testing.

As Weiss and Heckers (1999) have stated: "Functional trait studies... give us an estimate of the function of the brain prone to hallucinations, but cannot give us specific data regarding cerebral activity specifically during the hallucinatory state ('functional state')". It is with this in mind that the first so-called 'symptom capture' protocols were put into place, recording participants while they were hallucinating. McGuire et al. (1993) reported increased blood flow to Broca's area, the left anterior cingulate gyrus, and the left temporal lobe during hallucinations, while Suzuki et al.'s (1993) results found that the hallucinatory state was associated with a significant increase of activity in the left superior temporal cortex and anterior cingulate gyrus, closely mirroring the McGuire group's findings. Silbersweig et al. (1995) then introduced a breakthrough

method of tracking the neural signature of the auditory hallucination; scanning patients continually using positron emission tomography (PET) and having them press a button to indicate the start of an AH, then press a second button to indicate the end of the AH. By eliminating confounding factors associated with testing in different sessions, the Silbersweig group (1995) was able to obtain relatively state-specific data showing AHs to be associated with increased bilateral activity of the hippocampus, parahippocampal gyrus, and thalamus, as well as the right ventral striatum and right anterior cingulate gyrus.

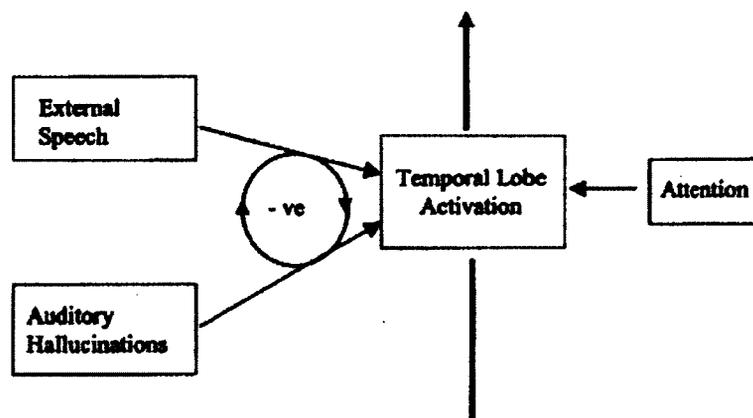
Dierks and colleagues (1999) expanded these findings by showing evidence that the primary auditory cortex is involved in the experience of auditory hallucinations. A similar methodology of having patients indicate hallucinating and quiescent states showed activation of the left inferior parietal and left middle frontal gyrus, the temporal lobes and the frontal lobes, in addition to bilateral activation of the superior temporal gyri (Lennox et al, 2000). However, this latter study also examined the unique activation pattern of each subject, and saw that the anterior cingulate, thalamus, cerebellum, and parahippocampal gyrus were differentially activated among the participants, never showing the same activation pattern, and possibly reflecting the unique nature of the experience for each individual. These studies, as well as others (Woodruff et al, 1997), show that AHs activate the same temporal cortical area activated by verbal auditory speech and inner speech (Shergill et al, 2000), suggesting that hallucinations may compete with exogenous and endogenous sound input for temporal cortical activation. In a recent meta-analysis, it was suggested that the state of experiencing AHs is primarily associated with cortical areas involved in speech production (e.g. Broca's area), while the

trait of being prone to AHs is associated with altered activation of cortical areas involved in speech perception (e.g. auditory cortex; Kuhn & Gallinat, 2010).

Auditory verbal imagery has been used as an easily accessible model for AHs, albeit with mixed results. During auditory verbal imagery, prominent frontal lobe activation has been noted (Silbersweig & Stern, 1998), a finding not replicated in functional imaging studies of AHs. However, it is thought that this frontal activation indicates voluntary conjuring of auditory verbal imagery as compared to the automatic, uncontrolled nature of AHs (Silbersweig & Stern, 1998). Conversely, activation of the primary sensory cortex (thought to be a key event in the experience of AHs as 'real') has been observed in AHs, whereas it has not been observed in consciously controlled auditory verbal imagery studies (McGuire et al., 1996). There are also some key areas of overlapping activation between these two conditions (McGuire et al., 1996); PET imaging has shown both AHs and auditory verbal imagery to activate the anterior cingulate and posterior superior temporal gyrus (STG).

It has been shown that there are alterations of the auditory cortical response to speech in schizophrenia patients with AHs (Woodruff et al., 1997). In patients scanned both during and after AH occurrence, activation of the temporal cortex, specifically the right medial temporal gyrus, was attenuated during AH occurrence when external speech was presented. This result was echoed in a case study involving a patient with chronic AHs; this patient showed elevated activity of the right medial temporal and left superior temporal gyri during the absence of external speech (and, hence, presence of AHs) which disappeared in the presence of real external speech (Bentaleb et al., 2002). Thus it can be seen that AHs activate the auditory cortex, and even compete with external speech for

attentional resources. This model of competition within the auditory cortex has been dubbed the 'saturation hypothesis' (Woodruff et al., 1997) and is demonstrated in Figure 1 (Woodruff, 2004, pg. 82). Accordingly, temporal lobe activation is represented by the vertical arrow in the centre of the figure, with this activation arising from both external speech and auditory hallucinations (as indicated by arrows). The circle between external speech and AH activation indicates a reciprocal relationship between these stimuli, as is indicated by the saturation hypothesis. Finally, temporal lobe activation is modulated by attention, which alters the general responsiveness of the temporal cortex whereby the more attention is allocated to external speech or auditory hallucinations, the greater the temporal lobe activation.



*Figure 1.* Model of the Saturation Hypothesis

It has also been suggested that increased sensitivity to specific speech characteristics increase the chance of experiencing AHs (Woodruff, 2004). Certainly, schizophrenia patients with AHs showed increased auditory cortex responsiveness compared to those patients without AHs (Woodruff et al., 1998). It has been shown in some studies that there is a right lateralized response of the auditory cortex (Woodruff et

al., 1997), that prosodic processing is also mainly lateralized to the right (Buchanon et al., 2000), and that passive listening to happy-sounding vs. happy-meaning speech amplifies this right cortical response in normal controls (Mitchell et al., 2003). However, this latter effect was reversed in schizophrenia patients, with happy-sounding (vs. happy-meaning) sentences enhancing temporal activity on the left side rather than the right (Mitchell & Woodruff, 2001), suggesting that the areas responsible for prosody processing are reversed in schizophrenia. This could result in altered sensitivity to emotional content and problematic semantic processing, which generally occurs in the left temporal cortex.

### 1.7 Attention, and Attentional Deficits in Schizophrenia

Early theories of attention posited that attention selected certain incoming sensory attention for conscious awareness and processing, while filtering out the remaining sensory information. The first of these theories, entitled the early-filter theory (Broadbent, 1958), stated that attention worked in an all-or-nothing fashion, much like a light switch, selecting and filtering sensory information before the sensory signals attain meaning. The result of this being that the filtered sensory information is cast aside forever. This theory was quickly disproved by the work of Cherry (1953), who used a dichotic listening task in which participants shadowed the message in one ear while ignoring stimuli presented in the other. According to the early-filter theory, there should be no meaningful processing of the unattended message under these conditions. Yet, when performing this task, if half of a sentence is presented in one ear and then switches to the other, if the meaning of the shadowed sentence switches to the unshadowed ear, shadowing is disrupted with the participant experiencing confusion and switching to the

unshadowed ear (Treisman, 1960). This led Treisman (1964) to propose a modified theory of attentional filter whereby attention works more like an attenuator, allowing gradation in the amount of sensory information being processed, while still maintaining Broadbent's idea that filtering occurs at the sensory memory level.

Concurrent to the early-selection models, theorists were proposing late-selection filter models, hypothesizing that all input to the sensory receptors activate representations in long-term memory (Deutsch & Deutsch, 1963; Norman, 1968). Each of these long-term memory representations differ in pertinence (how well the representation fits into the context of the situation), with the input that creates the best combination of activation and pertinence being selected to enter awareness. However, it is very difficult to design an experiment that would allow for a response to two different pieces of sensory information. In light of this, the filter model was abandoned, but not before its limitations spawned a new question: why can't we respond to two different pieces of sensory information at once. With that, the capacity model of attention was brought into the theoretical world.

The capacity model of attention (Kahneman, 1973) assumes that our attentional resources are finite; we have only a certain amount of cognitive capacity that can be allocated to various tasks. Seeing as tasks differ in the amount of capacity they require, the number of tasks that can be performed at any one time depend on the attentional demands of each. Following on from that, the attentional resources required by one task will come at the expense of capacity available to other tasks. Knowing this, it is possible to measure the capacity demands of a task.

Within a capacity model of attention, there are capacity limitations. Research in this field has shown that there is an inverse relationship between difficulty of the primary task and performance on a secondary task (Johnston et al, 1970; Britton & Tesser, 1982; Tyler et al, 1979). The most extreme case of capacity limitations would involve serial processing, whereby only one stimulus can be processed at a time, therefore perceptual analysis of one stimulus must be completed before another can begin. The other extreme case is one of parallel processing, whereby multiple stimuli can be processed at the same time, however in a limited capacity model, individual cognitive operations would be slower when processing more than one task at once. The results of the dichotic listening task presented earlier (Treisman, 1960) seem to point to parallel processing, as two different stimuli can be processed at once. However, the resulting confusion from the semantic switch of ears indicates that such an action causes the finite resource of attention to reach its limit. In a groundbreaking study by Lindsay, Taylor, and Forbes (1968), participants were presented a brief tone and a spot, followed by another tone and spot after an inter-stimulus interval of 500ms. This comprised one trial. Each trial could involve any of four judgement tasks: deciding which of the tones was higher in pitch or intensity, and deciding which of the two spots was higher or leftward of the other. Within a block of trials, participants performed one, two or four of the tasks. The more judgements that had to be made, the worse the performance. This seems to suggest that processing occurred in a parallel manner when demands were lower and in a serial manner (resulting in lower accuracy due to sensory memory decay) when task demands were high.

The literature of divided attention appears to present a hybrid model: capacity limits are certainly present beyond a certain point and at a certain difficulty level, task processing appears to operate in a serial manner. While stimulus load is below the capacity limit, however, processing appears to be parallel. Thus, one can expect that a demanding task will monopolize a significant portion of the attentional resources available, causing performance in any other tasks to suffer. Certainly, deficits of attention are well documented in schizophrenia (Laurens et al., 2005; Braff, 1993). It has been noted that patients exhibiting positive symptoms have difficulty directing their attention appropriately (Posner et al., 1988; Maruff et al., 1995) and it has been suggested that attentional deficits in schizophrenia may arise from dysregulation of executive attention control processes (Frith, 1992; Early et al., 1989). Subsequently, patients with schizophrenia often experience an increased vulnerability to distraction by task-irrelevant stimuli (Braff, 1993), which may include AHs. Applying a capacity model theory to auditory hallucinations in schizophrenia, it is not difficult to imagine that the invasive, and often distressing, nature of AHs would usurp attentional resources which may be more appropriately directed to relevant goal-direct behaviours. Thus, even when performing one task visible to an observer, the patient experiencing hallucinations would have divided attention and an already drained capacity of attention. What remains to be seen is how much attention hallucinations demand and how this affects cognitive performance.

## 1.8 Event-Related Potentials

Within the fields of attention and information processing, the electroencephalographically (EEG)-derived event-related potentials (ERPs) provide an exquisitely sensitive method of indexing cognition that can both complement and clarify behavioural observations. The ERP waveform is elicited in response to a specific stimulus, such as tones or light flashes, or cognitive events, such as recognition, decision making or response to specific stimuli events. Specifically, ERPs represent an average of the neural activity that follows the onset of a stimulus. They are extracted from recorded brain activity by averaging an EEG window (called an epoch) that is time-locked to a specific stimulus or behavioural event, causing the random background noise of the EEG to cancel to zero, leaving behind a constant and invariant waveform. When recorded concurrently with behavioural measures of task performance, ERPs provide a fuller picture of the cognitive features underlying different arousal, mood and psychiatric states.

The averaged ERP plots voltage (microvolts:  $\mu\text{V}$ ) as a function of time (milliseconds: ms); the resultant waveform appears as a series of deflections or peaks. Conventionally, these components are described in terms of polarity (positive peaks labeled P; negative peaks labeled N), and sequence (ordinal position of peak) or peak latency of where the ERP typically occurs. In this manner, the third positive peak in the waveform may be labeled the P3 or the P300, as it is expected to occur approximately 300 ms after stimulus onset.

Classification of ERPs is generally divided into two types: the early-occurring exogenous components, and the later endogenous components. The exogenous ERPs are generally those occurring within 100 ms of stimulus onset and are so named because their

respective amplitudes and latencies are primarily determined by the properties of the eliciting stimulus, such as intensity and rate (Friedman & Squires-Wheeler, 1994). As such, they are relatively insensitive to psychological variables such as mood and attention (Roth, 1977). These ERPs are mainly generated in the primary sensory cortex and association areas of the brain (Chiappa, 1990). By contrast, the endogenous ERP components (latency > 100ms) are highly influenced by cognitive and psychological variables manifest upon the subject and are relatively independent of eliciting stimulus' physical characteristics (Pritchard et al, 1986).

The primary advantage of ERPs resides in the fact that one can probe aspects of information processing without requiring any active, overt response on the part of the subject, thus making them ideal in the cognitive study of psychiatric populations, which may be unable to perform behavioural tasks due to cognitive and/or motor deficits. Furthermore, ERPs provide a temporal resolution far superior to some of the more sophisticated imaging techniques (i.e. PET, fMRI), making this methodology far more suitable for capturing instantaneous changes in information processes. The auditory mismatch negativity (MMN) waveform, in particular, can be especially useful as not only does it not require any behavioural response, it does not even require the subject's attention to the stimuli due to its intrinsic nature as an index of automatic sensory perception (Näätänen, 2003). The MMN has also shown good test-retest stability across multiple sessions spaced up to one month apart (Pekkonen, Rinne & Näätänen, 1995), making it an excellent tool for assessing clinical populations over the course of an illness. In addition, the MMN is an inexpensive and easy to use tool which has been shown to objectively index general brain deterioration in clinical populations (Näätänen, 2000).

### 1.8.1 Mismatch Negativity

The mismatch negativity is an event-related potential that is elicited by any discriminable change in auditory stimulation; the resulting waveform is a negative peak with a frontal-topography maximum amplitude and an expected peak latency of 90-250ms. Generally, the MMN is generated by randomly inserting low-probability (i.e. rare) deviant auditory stimuli into a train of repetitive (i.e. standard) sounds. These auditory stimuli may deviate in any number of ways from the standard, with deviations in frequency, duration, intensity and location eliciting an MMN (Näätänen & Ahlo, 1997). Notable is the fact that the MMN occurs irrespective of whether or not one is consciously aware of, or attending to, such a change (Näätänen, 1982; Näätänen, 1992). The automaticity of the MMN generator processes is provided by findings of MMN being recorded, albeit with smaller amplitudes, in anesthetized animals (Ruusuvirta, Penttonen, & Korhonen, 1998), coma patients (Kane, Butler & Simpson, 2000), as well as during Stage-2 and Rapid Eye Movement (REM) sleep (Sabri, DeLugt & Campbell, 2000; Saalinen, Kaartinen, & Lyytinen, 1996). It is thought that the MMN is generated in response to a comparison of the novel stimulus with a well-formed sensory or 'echoic' memory trace of the standard auditory stimulus. When the incoming auditory stimulus differs from the existing memory trace, the MMN is generated.

Given the MMN's association with auditory sensory information processing, it makes sense that MMN generators are located bilaterally in the left and right supratemporal lobes, specifically in the auditory cortex (Rinne et al., 1999). Furthermore, different areas of the auditory cortex are associated with MMN generation in response to different deviances of auditory information. MMNs to linguistic information (i.e.

phonemes) on the other hand are generated in the left auditory cortex, specifically in the region of Wernicke's area (Rinne et al., 1999). In addition to the MMN generators in the temporal lobes, which are responsible for detection of sensory auditory deviance, there are also right-hemisphere dominant MMN generators in the frontal lobes. These generators are associated with involuntary attention switching to relevant stimuli (Giard et al., 1990), and it is thought that activation of the frontal MMN generators is triggered by the auditory cortex following detection of salient information. This is supported by data demonstrating a slight delay in frontal activation following auditory cortex activation (Rinne et al., 2000).

Within Näätänen's model (1992), automatic detection and processing of auditory stimuli, irrespective of focused attention on the stimuli, has two main functions: extraction of sensory information from the environment and switching of attention to novel, and potentially relevant, changes in the auditory environment. These occur during the short phase of sensory memory, lasting 150-200ms from stimulus onset, while the sensory features of the incoming information is integrated with those of the preceding stimulation. Within this model, the result of the completed sensory analysis is a stimulus representation as opposed to a fixed memory. Past auditory stimuli are then held in a pure-memory long phase auditory store, sometimes called echoic memory (Neisser, 1967), which fades after 10-20 seconds unless new representations are added. An essential part of this model is that stimulus processing is automatic, and, therefore, does not require or imply conscious sound perception. When a discrepancy is detected in the short memory phase between the incoming stimulus and past stimuli representation, a mismatch signal is generated to indicate the detection of acoustic change and an interrupt

signal is sent to the executive mechanisms (Näätänen, 1986). This signal may lead to conscious perception of the deviant acoustic stimuli if the signal is strong enough, and whether or not attention is strongly focused elsewhere.

The strength and speed (i.e. latency) of the MMN signal produced is related to both the size of the deviance (i.e. how different the novel stimuli is from the defined memory trace) and the probability of the deviance occurring and is independent of the requirements of the task. When attention is directed to the auditory stimuli in an anticipatory way, even weak stimuli may be perceived consciously. By contrast, if attention is strongly focused elsewhere, such as a primary task, it would require a very intrusive or salient stimulus to penetrate into consciousness. Should this happen, the stimulus is then evaluated to determine whether it is significant or not; insignificant stimuli are quickly discarded and attention is re-directed back to the original task without conscious perception of the intrusive sound, whereas significant stimuli, such as a threat or the sound of one's own name, will likely result in conscious perception of the stimulus and attention being switched to its source (Näätänen, 1992).

Paying attention to the MMN-eliciting stimuli can cause other deviant-related ERP components, such as the later occurring negativity at 200ms (N2b), which may overlap temporally and spatially with the MMN. The confounding influence of N2b-related processes in MMN studies can be controlled for by varying the nature/difficulty of a diversion task (e.g. reading a book, watching a movie, performing a visual task) during MMN elicitation, thus reducing the possibility of N2b contamination as attention is not actively directed to the auditory channel in which the MMN-eliciting stimuli are presented (Muller-Gass et al, 2005).

While the MMN is generally elicited in a laboratory using pure tones as both standard and deviant stimuli, this ERP component has proved sensitive to a wide range of simple and complex sounds, including speech. Used as an index of discrimination of linguistic stimuli, such as phonemes and consonant-vowel (CV) syllables, MMN amplitudes generally increase with easier discriminations and diminish, or are not elicited, if two phonemes or syllables are not discriminated by participants (Näätänen, 2001). Using a dense electrode array to examine regionalized hemispheric specialization of early auditory processing of non-phonetic (tones) and phonetic (vowels) sounds, Rinne and colleagues (1999) reported left-hemisphere (over the superior temporal gyrus) maximum MMN amplitudes in response to phonemes and stronger right hemisphere activation in response to tone like sounds. This early, pre-attentive, left-hemisphere predominant MMN indexing of auditory analysis of phonetic features is not evident with MMNs elicited by complex tones or foreign language phonemes (Näätänen et al, 1997). These observations support the classic view that the left hemisphere processes phonetic or semantic aspects of stimuli and is reinforced by the finding that magnetic MMNs elicited by duration changes in speech sounds are left hemisphere maximum while duration changes evoked by non-speech sounds are right hemisphere dominant (Takegatu et al, 2004). MMN has also been used as an index of voice discriminability, as shown in one study where participants were presented with a repetitive vowel sound spoken by a female which was interspersed with four 'deviant' stimuli consisting of the same vowel sound pronounced by a male speaker or one of three different female speakers (Titova & Näätänen, 2001). Here, an MMN was elicited by all deviant voices; the more dissimilar the deviant voice was (as rated by the participants), the larger the amplitude of the MMN.

It has also been demonstrated that native speakers exhibit a larger MMN to similar vowel sounds in their own language, as opposed to non-native speakers, to whom the discernable difference between the vowel sounds is presumably smaller (Peltola et al, 2003; Winkler et al, 1998; Näätänen et al, 1997). Subsequent magnetic measurements of this mother-tongue MMN (MMNm) enhancement in a Finnish population showed the left auditory cortex, specifically Wernicke's area, to be the focus of this effect (Rinne et al, 1999). A similar study, this time probing the effect of voice familiarity on the MMN, presented a single vowel (the /a/ in the French word "allô") to healthy control participants in three different voices: a standard ( $p = 0.85$ ), unfamiliar voice, an infrequent ( $p = 0.075$ ) unfamiliar voice, and an infrequent ( $p = 0.075$ ) familiar voice (Beauchemin et al., 2006). This resulted in a significantly larger MMN to the familiar voice (vs. the unfamiliar voice) at fronto-central sites and a larger MMN, albeit not significantly so, at frontal recording sites. When compared to a control group, for whom none of the voices were familiar, there was no significant difference in responses to the unfamiliar voices, however the experimental group showed significantly larger MMN amplitudes to the familiar voices. This suggests that the brain may be especially tuned to familiar voices as opposed to unfamiliar voices, perhaps due to a previously formed long-term memory trace for the familiar voice (Beauchemin et al., 2006). This result further suggests that, as previously suggested (Huotilainen, Kujala & Alku., 2001), there is a direct link between long-term memory and the feature-analysis system of short-term memory that detects acoustic features of stimuli.

The mismatch negativity, despite being predominantly moderated by 'bottom-up' processes, also appears to some degree, under specific conditions, sensitive to 'top-down'

processes including the availability of attentional resources. High demand processing tasks result in a significant decrease in MMN amplitude; as more resources are required for processing of a primary task, there is a corresponding drop-off in resources available to the MMN generator (Kramer et al, 1995). The lowered effectiveness of the generator is seen in the reduction of MMN amplitude.

MMN amplitude also seems to be sensitive to the nature of the diversion task used. The MMN elicited by to-be ignored intensity deviants was attenuated when participants were counting targets presented to the opposite ear, as opposed to when reading (Näätänen et al, 1993). This difference has been attributed to the greater attentional focus required by the counting task. A similar result of dampened MMN during a dichotic listening task as compared to reading as a diversion has been since replicated (Alain & Woods, 1997), indicating that MMN is indeed modulated with the diversion task, again implicating processing resource capacity as an important modulator of the mismatch negativity. However, a recent study reported that a diversionary task may, via increased cortical excitability, actually increase MMN amplitude (Muller-Gass, Stelmack, Campbell, 2005). Related to the issue of the effects of diversionary tasks on the MMN-indexed early auditory processes are studies focusing on the effects of sound context on hemispheric processing of speech stimuli. The finding that CV syllable deviants elicit a stronger MMNm in the right hemisphere when embedded in either a speech-sound or non-speech sound context than when presented alone (where the left-hemisphere MMNm is stronger than the right) has been interpreted to reflect a general right-hemisphere specialization for the analysis of contextual acoustic information (Kujala et al, 2002). A number of behavioural studies have also suggested that the basic

functional asymmetry of central speech processing is affected by acoustical disturbances, including background noise. For example, inactivation of the right hemisphere, but not of the left hemisphere by electroconvulsive therapy has worsened word perception in noisy backgrounds (Balonov & Deglin, 1970). As well, during dichotic listening tasks, perception of words presented to the right ear, but not the left ear, decreased in the context of noise as compared with silence (Galoonov, Korolyova, & Shourgaya, 1988; Koroleva & Shurgaya, 1997). In an investigation of background noise influence on magnetic brain responses to spoken sentences, noise was found to affect syntactical processes in both hemispheres but altered early auditory processes only in the right hemisphere (Herrmann et al, 2000). With respect to MMNs, CV-syllable deviants presented against a white noise background (vs. silence), while not affecting behavioural discriminability, diminished MMNm in the left hemisphere, increased MMN amplitude in the right hemisphere (Shtyrov et al, 1998), and increased activation of additional right auditory cortical structures not evidenced in silence (Shtyrov et al, 1999). Thus it seems that the addition of noise competitors at intensities which reduce speech/sound discriminability results in diminished MMNs (Salo et al, 1994; Martin et al, 1997; Martin et al, 1999) and displaces MMN-related activity to the right hemisphere during speech discrimination (Muller-Gass et al, 2001), presumably due to effects on peripheral auditory mechanisms (i.e. by shifting thresholds or reducing audibility). However, the findings by Shtyrov and colleagues suggest that these noise competitors also impact on central auditory processing in a manner that decreases involvement of the left hemisphere, while involvement of the right hemisphere increases. That there is more to hearing in noise competition than just the audibility of the signal at the peripheral

auditory level is supported by the observations that various background conditions result in different effects on speech recognition performance compared to silent conditions. Speech recognition performance is more deleteriously affected by speech competitors than non-speech competitors (Garstecki & Mulac, 1974; Van Tasell & Yanz, 1987), and is more affected by meaningful speech competitors than non-meaningful speech competitors (Sperry et al, 1997). MMN indexing of the effect of different types of real-life noises on central auditory processing of speech (CV-syllables) has shown MMNs to speech stimuli to be affected by noises more than non-speech stimuli. As well, whereas industrial noises and babble noises reduced MMNs to both stimulus types, only speech elicited MMNs were diminished by traffic noise (Kozou et al, 2005).

Considering the apparent involvement of a dysfunctional left hemisphere auditory cortex in hallucinatory experiences of schizophrenia patients, the modulating role of auditory competitors on hallucinations, and the sensitivity of MMN in indexing hemispheric asymmetric shifts in early central auditory processing, MMN may be a particularly suitable tool for probing brain mechanisms underlying hallucinations in schizophrenia.

### 1.8.2 MMN and Schizophrenia

Given the cognitive deficits associated with schizophrenia, and the view that the MMN provides a useful index of pre-attentive cognition, research into the mismatch negativity in affected patients has been a major point of interest since the first study linking the two was published (Shelley et al, 1991). In general, chronic schizophrenia patients exhibit robust MMN deficits (Javitt et al, 1993; Umbricht et al, 2003; Youn et al,

2002), especially to duration deviants (Michie, 2001), however MMN reduction in schizophrenia has been reported with frequency (Javitt et al., 1993; Hirayasu et al., 1998; Todd et al., 2008), intensity (Fisher et al., 2008a; Todd et al., 2008) and location (Alain et al., 2002) deviants as well. Methodologically, much of this work has employed a classic two-stimulus auditory oddball, whereby a rare auditory deviant is presented randomly within a train of repetitive standards. This approach has several drawbacks, particularly when testing clinical populations such as patients with schizophrenia. The most notable of these is that, given the time requirements of these paradigms, it is not feasible to obtain responses to more than two different deviant types. However, recent work has suggested that use of a multi-feature MMN paradigm, whereby MMNs to five deviants can be recorded in a relatively short period, is not only feasible (Fisher et al., 2008a), but indeed optimal as this paradigm is not only more efficient, but has shown increased sensitivity compared to traditional MMN tasks (Thonnessen et al., 2008). As different MMN deviant types may differentially probe information processing deficits, use of a multi-feature MMN paradigm will allow for greater accuracy in profiling these deficits (Thonnessen et al., 2008).

Though much of the work examining the MMN in schizophrenia has chosen to employ pure tone stimuli with deviations in simple sound features (Umbricht & Krjles, 2005), some studies have utilized speech sounds. In Kasai and colleagues' (2002) work examining preattentive perception of speech sounds in schizophrenia, participants were exposed to three different tasks designed to elicit MMN in response to changes in pure tone duration, changes in duration of a spoken vowel (Japanese vowel /a/) and across-phoneme (Japanese vowel /a/ vs. Japanese vowel /o/) changes. The results of this study

showed no difference in ERP amplitudes between schizophrenia patients and a matched sample of healthy controls for either the pure tone or vowel duration tasks. However, the schizophrenia patients (vs. controls) did exhibit abnormal lateralization during the phoneme duration task, as well as lower MMN amplitudes in both hemispheres in the across phoneme condition. That MMN amplitude was only affected within the across-phoneme condition suggests that schizophrenia is associated with dysfunction of the comparative processes of stimulus encoding, while formation and maintenance of sensory memory remains intact. Although not specifically examined in relation to hallucinatory symptomatology in these patients, the abnormal lateralization of the MMN during the phoneme duration condition in the absence of altered MMN amplitudes could be indicative of AH-modulated altered speech processing within schizophrenia.

The deficits observed in MMN generation appear to be somewhat specific to schizophrenia, as there have been no reported MMN alterations in any of the other major psychiatric disorders such as depression or bipolar disorder (Catts et al, 1995; Umbricht, 2003). This suggests that, within chronic schizophrenia, there is impairment of auditory sensory memory and context-dependent information processing at the level of the primary and secondary auditory cortices (Umbricht & Krljes, 2005).

MMN deficits have been shown to be associated with faulty NMDA receptor function in both animals (Javitt et al, 1996) and humans (Umbricht et al, 2000, 2004). It has been suggested that NMDA receptor deficiency is not only responsible for the observed MMN deficiencies, but also for the deficits in auditory discrimination commonly seen in schizophrenia patients (Javitt et al., 1996). These receptor deficiencies could be due to a loss of dendritic spines, a primary location of NMDA receptors

(Nimchinsky et al, 2002). Dendritic abnormalities, including loss of spines, have been previously noted in schizophrenia (Glantz & Lewis, 2000; Salisbury et al, 2004). Further evidence of the connection between NMDA receptors and the MMN stems from reports that memantine, an NMDA receptor blocker, increases MMN amplitude in healthy participants (Korostenskaja et al., 2007). However, several common antipsychotics with NMDA action, including clozapine (Umbricht et al., 1998), risperidone (Umbricht et al., 1999; Korostenskaja et al., 2006) and olanzapine (Korostenskaja et al., 2005) do not enhance MMN amplitude in schizophrenia, indicating that deficient NMDA receptor activation cannot completely account for the MMN deficits reported in schizophrenia.

In addition, MMN deficits appear to become more prominent as the probability of the deviant stimulus decreases (Umbricht & Krljes, 2005), an important finding given that the effect of deviant probability is thought to reflect efficiency of standard stimulus encoding. Pursuant to this, MMN deficits relative to controls are unaffected by prolonged ISIs, as demonstrated by a series of studies that found MMN amplitude in schizophrenia patients relative to controls was unaffected by ISIs ranging up to 3s (Javitt et al., 1998) and even as long as 4.5s (Shelley et al., 1999). Together, these findings support a view that the attenuation of MMN amplitudes in schizophrenia patients (vs. controls) is likely due to deficient stimulus encoding in schizophrenia, as opposed to faster decay of memory traces. This is further supported by reports of impaired tone-matching performance in patients being positively correlated with reduced MMN amplitude (Javitt, Shelley, & Ritter, 2000).

It is of note that the majority of studies examining MMN in schizophrenia make little or no effort to examine the effects of the associated syndromes or symptoms, a

troubling finding given the heterogeneous nature of the disease. Specific to this work, there has been minimal systematic study examining whether auditory hallucinations make a unique contribution to the overall deficit in mismatch negativity generation. This is surprising, given how well suited the MMN is to index AHs, especially in the context of previous work by Kozou et al (2005), whereby background noise (in this case as a sort of cocktail party effect) attenuates MMN amplitude. Pursuant to this, one could imagine that further distraction would attenuate the MMN further if AHs do indeed monopolize cognitive attentional resources. One study that did examine the correlation between MMN and auditory hallucinations, as measured by the Positive and Negative Syndromes Scale (Kay et al, 1987), found an initial correlation that disappeared upon follow-up analysis using a Bonferroni procedure (Hirayasu et al., 1998). Three other earlier studies looked for a correlation between MMN and auditory hallucinations: of these, one found no significant effect; however, it used a vague measure of hallucinations (Schall et al, 1999), while another divided patients with schizophrenia and schizoaffective disorder into groups of high- and low-level hallucinators by way of median split rather than grouping according to absolute presence vs.0 absence of AHs, and reported no difference in MMN amplitude between groups (Oades et al., 1996). The final study found a significant negative correlation between a measure of hallucinatory behaviour and left MMN equivalent current dipole power (Youn et al, 2002).

More recently, studies have been conducted examining the contribution of auditory hallucinations to MMN amplitude reduction in schizophrenia. One such study, examining the processing of speech and non-speech sounds in hallucinating (HP) and non-hallucinating (NP) schizophrenia patients (Fisher et al., 2008b), reported no

significant between-group differences, however there were interesting within-group patterns that emerged. The healthy controls exhibited significantly larger amplitudes to across phoneme deviants than to phoneme duration deviants. This finding, was mirrored in the NP group, but not in the HP group who exhibited similar frontal MMN amplitudes to all three deviant types. The absence of differential sensitivity of the anterior MMNs to different deviants suggests that each was processed in a similar manner by the HP group, perhaps due to some level of frontal lobe dysfunction. In fact, this infers that, in hallucinating patients, the across phoneme changes were not given enough “weight” (i.e. not allocated proper significance by the frontal lobes). This improper “weighting” of incoming stimuli could illuminate the mechanism underlying the presence of AHs: perhaps hallucinating patients’ own inner speech is not properly weighted to indicate its significance, therefore one’s own speech is processed similarly to the speech of another. If both incoming and self-generated speech are processed the same way, with no discrimination between them, it is reasonable to expect that they are experienced as being the same, thereby causing the belief that one’s own speech is alien in origin.

### 1.9 Summary, General Objectives and Overall Hypotheses

As more emphasis is placed on investigating individual symptoms within schizophrenia, the study of auditory hallucinations is becoming a larger field within research into this devastating illness. With this new found scientific focus, we move closer to understanding the underlying causes and nature of AHs. Although no comprehensive neurocognitive theory has satisfactorily explained why AHs are *perceived* in the absence of an external stimulus, brain-based approaches employing functional

neuroimaging to study these mental phenomena *in vivo* have progressed our understanding of the neural basis of hallucinations. Reports of abnormal activation of the left primary auditory cortex by the experience of AHs and its inhibition by external speech suggests, as several studies have indicated (Barta et al., 1997; Barta et al., 1990), that experiencing AHs and listening to external speech might be subserved by some common neurological substrates. If the final common path to AH experiences lies within the auditory cortex itself, it is reasonable to ask whether the temporal cortex of hallucinating patients processes sounds and speech normally; whether it is predisposed to aberrantly respond to contextual aspects of auditory input which may influence AH hallucinatory experience. Insights into the predisposition of the temporal cortex to respond to specific aspects of auditory signals preferentially is provided with positron emission tomography (PET), which has demonstrated that human brain regions involving the superior temporal gyrus (including the left planum temporale) respond specifically to voices as opposed to environmental sounds (Belin et al., 2000).

The degree to which this differential responsivity may reflect early pre-attentive processes, which may be uniquely dysfunctional in hallucinating schizophrenia patients, has only begun to be explored. However, the MMN, used to probe auditory central processing on a millisecond basis with no attentional task requirements, has consistently reported discrimination of speech sounds (vs. non-speech sounds) to occur predominantly in the left hemisphere (Rinne et al., 1999; Shtyrov et al., 2000; Takegata et al., 2004). In the limited research examining differences between the discrimination of speech and non-speech sounds in schizophrenia, patients have shown greater MMN amplitude deficits (compared to healthy volunteers) in the detection of phoneme (vowel) changes than in the

detection of non-phoneme (tone) changes (Kasai et al., 2002). Investigation into the influence of AHs on the processing of speech sounds (as indexed by the MMN) showed no statistical difference between hallucinating and non-hallucinating patient subgroups at frontal sites, despite different patterns of response to speech and tone stimuli within these groups and an overall deficit in MMN amplitudes for schizophrenia patients as a whole (Fisher et al., 2008b). Specifically, both the non-hallucinating and hallucinating patient groups exhibited significantly larger MMN amplitudes to across-phoneme auditory deviants (vs. phoneme duration and pure tone duration deviants), thought to be highly relevant in human auditory processing, while there was no difference in MMN amplitude across deviant types in hallucinating patients. This not only indicated that patient subgroups may show a differential MMN response, but suggested that the underlying mechanisms of auditory hallucinations may impact the processing of incoming auditory deviance. While these studies have revealed interesting differences moderated by hallucinatory symptomatology in schizophrenia, they have been limited by relatively modest hallucinatory activity as a result of limiting recruitment to controlled, stabilized patients. As suggested by the authors, in order to best understand the impact of auditory hallucinations on automatic, pre-conscious auditory processing, assessment of a population at peak intensity hallucinatory activity would be ideal.

## CHAPTER 2: MISMATCH NEGATIVITY IN SCHIZOPHRENIA WITH AND WITHOUT AUDITORY HALLUCINATIONS AS MEASURED BY A MULTI-FEATURE PARADIGM (Experiment 1)

### 2.1 Introduction

Despite being predominantly moderated by ‘bottom-up’ processes, the mismatch negativity also appears to be, under specific conditions, sensitive to ‘top-down’ processes including the availability of attentional resources. High demand processing tasks result in a significant decrease in MMN amplitude; as more resources are required for processing of a primary task, there is a corresponding drop-off in resources available to the MMN generator (Kramer et al., 1995; Alain & Woods, 1997). The lowered effectiveness of the generator is seen in the reduction of MMN amplitude. In addition, the MMN is an inexpensive and easy to use tool which has been shown to objectively index general brain deterioration in clinical populations (Näätänen, 2000), and is insensitive to medication effects, as neither anxiolytics (Kasai et al., 2002), haloperidol (Pekkonen et al., 2002), clozapine (Umbricht et al., 1998), risperidone (Umbricht et al., 1999) or olanzapine (Korostenskaja et al., 2005) affect the MMN.

In general, chronic schizophrenic patients exhibit robust auditory MMN deficits, with reduced amplitudes being consistently evident with duration deviants, and, to a lesser extent, with pitch deviants (Javitt et al., 1993; Michie, 2001; Umbricht et al., 2003; Youn et al., 2002). This deficit in MMN generation appears to be somewhat specific to schizophrenia, as there have been no reported MMN alterations in any of the other major psychiatric disorders such as depression or bipolar disorder (Catts et al., 1995; Umbricht et al., 2003). This suggests that, within chronic schizophrenia, there is impairment of

auditory sensory memory and context-dependent information processing at the level of the primary and secondary auditory cortices (Umbricht & Krljes, 2005).

It is of note that the majority of studies examining MMN in schizophrenia make little or no effort to examine the effects of the associated syndromes or symptoms, a troubling finding given the heterogeneous nature of the disease. Several studies, however, have examined the impact of AHs on the MMN through post-hoc correlations with symptom scale-derived hallucination ratings (Hirayasu et al., 1998; Schall et al., 1999; Youn et al., 2003; Kasai et al., 2002) and one study has directly examined patients with schizophrenia and schizoaffective disorder divided into groups of high- and low- level hallucinators (Oades et al., 1996), although this latter study used a median split rather than grouping according to absolute presence vs absence of AHs. As yet, there has been no systematic study directly examining whether auditory hallucinations make a unique contribution to the overall deficit in mismatch negativity generation. This is surprising, given how well suited the MMN is to index AHs, especially in the context of previous work by Kozou et al (2005), whereby background noise (in this case as a sort of cocktail party effect) attenuates MMN amplitude. Pursuant to this, one could imagine that further distraction would attenuate the MMN further if AHs do indeed monopolize cognitive attentional resources.

The primary objective of this study was to isolate a particular symptom of schizophrenia, auditory hallucinations, and quantify MMN differences between those expressing this symptom and those who did not, in order to examine the unique contribution auditory hallucinations make to acoustic change detection deficits observed in schizophrenia.

## 2.2 Materials and Methods

### 2.2.1 Experimental Participants

Twenty-four experimental volunteers, all presenting with a primary diagnosis of schizophrenia, were recruited from the Outpatient Schizophrenia Clinic of the Royal Ottawa Mental Health Centre (ROMHC). During an initial clinical interview (with the primary care physician) in which volunteers were assessed with respect to inclusion and exclusion criteria, both clinical history and ratings on the Positive and Negative Syndrome Scale (PANSS) for schizophrenia (Kay et al., 1989) were used for allocation of volunteers to hallucinating patient (HP) and non-hallucinating patient (NP) groupings. HPs (n=12; 9 males) were patients reporting a definite, consistent history of AHs over the course of their illness, exhibiting a score  $\geq 3$  (mild or greater hallucinatory experiences) on the hallucination item of the PANSS positive symptom scale (based on self-reported symptoms over the past month), and NPs (n=12; 10 males) were patients exhibiting a score of 1 on this item (hallucinatory experiences absent) and no previous consistent history of AHs.

The presence and/or absence of AHs were subsequently confirmed by the experimenter, who rated the patients on the AH subscale of the Psychotic Symptom Rating Scale (PSYRATS). This 11-item, 5-point (0-4) rating scale assesses hallucinations with respect to frequency, duration, severity and intensity of distress and also symptom specific dimensions of controllability, loudness, location, negative content, degree of negative content, beliefs about origin of voices, and disruption. HP and NP groups were matched as closely as possible with respect to age, gender, PANSS scores

(Positive Scale, Negative Scale and General Psychopathology Scale) and medication dosage (clinical equivalence in schizophrenia rating; Bezchlibnyk-Butler & Jeffries, 2005). A summary of participant demographics is given in table 1.

The study was conducted following approval of both the ROMHC and Carleton University Research Ethics Boards.

	HP	NP	HC
Age	44.25 (3.16)	45.67 (3.16)	39.75 (3.16)
Rx Clinical Equivalent in SCZ	5.00 (0.67)	3.17 (1.58)	-
PANSS Positive	16.45 (0.98)	11.00 (1.20)	-
PANSS Negative	14.45 (1.22)	13.75 (1.51)	-
PANSS General	27.73 (1.84)	21.25 (4.31)	-
PANSS Hallucination Item	3.64 (0.19)	-	-
PSYRATS	28.67 (0.69)	-	-

Table 1. Summary of participant demographics (mean  $\pm$ SE). \* = significant difference between groups ( $p < .05$ )

All patient participants were to be between the ages of 18-65. Patients were to be judged as clinically stable for the four weeks prior to testing (as indicated by no significant changes in symptoms or medications) and their primary medication was to be limited to one of the atypical anti-psychotics. All participants were required to understand spoken and written English, though participants were allowed to have a first language other than English. Due to the auditory requirements of the study, all participants had to demonstrate normal hearing according to an audiometric assessment, conducted by the primary investigator in the research laboratory, requiring thresholds of 25 dB (SPL) or

less (using a 'descending method of limits' procedure) to pure tones of 500 Hz, 1000 Hz, and 2000 Hz.

Participants were excluded if they meet any of the following criteria: co-morbid DSM-IV TR Axis I disorder; total PANSS score >65, reflecting an acute psychotic episode; current history of drug abuse or dependence; history of head injury resulting in loss of consciousness; diagnosis of epilepsy or any other neurologic disorder; electroconvulsive therapy (ECT) treatment within the previous year; significant cardiac illness; extrapyramidal symptoms (EPS) resulting in movement disorders which could affect ERP recordings; or abnormal audiometric assessment.

### 2.2.2 Control Participants

Twelve normal healthy control participants (HC; 7 males) were required to self-report negative psychiatric, medical, neurological and alcohol/drug abuse histories, to report non-use of medications, and display normal hearing, as above. Experimental and control groups were matched as closely as possible with respect to age and gender.

### 2.2.3 Study Procedure

Volunteers attended the laboratory for one test session. Testing was conducted around midday (11:00am-2:00pm) with participants being required to abstain from illicit drugs, medications (except for anti-psychotics and adjunct drugs), and alcohol beginning at midnight of the previous day. Upon arrival at the laboratory participants completed demographic questionnaires and underwent audiometric assessment. Following this, EEG electrodes were applied and volunteers were assessed using the continuous performance

multi-feature MMN paradigm (Näätänen, 2004), during which they were instructed to view a silent, neutral emotive video and to ignore the presented auditory stimuli.

#### 2.2.4 Hallucination Ratings

Hallucination ratings in HPs were assessed during the test session in order to assess the presence/absence of hallucination activity during the study. Subjective ratings were carried out in a manner similar to that used by Margo et al (1981), requiring volunteers to assess hallucinations experienced during the recordings on 3 dimensions: 1) duration (0 = no AHs; 7 = continuous AHs); 2) loudness (0 = not audible; 7 = extremely loud); and 3) clarity (0 = unintelligible; 7 = very clear). Overall, HPs reported mean ( $\pm$ SE) scores of 3.04 (0.33) for duration, 2.02 (0.20) for loudness, and 2.10 (0.29) for clarity of hallucinations experienced during the test session.

#### 2.2.5 Task Stimuli

In the multi-feature MMN paradigm, the standard stimuli were tones of 75 ms duration (including 5 ms rise and fall) composed of 3 sinusoidal partials of 500, 1000 and 1500 Hz. Note that the intensity of the 1000 Hz and 1500 Hz partials were lower than that of the 500 Hz by 3 dB and 6dB, respectively.

The deviant tones differed from the standard tones in frequency, duration, intensity, perceived location of sound origin or contained a gap in the middle of the tone. Except where stated, the deviants were identical to the standards. Presented through headphones, all stimuli (with the exception of the intensity deviants) were at a sound pressure level (SPL) of 70 dB with equal phase intensity in each channel. Half of the

frequency deviants were 10% higher (composed of 550, 1100, 1650 Hz partials) while the other half were 10% lower (450, 900 and 1350 Hz partials). Half of the intensity deviants were at 60 dB while the other half were at 80 dB. The perceived difference between the standard tone and the location deviant was approximately 90°; the change in perceived location of sound origin was obtained by creating a time difference of 800µs for half of the location deviants to the right channel and half of the deviants to the left. The duration deviant was only 25 ms, while the gap deviant was created by removing 7 ms (including 1 ms rise and fall) from the middle of the standard stimulus.

In each sequence, the first 15 tones were standards, followed by a sequence whereby every second tone as a standard ( $P = 0.5$ ) and every other one was one of the five deviants ( $P = 0.1$  each). The deviants were presented so that each deviant category was presented once every 5 deviants and 2 deviants of the same category were never presented consecutively. The interstimulus interval (ISI) was 500ms, and the stimuli were presented in 3 sequences of 5 minutes each (1845 stimuli) for a total of 15 minutes (5535 stimuli).

#### 2.2.6 EEG Recording and ERP Computation

MMNs were extracted from EEG activity recorded with an electrode cap with  $\text{Ag}^+/\text{Ag}^+-\text{Cl}^-$  ring electrodes at thirty-two scalp sites according to the 10-20 system of electrode placement, including three midline sites (frontal [ $F_z$ ], central [ $C_z$ ], parietal [ $P_z$ ]), as well as three left hemisphere (frontal [ $F_3$ ], central [ $C_3$ ], parietal [ $P_3$ ]) and three right hemisphere (frontal [ $F_4$ ], central [ $C_4$ ], parietal [ $P_4$ ]) scalp sites. Electrodes were also used to record left (LM) and right (RM) mastoid activity and electrodes were also placed on

the mid-forehead and nose to serve as ground and reference, respectively. Bipolar recordings of horizontal (HEOG) and vertical (VEOG) electro-oculogram activity were taken from supra-/sub-orbital and external canthi sites, respectively. All electrode impedances were kept below 5k $\Omega$ . Electrical activity was recorded using BrainVision Recorder software with an amplifier bandpass of 0.1 and 30 Hz, digitized at 500 Hz, and stored on hard-disk for later off-line analysis using BrainVision Analyzer software.

Electrical epochs (500 ms duration, beginning 100 ms pre-stimulus) were corrected for eye movement and eye blink activity using the Gratton & Coles algorithm which operates in the time and frequency domain (Gratton, Coles & Donchin, 1983). Any corrected epochs with EEG voltages exceeding  $\pm 100 \mu\text{V}$  were excluded from further analysis.

Epochs were separately averaged for each standard and deviant stimulus type and then digitally filtered using band pass 0.15-8 Hz (Leung et al., 2006) and a slope of 24 db/octave. MMN difference waveforms were derived by digital point-by-point subtraction of the standard stimulus values from those elicited by the deviant stimulus, and MMNs were assessed by quantifying peak negative amplitudes within a window of 80-220 ms. MMN peaks were picked as the most negative voltage (relative to average pre-stimulus baseline activity) within the analysis window and output was the average within five voltage points to the left and right of the peak amplitude (creating a total time window of 2 ms). MMN latency measurements were only measured at F<sub>z</sub>, the site of maximum amplitude. Analysis of the N100 was not completed

### 2.2.7 Data Analysis

Analyses were carried out using the Statistical Package for the Social Sciences (SPSS; SPSS Inc., Chicago, IL). In separate analyses, MMN amplitudes for each deviant type were subjected to repeated-measures analysis of variance (ANOVA) procedures with one between group (3 levels: HC, HP, NP) and two within group factors (laterality [left, midline, right], and frontality [limited to the frontal (F), central (C) and parietal (P) regions]). Analysis of MMN latency was similar, but ANOVAs did not contain a site factor. Where appropriate, Huynh-Feldt correction factors were applied to the degrees of freedom and these adjusted values have been reported. Significant ANOVA effects were followed-up with Bonferroni-adjusted pairwise comparisons.

Regardless of the presence or absence of significant main or interaction effects, planned comparisons involving between- and within-group pairwise comparisons with respect to laterality and frontality conditions (in order to examine group effects in the frontal part of the scalp, the site of maximum MMN amplitude) were carried out for hypothesis testing.

## 2.3 Results

### 2.3.1 MMN Amplitude

There were significant differences among the groups for the frequency, duration, intensity and location deviants.

The frequency-MMN (see Figure 2) showed main effects of laterality,  $F(1.69, 66) = 4.37, p = .023$ , and frontality,  $F(1.17, 66) = 59.63, p = .000$ , with maximal amplitudes at frontal and midline sites. Planned comparisons showed that, in the frontal region, HCs ( $M = -1.46\mu\text{V}, SE \pm 0.20$ ) showed a significantly larger MMN than NPs ( $M = -0.85\mu\text{V}, SE \pm 0.20; p = .035$ ). Followed-up further, this difference was localized to  $F_3$ , where HCs ( $M$

=  $-1.38\mu\text{V}$ ,  $SE \pm 0.18$ ) again showed larger amplitudes than NPs ( $M = -0.68\mu\text{V}$ ,  $SE \pm 0.18$ ;  $p = 0.010$ ). Interestingly, this planned comparison also revealed a significant difference ( $p = .044$ ) between HCs ( $M = -1.44\mu\text{V}$ ,  $SE \pm 0.24$ ) and HPs ( $M = -0.73\mu\text{V}$ ,  $SE \pm 0.24$ ) at  $F_4$ .

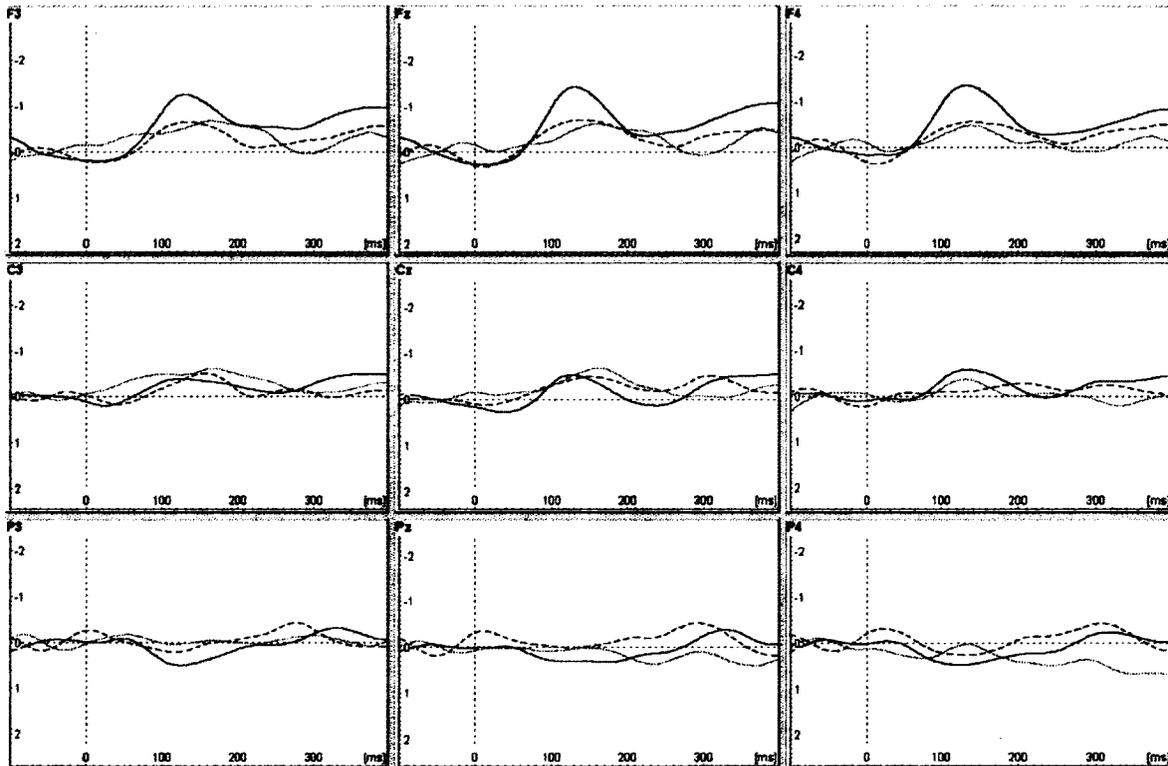


Figure 2. Grand averaged MMNs to frequency deviant across groups with HCs represented by solid line, HPs represented by dotted line and NPs represented by hashed line (units:  $\mu\text{V}$ ).

There were main effects of laterality,  $F(1.74, 57.52) = 9.77$ ,  $p = .000$ , and frontality,  $F(1.56, 51.44) = 83.28$ ,  $p = .000$ , for the duration MMN as well, again representing frontal and midline maximums (see Figure 3). However, this deviant also showed a main effect of group,  $F(2, 33) = 4.98$ ,  $p = .013$ , whereby HPs ( $M = -0.42\mu\text{V}$ ,  $SE \pm 0.12$ ) had smaller amplitudes than both NPs ( $M = -0.82\mu\text{V}$ ,  $SE \pm 0.12$ ;  $p = .023$ ) and HCs ( $M = -0.92\mu\text{V}$ ,  $SE \pm 0.12$ ;  $p = .005$ ).

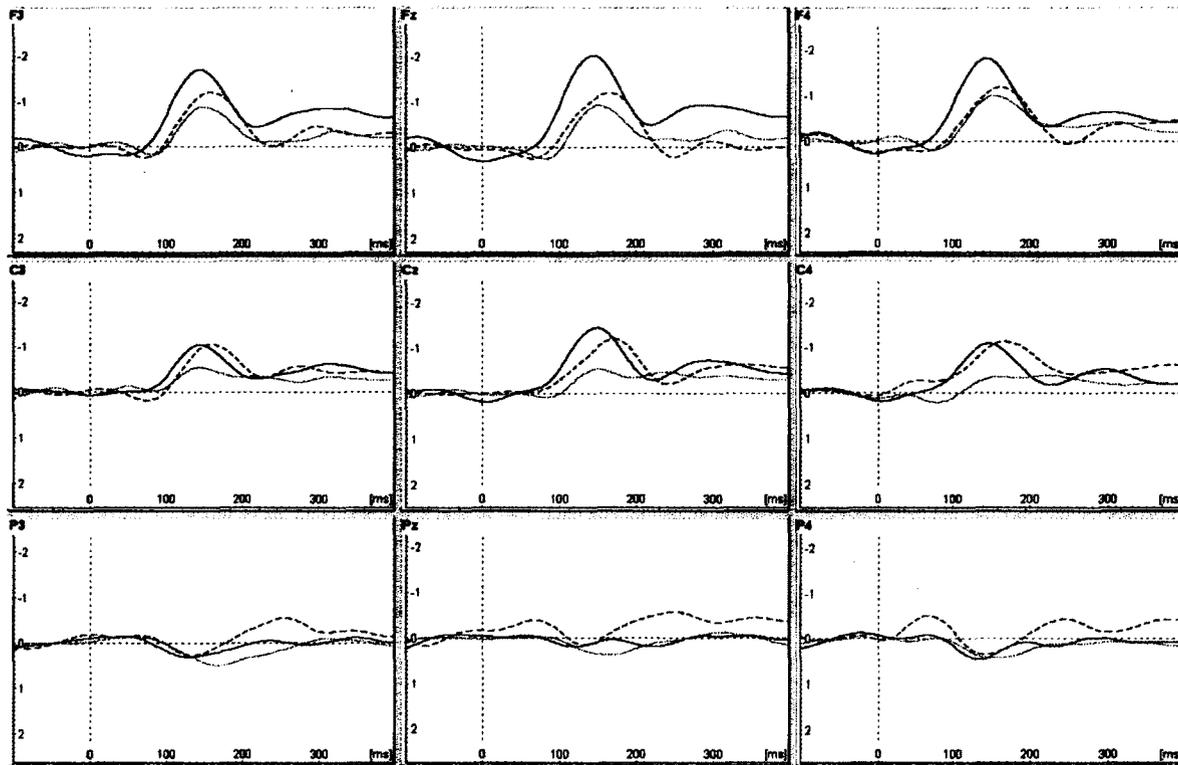


Figure 3. Grand averaged MMNs to duration deviant across groups with HCs represented by solid line, HPs represented by dotted line and NPs represented by hashed line (units:  $\mu\text{V}$ ).

The intensity-MMN (see Figure 4) showed main effects of laterality,  $F(1.36, 44.87) = 3.63, p = .050$ , and frontality,  $F(1.40, 46.29) = 70.28, p = .000$ , which revealed frontal and midline maximums. Planned comparisons, conducted independently of ANOVA results, of the interaction between laterality, frontality and group showed that HCs ( $M = -2.10\mu\text{V}, SE \pm 0.27$ ) had a significantly larger MMN than HPs ( $M = -1.13\mu\text{V}, SE \pm 0.27; p = .015$ ) at  $F_4$ .

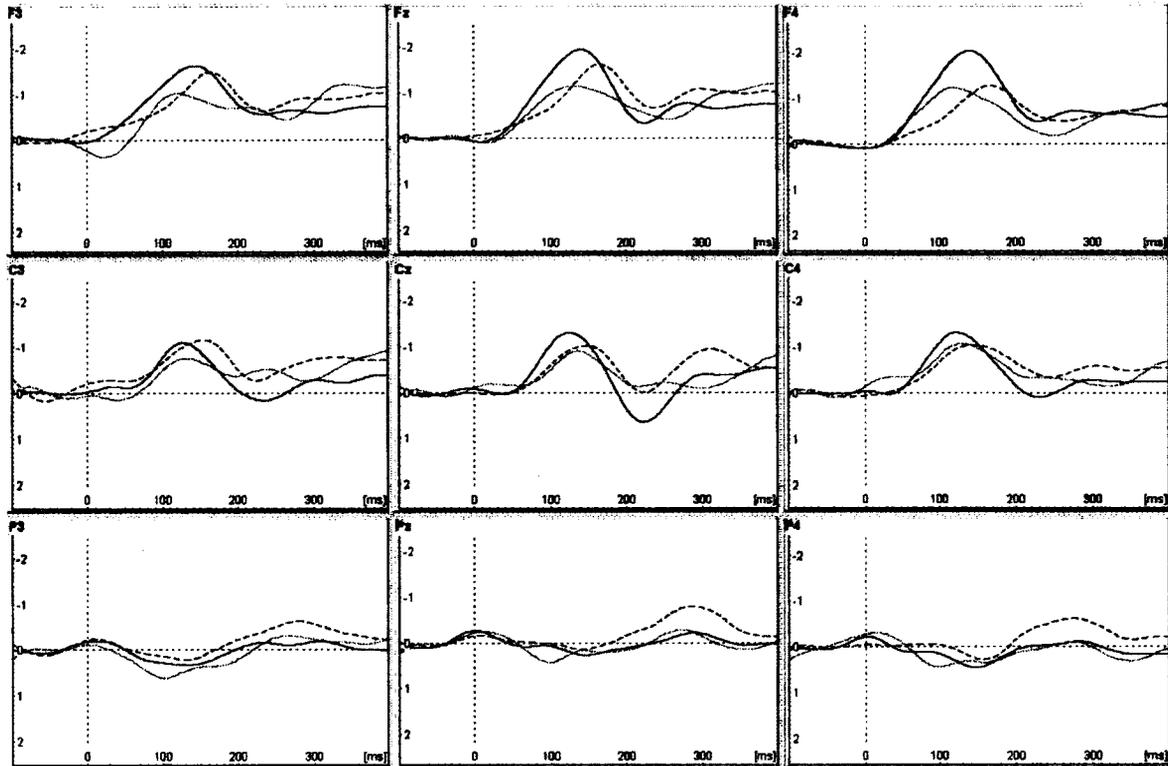


Figure 4. Grand averaged MMNs to loudness deviant across groups with HCs represented by solid line, HPs represented by dotted line and NPs represented by hashed line (units:  $\mu\text{V}$ ).

The MMN arising from the location deviant (see Figure 5) revealed a significant main effect of frontality,  $F(1.45, 48.02) = 84.093, p = .000$ , due to the frontal maximum exhibited, as well as a significant,  $F(3.91, 129.08) = 3.112, p = .018$ , laterality-by-frontality interaction. At each laterality, the frontal MMNs were greater than the central and parietal MMNs, while at the frontal sites,  $F_3$  ( $M = -1.26\mu\text{V}, SE \pm 0.12$ ) was significantly smaller than both  $F_z$  ( $M = -1.46\mu\text{V}, SE \pm 0.14$ ) and  $F_4$  ( $M = -1.52\mu\text{V}, SE \pm 0.13$ ).

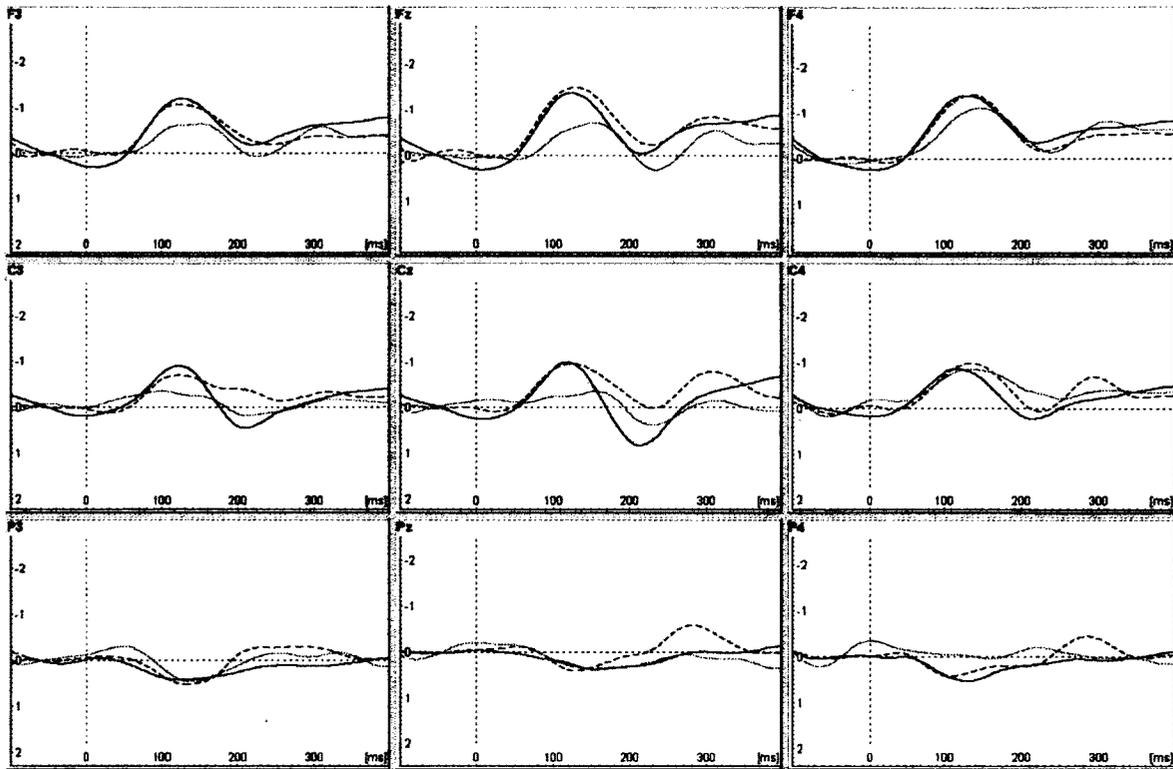


Figure 5. Grand averaged MMNs to location deviant across groups with HCs represented by solid line, HPs represented by dotted line and NPs represented by hashed line (units:  $\mu\text{V}$ ).

Significant main effects of laterality,  $F(2.00, 65.56) = 12.46, p = .000$ , and frontality,  $F(1.17, 38.64) = 109.15, p = .000$ , were reported for the gap-MMN (see Figure 6), due to the frontal and midline maximums seen overall. Planned comparison revealed no significant effects.

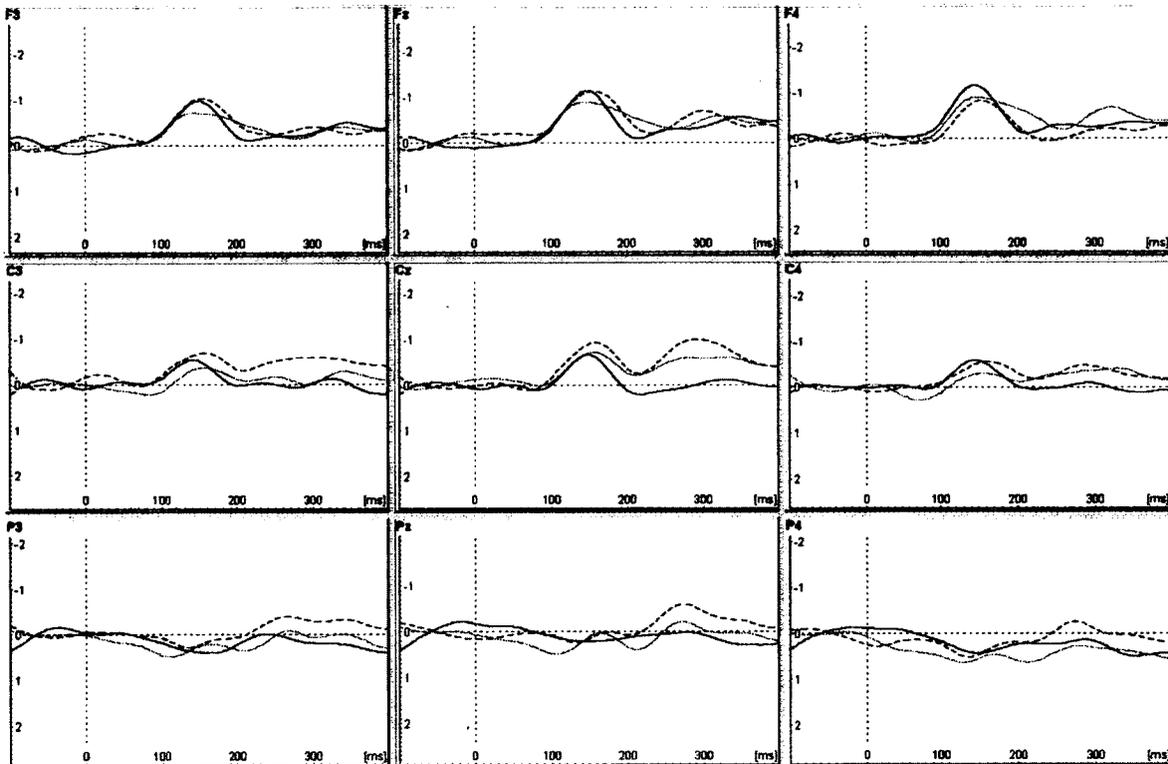


Figure 6. Grand averaged MMNs to gap deviant across groups with HCs represented by solid line, HPs represented by dotted line and NPs represented by hashed line (units:  $\mu\text{V}$ ).

### 2.3.2 MMN Latency

There were no significant between-group effects within each deviant type for MMN latency.

## 2.4 Discussion

This study painted an interesting picture of the differences seen across symptoms in schizophrenia. While other studies have examined the effects of AHs on the MMN (Oades et al., 1996; Hirayasu et al., 1998; Schall et al., 1999; Youn et al., 2003; Kasai et al., 2002), this has primarily been done by post-hoc correlations using hallucination-item ratings derived from various symptom scales. To our knowledge, this is the first study to directly compare MMNs in hallucinating and non-hallucinating patients with

schizophrenia. Furthermore, as recommended by Umbricht & Krjles in their meta-analysis of the MMN in schizophrenia, we have attempted to profile the MMN deficits in schizophrenia patients, albeit across two different subsets of schizophrenia, using a multi-feature paradigm that will allow for assessment of several acoustic feature dimensions, compared to the one or two features used in most research endeavours (Umbricht & Krjles, 2005).

Across studies, one of the most robust deficits seen in schizophrenia is that of a diminished MMN, especially to duration deviants (Michie et al., 2000; Umbricht & Krjles, 2005). While this study found smaller MMNs to duration deviants, this effect was limited to the HP group; there were no significant difference between NPs and HCs. This result has interesting implications for past and future research on the MMN in schizophrenia. The present findings suggest that the presence of auditory hallucinations in schizophrenia modulates the MMN to duration deviants in some way. Furthermore, this could indicate that the robust findings of an altered MMN to duration deviants is due to the composition of the testing populations used; that is to say these studies may have used samples whereby the majority, if not all, patients experienced auditory hallucinations. This suggests that careful choosing of patient volunteers should be exercised in order to ensure consistent results that can be replicated across studies. However, this isn't to say that auditory hallucinations are the only symptom that results in altered duration MMNs, but that a more focused study of the symptoms of schizophrenia and their unique contribution to pre-conscious auditory processing needs to be undertaken.

While it is important to know that duration MMNs are altered within a specific subset of patients with schizophrenia, it is also important to know why this occurs. While the processing of sound duration in humans is not yet fully understood, similar investigations of the auditory system in cats has led to the theory that auditory stimuli are partially processed at lower levels as a contiguous series of short duration epochs which are then recompiled in the auditory cortex (He, 1998). It follows that stimulus duration encoding may require more complex processing in the auditory cortex compared to other stimulus features, making the process more vulnerable to error due to auditory cortex defects (Michie et al, 2002). Perhaps, due to the intricate nature of the cortical computations involved, the processing of duration deviants is more sensitive to reductions in attentional resources in the auditory cortex stemming from the presence of, and the draining of resources by, auditory hallucinations.

Another possibility stems from the finding that acoustic energy sums over time, producing a perceived loudness increment with longer tones, as opposed to short tones (Scharf, 1978), raising the possibility that the observed deficit stems from an insensitivity to perceived loudness cues (Michie et al., 2002). While subsequent work ruled out this possibility in a general group of schizophrenia patients (Todd et al., 2001), it is possible that the presence of AHs usurps attentional resources from the auditory cortex, reducing its sensitivity to these small differences in perceived loudness.

Similar to the duration deviants, MMNs to the intensity (loudness) deviants were only altered in one patient subgroup; hallucinating patients showed a smaller MMN compared to healthy controls, while the NP group was not significantly different than either of the other two groups. When considered in the context of longer tones producing

perceived loudness increments (Scharf, 1978), it is possible that the deficits seen with duration and intensity deviants are related, whereby the reduction in available cortical resources result in reduced sensitivity to differences in stimulus intensity, be they perceived or absolute. In this situation, the smaller observed duration MMNs would be a direct result of an aberrant intensity evaluation component of the auditory cortex. One must also consider the possibility that these observed deficits are independent of each other, though they may both be separately related to a reduction in available attentional resources. This finding is particularly notable in that, to date, no other study has reported MMN deficits to intensity deviants in schizophrenia.

While planned comparisons revealed smaller frequency MMNs in both NPs and HPs compared to HCs (but not each other), these findings occurred in different regions. Smaller frequency MMNs were seen for HPs in the right frontal cortical region, whereas NPs had smaller MMNs than HCs in the left frontal cortical region. This could be due to a number of possible factors. Chief among the many possibilities is that these findings could be due to structural abnormalities of the brain that are unique to each subgroup, given that cortical abnormalities are consistently reported in schizophrenia (Andreasen et al., 1990; Barta et al., 1990; McLure et al., 1998; Weiss and Heckers, 1999; Shapleske et al., 2002).

These frequency MMN findings do raise some methodological considerations when testing patients with schizophrenia. While deficits in frequency MMN have been reported in schizophrenia, these results have been somewhat inconsistent (Michie et al., 2000; Umbricht & Krjles, 2005). Perhaps those studies not reporting a significant difference between groups employed a patient sample that was contained too great a mix

of hallucinating and non-hallucinating patients; in this case, one would expect the differences between the patients and controls to be eliminated due to excessive variability. Similarly, it is possible that those studies that did report a significant group effect employed a relatively homogeneous sample, whether they were comprised of mostly hallucinating or non-hallucinating patients. Regardless, this result suggests that care must be taken when selecting schizophrenic patients for participation in a study examining the MMN in response to frequency deviants.

One major limitation of this study is the modest level of hallucinatory activity expressed by HPs. It would be interesting to know how more intense auditory hallucinations would affect the mismatch process. One can reasonably expect that the current differences between HPs and the other groups would be exacerbated, however to what degree and whether other differences would emerge needs to be examined. While it is difficult to induce hallucinations, recruitment of participants with a more severe history of AHs could yield interesting results. Alternatively, one could employ a paradigm whereby participants signaled the onset and offset of hallucinations, with the task stimuli starting and stopping according to this. Also, given that all volunteers for our schizophrenia groups were outpatients, these participants were relatively high functioning compared to other patients with schizophrenia. MMN amplitudes have been positively correlated with general functioning, as scored by the Global Assessment of Functioning (GAF; Light & Braff, 2005), therefore it is unclear how well these findings can be generalized to more severe forms of schizophrenia. This could be resolved by replicating this study in acutely ill patients with schizophrenia as well as those who are stable, but still in need of hospitalization.

The use of the multi-feature MMN paradigm, ideal for studying psychiatric disorders such as schizophrenia, given that MMNs for multiple deviant types can be obtained in a short period of time, has allowed us to compile an extensive, detailed profile of pre-attentive acoustic processing in schizophrenia patients with and without auditory hallucinations. Use of this paradigm could be expanded to compare and contrast other specific symptoms within schizophrenia as well as within other mental illnesses such as bipolar disorder, Alzheimer's disease, and the mood disorders. Furthermore, it could be used to compare and contrast the effect of auditory hallucinations on pre-conscious auditory processing across diseases.

While the N100 was not examined within the context of this study, examination of this ERP waveform could be relevant to a study of schizophrenia, particularly in the presence of auditory hallucinations. It has been demonstrated that, while healthy controls exhibit a reduced N100 to their own voice during talking as opposed to listening, schizophrenia patients show no such reduction (Ford & Mathalon, 2005), particularly those prone to hallucinations (Heinks-Maldonado et al., 2007). It has not been described, however, whether this lack of an N1 reduction would manifest to pure-tone deviants under conditions of background noise, such as hallucinations. Given that recent work has shown the N100 component of the event-related potential to be functionally distinct from the MMN with regards to temporal properties and topography (Campbell et al., 2007), future research may look to examine this waveform and its relationship to altered MMNs in schizophrenia using the multi-feature paradigm.

It is our hope that this study will be the first step towards focused, research into specific schizophrenia symptomatology, so that a more detailed understanding of this

disease can emerge, possibly leading to focused treatments that effectively treat individual symptoms, and increasing the quality of life of those afflicted.

## CHAPTER 3: EFFECTS OF DEVIANT PROBABILITY ON THE ‘OPTIMAL’ MULTI-FEATURE MISMATCH NEGATIVITY (MMN) PARADIGM (Experiment 2a)

### 3.1 Introduction

The strength (i.e. amplitude) and speed (i.e. latency) of the mismatch negativity (MMN) signal produced is related to both the size of the deviance (i.e. how different the deviant stimulus is from the defined memory trace) and the probability of the deviance occurring and is independent of the requirements of the primary task (Näätänen et al., 2007). Increasing deviant probability leads to an attenuation of MMN amplitude (Näätänen et al., 1987; Sabri & Campbell, 2001), which is thought to be partially due to a weakened standard memory trace due to the reduction of standard stimulus presentations. This attenuation, however, may be more the result of deviant stimuli developing their own memory trace, leading to inhibition of MMN generation related to the standard (Ritter et al., 1992; Rosburg, 2004).

The recently developed “Optimum-1” multi-feature MMN paradigm (Näätänen et al., 2004) appears to be ideally suited for probing auditory processing, eliciting MMNs to five different pure-tone deviant types (frequency, duration, intensity, location and gap) in a relatively short period of time. Given this advantage over the traditional oddball design, the multi-feature MMN paradigm has been employed extensively in clinical research, notably to characterize MMN in schizophrenia (Fisher et al., 2008; Thonnessen et al., 2008), post-traumatic stress disorder (Menning et al., 2008) and Asperger syndrome (Kujala et al., 2010). However, of these five deviant types, frequency, duration and intensity deviants (obtained from auditory oddball paradigms) are overall most often reported in MMN literature and in some studies it may be useful to have access to a shorter (i.e. 3-stimulus) version of the multi-feature MMN paradigm. Due to the structure

of the multi-feature paradigm (i.e. repeating standard-deviant combinations), the omission of two deviants necessarily alters the probability of the remaining three deviants from 10% to 16.7%. While deviant probabilities greater than 16.7% have been successfully employed to elicit an MMN in a two-stimulus oddball (Sabri & Campbell, 2001; Sato et al., 2003), it is unclear what effect altering deviant probability will have on MMNs elicited by the multi-feature paradigm. There have been two previous attempts to measure alteration of the multi-feature paradigm (Jankowiak & Berti, 2007; Grimm et al., 2008), both of which merged a three-deviant version of the multi-feature paradigm with the classic Schröger-Wolff distraction paradigm (Schröger & Wolff, 1998). Additionally, both of these altered paradigms differed from the classic multi-feature paradigm in that they required active auditory discrimination and employed long (1500-2500 ms) stimulus-onset asynchronies. Furthermore, only the work by Jankowiak & Berti (2007) employed the established standard-deviant pattern of the original multi-feature MMN paradigm, finding a robust MMN to frequency, intensity and location deviants.

We examined whether a modified 3-stimulus version of the multi-feature paradigm elicited strong MMN waveforms and whether the amplitudes and latencies of these waveforms differed from those elicited by the standard 5-stimulus version of the multi-feature paradigm. We hypothesized that the modified 3-stimulus multi-feature paradigm would elicit robust MMN waveforms for all three deviant types, but that frontally-recorded MMN amplitudes in the original multi-feature paradigm would be larger than those in the modified paradigm. The aims of this study were two-fold: firstly, given that a 3-stimulus multi-feature paradigm may be useful for future research due to the shorter presentation time and focus on the three most used deviant types (frequency,

duration and intensity), we aimed to establish the validity of MMN waveforms from such a paradigm. Secondly, we wished to add to the understanding of MMN generation by elucidating the effect of altering deviant probabilities within the optimal MMN framework.

## 3.2 Materials and Methods

### 3.2.1 Study Participants

Participants were twenty-four healthy volunteers between the ages of 18-60. Participants were presented with either a 3-stimulus or 5-stimulus version of the 'optimal' multi-feature MMN paradigm. The twelve participants (3 females) that were presented with the 3-stimulus version of the multi-feature paradigm had an average age of 37.33 (SE = 4.02; Range: 22-59 years), while the twelve participants (5 females) that were presented with the 5-stimulus version had an average age of 39.75 (SE = 3.16; Range: 26-56 years). All participants were required to understand spoken and written English, in order to ensure adequate understanding of the study prior to signing consent; in both groups, all participants reported English as their native language, though some participants were fluently bilingual in French, as well. All participants had to demonstrate normal hearing according to an audiometric assessment, conducted by the primary investigator in the research laboratory, requiring thresholds of 25 dB (SPL) or less (using a 'descending method of limits' procedure) to pure tones of 500 Hz, 1000 Hz, and 2000 Hz.

Prior to attending the laboratory, potential participants completed a screening questionnaire over the telephone. Participants were excluded if they reported any of the

following criteria: DSM-IV TR Axis I disorder (American Psychiatric Association, 2000); history of drug abuse or dependence; history of head injury resulting in loss of consciousness; diagnosis of epilepsy or any other neurologic disorder; significant cardiac illness; movement disorders which could affect ERP recordings; or abnormal audiometric assessment.

### 3.2.2 Study Procedure

Testing was conducted around midday (11:00am-2:00pm) with participants being required to abstain from illicit drugs, medications, and alcohol beginning at midnight of the previous day. Upon arrival at the laboratory, following self-report of adherence to pre-testing abstinence, participants completed demographic questionnaires and underwent audiometric assessment. Following this, EEG electrodes were applied and volunteers were assessed using either the modified 3-stimulus or original 5-stimulus version of the continuous performance multi-feature MMN paradigm (Näätänen, 2004), during which they were instructed to view a silent, neutral emotive video and to ignore the presented auditory stimuli. All testing procedures were carried out in accordance with the Declaration of Helsinki and following the approval of the research ethics board of the Royal Ottawa Health Care Group.

### 3.2.3 Auditory Stimuli

Standard stimuli were tones of 75 ms duration (including 5 ms rise and fall) composed of 3 sinusoidal partials of 500, 1000 and 1500 Hz where the intensity of the 1000 Hz and 1500 Hz partials were lower than that of the 500 Hz by 3 dB and 6dB,

respectively. The deviant tones in the original 5-stimulus version ('Optimal-5') differed from the standard tones in frequency, duration, intensity, perceived location of sound origin or contained a gap in the middle of the tone. All stimuli were presented binaurally through headphones and at a sound pressure level (SPL) of 70 dB (with the exception of the intensity deviants) with equal phase intensity in each channel.

Half of the frequency deviants were 10% higher (composed of 550, 1100, 1650 Hz partials) while the other half were 10% lower (450, 900 and 1350 Hz partials). Half of the intensity deviants were at 60 dB while the other half were at 80 dB. The perceived difference between the standard tone and the location deviant was approximately 90°; the change in perceived location of sound origin was obtained by creating a time difference of 800 $\mu$ s for half of the location deviants to the right channel and half of the deviants to the left. The duration deviant was only 25 ms, while the gap deviant was created by removing 7 ms (including 1 ms rise and fall) from the middle of the standard stimulus. Except where stated, the deviants were identical to the standards.

In each sequence, the first 15 tones were standards, followed by a sequence whereby every second tone was a standard ( $P = 0.5$ ) and every other one was one of the five deviants ( $P = 0.1$  each). The deviants were presented so that each deviant category was presented once every 5 deviants and 2 deviants of the same category were never presented consecutively. The interstimulus interval (ISI) was 500ms, and the stimuli were presented in 3 sequences of 5 minutes each (600 stimuli) for a total of 15 minutes (1800 stimuli). The modified 3-stimulus version ('Optimal-3') was identical in all ways, except only frequency, duration and intensity deviants ( $P = .17$  each) were presented, resulting in 3 sequences of 3 minutes each (366 stimuli) for a total of 9 minutes (1098 stimuli). Of

note, the total number of each deviant presented (180 each) did not change across the two conditions, however due the removal of deviants in the 3-stimulus condition, the probabilities did change.

### 3.2.4 EEG Recording and ERP Computation

MMNs were extracted from EEG activity recorded with an electrode cap employing  $\text{Ag}^+/\text{Ag}^+-\text{Cl}^-$  ring electrodes at thirty-two scalp sites according to the 10-10 system of electrode placement, including three midline sites (frontal [ $F_z$ ], central [ $C_z$ ], parietal [ $P_z$ ]), as well as three left hemisphere (frontal [ $F_3$ ], central [ $C_3$ ], parietal [ $P_3$ ]) and three right hemisphere (frontal [ $F_4$ ], central [ $C_4$ ], parietal [ $P_4$ ]) scalp sites. Electrodes were also used to record left (LM) and right (RM) mastoid activity and electrodes were placed on the mid-forehead and nose to serve as ground and reference, respectively. Bipolar recordings of horizontal (HEOG) and vertical (VEOG) electro-oculogram activity were taken from supra-/sub-orbital and external canthi sites, respectively. All electrode impedances were kept below  $5\text{k}\Omega$ . Electrical activity was recorded using BrainVision Recorder software with an amplifier bandpass of 0.1 and 30 Hz, digitized at 500 Hz, and stored on hard-disk for later off-line analysis using BrainVision Analyzer software.

EEG epochs (500 ms duration, beginning 100 ms pre-stimulus) were corrected for residual eye movement and eye blink activity using the Gratton & Coles algorithm, which operates in the time and frequency domain (Gratton et al., 1983); any corrected epochs with EEG voltages exceeding  $\pm 100 \mu\text{V}$  were excluded from further analysis.

Within the multi-feature paradigm, epochs were separately averaged for each standard and deviant stimulus type and then digitally filtered using bandpass 0.15-8 Hz, (Leung et al., 2006) and a slope of 24 db/octave. The narrow band pass, previously used in a study of the Optimal MMN (Fisher et al., 2008), eliminates any extraneous high-frequency activity. MMN difference waveforms were derived by point-by-point subtraction of the standard stimulus values from those elicited by the deviant stimulus, and MMNs were assessed by quantifying peak negative amplitudes within a window of 80-220 ms. MMN peaks for each individual participant were picked as the most negative point within each condition's respective analysis window and output was the average within five voltage points (2ms) to the left and right of the peak amplitude. MMN latency measurements were only measured at F<sub>z</sub>, the site of maximum amplitude. Prior to peak picking, individual assessment of the presence of the MMN, as well as appropriate inversion at mastoids, was conducted within each participant for each deviant type.

### 3.2.5 Data Analysis

Analyses of MMN amplitudes and latencies were carried out using the Statistical Package for the Social Sciences (SPSS; SPSS Inc., Chicago, IL). In order to establish the presence of a true MMN, amplitudes at F<sub>z</sub> to all deviants and both conditions were compared to zero using a t-test. MMN amplitudes were subjected to mixed univariate analysis of variance (ANOVA) procedures with two within-subjects factors (laterality [left, right and midline] and region [limited to the frontal, central, and parietal regions]) and 1 between-subjects factor (group [Optimal-3 and Optimal-5]).

Where appropriate, Huynh-Feldt epsilon correction factors were applied to the degrees of freedom and the rounded adjusted degrees of freedom have been reported. Regardless of the presence or absence of significant main or interaction effects planned comparisons involving between-group comparisons with respect to laterality and region were carried out. Significant effects were followed-up with pairwise comparisons for greater specificity in reporting.

### 3.3 Results

#### 3.3.1 MMN Amplitude

All MMN amplitudes at F<sub>Z</sub> were significantly different from zero. The amplitudes ( $\pm$ SE) and 2-tailed t-test statistics are summarized in table 2.

Deviant	Mean Amplitude ( $\pm$ SE)	<i>t</i>	Significance
3-stim Duration	-1.83 $\mu$ V (0.19)	-9.67	<i>p</i> < .001
5-stim Duration	-2.05 $\mu$ V (0.27)	-7.67	<i>p</i> < .001
3-stim Pitch	-1.10 $\mu$ V (0.24)	-4.58	<i>p</i> = .001
5-stim Pitch	-1.56 $\mu$ V (0.21)	-7.51	<i>p</i> < .001
3-stim Intensity	-1.33 $\mu$ V (0.21)	-6.37	<i>p</i> < .001
5-stim Intensity	-2.10 $\mu$ V (0.25)	-8.53	<i>p</i> < .001

Table 2. Mean amplitudes ( $\pm$ SE) at F<sub>Z</sub> plus t-statistic and significance resulting from 2-tailed comparison of means against zero for all deviants in both conditions.

A general 3 (deviant type) x 3 (frontal sites) x 2 (group) ANOVA was calculated to examine between-deviant differences. There was a main effect of deviant,  $F(2, 44) = 6.33, p = .004$ , due to an overall significantly smaller pitch MMNs ( $M = -1.21, SE = .14$ ) compared to duration ( $M = -1.78, SE = .16; p = .002$ ) and intensity ( $M = -1.61, SE = .14; p = .022$ ) MMNs. When followed-up with group-by-deviant pairwise comparisons, it was

revealed that in the Optimal-3 condition, pitch MMNs ( $M = -.97$ ,  $SE = .20$ ) were significantly smaller than duration MMNs ( $M = -1.69$ ,  $SE = .22$ ;  $p = .004$ ), while in the Optimal-5 condition, pitch MMNs ( $M = -1.46$ ,  $SE = .20$ ) were significantly different than intensity MMNs ( $M = -1.99$ ,  $SE = .20$ ;  $p = .027$ ).

There was a further overall main effect of laterality,  $F(2,44) = 12.46$ ,  $p < .001$ , due to overall smaller amplitudes at  $F_3$  ( $M = -1.37$ ,  $SE = .10$ ) compared to  $F_z$  ( $M = -1.66$ ,  $SE = .12$ ) and  $F_4$  ( $M = -1.56$ ,  $SE = .13$ ). There were no significant main interactions.

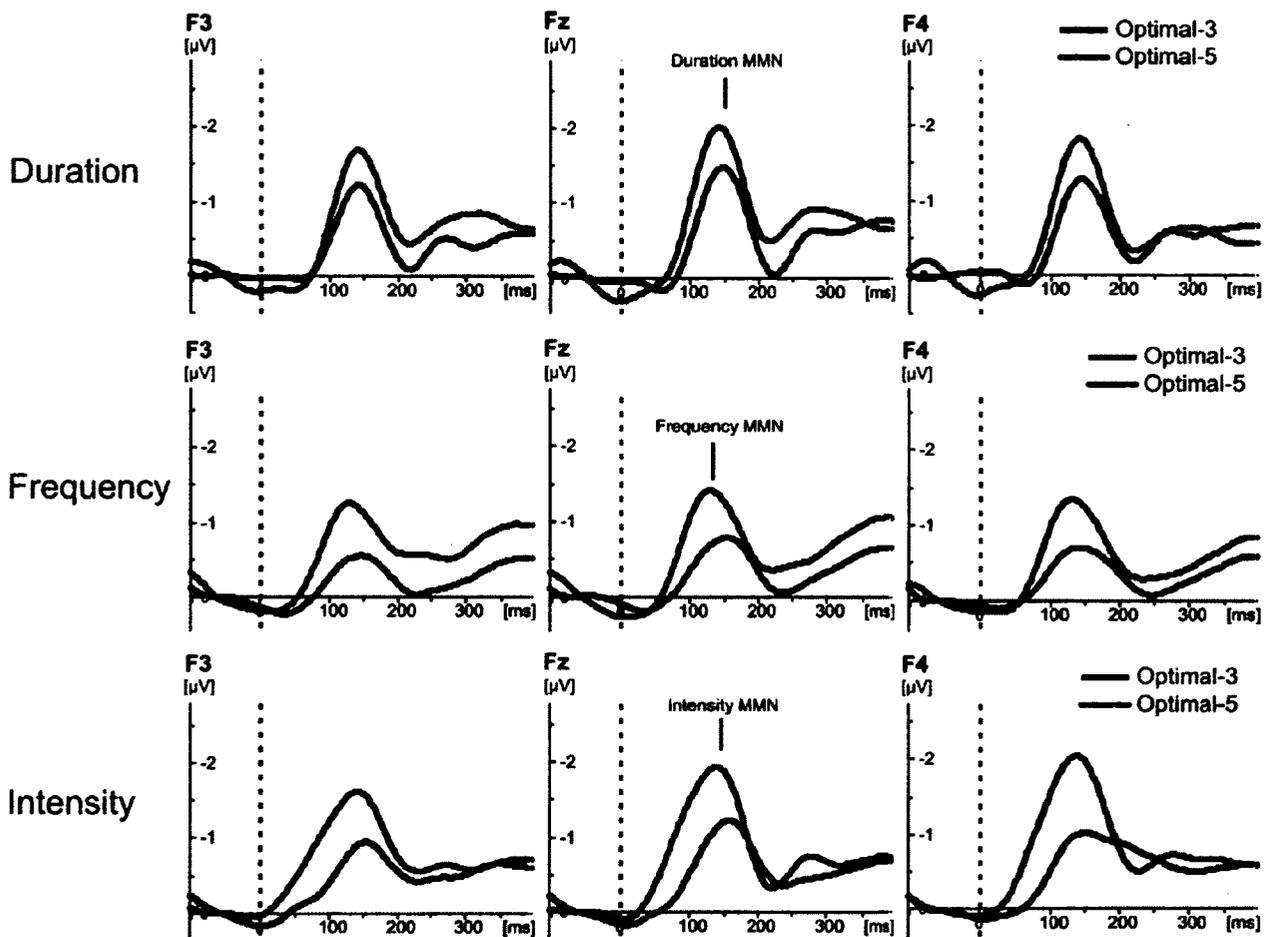


Figure 7. Subtracted waveforms showing mismatch negativity elicited by duration, frequency and intensity deviants at left ( $F_3$ ), midline ( $F_z$ ) and right ( $F_4$ ) frontal recording sites for Optimal-3 and Optimal-5 paradigms.

### 3.3.1.1 Duration MMN

There was a main effect of region,  $F(1, 30) = 95.84, p < .001$ , due to significantly ( $p < .001$ ) larger MMN amplitudes at frontal regions ( $M = -1.77 \mu\text{V}$ ,  $SE = .16$ ) compared to amplitudes at central ( $M = -1.03 \mu\text{V}$ ,  $SE = .10$ ) and parietal ( $M = .42 \mu\text{V}$ ,  $SE = .09$ ) regions, while central MMN amplitudes were significantly ( $p < .001$ ) larger than parietal amplitudes. There was a further main effect of laterality,  $F(2, 35) = 10.83, p = .001$ , which was due to significantly ( $p < .001$ ) larger amplitudes at midline sites ( $M = -.97 \mu\text{V}$ ,  $SE = .09$ ) compared to those at left ( $M = -.68 \mu\text{V}$ ,  $SE = .07$ ) and right ( $M = -.73$ ,  $SE = .09$ ) electrode sites.

There were no significant main interactions involving group. Planned comparisons of group-by-region and group-by-region-by-laterality revealed no significant differences between the Optimal-5 and Optimal-3 versions of the paradigm (see figure 7).

### 3.3.1.2 Pitch MMN

There was a main effect of region,  $F(1, 28) = 64.29, p < .001$ , observed power = 1.00, partial eta-square = .74, due to MMN amplitudes at frontal regions ( $M = -1.24 \mu\text{V}$ ,  $SE = .14$ ) being significantly ( $p < .001$ ) larger than amplitudes at central ( $M = -.55 \mu\text{V}$ ,  $SE = .11$ ) and parietal ( $M = .37 \mu\text{V}$ ,  $SE = .11$ ) regions, while central MMN amplitudes were significantly ( $p < .001$ ) larger than parietal amplitudes.

There was also a main effect of laterality,  $F(2, 44) = 4.58, p = .016$ , which was due to significantly smaller amplitudes at left sites ( $M = -.36 \mu\text{V}$ ,  $SE = .09$ ) compared to

those at midline ( $M = -.54 \mu\text{V}$ ,  $SE = .12$ ;  $p = .008$ ) and right ( $M = -.50$ ,  $SE = .08$ ;  $p = .048$ ) electrode sites.

There were no significant main interactions involving group. Planned comparisons of group-by-region showed no significance, while group-by-region-by-laterality analysis revealed that MMN amplitudes to Optimal-3 ( $M = -.77 \mu\text{V}$ ,  $SE = .19$ ) were significantly ( $p = .03$ ) smaller than those to Optimal-5 ( $M = -1.378$ ,  $SE = .19$ ) at site  $F_3$  (see figure 7).

### 3.3.1.3 Intensity MMN

There was a main effect of region,  $F(2, 35) = 78.22$ ,  $p < .001$ , due to MMN significantly ( $p < .001$ ) larger amplitudes at frontal regions ( $M = -1.61 \mu\text{V}$ ,  $SE = .14$ ) compared amplitudes at central ( $M = -.93 \mu\text{V}$ ,  $SE = .15$ ) and parietal ( $M = .39 \mu\text{V}$ ,  $SE = .14$ ) regions, while central MMN amplitudes were significantly ( $p < .001$ ) larger than parietal amplitudes.

There was also a main effect of group,  $F(1,22) = 4.49$ ,  $p = .046$ , due to overall larger MMN amplitudes to Optimal-5 ( $M = -.94 \mu\text{V}$ ,  $SE = .15$ ) compared to Optimal-3 ( $M = -.49 \mu\text{V}$ ,  $SE = .15$ ).

There were no significant main interactions. Planned comparisons of region-by-group interactions showed a significant difference ( $p = .013$ ) between MMN amplitudes elicited by Optimal-5 ( $M = -1.99 \mu\text{V}$ ,  $SE = .20$ ) and Optimal-3 ( $M = -1.22 \mu\text{V}$ ,  $SE = .20$ ) at frontal sites only. When followed up further with a region-by-laterality-by-group analysis, MMN amplitudes elicited by Optimal-5 were found to be significantly larger

than those elicited by Optimal-3 at  $F_3$  ( $p = .013$ ),  $F_Z$  ( $p = .026$ ) and  $F_4$  ( $p = .016$ ), as shown in figure 7.

### 3.3.2 MMN Latency

There was no significant difference between groups regarding MMN latency for any of the three deviants.

## 3.4 Discussion

Given the framework of the multi-feature MMN paradigm, wherein each standard is followed by a deviant in an alternating pattern, we were afforded a unique opportunity to examine the effect of altering deviant probability while holding the probability of the standard constant. Increasing the deviant probability (from  $P = .1$  to  $P = .17$ , as in Optimal-3) resulted in MMN waveforms that appeared to be attenuated, with MMNs to the frequency and intensity deviants being significantly smaller than those obtained with Optimal-5. It is unclear whether reduction of MMN amplitudes with increased deviant probability is specific to frequency and intensity deviants, with the duration deviant amplitudes being relatively unaffected. A previous attempt to examine MMNs derived from a modified 3-stimulus multi-feature paradigm reported elicitation of robust MMNs to frequency, intensity and location deviants but did not compare these to those elicited by the original Optimal-5 paradigm (Jankowiak & Berti, 2007). While visual inspection of the waveforms suggests minimal effect of increasing deviant probability on duration MMN amplitude, further work will need to be conducted to determine whether this

deviant is relatively insensitive to increasing deviant probability and at what point such increases will significantly affect amplitude.

It has been previously reported that increasing deviant probability leads to an attenuation of MMN amplitude (Näätänen, 1987; Sabri & Campbell, 2001), with this attenuation resulting from either a weakened standard memory trace (due to a reduction of standard stimuli) or the development of separate deviant memory traces. Because the multi-feature MMN paradigm requires an alternating standard-deviant pattern, this prevents a reduction the ratio of deviants-to-standards or overall percentage of deviants and standards, as each necessarily comprise 50% of the presented stimuli. Therefore, this study corroborates previous work suggesting reduced MMN amplitudes following increases in the probability of deviant presentation are the result of deviant stimuli developing their own memory trace and inhibiting MMN generation related to the standard (Ritter et al., 1992; Rosburg, 2004).

While certainly there is a downside to the Optimal-3 in terms of reduced MMN amplitude to frequency and intensity deviants, it must be noted that this paradigm elicited clear, identifiable MMN components to all three deviant types and at a time savings of 40%, obtained through the elimination of 702 stimuli. This preliminary evidence suggests that the Optimal-3 paradigm may be useful in cases where experimenters would like to obtain only frequency, duration and intensity MMNs and/or would like to obtain MMN data in a period of time even shorter than needed for the relatively quick Optimal-5 version of this paradigm. Specifically, the Optimal-3 paradigm may be useful for acutely ill clinical populations that are unable to tolerate long test sessions, such as acute schizophrenia patients, bipolar patients with psychotic features and patients with

Alzheimer's disease, or for ERP test batteries that wish to include a rapid, yet thorough, MMN paradigm. Certainly in the case of schizophrenia research, reporting of frequency, duration and intensity deviants would be consistent with the majority of MMN research, which focuses primarily on these three deviant types while generally omitting or ignoring location and gap deviants (Umbricht & Krljes, 2005).

This study has several limitations, including the use of two separate sub-groups rather than repeated testing of the same population. We do, however, feel this limitation is minimized by the fact that healthy, matched populations were used in testing. Future research may wish to better elucidate the impact of progressive increases of deviant probability by comparing four-, three- and two-deviant versions of the multi-feature MMN paradigm to the original five-deviant version.

## CHAPTER 4: EFFECTS OF AUDITORY HALLUCINATIONS ON THE MISMATCH NEGATIVITY (MMN) IN SCHIZOPHRENIA AS MEASURED BY A MODIFIED 'OPTIMAL' MULTI-FEATURE PARADIGM (Experiment 2b)

### 4.1 Introduction

The mismatch negativity (MMN) is elicited by any discriminable change in auditory stimulation (Näätänen, 1992); these auditory stimuli may deviate in any number of ways from the standard, with deviations in frequency, duration, intensity and location (among others) eliciting an MMN (Näätänen & Ahlo, 1997). In the majority of studies, the MMN is generated by randomly inserting a single low-probability (i.e. rare) deviant auditory stimulus into a train of repetitive (i.e. standard) sounds. The recently developed "Optimum-1" multi-feature MMN paradigm (Näätänen et al., 2004), however, elicits MMNs to five different pure-tone deviant types (frequency, duration, intensity, location and gap) in a relatively short period of time. Given the advantage in efficiency over the traditional oddball design, the multi-feature MMN paradigm has been employed recently in clinical research, notably to characterize MMN in post-traumatic stress disorder (Menning et al., 2008), Asperger syndrome (Kujala et al., 2010) and schizophrenia (Fisher et al., 2008a; Thonnessen et al., 2008). However, of these five deviant types, frequency, duration and intensity deviants (obtained from auditory oddball paradigms) are overall most often reported in MMN literature, leading to the development of the even shorter Optimal-3 (i.e. 3-deviant) version of the multi-feature MMN paradigm (Fisher et al., 2011a).

MMN abnormalities are marked in schizophrenia (Näätänen and Kähkönen, 2009) and appear to be specific to this disorder, as no consistent MMN alterations have been observed in any of the other major psychiatric disorders such as bipolar disorder or

depression (Umbricht et al., 2003; Catts et al., 1995). An emerging school of thought suggests that research in schizophrenia should examine the effects of the associated syndromes or symptoms on correlates of cortical function, such as the MMN; as such, there is a burgeoning literature examining whether auditory hallucinations make a unique contribution to the overall deficit in MMN generation (Hirayasu et al., 1998; Oades et al., 1996; Schall et al., 1999; Youn et al., 2002). Overall, these efforts have tended to focus on correlations between MMN amplitude and self-report measures of hallucinations with uneven results, though the two studies that did find significant correlations reported that as measures of hallucinations increase there is a corresponding decrease in MMN amplitude (Hirayasu et al., 1998, Youn et al., 2002). In the only study to date to directly compare schizophrenia patients with clear, persistent auditory hallucinations to those with no auditory hallucinations, it was reported that hallucinating patients showed a globally reduced MMN to duration (vs. healthy controls and non-hallucinating patients) and intensity deviants (vs. healthy controls), while non-hallucinating patients were not significantly different than healthy controls (Fisher et al., 2008a).

The primary aims of this study were two-fold: firstly, we wished to compare the change detection response of SZ patients with AHs and healthy controls at frontal recording sites within a modified 3-deviant (frequency, duration and intensity) multi-feature paradigm. Secondly, we wished to probe the relationship between trait measures of AHs and MMN generation in schizophrenia. We hypothesized that schizophrenia patients would elicit smaller MMN waveforms for all three deviant types compared to healthy controls, and smaller MMN amplitudes in SZs would associated with larger

scores on trait measures of AVHs. Additionally, we engaged in an exploratory investigation on the effects of state measures of AHs and MMN in schizophrenia.

## 4.2 Materials and Methods

### 4.2.1 Experimental Participants

Twelve patient volunteers, all presenting with a primary diagnosis of schizophrenia and following a stable regimen of medication, were recruited from the Outpatient Schizophrenia Clinic of the Royal Ottawa Mental Health Centre (ROMHC). During an initial clinical interview (with the primary care physician) in which volunteers were assessed with respect to inclusion and exclusion criteria, both clinical history and ratings on the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1989) for schizophrenia were used for recruitment. For study inclusion, all patients reported a definite, consistent history of AHs over the course of their illness, exhibiting a score  $\geq 3$  (mild or greater hallucinatory experiences) on the hallucination item of the PANSS positive symptom scale (based on clinician ratings of self-reported symptoms over the past month).

The tendency to experience AHs was subsequently confirmed by a study investigator (DF), who rated the patients on the AH subscale of the Psychotic Symptom Rating Scale (PSYRATS; Haddock et al., 1999). This 11-item, 5-point (0-4) rating scale assesses trait hallucinations with respect to frequency, duration, severity and intensity of distress and also symptom specific dimensions of controllability, loudness, location, negative content, degree of negative content, beliefs about origin of voices, and disruption. A summary of participant characteristics is given in table 3.

Table 3. *Summary of participant demographics and trait questionnaires (mean  $\pm$  SE)*

	Patients	Controls
Age	41.31 (2.79)	37.33 (4.02)
Handedness (EHI)	0.64 (0.15)	0.71 (0.13)
Years of education	13.8 (1.07)	15.83 (0.67)
PSYRATS	25.92 (6.84)	-
PANSS Positive Symptom	21.55 (1.12)	-
PANSS Negative Symptom	19.82 (1.56)	-
PANSS Hallucination Item	4.00 (0.14)	-
PANSS General Psychoticism	40.82 (2.65)	-

All patients were required to be primarily right handed, as indicated by a score greater than 0.5 on the Edinburgh Handedness Inventory (EHI; Oldfield, 1971), between the ages of 18 and 65, and to have a primary DSM-IV TR diagnosis of schizophrenia, paranoid subtype, as assessed with Structured Clinical Interview DSM-IV Psychotic Screen (SCID-P) by their primary care physician.

Patients also had to be clinically stable for the 4 weeks prior to testing, having no significant changes in symptoms or medications. Patients' primary medication was limited to one of the atypical anti-psychotics. All participants were required to understand spoken and written English, although English did not need to be their first language. Normal hearing via audiometric assessment was a requirement and was evidenced by auditory sound pressure level (SPL) thresholds of 25 dB or less (using a 'descending method of limits' procedure) to pure tones of 500 Hz, 1000 Hz, and 2000 Hz.

Participants were excluded if they met any of the following criteria: co-morbid Axis I disorder as defined by DSM-IV TR criteria; current history of drug abuse or dependence; head injury resulting in the loss of consciousness within the last year; a neurologic disorder including epilepsy; primary treatment with a first generation neuroleptic such as haloperidol; electro-convulsive therapy (ECT) treatment within the last year; significant cardiac illness; extrapyramidal symptoms (EPS) resulting in movement disorders which would disrupt the ERP recordings; or audiometric assessment significantly above 25 dB (SPL) on each level of pure tones.

#### 4.2.2 Control Participants

Normal participants (HC) were twelve healthy volunteers, who, for exclusion/inclusion purposes, were required to self-report negative psychiatric, medical, neurological and alcohol/drug abuse histories, to report non-use of medications, and display normal hearing. None of the HCs had an immediate family history of psychosis. Experimental and control groups were matched as closely as possible with respect to age and gender. While not specifically controlled for, the groups did not significantly differ on years of education ( $p = .11$ ).

#### 4.2.3 Study Procedure

Testing was conducted around midday (11:00am-2:00pm) with participants being required to abstain from illicit drugs, medications, and alcohol beginning at midnight of the previous day. Participants were also instructed to abstain from both caffeine and cigarettes for at least an hour prior to the session. Upon arrival at the laboratory,

following self-report of adherence to pre-testing abstinence, participants completed demographic questionnaires and underwent audiometric assessment. Following this, EEG electrodes were applied and volunteers were assessed using a modified 3-stimulus version (Fisher et al., 2010) of the multi-feature MMN paradigm (Näätänen et al., 2004), during which they were instructed to view a silent, neutral emotive video and to ignore the presented auditory stimuli. All testing procedures were carried out in accordance with the Declaration of Helsinki and following the approval of the research ethics board of the Royal Ottawa Health Care Group.

#### 4.2.4 Auditory Stimuli

Standard stimuli were tones of 75 ms duration (including 5 ms rise and fall) composed of 3 sinusoidal partials of 500, 1000 and 1500 Hz where the intensity of the 1000 Hz and 1500 Hz partials were lower than that of the 500 Hz by 3 dB and 6dB, respectively. The modified 3-stimulus version of the multi-feature MMN paradigm presented only frequency, duration and intensity deviants. All stimuli were presented binaurally through headphones and at a sound pressure level (SPL) of 70 dB (with the exception of the intensity deviants) with equal phase intensity in each channel.

Half of the frequency deviants were 10% higher (composed of 550, 1100, 1650 Hz partials) while the other half were 10% lower (450, 900 and 1350 Hz partials). Half of the intensity deviants were at 60 dB while the other half were at 80 dB. The duration deviant was only 25 ms. Except where stated, the deviants were identical to the standards.

In each sequence, the first 15 tones were standards, followed by a sequence whereby every second tone was a standard ( $P = 0.5$ ) and every other one was one of the

three deviants ( $P = 0.17$  each). The deviants were presented so that each deviant category was presented once every 3 deviants and 2 deviants of the same category were never presented consecutively. The stimulus onset asynchrony (SOA) was 500ms, and the stimuli were presented in 3 sequences of 3 minutes each (366 stimuli) for a total of 9 minutes (1098 stimuli).

#### 4.2.5 EEG Recording and ERP Computation

MMNs were extracted from EEG activity recorded with an electrode cap positioning  $\text{Ag}^+/\text{Ag}^+-\text{Cl}^-$  ring electrodes at thirty-two scalp sites according to the 10-10 system of electrode placement, including three midline sites (frontal [F<sub>Z</sub>], central [C<sub>Z</sub>], parietal [P<sub>Z</sub>]), as well as three left hemisphere (frontal [F<sub>3</sub>], central [C<sub>3</sub>], parietal [P<sub>3</sub>]) and three right hemisphere (frontal [F<sub>4</sub>], central [C<sub>4</sub>], parietal [P<sub>4</sub>]) scalp sites. Electrodes were also used to record left (LM) and right (RM) mastoid activity and electrodes were placed on the mid-forehead and nose to serve as ground and reference, respectively. Bipolar recordings of horizontal (HEOG) and vertical (VEOG) electro-oculogram activity were taken from supra-/sub-orbital and external canthi sites, respectively. All electrode impedances were kept below 5k $\Omega$ . Electrical activity was recorded using BrainVision Recorder software and a BrainVision Quickamp amplifier (Brain Products, GmbH) with bandpass settings of 0.1 and 30 Hz, digitized at 500 Hz, and stored on hard-disk for later off-line analysis using BrainVision Analyzer software.

EEG epochs (500 ms duration, beginning 100 ms pre-stimulus) were corrected for residual eye movement and eye blink activity using the Gratton & Coles algorithm, which

operates in the time and frequency domain (Gratton et al., 1983); any corrected epochs with EEG voltages exceeding  $\pm 100 \mu\text{V}$  were excluded from further analysis.

Within the multi-feature paradigm, epochs were separately averaged for each standard and deviant stimulus type and then digitally filtered using a bandpass of 0.15-8 Hz, (Leung et al., 2006) and a slope of 24 db/octave. The narrow band pass, previously used in a study of the multi-feature MMN (Fisher et al., 2008a; Fisher et al., 2010), eliminates any extraneous high-frequency activity. MMN difference waveforms were derived by point-by-point digital subtraction of the standard stimulus values from those elicited by the deviant stimulus, and MMNs were assessed by quantifying peak negative amplitudes within a window of 80-220 ms. MMN peaks for each individual participant were picked as the most negative point within each condition's respective analysis window and output was the average within five voltage points (10 ms) to the left and right of the peak amplitude. MMN latency measurements were only measured at  $F_z$ , the site of maximum amplitude. Prior to peak picking, individual visual assessment of the presence of the true MMN, as well as appropriate polarity inversion at mastoids, was conducted within each participant for each deviant type.

#### 4.2.6 Hallucination State Ratings (HSR)

Upon completion of the MMN paradigm, patients completed a rating scale, similar to that used by Margo et al. (1981), asking them to indicate the nature of their hallucinations experienced during the recordings on 5 dimensions: 1) duration (1= no AVHs, 7= continuous AVHs); 2) loudness (1= not audible, 7= extremely loud); 3) clarity

(1= unintelligible, 7= very clear); 4) distress (1 = not distressing, 5 = very distressing); and 5) control (1 = complete control over voices, 7 = no control over voices).

#### 4.2.7 Data Analysis

Analyses of MMN amplitudes and latencies were carried out using the Statistical Package for the Social Sciences (SPSS; SPSS Inc., Chicago, IL). MMN amplitudes were subjected to mixed univariate analysis of variance (ANOVA) procedures with two within-subjects factors (deviant [duration, frequency and intensity] and electrode site [limited to F<sub>3</sub>, F<sub>Z</sub> and F<sub>4</sub>]) and one between-subjects factor (group [SZ patients and HCs]). MMN latencies, derived only from F<sub>Z</sub> (the site of maximum amplitude), were subjected to a similar analysis, however electrode site was not included as a factor.

Where appropriate, Huynh-Feldt epsilon correction factors were applied to the degrees of freedom and the rounded adjusted degrees of freedom have been reported. Regardless of the presence or absence of significant main or interaction effects, planned comparisons involving between-group comparisons with respect to laterality and region were carried out. Significant effects were followed-up with pairwise comparisons for greater specificity in reporting.

In order to examine the correlation between MMN amplitude and state and trait hallucination severity, one-tailed Spearman's rho correlations were conducted between MMN amplitude at frontal sites and hallucination measures (PSYRATS, HSRs). Correlations between MMNs and PANSS scores were also performed to describe any significant relationship with positive symptom, negative symptom and general psychopathology scores.

### 4.3 Results

#### 4.3.1 MMN Amplitude

A general 3 (deviant type) x 3 (frontal sites) x 2 (group) ANOVA was calculated to examine between-deviant differences across groups at each of the maximal recording regions. There was a main effect of deviant,  $F(2, 44) = 5.86, p = .006, \eta^2_{\text{partial}} = .33$ , observed power = .77, due to an overall significantly smaller frequency MMN ( $M = -0.87 \mu\text{V}, SE = .15$ ) compared to duration ( $M = -1.35 \mu\text{V}, SE = .14; p = .003$ ) MMN. There was a further overall main effect of laterality,  $F(2,44) = 9.39, p < .002, \eta^2_{\text{partial}} = .79$ , observed power = 1.00, due to overall larger amplitudes at  $F_z$  ( $M = -1.27 \mu\text{V}, SE = .11$ ) compared to  $F_3$  ( $M = -1.00 \mu\text{V}, SE = .10; p < .001$ ) and  $F_4$  ( $M = -1.06 \mu\text{V}, SE = .14; p = .003$ ). There were no significant main group effects.

Planned comparisons involving group revealed a significant difference between HCs and SZ patients for duration deviants ( $p = .029; \eta^2_{\text{partial}} = .20$ , observed power = .61), due to overall larger MMN amplitudes for HCs ( $M = -1.69 \mu\text{V}, SE = .20$ ) compared to patients ( $M = -1.02 \mu\text{V}, SE = .20$ ). When followed up further to include the effects of electrode site (Figure 8), this effect was found to be limited to  $F_4$ , where HCs ( $M = -1.74 \mu\text{V}, SE = .24$ ) had significantly larger amplitudes to duration deviants compared to SZ patients ( $M = -.72 \mu\text{V}, SE = .24; p = .006; \eta^2_{\text{partial}} = .30$ , observed power = .84). There was also a trend for duration MMNs to be larger for HCs compared to SZ patients at site  $F_z$  ( $p = .06; \eta^2_{\text{partial}} = .15$ , observed power = .49). The two groups did not differ for either frequency or intensity MMNs (Figure 8).

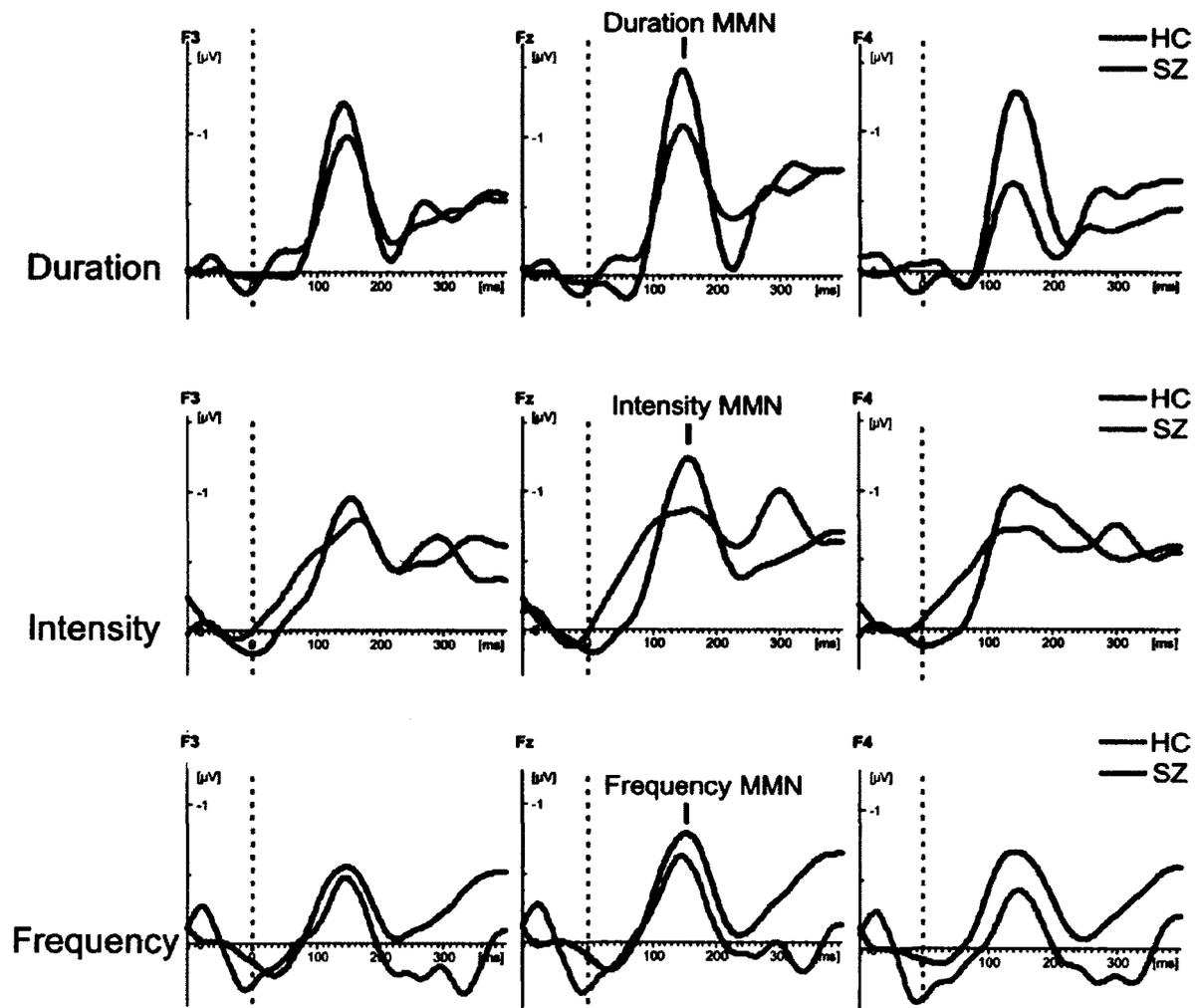


Figure 8. Subtracted waveforms showing mismatch negativity elicited by duration, frequency and intensity deviants at left ( $F_3$ ), midline ( $F_z$ ) and right ( $F_4$ ) frontal recording sites for schizophrenia patients and healthy controls.

#### 4.3.2 MMN Latency

There was no significant difference between groups regarding MMN latency for any of the three deviants, nor were there any differences between the three latencies.

#### 4.3.3 Correlations

PSYRATS scores were positively (i.e. as PSYRATS increases, MMN decreases) correlated with duration MMN amplitudes at  $F_4$  ( $\rho_s = .61, p = .022$ ) and  $F_Z$  ( $\rho_s = .55, p = .039$ ), with intensity MMN amplitudes at  $F_4$  ( $\rho_s = .67, p = .011$ ) and with frequency MMN amplitudes at  $F_4$  ( $\rho_s = .66, p = .013$ ) and  $F_Z$  ( $\rho_s = .60, p = .024$ ). There were no significant correlations between MMN amplitude and HSRs.

Correlation analysis of MMN amplitudes and PANSS scores revealed duration MMN amplitudes at  $F_3$  to be positively (i.e. as score increases, MMN decreases) correlated with positive symptom ( $\rho_s = .71, p = .011$ ) and general psychoticism (GP;  $\rho_s = .61, p = .030$ ) scales, as well as with the hallucination item ( $\rho_s = .62, p = .027$ ) of the positive symptom scale. There were additional significant positive (i.e. as score increases, MMN decreases) correlations between duration MMN amplitudes at  $F_Z$  and the positive symptom scale ( $\rho_s = .78, p = .004$ ), general psychoticism scale ( $\rho_s = .70, p = .013$ ), and the hallucination item ( $\rho_s = .62, p = .027$ ) of the positive symptom subscale. There were no significant correlations between PANSS negative symptom scores and MMN amplitudes.

#### 4.4 Discussion

In this study, we compared the automatic auditory change detection mechanism (as indexed by the MMN) of SZ patients with that of healthy controls within a modified version of the 'optimal' multi-feature MMN paradigm (Näätänen et al., 2004). To our knowledge, this is the first study to assess the MMN in SZ using a modified version of the multi-feature MMN paradigm, and, more specifically, using the recently introduced Optimal-3 paradigm (Fisher et al., 2010).

Consistent with previous research (Umbricht & Krljes, 2005), patients with SZ exhibited a significantly smaller duration MMN compared to healthy controls. What is notable about this finding is that the difference was observed using a shorter duration deviant, supporting the notion that reduced MMN in schizophrenia can be observed with both duration increments (Shelley et al., 1991; Schall et al., 1998; Todd et al., 2008) and decrements (Fisher et al., 2008b; Horton et al., 2010). Conversely, there was no statistical difference in the frequency or intensity MMN amplitudes of schizophrenia patients compared to healthy controls.

While duration MMN results have been consistently supported (Catts et al., 1995; Michie et al., 2000), reports of altered frequency and intensity MMN in schizophrenia have been less consistent (Fisher et al., 2008a; Dulude et al., 2010; Javitt et al., 2000; Todd et al., 2008; Umbricht & Krljes, 2005). It has been previously reported that patients have a greater propensity to exhibit a reduced frequency-MMN amplitudes (vs. healthy controls) when deviant probability is minimized (Javitt et al., 1998; Shelley et al., 1999), degree of deviance is large (Javitt et al., 1998; Shelley et al., 1999) and SOA is short (Javitt et al., 1998; Michie et al., 2000). Additionally, in schizophrenia, reduced frequency MMN appears to be more prevalent in older patients with a longer duration of illness (Todd et al., 2008). Unfortunately, within the current MMN paradigm, deviant probability is not minimized ( $p = 0.17$ ), degree of deviance is moderate ( $df = 10\%$ ) and SOA is not short ( $SOA = 575$  ms) and these factors may have minimized the difference between SZ patients and controls despite the fact our SZ group tended to be older. A recent investigation observed smaller frequency MMNs in patients with relatively short (300 ms) SOA, suggesting that this particular deficit may reflect aberrant temporal

processing in this population (Horton et al., 2010). It should be noted, however, that differences between SZs with AHs and HCs have been obtained within a paradigm with identical standard and frequency deviant stimuli and the same SOA (Fisher et al., 2008a), suggesting that while the current paradigm may not be ideal for elucidating patient-control differences, it likely does not eliminate them.

Todd et al. (2008) found that patients early in the illness demonstrate significant reduction of intensity-MMNs (vs. age-matched controls), while patients with longer duration of illness show no reduction of intensity-MMN in patients vs. age-matched controls. The participants in our study seem better match the age range of Todd et al.'s (2008) long duration of illness patients (and corresponding matched controls), therefore the lack of intensity-MMN differences between participant groups may be at least in part due to age-related decline in MMN amplitude reported in this study.

PSYRATS scores were positively correlated with duration MMN amplitudes at F<sub>4</sub> and with intensity MMN amplitudes at F<sub>Z</sub> and F<sub>4</sub> indicating that in schizophrenia patients, increased auditory hallucinations are associated with reduced amplitude of duration and intensity MMNs. Previous attempts to correlate MMN amplitude and self-report measures of hallucinations have yielded uneven results, however two studies have reported that as AH scores increase there is a corresponding decrease in MMN amplitudes (Hirayasu et al., 1998, Youn et al., 2002). Furthermore, schizophrenia patients who experience AHs have been shown to have reduced duration, intensity and frequency MMNs compared to HCs and reduced duration MMN compared to schizophrenia patients without auditory hallucinations (Fisher et al., 2008a). Recent neuroimaging work has shown increased PSYRATS scores to be correlated with reduced activity of the left

superior temporal region during the presence of an external auditory competitor (Plaze et al., 2006). The negative correlation between left temporal activity and predisposition to experience AHs was interpreted as reflecting competition between AHs and incoming auditory stimuli for finite resources in the auditory cortex. Additionally, it has been suggested that the brains, and specifically the auditory cortex, of schizophrenia patients prone to AHs are “tuned” to preferentially process internally generated auditory signals (such as AHs) at the expense of external auditory processing (Ford et al., 2009). Similar to previous findings (Kuhn & Gallinat, 2010), this group reported reduced activation of left primary auditory cortex to incoming auditory stimuli in SZ patients prone to AHs, which may reflect competition for resources between internally- and externally-generated auditory events, progressive reduction of left auditory cortex (Heschl’s Gyrus; Salisbury et al., 2007), or both. Given that the left auditory cortex has been identified as the site of MMN generation for tone deviants (Näätänen et al., 2007), altered activation of this cortical area in patients prone to AHs likely results in reduced function of the auditory change detector (i.e. reduced MMNs). Furthermore, as the state (vs. trait) of actively experiencing AHs has been primarily linked to brain regions involved in speech production (such as Broca’s area) rather than the auditory cortex (site of MMN generation), this explains our findings of MMN alteration being related to trait (PSYRATS), but not state (HSRs), measures of AHs. Thus, the current finding may provide additional evidence corroborating previous reports of SZ patients preferentially processing AHs, rather than incoming external stimuli. Furthermore, it supports the suggestion that the MMN is crucially relevant as a marker of AH-related altered auditory

processing in schizophrenia (Northoff & Qin, 2011), albeit to the predisposition (or trait) to experience AHs, rather than the active state of experiencing AHs.

Related to correlations with PSYRATS scores, duration MMN amplitudes at F<sub>3</sub> and F<sub>z</sub> were positively correlated (i.e. as PANSS scores increase, MMN amplitudes decrease) with PANSS positive scale, hallucination item and GP scores. It should be noted, that the hallucination item of the PANSS does not exist independently, but is part of the PANSS positive scale. This presents the possibility that the relationship between PANSS positive scale scores and MMN amplitudes is driven by variation in the hallucination item, an interpretation previously reported in schizophrenia patients with AHs (Youn et al., 2002). Furthermore, auditory hallucinations, a hallmark symptom of psychoticism in schizophrenia, may also be driving the positive correlation between PANSS GP scores and duration MMN amplitude. This suggestion is further strengthened by the fact that there was no correlation between MMN amplitudes and PANSS negative scale scores, suggesting specificity in the relationship with positive symptoms, and AHs in particular. There is, however, the possibility that reduced duration MMNs are associated with a general increase in psychoticism, with PANSS positive symptom and hallucination item scores representing part, though not all, of this correlation.

There are several limitations to this study, including the use of a single patient population (vs. hallucinating and non-hallucinating sub-groups) and the modest level of hallucinatory activity expressed by our schizophrenia patients. Employing an additional non-hallucinating schizophrenia population would allow us to better separate the effects of AHs from the general effects of schizophrenia on the MMN. Furthermore, the differences between schizophrenia patients and healthy controls might be exacerbated

by increased AH activity in our patient population. Additionally, while the Optimal-3 paradigm offers significant time advantages, it may not be as sensitive as the original five deviant multi-feature MMN paradigm. The limited findings reported may be due to the reduced frequency- and intensity- MMNs elicited by the Optimal-3 (compared to the original 5-deviant paradigm; Fisher et al., 2010), creating somewhat of a floor effect. Future studies may look to employ larger sample sizes so as to have sufficient power to address this issue in a more definitive manner.

In summary, this study is the first to examine schizophrenia patients within a modified (3-deviant) multi-feature MMN paradigm and, as such, the first study to report a significant difference in duration MMN amplitude between schizophrenia patients and healthy controls within such a paradigm. This corroborates previous research reporting a robust duration MMN deficit in schizophrenia (Näätänen & Kähkönen, 2009; Umbricht & Krljes, 2005) and validates the ability of the newly developed Optimal-3 multi-feature MMN paradigm to detect this. Finally, our findings support the burgeoning research suggesting that the presence of auditory hallucinations may make a significant contribution to widely-reported MMN deficits in schizophrenia.

## CHAPTER 5: ALTERATIONS OF MISMATCH NEGATIVITY (MMN) IN SCHIZOPHRENIA PATIENTS WITH AUDITORY HALLUCINATIONS EXPERIENCING ACUTE EXACERBATION OF ILLNESS (Experiment 3a)

### 5.1 Introduction

As more emphasis is placed on investigating individual symptoms within schizophrenia, the study of auditory hallucinations (AH) is becoming a larger field within research into this devastating illness (Ford et al., 2012). With this new found scientific focus, we move closer to understanding the underlying causes and nature of AHs.

Among the brain-based methods used to explore the neural underpinnings of AHs is the mismatch negativity (MMN), used to probe central auditory processing on a millisecond basis with no attentional task requirements. In the limited research examining differences between the discrimination of acoustic change in schizophrenia, hallucinating patients have been shown to exhibit significantly attenuated MMN amplitudes to duration deviants (vs. healthy controls and non-hallucinating patients) and intensity deviants (vs. healthy controls), as well as attenuated MMN amplitudes to frequency deviants (vs. healthy controls; Fisher et al., 2008a). In contrast, research examining the contribution of AHs to deficits in the processing of speech sounds showed no statistical difference between hallucinating and non-hallucinating patient subgroups at frontal sites, despite different patterns of response to speech and tone stimuli within these groups and an overall deficit in MMN amplitudes for schizophrenia patients as a whole (Fisher et al., 2008b). Specifically, both the non-hallucinating patient and healthy control groups exhibited significantly larger MMN amplitudes to across-phoneme auditory deviants (vs. phoneme duration and pure tone duration deviants), thought to be highly relevant in human auditory processing, while there was no difference in MMN amplitude across

deviant types in hallucinating patients. This not only indicated that patient subgroups may show a differential MMN response, but suggested that the underlying mechanisms of auditory hallucinations may impact the processing of incoming auditory deviance. While these two studies revealed interesting differences moderated by hallucinatory symptomatology in schizophrenia, both were limited by relatively modest AH activity as a result of limiting recruitment to controlled, stabilized patients. As suggested by the authors, in order to best understand the impact of auditory hallucinations on automatic, pre-conscious auditory processing, assessment of a population at peak intensity hallucinatory activity would be ideal.

One objective of this study, using MMN to multiple pure-tone deviants recorded from multiple scalp sites, is to compare hallucinating schizophrenia patients (SZ) with respect to left and right hemisphere differences in deviance detection during an acute psychotic episode requiring hospitalization, during which time symptoms of psychosis, including auditory hallucinations, are likely to be at their most severe. Employing the multi-feature auditory stimulus paradigm proposed by Näätänen and colleagues (2004), it is hypothesized that during hospitalization deviant detection, as expressed by MMN, will be reduced in SZs compared to non-patient healthy controls (HC). Furthermore, it is expected that alteration of auditory change detection, as indexed by MMN amplitude, will be associated with measures of AH state and trait, such that smaller MMNs are observed in patients with more severe AH trait and during exacerbations of AH state.

The suggestion that AHs may drive the normal hearing apparatus (temporal cortex) and compete with external speech for attentional/processing resources allocated to that apparatus (Woodruff, 2004; Woodruff et al., 1997) is supported by the finding of

some studies that AHs are reduced when listening to external speech (Slade, 1974; Margo, Helmsley, & Slade, 1981). Furthermore, compared to healthy controls, who exhibit fMRI-indexed bilateral temporal activation during external speech perception (Bentaleb et al., 2002), schizophrenia patients experiencing severe hallucinations evidenced marked right temporal cortical hypo-responsivity to auditory perception of speech (Woodruff et al., 1997). Given that the responsivity of the auditory cortex varies according to 'host-specific' and contextual qualities of auditory signals (Belin et al., 2000), examining the influence of factors modulating central response to incoming auditory stimuli may provide a unique approach for understanding pathophysiological brain mechanisms underlying AHs and their effects on a pre-attentive cognition. Central processing beyond the peripheral auditory mechanism is affected by speech competitors such as background noise (and, perhaps, auditory hallucinations) and is reflected at the pre-attentive level by reductions in MMN and regional displacement of maximal amplitudes from left to right hemisphere (Shtyrov et al., 1998; Shtyrov et al., 1999; Muller-Gass et al., 2001; Kujala et al., 2002). By assessing patients during acute exacerbation of illness severe enough to require hospitalization, we will be able to observe how acute exacerbation of hallucinatory symptoms may drive/inhibit central processing.

## 5.2 Materials and Methods

### 5.2.1 Experimental Participants

Twelve experimental volunteers, all presenting with a primary diagnosis of schizophrenia, were recruited from the Inpatient Schizophrenia Clinical Unit of the Royal Ottawa Mental Health Centre (ROMHC). During an initial clinical interview (with the primary care physician) volunteers were assessed with respect to inclusion and exclusion criteria according to clinical history, and ratings on the Positive and Negative Syndrome Scale (PANSS; Kay, Opler & Lindenmeyer, 1989) for schizophrenia. At the time of admission to the study, all experimental participants were experiencing acute exacerbation of their illness, as indicated by a total PANSS score between 60-120 (Sechter et al., 2002). All patients reported a current history of AHs at the time of acute illness, exhibiting a score  $\geq 3$  ("mild or greater hallucinatory experiences"; range 1-6) on the hallucination item of the PANSS positive symptom scale (based on physician assessment).

The presence of AHs was subsequently confirmed by the experimenter (DF), who rated the patients on the AH subscale of the Psychotic Symptom Rating Scale (PSYRATS) by means of a semi-structured interview. This 11-item, 5-point (0-4) rating scale assesses hallucinations with respect to frequency, duration, severity and intensity of distress and also symptom specific dimensions of controllability, loudness, location, negative content, degree of negative content, beliefs about origin of voices, and disruption.

All patient participants were primarily right-handed, as per the Edinburgh Handedness Inventory (EHI; Oldfield, 1971), and between the ages of 18-55. All patients entering the study had a primary DSM-IV TR diagnosis of schizophrenia, paranoid subtype, as assessed by a structured clinical interview (SCID-P; Frist et al., 2001) and

were acutely ill at the time of assessment. Their primary medication was limited to one of the atypical anti-psychotics. All participants were able to understand spoken and written English. Due to the auditory requirements of the study, all participants were required to demonstrate normal hearing according to an audiometric assessment, conducted by the primary investigator in the research laboratory, and were able to detect pure tones of 500 Hz, 1000 Hz, and 2000 Hz at an intensity of 25 dB (SPL) or less.

Participants were excluded if they met any of the following criteria: co-morbid DSM-IV TR Axis I disorder; current history of drug abuse or dependence; recent (one year) history of head injury resulting in loss of consciousness; diagnosis of epilepsy or any other neurologic disorder; treatment with anxiolytics or anti-depressants; electro-convulsive therapy (ECT) treatment within the previous year; significant cardiac illness; extrapyramidal symptoms (EPS) resulting in movement disorders which could affect ERP recordings; or abnormal audiometric assessment.

### 5.2.2 Control Participants

Healthy control participants (HC) were fifteen right-handed, healthy volunteers, with negative psychiatric, medical, neurological and alcohol/drug abuse histories (by self-report), reporting non-use of medications, and displaying normal hearing. Experimental and control groups were matched with respect to age and gender. Two-tailed independent samples t-tests were used to compare group means on demographic variables. While attempts were made to match the groups for years of education this proved to be difficult as schizophrenia patients who are more likely to require hospitalization tend to have an early age of onset (Olfson et al., 2011), which interferes with schooling. As such, there

was a significant difference,  $t = -3.45$ ,  $p = .004$ , between groups on years of education.

Participant demographics are shown in table 4.

*Table 4. Summary of participant demographics and trait questionnaires (mean  $\pm$  SE) for experiment 3a*

	Patients	Controls
Age	30.60 (3.41)	31.67 (3.03)
Years of education	12.07 (0.92)	16.07 (0.69)
PSYRATS	25.22 (3.26)	-
PANSS Positive Symptom	19.43 (1.59)	-
PANSS Negative Symptom	19.71 (1.48)	-
PANSS Hallucination Item	3.57 (0.57)	-
PANSS General Psychopathology	35.29 (1.01)	-
HSR-Duration	2.73 (0.62)	
HSR-Loudness	2.82 (0.54)	
HSR-Clarity	3.45 (0.82)	

### 5.2.3 Study Design

Following the signing of an informed consent, volunteers attended the Clinical Neuroelectrophysiology and Cognitive Research Laboratory at the Royal Ottawa Mental Health Centre. For experimental participants, the test session took place as close as possible to hospital admission and before stabilization of acute exacerbation of symptoms. The study was conducted following approval of both the Research Ethics Board of the Royal Ottawa Health Care Group (ROHCG) and the Carleton University Ethics Committee for Psychological Research.

#### 5.2.4 Study Procedure

Testing was conducted around midday (12:30 p.m.-2:30 p.m.) with participants being required to abstain from drugs, medications (except for anti-psychotics and adjunct drugs), and alcohol beginning at midnight of the previous day. Upon arrival at the laboratory, participants completed demographic questionnaires and underwent audiometric assessment. Following this, EEG electrodes were applied and volunteers were assessed with respect to the electrophysiological paradigm, during which they were instructed to view a silent, neutral emotive video and to ignore the presented auditory stimuli. Rest intervals of ~1 minute were inserted between each of the test blocks of the MMN paradigm.

#### 5.2.5 Task Stimuli: 5-deviant 'Optimal' Multi-Feature MMN

This study employed the 5-deviant multi-feature MMN paradigm developed by Näätänen et al. (2004), exactly as described in Experiment 1. Briefly, the deviant tones differed from the standard tones in frequency, duration, intensity, perceived location of sound origin or contain a gap in the middle of the tone. Except where stated, the deviants were identical to the standards.

In each test block, the first 15 tones were standards, followed by a sequence whereby every second tone was a standard ( $P = 0.5$ ) and every other one was one of the five deviants ( $P = 0.1$  each). The deviants were presented so that each deviant category is presented once every 5 deviants and 2 deviants of the same category are never presented

consecutively. The stimuli were presented in 3 blocks of 5 minutes each (1845 stimuli) for a total of 15 minutes (5535 stimuli).

#### 5.2.6 Hallucination State Ratings (HSR)

HSRs in patients were assessed following the MMN paradigm. Subjective ratings were carried out in a manner similar to that used by Margo et al (1981), requiring SZs to assess subjective aspects of hallucinations experienced during the electrophysiological recording on 3 dimensions: 1) duration (1 = no AHs; 7 = continuous AHs); 2) loudness (1 = not audible; 7 = extremely loud); and 3) clarity (1 = unintelligible; 7 = very clear)

#### 5.2.7 EEG Recording and ERP Computation

MMNs were extracted from EEG activity recorded from  $\text{Ag}^+/\text{Ag}^+-\text{Cl}^-$  ring electrodes at thirty-two scalp sites according to the 10-20 system of electrode placement, including three midline sites (frontal [ $F_z$ ], central [ $C_z$ ], parietal [ $P_z$ ]), as well as three left hemisphere (frontal [ $F_3$ ], central [ $C_3$ ], parietal [ $P_3$ ]) and three right hemisphere (frontal [ $F_4$ ], central [ $C_4$ ], parietal [ $P_4$ ]) scalp sites. Electrodes were also used to record left (LM) and right (RM) mastoid activity and electrodes were placed on the mid-forehead and nose to serve as ground and reference respectively. Bipolar recordings of horizontal (HEOG) and vertical (VEOG) electro-oculogram activity were taken from supra-/sub-orbital and external canthi sites, respectively. All electrode impedances were kept below  $5\text{k}\Omega$ . Electrical activity was recorded at a sampling rate of 500 Hz using Brain Vision Recorder software with an amplifier bandpass of 0.1 and 70 Hz, and stored on hard-disk for later off-line analysis.

Electrical epochs (500 ms duration, beginning 100 ms pre-stimulus) with EEG or EOG voltages exceeding  $\pm 75 \mu\text{V}$  were excluded from the analysis and the remaining artifact-free epochs, were corrected for residual eye movement and eye blink activity using an algorithm operating in the time and frequency domain (Gratton, Coles, & Donchin, 1983).

Within the MMN test paradigm, epochs were separately averaged for standard stimuli and for each deviant stimulus type and then digitally filtered using a bandpass of 0.15-8 Hz (Leung et al., 2006) and a slope of 24 db/octave. For each site and deviant type, MMN difference waveforms were derived from point-by-point subtraction of the standard stimulus values from those elicited by the deviant stimulus, and MMNs were assessed by quantifying peak negative amplitudes within a custom-tailored window derived from an inspection of the grand-averaged waveform from each condition. MMN latency values were only measured at F<sub>z</sub>, the site of maximum amplitude. For all deviant types in all participants, MMN waveforms were visually inspected to ensure appropriate inversion at mastoids.

### 5.2.8 Data Analysis

Separate analyses were carried out for each of the five deviant types using the Statistical Package for the Social Sciences (SPSS; SPSS Inc., Chicago, IL). MMN amplitudes were subjected to mixed univariate analysis of variance (ANOVA) procedures with one between-group (2 levels: HC, HP) and two within-group factors (laterality [left, central, right], and region [limited to the frontal (F), and central (C) regions]).

Analyses of MMN latency and HSR (duration, intensity, clarity) scores were performed with independent samples t-tests.

Where appropriate, Huynh-Feldt epsilon correction factors were applied to the degrees of freedom and the adjusted F-values are reported. Significant effects were followed-up with pairwise comparisons. Any unexpected significant results (i.e. those that could not be predicted with previous empirical evidence) that require follow-up were analyzed with Bonferroni-adjusted pairwise comparisons, in order to guard against type I error. However, for planned comparisons (i.e. those supported by previous research and relevant to hypotheses), no alpha correction was used. It has been pointed out that Bonferroni adjustments, when applied too liberally, not only significantly reduce power (to as low as 33%; Jennions & Moller, 2003), but also greatly increase the chance of Type II error to somewhere between 39-66% (Nakagawa, 2004). It goes to say, that Type II error is just as undesirable as Type I error, and it has been suggested that Bonferroni adjustments may harm a study, rather than help it (Rothman, 1990; Perneger, 1998; Perneger, 1999). Furthermore, if a hypothesis is constructed properly, that is to say it necessitates detailed measurements, it is much less likely that significant results will be found; a paradox named the hyper-Red Queen phenomenon (Moran, 2003). Therefore, in cases where statistical examination is warranted by previous empirical research, no Bonferroni adjustments were made.

Relationships of frontal MMNs, site of maximum amplitude, to medication (chlorpromazine equivalent score) and symptom ratings (including PSYRATS, PANSS and HSR scores) were examined with two-tailed correlational (Spearman's  $\rho$ ) statistics. Spearman's  $\rho$  was specifically chosen given the relatively small sample size, as it is more

resistant to the effects of potential outliers than other correlational methods, such as Pearson's  $r$ .

### 5.3 Results

#### 5.3.1 MMN Amplitude

Analysis of duration MMN revealed a main effect of region,  $F(1,23) = 26.81$ ,  $p < .001$ , due to significantly larger amplitudes at frontal ( $M = -1.53 \mu\text{V}$ ,  $SE = .12$ ) than central ( $M = -.84 \mu\text{V}$ ,  $SE = .11$ ) electrodes. There was also a main effect of group,  $F(1,23) = 5.21$ ,  $p = .032$ , due to significantly smaller MMN amplitudes in SZs ( $M = -.96 \mu\text{V}$ ,  $SE = .15$ ) compared to HCs ( $M = -1.41 \mu\text{V}$ ,  $SE = .13$ ). Planned comparisons showed significantly reduced duration MMN amplitudes for SZs ( $M = -.75 \mu\text{V}$ ,  $SE = .14$ ) compared HCs ( $M = -1.26 \mu\text{V}$ ,  $SE = .13$ ) in the left hemisphere ( $p = .014$ ). Additionally, in the frontal region, significantly reduced amplitudes were seen for SZs ( $M = -1.24 \mu\text{V}$ ,  $SE = .19$ ) compared to HCs ( $M = -1.82 \mu\text{V}$ ,  $SE = .16$ ;  $p = .03$ ). Finally, planned comparisons of the site x region x group interaction revealed significantly reduced duration MMN amplitudes for SZs (vs. HCs) at  $F_3$  ( $p = .017$ ) and  $F_Z$  ( $p = .033$ ), as shown in figure 9.

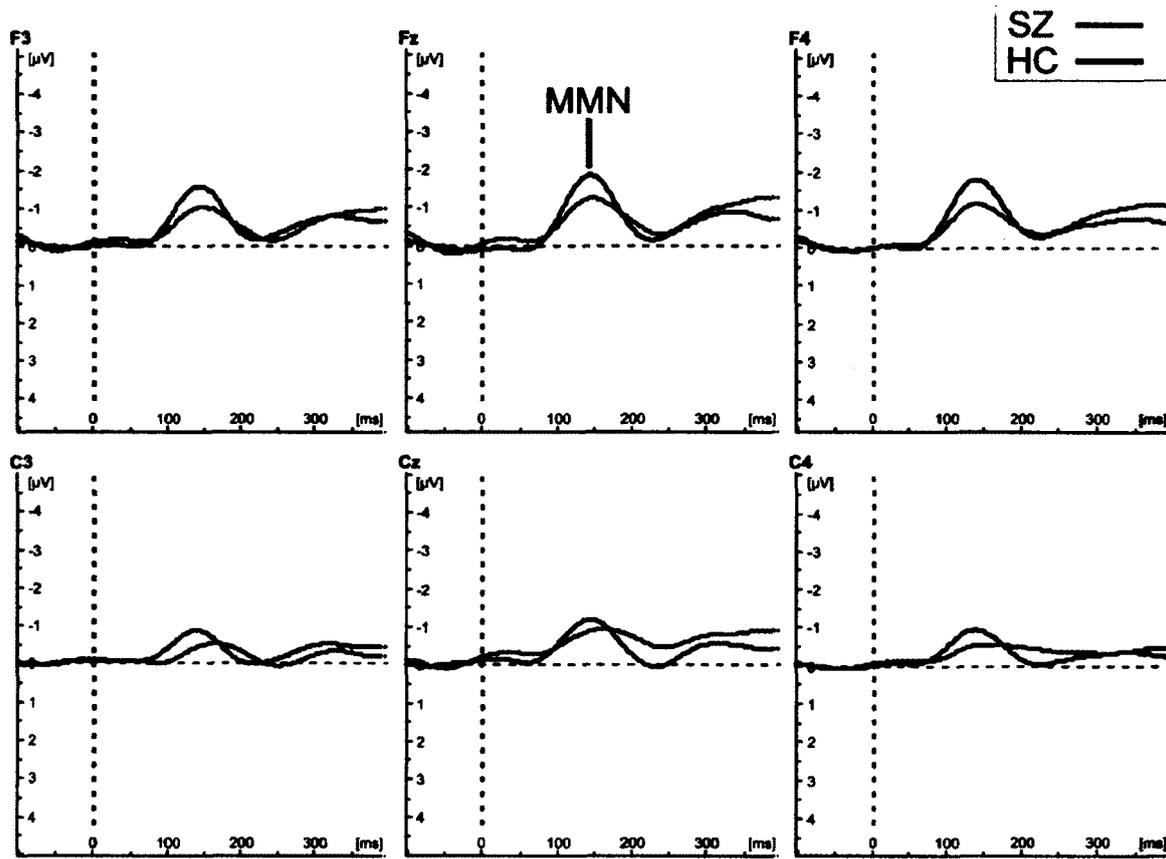


Figure 9. Grand averaged duration MMN waveforms for schizophrenia inpatients (SZ) and healthy controls (HC).

Regarding gap MMN, there was a main effect of region,  $F(1,23) = 29.54, p < .001$ , due to larger amplitudes at frontal ( $M = -.94 \mu\text{V}, SE = .12$ ) than at central ( $M = -.49 \mu\text{V}, SE = .08$ ) sites, as well as a trend for overall group differences,  $F(1,23) = 3.37, p = .079$ , due to reduced amplitudes for SZs ( $M = -.53 \mu\text{V}, SE = .15$ ) compared to HCs ( $M = -.90 \mu\text{V}, SE = .13$ ). Planned comparisons of gap MMN found that, at central sites, there was a significant difference ( $p = .011$ ) between SZs ( $M = -.25 \mu\text{V}, SE = .13$ ) and HCs ( $M = -.73 \mu\text{V}, SE = .12$ ). When followed-up to account for site (figure 10), a significant reduction of SZ amplitudes (vs. HCs) at  $C_3$  ( $p = .026$ ) and  $C_z$  ( $p = .018$ ) was revealed.

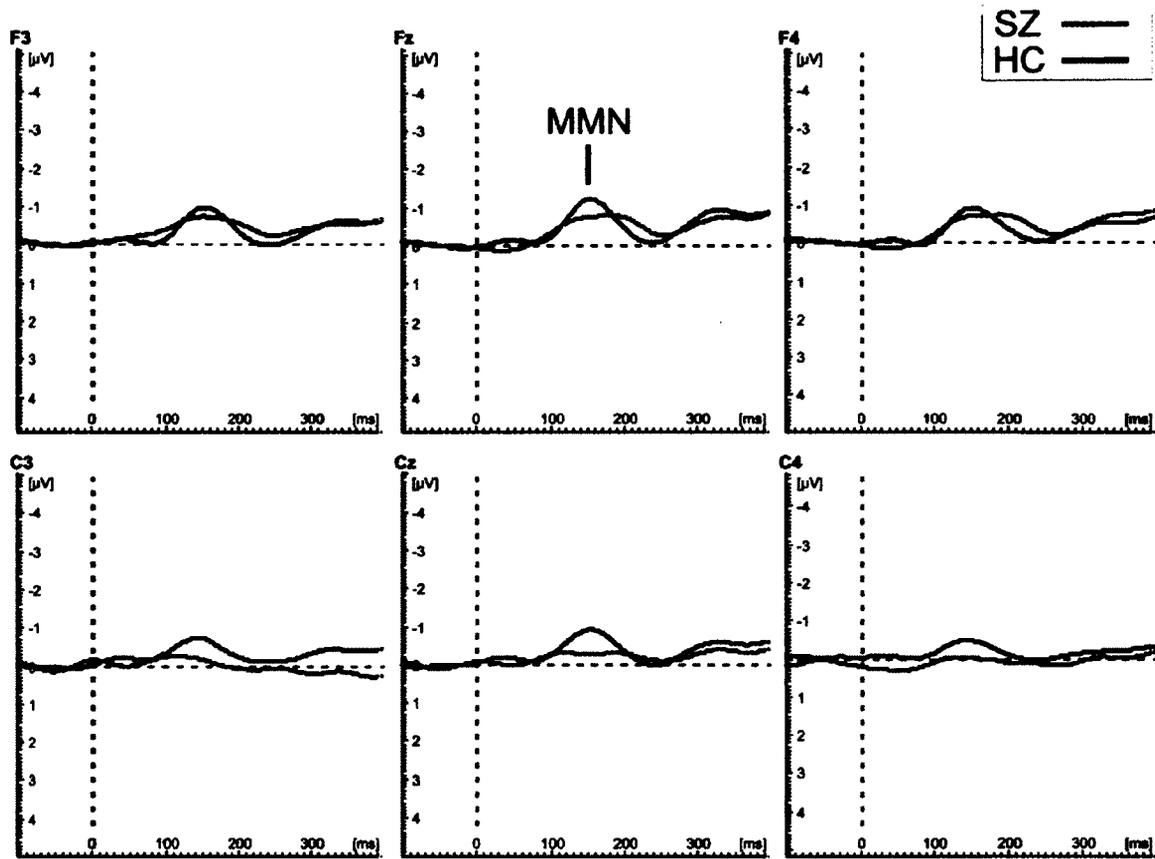


Figure 10. Grand averaged gap MMN waveforms for schizophrenia inpatients (SZ) and healthy controls (HC).

There was a significant main effect of region for intensity MMN amplitudes,  $F(1,23) = 28.86$ ,  $p < .001$ , due to larger amplitudes at frontal ( $M = -1.72 \mu\text{V}$ ,  $SE = .17$ ) regions than at central regions ( $M = -.66 \mu\text{V}$ ,  $SE = .13$ ). Planned comparisons revealed a significant between-group difference at  $C_3$  ( $p = .024$ ; figure 11) due to HCs ( $M = -1.09 \mu\text{V}$ ,  $SE = .16$ ) having significantly larger amplitudes than SZs ( $M = -.49 \mu\text{V}$ ,  $SE = .19$ ).

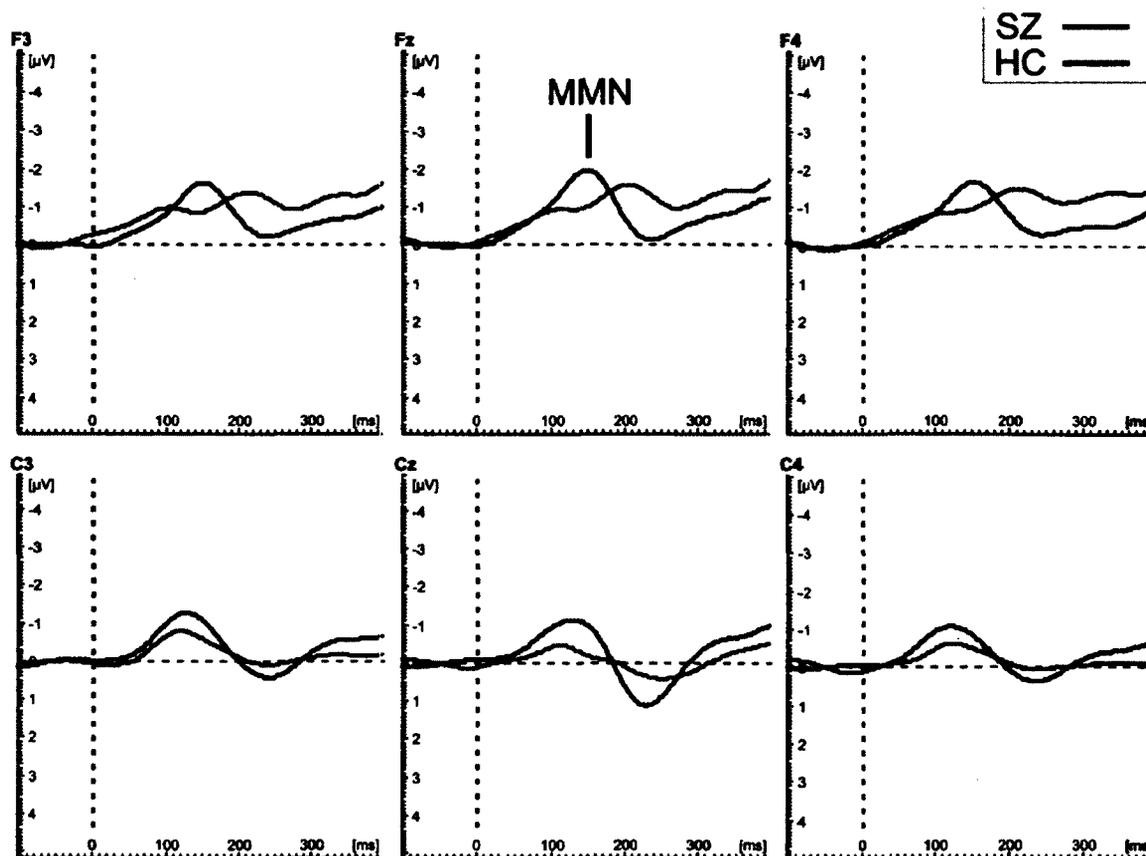


Figure 11. Grand averaged intensity MMN waveforms for schizophrenia inpatients (SZ) and healthy controls (HC).

Within the analysis of location MMN, there was a main effect of region,  $F(1,23) = 4.20, p = .05$  (frontal:  $M = -.96 \mu\text{V}, SE = .10$ ; central:  $M = -.71 \mu\text{V}, SE = .13$ ), as well as a region  $\times$  site  $\times$  group trend,  $F(2,46) = 2.65, p = .081$ . Follow-up of the region  $\times$  site  $\times$  group trend revealed a significant difference ( $p = .039$ ) between SZs ( $M = -.70 \mu\text{V}, SE = .18$ ) and HCs ( $M = -1.24 \mu\text{V}, SE = .16$ ) at  $F_4$  only (Figure 12).

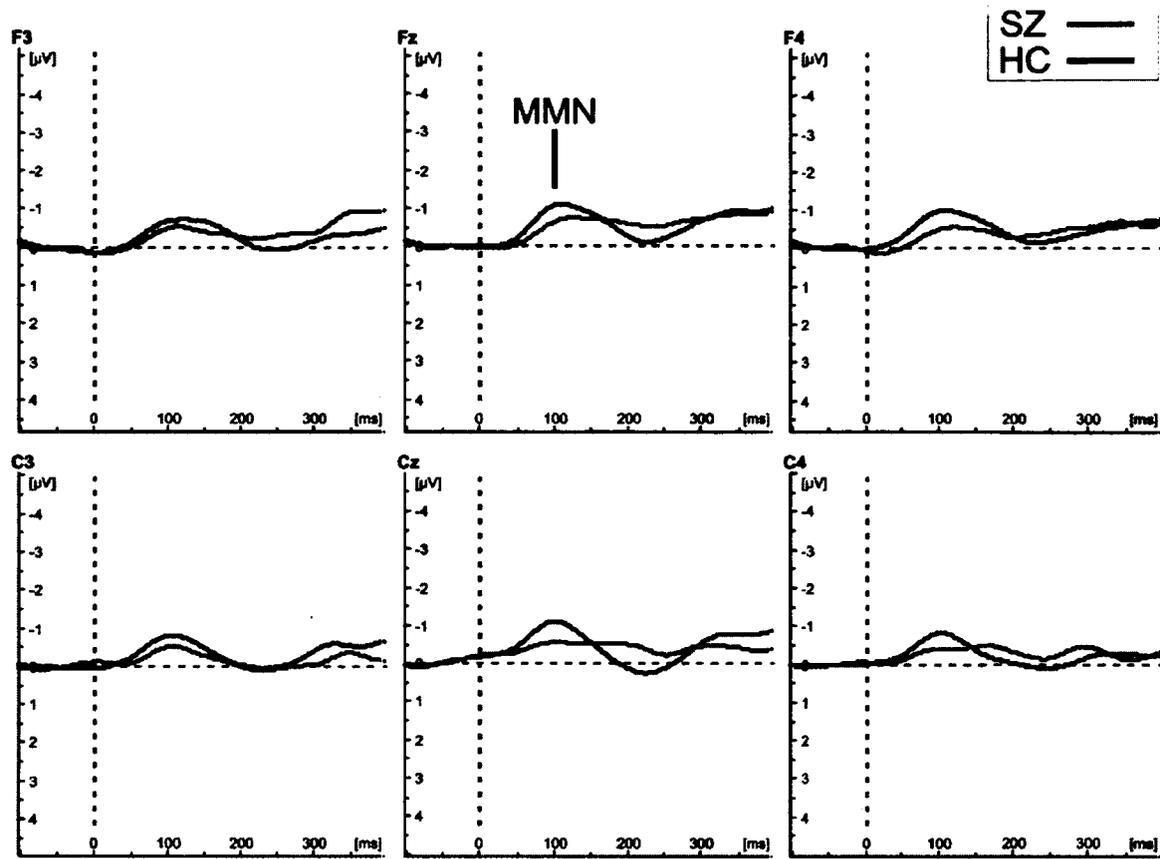


Figure 12. Grand averaged location MMN waveforms for schizophrenia inpatients (SZ) and healthy controls (HC).

Finally, analysis of frequency MMN revealed a main effect of region,  $F(1,23) = 11.77, p = .002$ , due to significantly larger frontal ( $M = -1.22 \mu\text{V}$ ,  $SE = .13$ ) than central ( $M = -.86 \mu\text{V}$ ,  $SE = .09$ ) amplitudes. Planned comparisons resulted in no significant between-group differences (Figure 13).

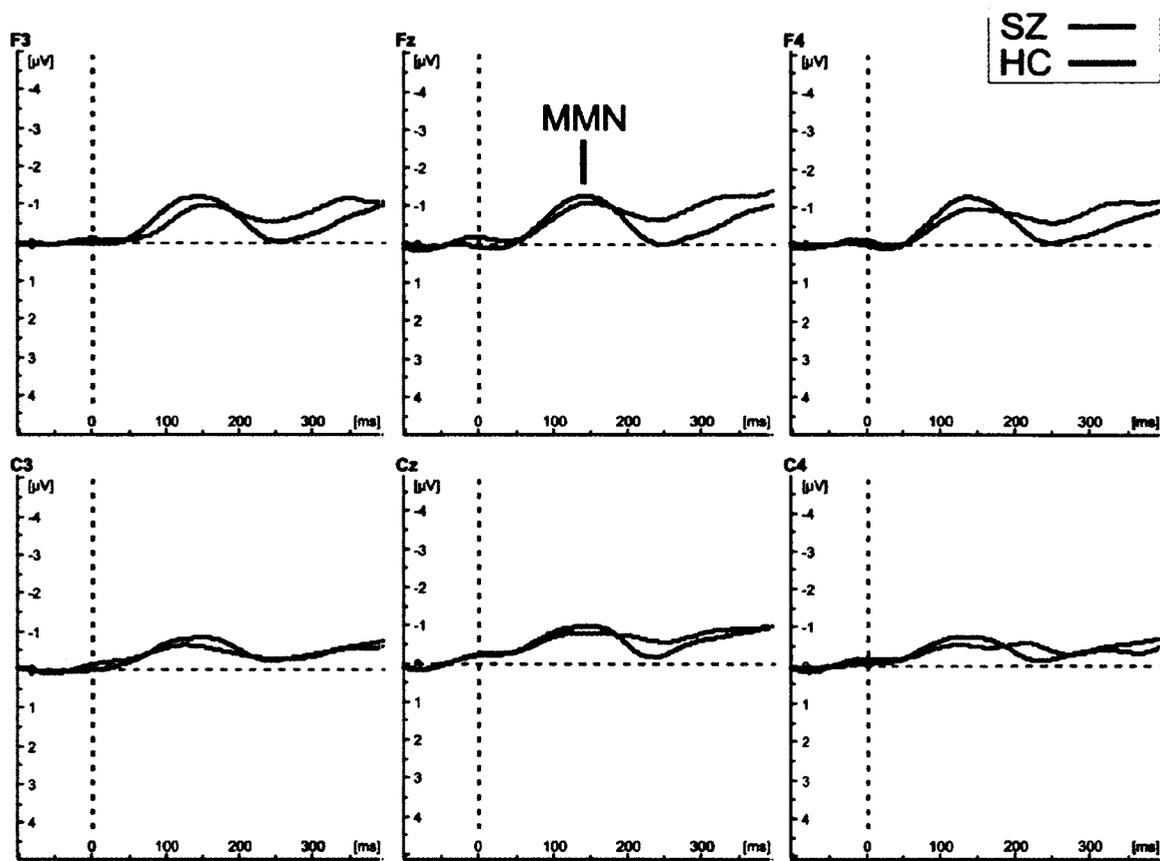


Figure 13. Grand averaged frequency MMN waveforms for schizophrenia inpatients (SZ) and healthy controls (HC).

### 5.3.2 MMN Latency

There were no significant main or interaction effects. Planned comparisons revealed no significant differences between groups.

### 5.3.3 Correlations

HSR-Duration ratings were negatively correlated with gap MMN amplitudes at  $F_4$  ( $\rho = -.82, p = .002$ ) and  $F_z$  ( $\rho = -.83, p = .001$ ). HSR-Loudness ratings were negatively correlated with gap MMN amplitudes at  $F_4$  ( $\rho = -.63, p = .037$ ) and  $F_z$  ( $\rho = -.85, p <$

.001). HSR-Clarity ratings were negatively correlated with gap MMN amplitudes at F<sub>4</sub> ( $\rho = -.72, p = .013$ ) and F<sub>z</sub> ( $\rho = -.65, p = .03$ ). While there were no significant correlations between PANSS scores and MMN amplitudes, there were correlations between duration MMN latency and PANSS Negative symptom ( $\rho = .82, p = .025$ ) and General Psychopathology ( $\rho = .84, p = .036$ ) scores. Finally, there was a significant negative correlation between location MMN amplitudes at F<sub>4</sub> and medication dosage ( $\rho = -.72, p = .043$ ).

#### 5.4 Discussion

Continuing in the trend of investigating individual symptoms, such as auditory hallucinations, within schizophrenia, this study examined the neural correlates of auditory change detection (as indexed by the MMN) in hallucinating schizophrenia patients (SZ) during an acute psychotic episode requiring hospitalization, during which time symptoms of psychosis, including auditory hallucinations, were expected to be at their most severe. Overall, despite the relatively modest hallucinatory activity experienced by these patients while acutely ill, we report deficits in MMN amplitude across several deviant types.

Among the most robust neuroelectrophysiological findings in schizophrenia is a reduced duration MMN. Not only was this the first reported MMN deficit in schizophrenia (Shelley et al., 1991), it has been replicated many times over with both duration increments (Shelley et al., 1991; Schall et al., 1998; Todd et al., 2008) and decrements (Fisher et al., 2008b; Horton et al., 2010). Recently, duration MMN deficits in schizophrenia have been reported in both the original, 5-deviant multi-feature paradigm (Fisher et al., 2008a) and modified Optimal-3 paradigm (Fisher et al., 2011b).

Consistent with this previous research, SZ patients exhibited a significantly smaller duration MMN compared to healthy controls overall, but particularly at F<sub>3</sub> and F<sub>Z</sub>. Both of these findings are consistent with previous literature; duration MMN deficits at F<sub>Z</sub> have been commonly reported in schizophrenia in general, as well as in patients with auditory hallucinations (Fisher et al., 2008a; Fisher et al., 2011b). Similarly, recent investigation of the neuromagnetic (MEG) analog of the MMN, the MMNm, using the 'Optimal' 5-deviant multi-feature paradigm reported duration MMNm deficits, but only in the left hemisphere (Thonnessen et al., 2008). Interestingly, an earlier investigation that found duration MMN deficits, reported at F<sub>3</sub>, to be related to attenuated activity of left superior temporal gyrus found the magnitude of this deficit to be related to scores on the hallucinatory behaviour subscale of the PANSS (Hirayasu et al., 1998). Thus, given the consistent AHs reported by the current participants, it is perhaps not surprising that duration MMN deficits show a left-central distribution.

We also report significant positive correlations between duration MMN latency and both the negative symptom and general psychopathology subscales of the PANSS, indicating that larger scores on these subscales are associated with larger (i.e. slower) MMN latencies. Previously, increased negative symptoms have been correlated with MMN amplitude (Grzella et al., 2001), but this is the first report, to our knowledge, to report an association between PANSS negative scores and MMN latency. The negative symptom scale of the PANSS is associated with cognitive, affective and social deficits (including symptoms of avolition, blunted affect, etc...), while the general psychopathology scale is associated with overall illness severity, including cognitive

deficits and perceptual disorganization. Given this, one might expect increased scores on these subscales of the PANSS to be associated with delays in central auditory processing.

This study is the first, to our knowledge, to report a significant difference in MMN amplitude between schizophrenia patients and healthy controls to gap deviants, albeit at central recording sites only. However, evidence suggests that the topography of the MMN to gaps embedded in spectrally rich auditory stimuli, such as those used in this experiment, is more posterior than that seen with other deviant types, with MMN maxima encompassing both frontal and central recording sites (Takegata, Heikkilä & Näätänen, 2009).

Processing of silent gaps in the order of milliseconds is crucial in speech perception. Relatedly, activation in response to the gap deviant has been reported in the left fusiform gyrus (Fisher & Knott, 2009), which has been implicated in semantic processing (such as detection and processing of gaps in and between words) during presentation of auditory stimuli (Binder et al., 1997), with greater activation of the fusiform gyrus seen during the presentation of spectrally rich stimuli, such as words (Demonet et al., 1992). There is also some suggestion that the fusiform gyrus may be involved in the production of mental imagery (Wise et al., 2000) and activation of the fusiform gyrus has been reported during non-clinical auditory hallucinations (Barkus et al., 2007). As such, the gap deviant may be sensitive to cortical activation during the presence of auditory hallucinations. Consistent with this suggestion, albeit in the opposite direction predicted, gap MMN amplitudes at right- and midline-frontal sites increased with corresponding increases in hallucinatory state loudness, duration and clarity. Although this is inconsistent with our hypothesis, it may fit with previous findings that

environmental conditions (in this case, auditory hallucinations) during the diversionary task could actually increase MMN amplitude via increased cortical excitability (Muller-Gass et al., 2005). Specifically, activation of shared cortical areas by low-to-moderate auditory hallucinations may result in a hyper-excitability of gap MMN generators, resulting in increased gap MMN amplitudes with increases in auditory hallucinations. However, why this effect is specific to gap MMN, and whether this effect would be seen with more intense (or an absence of) hallucinatory states, must be examined further.

Given that this is the first study to report decreases in gap MMN amplitude in schizophrenia and alteration of these amplitudes with hallucinatory state, the interpretation of these findings is somewhat unclear. It could be that, since previous studies examined gap MMN in stable schizophrenia patients, this deficit is unique to the acute illness. Alternatively, it could be that the acute illness potentiates the impact of other factors, such as auditory hallucinations. Future replications of this finding will be necessary to further elucidate the neural underpinnings of this reported MMN deficit.

Following up on a region x site x group trend, there was a significant between-group difference that emerged for SZs to have a reduced right frontal (F<sub>4</sub>) location MMN amplitude compared to HCs. This difference is notable for two main reasons. Firstly, previous neuroimaging work examining the cortical correlates of sound location (vs. sound identity) reports significant right dominant activation of the IPL, as well as the superior parietal and prefrontal region (Alain et al., 2001; Arnott et al., 2005). An extension of this work examining activation of the IPL during sound localization demonstrated the right IPL to be involved in the active (working memory related) monitoring and updating of sound location, independent of task responding (Alain, He, &

Grady, 2008). Specifically, it has been suggested that the inferior and superior parietal cortex play an important role in localizing and remembering sound locations (Alain et al., 2001; Rämä et al., 2004; Arnott et al., 2005), which would be important in the memory trace formation requisite in the elicitation of the MMN. With this in mind, these reports suggest that violation of the location of an established memory trace recruits the IPL in processing, despite the absence of an active task, in order to pre-attentively assess the incoming deviant stimulus. As such, we might expect that SZ patients would show a right-sided reduction in location MMN, given the importance of this hemisphere is location processing.

Relatedly, SZ patients with AHs have been reported to have anatomical differences in and around the right temporoparietal junction (rTPJ), a region associated with the auditory “where” pathway, depending on whether hallucinations were experienced as originating inside or outside the head (Plaze et al., 2011). Specifically, patients who experienced auditory hallucinations as being outside the head showed reduced white matter in the right superior temporal gyrus (in the vicinity of the rTPJ), suggesting structural compromise in the dorsal stream that communicates information related to the spatial location of sounds (Plaze et al., 2011). As such, location MMN, particularly recorded from right frontal electrodes, may prove to be a useful as an index of the experienced spatial location of auditory hallucinations.

This finding is somewhat tempered, however, by a significant negative correlation between location MMN amplitude at F<sub>4</sub> and medication dosage (as indexed by chlorpromazine equivalents). While previous work has shown the MMN to be insensitive to neuroleptic effects, this previous work focused on duration (Korostenskaja et al., 2005)

and frequency (Umbricht et al., 1998; 1999) deviants. It may be that auditory detection of location deviance is more sensitive to the effects of antipsychotic medication as compared to duration or frequency deviance. Certainly, in previous work with schizophrenia outpatients, there was no significant between-group difference for location MMN (Fisher et al., 2008a). Of course, one must also be mindful that correlation does not equal causation and that the association between location MMN amplitudes at F<sub>4</sub> and medication dosage may be mediated by a third, unknown factor. By way of example, medication dosage may be a proxy for treatment resistance (perhaps due to compromised white matter integrity of STG and rTJP; Plaze et al., 2011), with treatment resistant patients being more likely to exhibit location MMN deficits. In the meantime, the reported group difference observed for location MMN must be treated with caution until further research can determine whether this deficit observed in schizophrenia is due to the illness itself or an artifact of medication effects.

Previously, schizophrenia patients have been reported to exhibit deficits of intensity MMN amplitude compared to healthy controls (Fisher et al., 2008a; Todd et al., 2008). We report a similar finding, but only at the left central recording site. While MMN amplitudes tend to be maximal at frontal electrodes, MMN generators are known to have a fronto-central orientation (Näätänen et al. 2007), thereby including central electrodes as reasonable recording sites of interest.

As reported earlier (Fisher et al., 2008a), It is possible that the deficits seen with duration and intensity deviants are related, with a reduction in available cortical resources (e.g. by usurping of these resources by AHs) resulting in reduced sensitivity to differences in stimulus intensity. Additionally, several findings have suggested that the

duration MMN (Frodl-Bauch et al., 1997; Kaukoranta et al., 1989; Sams et al., 1991) and intensity MMN (Lounasmaa et al., 1989; Sams et al., 1991) generators are localized in the same general cortical area. Indeed, the lateralization of the between-group difference in this particular study (i.e. left) is consistent with the expected and observed left lateralized deficit to duration MMN in schizophrenia even if the observed difference for intensity MMN was seen somewhat more posterior.

In this study, we found no group differences for frequency MMN. Indeed, compared to the robust findings associated with duration MMN, reports of altered frequency MMN in schizophrenia have been less consistent (Näätänen & Kahkonen, 2008; Umbricht & Krljes, 2005). Previous reports have identified several conditions that facilitate reductions of frequency-MMN amplitudes in SZ patients (vs. healthy controls): small deviant probability (Javitt et al., 1998; Shelley et al., 1999); large degree of deviance (Javitt et al., 1998; Shelley et al., 1999); and short SOA (Javitt et al., 1998; Michie et al., 2000). Additionally, in schizophrenia, reduced frequency MMN appears to be more prevalent in older patients with a longer duration of illness (Todd et al., 2008). Unfortunately, within the current MMN paradigm, deviant probability is not minimized ( $p = 0.10$  vs.  $p = 0.05$  or lower in Javitt et al., 1998), degree of deviance is moderate ( $df = 10\%$  vs.  $df = 20\%$  or higher in Javitt et al., 1998) and SOA is not short (SOA = 575 ms vs. 150 ms in Javitt et al., 1998) and these factors may have minimized the difference between SZ patients and controls. It should be noted, however, that differences between SZs with AHs and HCs have been previously obtained within an identical paradigm (Fisher et al., 2008a), however this study employed an older patient population, potentially increasing the chance of obtaining group differences (Todd et al., 2008).

There are several limitations to this study, including the use of a single patient population (vs. hallucinating and non-hallucinating sub-groups) and the modest level of hallucinatory activity expressed by our schizophrenia patients despite acute exacerbation of illness requiring hospitalization. Employing an additional non-hallucinating schizophrenia population, though difficult to recruit, would allow us to better separate the effects of AHs from the general effects of schizophrenia on the MMN in an acutely ill population. As an alternative, if a matching non-hallucinating sub-group cannot be found, the use of a group that is less homogeneous on measures of AHs would better allow for post-hoc elucidation of relationships between AHs (particularly AH trait) and MMN amplitudes. In this particular sample there was a limited range of AH activity; with less variance in AH symptomatology and a relatively small sample size, it is less likely that correlations will be statistically significant. Conversely, where there is greater variance, existing correlational relationships are more likely to emerge. Future studies may also wish to combine the use of electrophysiological measures with structural data, such as structural magnetic resonance imaging and/or diffusion tensor imaging, in order to explore the potential underlying structural correlates of observed deficits in acoustic change detection.

In summary, this study corroborates previous research reporting a robust duration MMN deficit in schizophrenia (Näätänen & Kähkönen, 2009; Umbricht & Krljes, 2005), as well as reporting gap MMN and location MMN deficits in schizophrenia inpatients with persistent auditory hallucinations. These findings offer further support to previous work suggesting that the presence of auditory hallucinations may make a significant contribution to the widely reported MMN deficits in schizophrenia.

## CHAPTER 6: AUDITORY MISMATCH NEGATIVITY (MMN) IN ACUTELY ILL AND CURRENTLY STABLE SCHIZOPHRENIA PATIENTS WITH AUDITORY HALLUCINATIONS (Experiment 3b)

### 6.1 Introduction

Previous work examining the effects of auditory hallucinations (AH) on auditory change detection processing has indicated that patient subgroups (HPs vs. NPs) show a differential MMN response, indicating that the underlying mechanisms of auditory hallucinations may impact the processing of incoming auditory deviance (Fisher et al., 2008a; Fisher et al., 2008b). Following on from these studies, both of which were limited by relatively modest hallucinatory activity as a result of limiting recruitment to controlled, stabilized patients, it was proposed that assessment of a population currently experiencing acute exacerbation of symptoms (and, therefore, likely at peak intensity hallucinatory activity) would be ideal (Experiment 3a). This study also found reductions of MMN amplitude in SZ in-patients with AHs, as well as several correlations between AH symptoms and measures of MMN. However, it is not clear whether the nature of the MMN deficits observed change depending on whether the AHs occur within the context of acute exacerbation of psychotic symptoms (requiring hospitalization) or within stable symptomatology.

One objective of this study, using MMN to multiple pure-tone deviants recorded from multiple scalp sites, is to compare schizophrenia patients with AHs currently requiring in-patient hospitalization due to an acute psychotic episode (SZI) to community-dwelling schizophrenia patients with persistent AHs and stable symptomatology (SZO). Employing the multi-feature auditory stimulus paradigm proposed by Näätänen and colleagues (2004), it is hypothesized that auditory change

detection, as expressed by the MMN, will be reduced in SZIs compared to SZOs. Furthermore, it is expected that MMN reductions in SZIs will be associated with measures of AH state and trait, such that SZIs will report higher AH trait and state scores.

It is our hope that by comparing patients with shared symptomatology, but different presentations of their illness, we will be able to observe how acute exacerbation of symptoms may affect pre-conscious auditory processing in the brain so as to better understand the fluctuations of illness severity within schizophrenia and their effects on cognition.

## 6.2 Materials and Methods

### 6.2.1 Experimental Participants

Twenty-four experimental volunteers, all presenting with a primary diagnosis of schizophrenia, were recruited from the Inpatient Schizophrenia Clinical Unit (SZI; n = 12) and Outpatient Schizophrenia Clinic (SZO; n = 12) of the Royal Ottawa Mental Health Centre (ROMHC). During an initial clinical interview (with the primary care physician) volunteers were assessed with respect to inclusion and exclusion criteria according to clinical history, and ratings on the Positive and Negative Syndrome Scale (PANSS; Kay, Opler & Lindenmeyer, 1989) for schizophrenia. At the time of admission to the study, all SZIs were experiencing acute exacerbation of their illness as indicated by a total PANSS score between 60-120 (Sechter et al., 2002). All SZOs were judged as clinically stable for the four weeks prior to testing (as indicated by no significant changes in symptoms or medications, as well as a total PANSS score < 65). All participants

reported a current history of AHs, exhibiting a score  $\geq 3$  (“mild or greater hallucinatory experiences”; range 1-6) on the hallucination item of the PANSS positive symptom scale (based on physician’s assessment of symptoms).

In both groups, the presence of AHs was subsequently confirmed by the experimenter (DF), who rated the patients on the AH subscale of the Psychotic Symptom Rating Scale (PSYRATS) by means of a semi-structured interview. This 11-item, 5-point (0-4) rating scale assesses hallucinations with respect to frequency, duration, severity and intensity of distress and also symptom specific dimensions of controllability, loudness, location, negative content, degree of negative content, beliefs about origin of voices, and disruption. In addition to the PANSS and PSYRATS, assessments included a general medical/health questionnaire. Participant demographics are presented in Table 5.

*Table 5. Summary of participant demographics and trait questionnaires (mean  $\pm$  SE) for SZIs and SZOs in Experiment 3b.*

	SZI	SZO
Age	30.60 (3.41)	44.25 (3.15)
PSYRATS	25.22 (3.26)	28.67 (1.20)
PANSS Positive Symptom	19.43 (1.59)	16.45 (0.98)
PANSS Negative Symptom	19.71 (1.48)	14.45 (1.21)
PANSS Hallucination Item	3.57 (0.57)	3.63 (0.19)
PANSS General Psychopathology	35.29 (1.01)	27.72 (1.84)

Two-tailed independent samples t-tests were used to compare group means on demographic variables. While the groups did not significantly differ on PSYRATS scores, PANSS positive symptom scores, PANSS AH-item scores or neuroleptic dosage, there were some group differences. First, there was a significant difference,  $t = -2.94$ ,  $p = .008$ , of age, with SZOs being significantly older than SZIs. There were also significant between group differences on PANSS negative symptom scores,  $t = 2.70$ ,  $p = .015$ , and on PANSS general psychopathology scores,  $t = 2.96$ ,  $p = .009$ ; in both cases, the differences were due to larger scores in SZIs compared to SZOs.

All patient participants were primarily right-handed, as per the Edinburgh Handedness Inventory (EHI; Oldfield, 1971), and between the ages of 18-60. All patients entering the study had a primary DSM-IV TR diagnosis of schizophrenia, paranoid subtype, as assessed by a structured clinical interview (SCID-P; Frist et al., 2001) and SZIs were acutely ill at the time of assessment. For both groups, primary medication was limited to one of the atypical anti-psychotics. All participants were able to understand spoken and written English. Due to the auditory requirements of the study, all participants were required to demonstrate normal hearing according to an audiometric assessment, conducted by the primary investigator in the research laboratory, and were able to detect pure tones of 500 Hz, 1000 Hz, and 2000 Hz at an intensity of 25 dB (SPL) or less.

Participants were excluded if they met any of the following criteria: co-morbid DSM-IV TR Axis I disorder; current history of drug abuse or dependence; recent (one year) history of head injury resulting in loss of consciousness; diagnosis of epilepsy or any other neurologic disorder; treatment with anti-depressants; electro-convulsive therapy

(ECT) treatment within the previous year; significant cardiac illness; extrapyramidal symptoms (EPS) resulting in movement disorders which could affect ERP recordings; or abnormal audiometric assessment.

### 6.2.2 Study Design

Following the signing of an informed consent, volunteers attended the Clinical Neuroelectrophysiology and Cognitive Research Laboratory at the Royal Ottawa Mental Health Centre. For SZIs, the test session took place as close as possible to hospital admission and before stabilization of acute exacerbation of symptoms. The study was conducted following approval of both the Research Ethics Board of the Royal Ottawa Health Care Group (ROHCG) and the Carleton University Ethics Committee for Psychological Research.

### 6.2.3 Study Procedure

Testing was conducted around midday with participants being required to abstain from drugs, medications (except for anti-psychotics and adjunct drugs), and alcohol beginning at midnight of the previous day. Upon arrival at the laboratory, participants completed demographic questionnaires and underwent audiometric assessment. Following this, EEG electrodes were applied and volunteers were assessed with respect to the electrophysiological paradigm, during which they were instructed to view a silent, neutral emotive video and to ignore the presented auditory stimuli. Rest intervals of ~1 minute were inserted between each of the test blocks of the MMN paradigm.

#### 6.2.4 Task Stimuli: 5-deviant 'Optimal' Multi-Feature MMN

This study employed the 5-deviant multi-feature MMN paradigm developed by Näätänen et al. (2004), exactly as described in Experiment 1. Briefly, the deviant tones differed from the standard tones in frequency, duration, intensity, perceived location of sound origin or contain a gap in the middle of the tone. Except where stated, the deviants were identical to the standards.

In each test block, the first 15 tones were standards, followed by a sequence whereby every second tone is a standard ( $P = 0.5$ ) and every other one is one of the five deviants ( $P = 0.1$  each). The deviants were presented so that each deviant category is presented once every 5 deviants and 2 deviants of the same category are never presented consecutively. The stimuli were presented in 3 blocks of 5 minutes each (1845 stimuli) for a total of 15 minutes (5535 stimuli).

#### 6.2.5 Hallucination State Ratings (HSR)

HSRs in patients were assessed following the MMN paradigm. Subjective ratings were carried out in a manner similar to that used by Margo et al (1981), requiring participants to assess subjective aspects of hallucinations experienced during the electrophysiological recording on 3 dimensions: 1) duration (1 = no AHs; 7 = continuous AHs); 2) loudness (1 = not audible; 7 = extremely loud); and 3) clarity (1 = unintelligible; 7 = very clear)

#### 6.2.6 EEG Recording and ERP Computation

MMNs were extracted from EEG activity recorded from  $\text{Ag}^+/\text{Ag}^+-\text{Cl}^-$  ring electrodes at thirty-two scalp sites according to the 10-20 system of electrode placement, including three midline sites (frontal [ $F_z$ ], central [ $C_z$ ], parietal [ $P_z$ ]), as well as three left hemisphere (frontal [ $F_3$ ], central [ $C_3$ ], parietal [ $P_3$ ]) and three right hemisphere (frontal [ $F_4$ ], central [ $C_4$ ], parietal [ $P_4$ ]) scalp sites. Electrodes were also used to record left (LM) and right (RM) mastoid activity and electrodes were placed on the mid-forehead and nose to serve as ground and reference respectively. Bipolar recordings of horizontal (HEOG) and vertical (VEOG) electro-oculogram activity were taken from supra-/sub-orbital and external canthi sites, respectively. All electrode impedances were kept below  $5\text{k}\Omega$ . Electrical activity was recorded at a sampling rate of 500 Hz using Brain Vision Recorder software with an amplifier bandpass of 0.1 and 70 Hz, and stored on hard-disk for later off-line analysis.

Electrical epochs (500 ms duration, beginning 100 ms pre-stimulus) with EEG or EOG voltages exceeding  $\pm 75 \mu\text{V}$  were excluded from the analysis and the remaining artifact-free epochs, were corrected for residual eye movement and eye blink activity using an algorithm operating in the time and frequency domain (Gratton, Coles, & Donchin, 1983).

Within the MMN test paradigm, epochs were separately averaged for standard stimuli and for each deviant stimulus type and then digitally filtered using a bandpass of 0.15-8 Hz (Leung et al., 2006) and a slope of 24 db/octave. For each site and deviant type, MMN difference waveforms were derived from point-by-point subtraction of the standard stimulus values from those elicited by the deviant stimulus, and MMNs were assessed by quantifying peak negative amplitudes within a custom-tailored window

derived from an inspection of the grand-averaged waveform from each condition. MMN latency values were only measured at F<sub>z</sub>, the site of maximum amplitude. For all deviant types in all participants, MMN waveforms were visually inspected to ensure appropriate inversion at mastoids.

### 6.2.7 Data Analysis

Separate analyses were carried out for each deviant type using the Statistical Package for the Social Sciences (SPSS; SPSS Inc., Chicago, IL). MMN amplitudes were subjected to mixed univariate analysis of variance (ANOVA) procedures with one between-group (2 levels: SZI, SZO) and two within-group factors (laterality [left, central, right], and region [limited to the frontal (F), and central (C) regions]).

Analyses of MMN latency and hallucination rating scale (duration, intensity, clarity) scores were performed with independent samples t-tests.

Where appropriate, Huynh-Feldt epsilon correction factors were applied to the degrees of freedom and the adjusted F-values are reported. Significant effects were followed-up with pairwise comparisons. Any unexpected significant results (i.e. those that could not be predicted with previous empirical evidence) that require follow-up were analyzed with Bonferroni-adjusted pairwise comparisons, in order to guard against type I error. However, for planned comparisons (i.e. those supported by previous research and relevant to hypotheses), no alpha correction was used. It has been pointed out that Bonferroni adjustments, when applied too liberally, not only significantly reduce power (to as low as 33%; Jennions & Moller, 2003), but also greatly increase the chance of Type II error to somewhere between 39-66% (Nakagawa, 2004). It goes to say, that Type

II error is just as undesirable as Type I error, and it has been suggested that Bonferroni adjustments may harm a study, rather than help it (Rothman, 1990; Perneger, 1998; Perneger, 1999). Furthermore, if a hypothesis is constructed properly, that is to say it necessitates detailed measurements, it is much less likely that significant results will be found; a paradox named the hyper-Red Queen phenomenon (Moran, 2003). Therefore, in cases where statistical examination is warranted by previous empirical research, no Bonferroni adjustments were made.

## 6.3 Results

### 6.3.1 MMN Amplitude

Analysis of duration MMN found a significant main effect of region,  $F(1, 21) = 12.47, p = .002$ , due to significantly larger MMN amplitudes at frontal ( $M = -1.09 \mu\text{V}$ ,  $SE = .11$ ) compared to central ( $M = -.66 \mu\text{V}$ ,  $SE = .11$ ) sites. There were no other significant main or interaction effects, nor were significant group differences found with planned comparisons.

Pitch MMN also displayed a significant main effect of region,  $F(1,21) = 6.99, p = .015$ , also due to significantly larger MMN amplitudes at frontal ( $M = -1.00 \mu\text{V}$ ,  $SE = .16$ ) compared to central ( $M = -.68 \mu\text{V}$ ,  $SE = .13$ ) sites. There were not any other significant main or interaction effects, nor were significant group differences found with planned comparisons.

A significant main effect of region was also found for gap MMN,  $F(1,21) = 14.25, p = .001$ , due to larger frontal ( $M = -0.92 \mu\text{V}$ ,  $SE = .19$ ) MMN amplitudes compared to those at central ( $M = -.34 \mu\text{V}$ ,  $SE = .09$ ) sites. No other significant main or

interaction effects were observed, nor were significant group differences found with planned comparisons.

Analysis of intensity MMN revealed a main effect of region,  $F(1,21) = 13.74$ ,  $p = .001$ , due to larger frontal ( $M = -1.45 \mu\text{V}$ ,  $SE = .22$ ) MMN amplitudes compared to those at central ( $M = -.61 \mu\text{V}$ ,  $SE = .17$ ) sites. There were no other main or interaction effects, nor did were any group differences seen with planned comparisons.

Finally, analysis of location MMN followed the same pattern, with no main or interaction effects aside from a main effect of region,  $F(1,21) = 6.79$ ,  $p = .016$ , due to significantly larger frontal ( $M = -.99 \mu\text{V}$ ,  $p = .14$ ) MMN amplitudes compared to those in the central ( $M = -.62 \mu\text{V}$ ,  $p = .14$ ) region.

Group comparisons of MMNs to each deviant can be seen in figure 14.

### 6.3.2 MMN Latency

There were no significant main or interaction effects. Planned comparisons revealed no significant differences between groups.

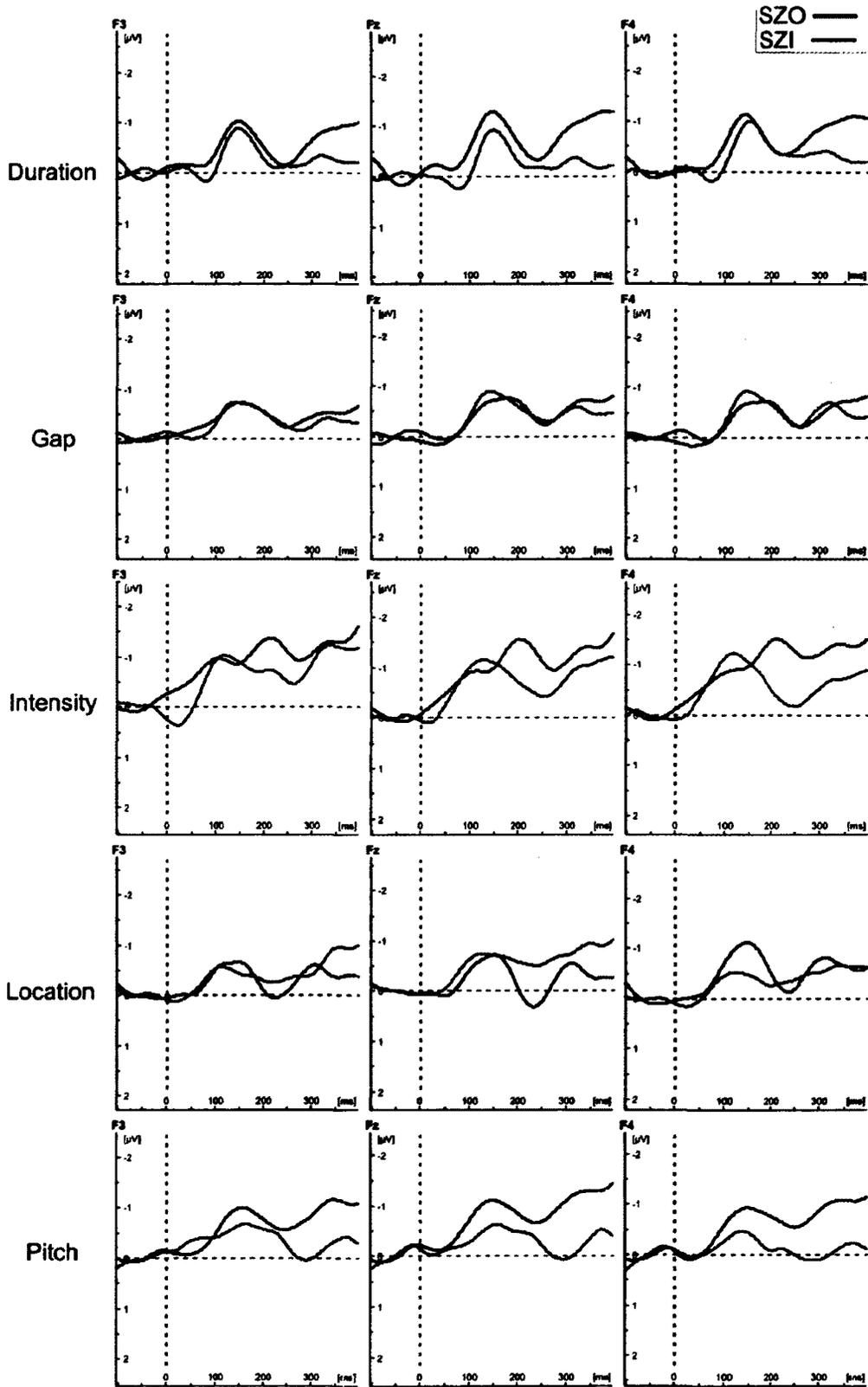


Figure 14. Grand averaged MMN waveforms for schizophrenia inpatients (SZI) and schizophrenia outpatients (SZO) elicited by all five deviant types

### 6.3.3 Hallucination State Ratings

There were no significant differences between groups on HSRs (see Table 6 for mean HSR values).

Table 6. *Hallucination state ratings (mean  $\pm$  SE) for SZIs and SZOs.*

	SZI	SZO
HSR-Duration	2.73 (0.62)	2.92 (0.50)
HSR-Loudness	2.82 (0.54)	1.96 (0.19)
HSR-Clarity	3.45 (0.82)	2.06 (0.37)

## 6.4 Discussion

The primary aim of this study was to determine whether the deficits in MMN generation seen with auditory hallucinations in schizophrenia are affected by whether or not the person is currently experiencing an acute exacerbation of psychosis. While the MMN for all deviant types showed appropriate distribution across the scalp (as reflected by larger amplitudes at frontal electrodes compared to central recording sites), there was minimal difference between the groups. It is notable that no group differences emerged on any electrophysiological measure, despite the fact that there was a significant difference between groups on PANSS Negative and GP scores. This suggests that, despite the fact that there is a correlation between these scores and MMN latencies in SZIs, as reported in Experiment 3a, these do not appear to be sufficient for differences to appear between SZIs and SZOs. Instead, it may be that a significant difference on measures of AH trait or state, neither of which was observed, is necessary for group differences in MMN measures to appear. Previously, in schizophrenia patients who

differed on AH measures (but not measures of negative symptoms or general psychopathology), group differences were observed (Fisher et al., 2008a). Taken together, this suggests that the presence of auditory hallucinations may have a primary importance in the development of auditory change detection deficits in schizophrenia and that, while negative symptoms and general psychopathology certainly contribute to these alterations, they appear to be of lesser importance on this measure, though they are of great importance to the overall functioning and well-being of the individual. From a practical perspective, this preliminary finding suggests that the current status of SZ patients (SZI or SZO) does not affect the MMN and, therefore, research using either group can be directly compared. Of course, further investigation into this issue through replication should be conducted to verify this particular interpretation of our findings.

One limitation of this particular study is that, while the SZIs who participated were experiencing acute exacerbation of their illness, they did not differ from SZOs on AH trait or state symptomatology. This likely limited our ability to detect group differences between SZ inpatients and outpatients. What remains to be seen is whether this is indicative of the general schizophrenia population or an artifact of this particular sample. Certainly, given the persistent nature of AHs in the general schizophrenia community it may be that, for those afflicted, measures of AH trait remain relatively stable over the course of the illness, with fluctuations of negative symptoms and general psychopathy being more predictive of acute hospitalization.

Another limitation of this study is the significant difference in age between the two groups. Given the population being studied, the age differences are not surprising. A study of psychiatric hospitalizations for schizophrenia in Canada found the highest

number of hospitalizations to be among male patients in their 20s and 30s, with a decrease in acute hospitalizations for male patients, suggesting some stabilization of the illness, seen starting around the age of 40 (Public Health Agency of Canada, 2002); as such, given the course of this illness, a difference in age (while accurately representing each group) may be nearly unavoidable. Certainly, the average age of SZIs corresponds with the increased hospitalizations reported among individuals in that age bracket and the average age of SZOs corresponds with the relative stability in the illness beginning around age 40. Furthermore, given that both groups are relatively young and displayed good hearing, it is unlikely that advancement of age would have affected these null findings. This is supported by a previous study examining the effects of age on MMN amplitude in schizophrenia, which found minimal change between the ages of 30 and 50 (Kiang et al., 2009). Indeed, when the analyses of MMN measures were re-run including age as a covariate, the reported findings did not change in any substantial way.

Another factor that warrants discussion is the lack of difference between medication dosage, as indicated by chlorpromazine equivalents. While at first it may seem surprising that there is no difference between these groups, one of the most common reasons for acute exacerbation of illness is discontinuation of antipsychotic medication. Thus, once in an acute care setting, patients are often placed back on their maintenance dose (or at a similar dosage); the patients then remain hospitalized while the medication takes effect (which may vary depending on how long they were off their neuroleptics) and to determine whether a higher maintenance dosage of neuroleptics is needed to stabilize symptoms. For this reason, medication dosage of SZIs is often at or

near the level that would have been used when that particular patients was living in the community (i.e. an SZO).

In summary, we found no significant differences on measures of auditory change detection to pure tones (MMN amplitudes or latencies) among schizophrenia in-patients and outpatients, despite differences in age, PANSS negative symptom score and PANSS GP score. The two groups did not differ on measures of AH trait, which has previously been associated with alterations in MMN amplitude. These findings tentatively suggest that acute exacerbation of schizophrenia, requiring hospitalization, is not sufficient to exacerbate observed MMN deficits among patient groups matched for hallucinatory intensity. It remains to be seen if acute exacerbation of AH state or trait would worsen such deficits

## CHAPTER 8: GENERAL SUMMARY

Overall, this series of studies has used novel methodology to elucidate new and interesting findings about auditory hallucinations in schizophrenia and their relationship with central auditory processing, as indexed by the auditory mismatch negativity. Among the strengths of these studies is the probing of MMNs across multiple deviant types in schizophrenia patients, as previously recommended in a related meta-analysis (Umbricht & Krjles, 2005). We employed both the original 5-deviant optimal multi-feature MMN paradigm (Näätänen et al., 2004), as well as a modified 3-deviant version that probed duration, frequency and intensity deviants (Fisher et al., 2011a). The obtained results demonstrated that either the Optimal-5 or Optimal-3 appear to be suitable for examining auditory change dysfunction in schizophrenia. Another major strength of study 1, in particular, is the direct comparison of MMNs in hallucinating and non-hallucinating patients with schizophrenia, the first study to do so.

Using a multi-feature methodology yielded several interesting findings. As stated previously, one of the most robust deficits seen in schizophrenia is that of a diminished duration MMN (Michie et al., 2000; Umbricht & Krjles, 2005). True to form, we reported reduced duration MMN amplitudes compared to healthy controls in all studies. In study 1, we reported smaller duration MMNs (vs. HCs), however only in the HP group; there was no significant difference between NPs and HCs. Follow-up of this finding found duration MMN deficits in schizophrenia patients with persistent AHs who were community dwelling outpatients (experiment 2b), as well as acutely ill inpatients (experiment 3a). We suggest, based on these findings, that it may be the presence of

auditory hallucinations that diminishes duration MMN, as opposed to current illness status, as there was no significant difference between the duration MMN amplitudes of inpatients and outpatients, despite the former being currently rated as more ill, particularly related to negative symptoms and general psychopathology (experiment 3b). This suggestion that duration MMN may be negatively affected by the presence of auditory hallucinations was supported by correlations indicating that as measures of auditory hallucination trait increase (i.e. PSYRATS, PANSS hallucination item), duration MMN amplitudes at frontal sites decrease.

Intensity MMN amplitudes were also found to be significantly different in schizophrenia patients with auditory hallucinations (vs. HCs), but only during presentation of the original, 5-deviant multi-feature paradigm. Similar to our findings with duration MMN, we observed intensity deviant deficits irrespective of inpatient or outpatient status, though deficits in outpatients were more anterior in their distribution. While no significant between-group differences were observed between HPs and HCs, intensity MMN amplitudes in response to the Optimal-3 paradigm were correlated with PSYRATS scores such that as hallucinatory trait scores increase, MMN amplitudes decrease.

Compared to the robust findings associated with duration MMN, and, increasingly, intensity MMN, reports of altered frequency MMN in schizophrenia have been less consistent (Näätänen & Kahkonen, 2008; Umbricht & Krljes, 2005). In line with this inconsistency, deficits in frequency MMN were observed in both hallucinating and non-hallucinating schizophrenia outpatients (albeit with different topographic distribution) with the Optimal-5 paradigm, but not with hallucinating inpatients (using the

Optimal-5) or hallucinating outpatients (using the Optimal-3). It may be that frequency MMN deficits were not observed in the younger inpatients as reduced frequency MMN appears to be more prevalent in older patients with a longer duration of illness (Todd et al., 2008). However, given that deficits were observed in both HPs and NPs and not replicated subsequently, it may simply be that frequency MMN is relatively unaffected by the presence of auditory hallucinations and, instead, is more sensitive to an as yet unidentified factor.

Of the observed reductions in amplitude of auditory change deviants, gap and location deviant deficits were only seen in schizophrenia patients requiring hospitalization (vs. outpatients), although gap and location deviants were not probed with the Optimal-3 paradigm. To our knowledge, there have been no previous reports of a significant difference in MMN amplitude between schizophrenia patients and healthy controls to gap deviants. Due to the lack of previous findings, any interpretation of this group difference is purely speculative, however we suggest that the presence of this particular deficit in inpatients only may be a result of the acute illness potentiating the impact auditory hallucinations on auditory change detection. However, studies employing both hallucinating and non-hallucinating inpatients are needed to rule out the alternative explanation that this deficit is unique to the acute illness, irrespective of the presence or absence of specific symptoms.

Similarly, location MMN amplitude reductions were only seen in schizophrenia inpatients, not in stable outpatients. Compared to gap MMN findings, however, interpretations of intensity MMN results are further muddied by a significant negative correlation between location MMN amplitude and medication dosage. It remains to be

seen if this correlation is due to the auditory detection of location deviance being more sensitive to the effects of antipsychotic medication (vs. other deviants which are insensitive to neuroleptics) or whether medication dosage may be a marker of another factor, such as treatment resistance. However, given that hallucinating schizophrenia patients appear to have structural differences in white matter in and around the right auditory cortex depending on whether hallucinations are experienced as being inside the head or outside the head, intensity MMN may be an important tool in future studies of AHs.

Overall, despite the relatively modest hallucinatory activity experienced by schizophrenia patients with currently stable symptomatology and those with acute exacerbation of illness, we report deficits in MMN amplitude across several deviant types. This suggests that the presence of auditory hallucinations interferes with cognitive processing of incoming auditory stimuli, particularly as it relates to auditory change detection. This particular deficit, however, appears to be one of several deficits in auditory processing seen in such patients, as auditory hallucinations have been implicated in deficient processing of auditory targets, auditory distractors, and the auditory steady-state response (among others), as well as deficient auditory sensory gating mechanisms (Ford et al., 2012).

All of the studies reported here are limited by the modest level of hallucinatory activity expressed by the hallucinating participants under study. Though it was a stated goal of this thesis, it remains to be seen how increasingly intense auditory hallucinations affect the mismatch process. As such, future studies may wish to target those patients with a stronger presence of AHs, irrespective of inpatient or outpatient status.

Additionally, use of a symptom-capture paradigm (wherein hallucinating patients signal the onset and offset of hallucinations) during the presentation of auditory stimuli would allow for better comparison of hallucinating and non-hallucinating states.

Another potential perspective of exploring the effects of auditory hallucinations on auditory change detection would be to explore differences between psychosis patient groups with auditory hallucinations (e.g. comparing MMN responses of schizophrenia patients with auditory hallucinations against those of patients with auditory hallucinations resulting from drug-induced psychosis). This would allow for better elucidation of which deficits are due to the simple presence of auditory hallucinations, compared to those within the context of schizophrenia. Relatedly, future studies may wish to examine whether deficits of central auditory processing (including change detection) are observed in healthy individuals with auditory hallucinations (but no other symptoms of psychosis).

Future studies may also wish to combine the use of electrophysiological (or magnetoencephalographic) measures with structural data, such as that obtained with magnetic resonance imaging and/or diffusion tensor imaging, in order to explore the potential underlying grey and white matter correlates of observed deficits in acoustic change detection.

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APPENDIX A: AH Subscale of the Psychoticism Rating Scale (PSYRATS; Haddock et al., 1999)

A. Auditory Hallucinations

1. Frequency

Voices not present or present less than once a week	0
Voices occur at least once a week	1
Voices occur at least once a day	2
Voices occur at least once an hour	3
Voices occur continuously or almost continuously	4

2. Duration

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

3. Location

No voices present	0
Voices sound like they are inside head only	1
Voices outside the head, but close to ears or head Voices inside head may also be present	2
Voices sound like they are inside or close to ears and outside head away from ears	3
Voices sound like they are outside the head only	4

4. Loudness

Voices not present	0
Quieter than own voice, whispers	1
About the same loudness as own voice	2
Louder than own voice	3
Extremely loud, shouting	4

5. Beliefs re: origin of voices

Voices not present	0
Believes voices to be solely internally generated and related to self	1
Holds <50% conviction that voices originate from external causes	2
Holds >50% (but <100%) conviction that voices originate from external causes	3
Believes voices are solely due to external causes	4

<b>6. Amount of negative content of voices</b>	
No unpleasant content	0
Occasional unpleasant content (<10%)	1
Minority of voice content is unpleasant or Negative (<50%)	2
Majority of voice content is unpleasant or Negative (>50%)	3
All of the voice content is unpleasant or negative	4
<b>7. Degree of negative control</b>	
Not unpleasant or negative	0
Some degree or negative content, but not personal comments relating to self or family	1
Personal verbal abuse, comments on behaviour	2
Personal verbal abuse relating to self-concept	3
Personal threats to self (threats to harm self or family, extreme instructions, commands to harm self or others)	4
<b>8. Amount of distress</b>	
Voices not distressing at all	0
Voices occasionally distressing, majority not distressing (<10%)	1
Minority of voices distressing (<50%)	2
Majority of voices distressing, minority not distressing (>50%)	3
Voices always distressing	4
<b>9. Intensity of distress</b>	
Voices not distressing at all	0
Voices slightly distressing	1
Voices are distressing to a moderate degree	2
Voices are very distressing, although subject could feel worse	3
Voices are extremely distressing, feel the worst he/she could possibly feel	4

10. Disruption to life caused by voices
- |  |   |
|--|---|
| No disruption to life, able to maintain social/family relationships (if present)   | 0 |
| Voices cause minimal amount of disruption to life  | 1 |
| Voices cause moderate amount of disruption to life causing some disturbance to daytime activity and/or family and social activities. | 2 |
| Voices cause severe disruption to life so that hospitalization is usually necessary.   | 3 |
| Voices cause complete disruption of daily life requiring hospitalization.  | 4 |
11. Controllability of voices
- |  |   |
|--|---|
| Subject believes they can have control over the voices and can always bring on or dismiss the voices at will.  | 0 |
| Subject believes they can have some control over the voices on the majority of occasions   | 1 |
| Subject believes they can have some control over the voices approximately half the time  | 2 |
| Subject believes they can have some control over the voices, but only occasionally. The majority of the time the subject experiences voices that are uncontrollable. | 3 |
| Subject has no control over when the voices occur and cannot dismiss or bring them on at all.  | 4 |

## APPENDIX B: Hallucination State Ratings (HSR)

**Hallucination Ratings****Task \_\_\_\_\_**

Please rate your auditory hallucinations (“voices”) based on how they appeared during the previous task

**Duration**

No Hallucinations	1	2	3	4	5	6	7	Continuous
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**Loudness**

Not audible loud	1	2	3	4	5	6	7	Extremely
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**Clarity**

Unintelligible	1	2	3	4	5	6	7	Very clear
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## APPENDIX C: Edinburgh Handedness Inventory (Oldfield, 1971)

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 ++. In 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)