Electrophysiological and Behavioral Indices of
Acoustic Change Detection and Involuntary Attention Switches
in Schizophrenia

Jemeen Horton

Thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of
the requirement for the degree of

Doctorate of Philosophy

Department of Psychology

Carleton University

Ottawa, Ontario

© August 2007

Library and
Archives Canada

Bibliothèque et
Archives Canada

Published Heritage
Branch

Direction du
Patrimoine de l'édition

395 Wellington Street
Ottawa ON K1A 0N4
Canada

395, rue Wellington
Ottawa ON K1A 0N4
Canada

Your file Votre référence

ISBN: 978-0-494-33493-5

Our file Notre référence

ISBN: 978-0-494-33493-5

NOTICE:

The author has granted a non-exclusive license allowing Library and Archives Canada to reproduce, publish, archive, preserve, conserve, communicate to the public by telecommunication or on the Internet, loan, distribute and sell theses worldwide, for commercial or non-commercial purposes, in microform, paper, electronic and/or any other formats.

The author retains copyright ownership and moral rights in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author's permission.

AVIS:

L'auteur a accordé une licence non exclusive permettant à la Bibliothèque et Archives Canada de reproduire, publier, archiver, sauvegarder, conserver, transmettre au public par télécommunication ou par l'Internet, prêter, distribuer et vendre des thèses partout dans le monde, à des fins commerciales ou autres, sur support microforme, papier, électronique et/ou autres formats.

L'auteur conserve la propriété du droit d'auteur et des droits moraux qui protègent cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

In compliance with the Canadian Privacy Act some supporting forms may have been removed from this thesis.

Conformément à la loi canadienne sur la protection de la vie privée, quelques formulaires secondaires ont été enlevés de cette thèse.

While these forms may be included in the document page count, their removal does not represent any loss of content from the thesis.

Bien que ces formulaires aient inclus dans la pagination, il n'y aura aucun contenu manquant.

Canada

ABSTRACT

Neurocognitive deficits including abnormal pre-attentive processing have been established in schizophrenia. The mismatch negativity (MMN) is a scalp-recorded event-related potential (ERP) reflecting an automatic auditory change detector mechanism. According to a pre-attentive activation model, the deviance-elicited MMN triggers involuntary processes involved in the shifting of attention towards initially unattended stimuli. Diminished MMNs extracted from passive, non-task paradigms are a robust finding in the schizophrenia literature however their impact on higher-order attentional processes and task performance has yet to be examined. The purpose of the present dissertation was threefold: a) to replicate findings of abnormal MMN to frequency and duration deviants in a passive auditory oddball paradigm recorded from 21 schizophrenics and 19 controls (Experiment 1); b) to examine the impact of aberrant MMNs to frequency deviants on task proficiency and ERPs recorded from 10 schizophrenics and 11 controls (Experiment 2) and c) to examine the impact of aberrant MMNs to duration deviants on task proficiency and ERPs recorded from 20 schizophrenics and 14 controls (Experiment 3); the latter two objectives being carried out with a novel distraction paradigm which embeds deviant distractors within target stimuli. This paradigm is known to elicit behavioral and ERP distraction indices triggered by memory-based detections of small changes in the acoustic environment; distraction effects are evidenced by reduced detection of and prolonged reaction time to task targets and by elicitation of 3 sequential ERP components (MMN, P3a and RON). Results from Experiment 1 revealed that MMN amplitude to frequency and duration deviants were significantly reduced in the schizophrenics compared to the controls and that MMN

latency to frequency deviants was significantly shorter in the schizophrenics. Although MMN amplitude was also significantly reduced to frequency deviants in Experiment 2 and to the long duration deviant in Experiment 3, there were no statistically significant differences between the schizophrenics and the controls in terms of behavioural or electrophysiological indices of distraction. Overall, although the results from these experiments support dysfunctional auditory sensory memory processes in schizophrenia, these early change detector aberrations do not appear to convey a significant impact on distractibility beyond that seen in healthy controls.

AUTHOR'S NOTE

This journey has been a very long one and there have been many people who have helped me along the way. First and foremost, my sister Reeann who gave me the most valuable gift of all – time. As a single parent from my 2nd year of university, this journey became a delicate balancing act between my responsibilities as a parent and personal dreams for my future. Without the enduring support of my sister to care for Josh while I was working, I never would have reached this point and for that I am eternally grateful. I also want to thank my brother-in-law Hugh for always welcoming my son and for being such a positive role model for a young boy who has grown up without a father.

And to all of my friends and mentors along the way who have always remained positive, I am also very grateful. I would like to specifically mention Heather, a constant presence in my life for the past several years, who never ceased to listen to my endless complaints and tribulations. I would also like to thank my advisors, Verner Knott and John Logan for their support, guidance and patience, as well as to Anne and the others in the lab for always supporting me and for being there when I needed help.

It was a pleasure for me to meet all of the people who volunteered to participate in my experiments. It was a great experience to meet so many different people who were so eager to participate and to put forth their best efforts to help me. Thank-you very much! I wish all of the patients hope and happiness for the future. Schizophrenia is a devastating disorder and I was so enlightened by many of the stories I heard. It was a very rewarding and fulfilling experience; one that I think has made me a better person.

Finally, last but surely not least, I want to thank Josh, my wonderful baby who has grown up along with me for the past 12 and half years. You have given meaning to all of my hard work and the drive for me to create a better future for both of us.

TABLE OF CONTENTS

Abstract	ii
Author's Note	iv
Table of Contents.....	vi
List of Tables.....	ix
List of Figures.....	x
1.0 General Introduction	
1.1 Introduction to Schizophrenia.....	2
1.2 Clinical Features	2
1.3 Cognitive Deficits	3
1.4 Attentional Dysfunction.....	5
1.5 Pre-Attentive Information Processing.....	8
1.6 Simple Tone Matching Performance	11
1.7 Event-Related Potentials	16
1.8 The Mismatch Negativity	23
1.9 MMN and Schizophrenia.....	31
1.10 Rationale and Hypotheses for Experiment 1	45
2.0 <i>Experiment 1: MMNs to duration and frequency deviants in schizophrenics and controls</i>	
2.1 Method	
2.1.2 Participants.....	48
2.1.3 Stimuli.....	49
2.1.4 Procedure	50
2.1.5 Recording.....	51
2.1.6 Analysis.....	52
2.2 Results	
2.2.3 Participant Characteristics	53
2.2.4 Frequency Deviant Conditions	54
2.2.5 Duration Deviant Conditions	58
2.2.6 MMN and Clozapine.....	59
2.2.7 MMN and Psychopathology Ratings	61
2.2.8 Intellectual and Digit Span Performance.....	61
2.3 Discussion	62

3.0	Distraction.....	77
3.1.1	The P3a ERP	78
3.1.2	ERP Distraction Paradigms.....	83
3.1.3	Schröger's Auditory Distraction Paradigm.....	83
3.1.4	Pre-attentive Activation Model.....	84
3.1.5	MMN and Conscious Detection of Auditory Deviance	88
3.1.6	Application of Schröger's Paradigm	90
3.1.7	Summary	94
3.1.8	Experiment 2 and Experiment 3: Rationale and Hypotheses.....	95
4.0	<i>Experiment 2: ERP and behavioral correlates of auditory distraction induced by frequency deviants in schizophrenics and controls</i>	
4.1	Method	
4.1.2	Participants.....	97
4.1.3	Stimulus Paradigm.....	98
4.1.4	Study Procedure	99
4.1.5	ERP Recordings	99
4.1.6	Behavioural Measures.....	101
4.1.7	Statistical Analyses	
4.1.7.1	ERP Measures	101
4.1.7.2	Behavioural Measures.....	102
4.2	Results	
4.2.1	Participant Characteristics	103
4.2.2	Behavioural Measures	
4.2.2.1	Reaction Time	104
4.2.2.2	Response Accuracy	104
4.2.3	ERP Measures	
4.2.3.1	MMN.....	106
4.2.3.2	P3a.....	107
4.2.3.3	RON	108
4.2.4	Correlations	
4.2.4.1	Reaction Time and ERPs	110
4.2.4.2	Clozapine	111
4.2.4.3	Psychopathology Ratings.....	111
4.2.4.4	Neuropsychological Performance	111
5.0.	<i>Experiment 3:ERP and behavioural correlates of auditory distraction induced by duration deviants in schizophrenics and controls</i>	
5.1	Method	
5.1.2	Participants.....	113
5.1.3	Stimulus Paradigm.....	113

5.1.4	Study Procedure	114
5.1.5	ERP Recordings	115
5.1.6	Behavioural Measures	116
5.1.7	Statistical Analyses	
5.1.7.1.	ERP Measures	117
5.1.7.2	Behavioural Measures	118
5.2	Results	
5.2.1	Participant Characteristics	118
5.2.2	Behavioural Measures	
5.2.2.1	Reaction Time	119
5.2.2.2	Response Accuracy	120
5.2.3	ERP Measures	
5.2.3.1	MMN	121
5.2.3.2	P3a	122
5.2.3.3	RON	123
5.2.4	Correlations	
5.2.4.1	Reaction Time and ERPs	125
5.2.4.2	Clozapine	125
5.2.4.3	Psychopathology Ratings	125
5.2.4.4	Neuropsychological Performance	126
6.0	Discussion	127
6.1.	Experiment 2	128
6.2	Experiment 3	139
7.0	Overall Summary	145
8.0	References	147
9.0	Appendices	161

LIST OF TABLES

Table 1	MMN-Duration Studies in Schizophrenia
Table 2	MMN-Frequency Studies in Schizophrenia
Table 3	MMN in Schizophrenia at varied levels of deviant probability and ISI
Table 4	MMN in Schizophrenia as a function of pitch change
Table 5	Demographic Characteristics of Patients and Controls
Table 6	Means ($\pm$ SD) of averaged EEG sweeps to frequency deviants
Table 7	Mean ($\pm$ SD) peak MMN amplitudes and latencies at FZ to frequency deviants
Table 8	Means ($\pm$ SD) of averaged EEG sweeps to duration deviants
Table 9	Mean ($\pm$ SD) peak MMN amplitudes and latencies at FZ to duration deviants
Table 10	Estimates of effect size
Table 11	Demographic Characteristics of Patients and Controls
Table 12	Mean ($\pm$ SD) reaction time (ms), correct responses (%) and no-responses (%)
Table 13	Means ($\pm$ SD) of averaged EEG sweeps to frequency deviants
Table 14	Mean ($\pm$ SD) peak MMN amplitudes and latencies at FZ to frequency deviants
Table 15	Mean ($\pm$ SD) peak P3a amplitudes and latencies at CZ to frequency deviants
Table 16	Mean ($\pm$ SD) peak RON amplitudes and latencies at FZ to frequency deviants
Table 17	Demographic Characteristics of Patients and Controls
Table 18	Mean ($\pm$ SD) reaction time (ms), correct responses (%) and no-responses (%)
Table 19	Means ($\pm$ SD) of averaged EEG sweeps to duration deviants
Table 20	Mean ($\pm$ SD) peak MMN amplitudes and latencies at FZ to duration deviants
Table 21	Mean ($\pm$ SD) peak P3a amplitudes and latencies at CZ to duration deviants
Table 22	Mean ($\pm$ SD) peak RON amplitudes and latencies at FZ to frequency deviants

LIST OF FIGURES

- Figure 1 Grand averaged ERP waveforms for controls and patients at FZ for a) 20% Δf , b) 10% Δf , and c) 5% Δf deviants
- Figure 2 Grand averaged ERP waveforms for controls and patients at FZ for a) long duration (100ms) and b) short duration (50ms) deviants
- Figure 3 Illustration of the distraction paradigm with the task-relevant stimulus dimension being duration (equiprobably presented short and long duration tones) and the task-irrelevant stimulus dimension being frequency (including a frequent standard and an infrequent deviant frequency). Subjects discriminate between short and long duration stimuli. From “Behavioural and Electrophysiological Effects of Task-Irrelevant Sound Change: A New Distraction Paradigm,” by E. Schröger and C. Wolff, 1998, Cognitive Brain Research, 7, p. 73.
- Figure 4 Schröger’s (1997) model explaining the conscious detection of deviant sounds forming an irregularity with respect to some discrete repetitive stimulation as the result of a preattentive operating detection system. This system extracts actual stimulus information and invariances of recent stimulation into presentations of sensory memory, compared these representations on a feature-specific basis, generates appropriate mismatch signals proportional to the detected discrepancy and accumulates this information into an integrated mismatch signal. If a variable threshold is exceeded, subsequent processes may be activated that result for example, in a button-press response, indicating that the participant consciously detected the deviant. From” On the Detection of Auditory Deviations: A Pre-Attentive Activation Model,” by E. Schröger, Psychophysiology, 34, p. 246
- Figure 5 Grand averaged ERP waveforms for controls and patients for a) 20% Δf , b) 10% Δf , and c) 5% Δf deviants
- Figure 6 Grand averaged ERP waveforms for controls and patients for a) long duration (100ms) and short duration (50ms) deviants

1.0 General Introduction

This dissertation explored information-processing dysfunction in schizophrenia utilizing non-invasive neuroelectrophysiological measurement approaches. The mismatch negativity (MMN) component of the scalp-recorded event-related potential (ERP) was utilized as a primary tool to examine pre-attentive processing abnormalities of acoustic sensory information, and to investigate the relationship of aberrant MMNs to behavioural and neuroelectrophysiological indices of task performance efficiency in schizophrenia.

Using electrophysiological scalp recordings to elucidate neurophysiological mechanisms underlying pre-attentive, perceptual and cognitive processing is a common research approach in the cognitive neuroscience literature. In combination with behavioural measures, ERPs facilitate the development of a comprehensive picture of information processing and the examination of underlying cerebral processes.

The mismatch negativity is an automatic, attention-independent ERP index of auditory deviance detection. Given that the MMN is the earliest physiologically measurable brain response capable of differentiating between usual and unusual auditory stimulus events, its stimulus-eliciting parameters and its relationship to task performance was examined as a means of probing distractor processing and distraction vulnerability in schizophrenia.

1.1 Introduction to Schizophrenia

Of all of the psychiatric disorders, schizophrenia has the most severe impact on emotional status, cognition, and overall functional ability. Schizophrenia is chronic in nature, with initial signs of clinical symptomatology typically presenting in early adulthood and enduring throughout adult life. Clinical outcome is often bleak, characterized by life-long struggles between periods of acute illness of hallucinations and delusions, interspersed between lengthy periods of social isolation, interpersonal dysfunction and apathy. The psychological consequences, as demonstrated by suicide rates are immense, the highest among all psychiatric illnesses. One in every four sufferers of schizophrenia attempts suicide and one in every ten succeed (American Psychiatric Association, 1994).

It is estimated that approximately twenty million people worldwide are afflicted by schizophrenia (Hafner & der Heiden, 1997). In any given year, approximately one percent of the general population suffers from this illness (American Psychiatric Association, 1994). The direct and indirect costs are significant; approximately four billion dollars are spent annually on management of the disease (Goeree et al., 1999).

1.2 Clinical Features

Schizophrenia is characterized by a multifaceted array of clinical symptoms including marked disturbances of thought and perception, bizarre behaviour, loss of contact with reality and/or self, and an inability to undertake daily functional activities. The Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 1994) broadly categorizes the diagnostic criteria of schizophrenia into two

dimensions, positive and negative (American Psychiatric Association, 1994). Positive symptoms include hallucinations and delusions, while negative symptoms include flat affect, alogia (i.e., restrictions in the fluency and productivity of thought and speech) and avolition (i.e., lack of initiation in goal-directed behaviours). The former reflect excess, or distortion of normal functions, while the latter represent diminished or absence of normal functions. The DSM-IV diagnostic criteria for schizophrenia also include neurocognitive deficits. A commonly held belief is that the symptomatic expression of schizophrenia is related to disordered attentional and information-processing systems that subsequently give rise to disordered and fragmented thought processes (Nuechterlein & Dawson, 1984).

1.3 Cognitive Deficits

The idea that schizophrenia is associated with cognitive deficits has a long history. Emil Kraepelin, a German psychiatrist provided the first diagnostic criteria for schizophrenia and introduced the term “dementia praecox” to describe a cluster of disorders with symptoms of intellectual deterioration (“dementia”), occurring at a relatively young age (“praecox”) (Kraepelin, 1919). In Kraepelin’s efforts to describe schizophrenia, he documented a cluster of abnormal mental processes, including “the weakening of judgement, of mental and creative ability...” and “a certain unsteadiness of attention” (Kraepelin, 1919). A contemporary of Kraepelin, Eugen Bleuler (1911), coined the term schizophrenia (schizo, “split; phreno, “mind”) and also supported the pervasiveness of cognitive dysfunction in schizophrenia. According to Bleuler,

individuals with schizophrenia were “incapable of holding the train of thought in the proper channels” and observed that “acute attention is lacking” (Bleuler, 1911). Bleuler (1911) also spoke of a vulnerability to distraction in schizophrenics, “the selectivity which normal attention ordinarily exercises among the sensory impressions can be reduced to zero so that almost everything reaches the senses”.

Since these very early accounts of cognitive and attentional abnormalities in schizophrenia, a wealth of research has accumulated concerning cognitive functioning in schizophrenia. The vast majority of this research has established that individuals with schizophrenia show cognitive dysfunction including deficits in executive functions (Goldberg, Saint-Cry, Weinberger, 1990), concept formation (Hagger et al., 1993), auditory and visual memory (Schwartz, Rosse, & Deutsch, 1992), working memory (Goldman-Rakic, 1994) and attention (Addington, Addington, & Gasbarre, 1997). In addition, schizophrenics demonstrate an enhanced susceptibility to distraction and are impaired in their ability to inhibit irrelevant and/or redundant stimuli (McGhie & Chapman, 1965). On standardized cognitive tasks, schizophrenics score one to two standard deviations below the general population (Bilder, 1997).

Cognitive dysfunction in schizophrenics correlates highly with the presence of negative rather than positive symptoms (Green, 1996). Negative symptoms, in comparisons to positive ones, are considered stable features of schizophrenia, and in general, are unaffected by treatment with conventional pharmacological interventions (Meltzer & McGurk, 1999).

Cognitive deficits are a major factor in determining occupational and functional rehabilitation, and outcome in schizophrenia. It has become increasingly apparent that these deficits play a greater predictive role than typical clinical symptomatology in estimating functional status (Harvey, Howabitz, Parrella, White, Davidson et al., 1998). This is illustrated statistically by regression models where impaired cognitive processes account for a larger portion of the variance (i.e., functional outcome) than positive or negative symptoms (Harvey et al., 1998). Premorbid academic, occupational and social dysfunction, early onset, and poor treatment response are positively associated with severity of cognitive impairment (Heaton & Crowley, 1981; Bilder, Turkel, Lipschutz-Broch & Lieberman, 1992).

1.4 Attentional Dysfunction

Attentional dysfunction holds a prominent role in the literature on cognition in schizophrenia. Disordered attentional processes are considered core features in the symptomatic development of schizophrenia (Braff, 1993; Nuechterlein & Dawson, 1984). Intact attention is fundamental to more complex, higher-order intellectual and information processing functions and thus, successful performance on neurocognitive tests. Attentional dysfunction appears to be a trait rather than a state feature of schizophrenia, in that disturbances of attention have been documented during all phases of this illness (Wohlberg & Kornetsky, 1973), are present in neuroleptic naïve individuals (Asarnow & MacCrimmon, 1978), and have been observed in first-degree relatives (Nuechterlein & Dawson, 1984).

Efforts to explain the nature of attentional dysfunction in schizophrenia have relied mainly on models of selective attention and capacity theories. Donald Broadbent's "Filter Theory of Attention" (1958) has served as the basis for many selective attention models and has been applied to schizophrenia. According to Broadbent's model, all incoming stimuli impinging on the sensory organs are briefly stored in a sensory buffer, while the physical features of these inputs are analyzed in parallel. Sensory information is transduced in the brain in the form of neural representations, which Broadbent referred to as "channels" of information. While all sensory information inputs are analyzed in parallel, a selective filter selects a single channel of information based on the desired attributes. According to Broadbent, this single channel of information is passed on to a higher-level processing stage, which is of limited capacity (i.e. attention); all other channels of information decay rapidly. This theory is often referred to as an "early selection theory" because the filtering process occurs early in the pathway of information processing. The premises of this theory are based on findings from dichotic listening tasks (i.e., dual task paradigms) where separate channels of information were presented to an attended channel (i.e., right ear) and to an unattended channel (i.e., left ear). Because Broadbent noted that subjects were only able to recall information present to the attended channel, he concluded that input to the unattended channel was filtered (blocked) before reaching awareness.

Applied to schizophrenia, Broadbent's model suggests that attentional dysfunction reflects an abnormal selective filtering mechanism that allows an overload of sensory inputs to reach the limited capacity processor. This defect prevents effective inhibition of

non-relevant events, which in turn, leads to an overabundance of superfluous sensory inputs competing for attentional resources, thus creating a state of informational overload. Such a large burden placed on the brain's capacity to process information would likely interfere with working memory systems, giving rise to loose associations, resulting in cognitive fragmentation and the emergence of perceptual distortions, delusional belief systems and formal thought disorder. This "informational overload" hypothesis is supported by findings from selective attention studies, which show that schizophrenics are impaired in their ability to sort irrelevant from relevant inputs and to selectively attend to target stimuli (Nuechterlein & Dawson, 1984). Based on these observations, the informational overload hypothesis of schizophrenia and its implications for the manifestation of psychotic symptomology has been widely accepted in the schizophrenia literature (Nuechterlein & Dawson, 1984; Braff, 1993; Rund, 1989).

A frequently cited article in the schizophrenia literature (McGhie & Chapman, 1961) synthesized an argument in support of a deficient internal screening mechanism, "If gating is defective, inhibition and selectively fail, and consciousness is flooded with an undifferentiated and involuntary tide of sensory data, sweeping away the stable constructs of reality" (p.104). As illustrated by the following quote, the existence of a deficient sensory/informational filter is also supported by a subjective account of a schizophrenia sufferer: "My mind has to be here, there and everywhere. When my family gets together I cannot concentrate on what just one person is trying to say to me" (Freedman et al., 1991, p.234).

Theories of attention based on limited resource capacity and allocation (Kahneman, 1973) also appear useful for delineating the nature of the attentional dysfunction in schizophrenia. A particular emphasis of limited resource pool theories of attention is that individuals differ in size of their intrinsic resource pool, and the means and efficiency by which they allocate their resources. In the context of attentional dysfunction, schizophrenics possess an overall reduction of their available processing resources and moreover, their ability to efficiently allocate attentional resources to specific targets is disordered.

Deficits in attention in schizophrenia have been profiled using a variety of techniques including auditory oddball tasks (Knott et al., 1999), sensorimotor gating (i.e. prepulse inhibition and P50 gating) (Adler et al., 1982), smooth pursuit eye movement (Holzman, 1987; Abel et al., 1991), skin conductance orienting response (Bernstein, 1987), span of apprehension (Asarnow et al., 1991), visual backward masking (Saccuzzo, Hirt & Spencer, 1974), continuous performance tasks (Asarnow & MacCrimmon, 1978; Walker, 1981), reaction time (Rodnick & Shakow, 1940) and ERPs (Roth, Horvath, Pfefferbaum, & Kopell, 1980).

1.5 Pre-attentive Information Processing

For the most part, information processing dysfunction in schizophrenia has been examined in experimental conditions where attentional resources are engaged by and consciously drawn directly to a particular task event. Task demands in these conditions often require execution of a behavioural response of some kind. Based on the complex

nature of these tasks, activation of multiple brain regions are required for task performance, including the prefrontal cortex, the neural region that subserves attention. Investigations aimed at studying routine, automatic mental processes that occur in the absence of attention, and that are dependent on more discrete, limited areas of the cortex, have more recently begun to emerge in the literature. Fundamental questions exist concerning whether cognitive dysfunction in schizophrenia is so pervasive that it extends to pre-perceptual information processing, the sensory prerequisites of perception (Javitt, Strous, Grochowski, Ritter, & Cowan, 1997). Thus, a primary goal in the study of sensory-based, rather than attention-dependent processes is to identify the simplest task on which performance is impaired, so as to determine key mechanisms underlying higher-order cognitive dysfunctions.

Cognitive psychology typically categorizes memory into 3 functional classes: sensory memory, working memory and long-term memory. Long-term memory is a storage system with an extremely large capacity that is responsible for storing information on a relatively permanent basis (e.g. persistent for decades). Sensory and working memory systems on the other hand hold information for much shorter periods, sensory memory up to a few seconds and working memory up to 10 seconds (rehearsal facilitated prolonged storage). Research suggests that sensory memory has a much larger (transient) storage capacity than working memory. The sensory register has to be large enough to store all of the information imposed on sensory receptors. Sensory memory (i.e., sensory register) is a system designed to store a representation of information from the environment (i.e., external inputs). Thus one function of sensory memory is to create and store a useful

representation. Another function is to “hold” this information until other cognitive processes are capable of interpreting the event or to add meaning to it. Two sensory memory systems have been identified; echoic and visual, representing temporary storage of auditory and visual information respectively. Working memory refers to the ability to form, store and manipulate new transient memory traces for immediate use (i.e., to engage in complex tasks such as language comprehension, concept formation etc.,) and to store information temporarily retrieved from long-term memory stores relevant for moment-to-moment mental activity (Baddeley, 1986). In Baddeley’s (2000) concept of working memory, four components are included; the central executive component of the prefrontal cortex, two modality-specific, transient “slave” subsystems, the phonological loop and the visuo-spatial sketchpad, as well as an episodic buffer. The episodic buffer stores multidimensional representations, information that is integrated across modalities. The prefrontal cortex is believed to play a key role in working memory systems.

Recent research supports a close link between sensory and working memory systems. Although the exact neural underpinnings between these two functionally different domains of memory has yet to be fully determined, there is direct evidence linking neurons in the auditory cortex that are responsible for transient storage of acoustic sensory information to the neural circuitry that subserves working memory. Single-neuron activity recording studies on monkeys have demonstrated that sensory neurons responsible for selective feature processing activate feature selective neurons in the prefrontal cortex (Romo, Brody, Herababdez, & Lemus, 1999). Thus, there appears to be a dynamic interplay between the auditory sensory cortex and the prefrontal cortex;

feedforward and feedback connections within the sensory cortical areas and the prefrontal cortex (Wang, 2001).

Working memory deficits in schizophrenia have been identified in classical working memory tasks that primarily engage prefrontal circuitry (Holzman & Goldman-Rakic, 1995) and that are highly dependent upon the functioning of the central executive system. Dysfunctional working memory has been proposed as a cognitive analogue to formal thought disorder in schizophrenia (Goldman-Rakic, 1994). In contrast, the integrity of information-processing within the sensory memory systems has been less comprehensively studied. It seems only logical that a generalized deficit in this very early stage of information processing where pertinent sensory information is extracted to create functionally accessible perceptual experiences would have a significant impact on higher cortical functions.

Deficits in low-level information-processing can be probed by examining sensory memory (i.e., auditory/echoic sensory memory). The critical brain substrate for auditory sensory memory, or “echoic” memory, is localized to the auditory cortex in the region of the superior temporal plane (Colombo, D’Amato, Rodman, Gross, 1990).

1.6 Simple Tone Matching Performance

The integrity of the auditory memory system in schizophrenia has been examined behaviourally by using a simple tone-matching task (i.e., basic auditory discrimination) (Rabinowicz, Silipo, Goldman, & Javitt, 2000; Javitt, Liederman, Cienfuegos, Shelley, 1999, Javitt, Strous, Grochowski, Ritter, & Cowan, 1997; Strous, Cowan, Ritter, & Javitt,

1995). In this task, tone pairs are presented and the participant is asked to determine whether the second tone is different or the same as the first. Since routine processing of basic acoustic input requires only limited regions of the cortex (Rabinowicz et al, 2000), this paradigm is useful for studying very early stages of auditory information processing. Moreover, the fast presentation of tones (i.e., < 1 second) and short intertone intervals (i.e., 300 ms) prevent active rehearsal of acoustic inputs, thus reducing the influence of frontal systems activation on task performance (Rabinowicz et al, 2000). In addition, no-delay tone discrimination conditions are also employed to examine the effect of task difficulty on performance (i.e., smaller pitch differences) (Javitt et al., 1997).

Strous and colleagues (1995) examined tone-matching performance in schizophrenics relative to controls in three conditions: easy, where participants are requested to discriminate tones differing in frequency by 20%, intermediate (10% Δf) and difficult (5% Δf). In the no-delay condition, although tone-matching performance across groups did not significantly differ, a trend toward poorer performance in the schizophrenic group in the 5% Δf condition was noted. By contrast, tone discrimination in the schizophrenic group was significantly poorer compared to controls across all three pitch change levels with a 300 ms inter-tone interval (ITI). Moreover, it was found that performance in the schizophrenic group in the 20% Δf condition was behaviourally similar (i.e., accuracy) to that of control subjects in the 5% Δf condition. Collectively, these findings suggest that individuals with schizophrenia have elevated thresholds for tone discrimination when a brief interval of 300 ms is introduced between tone pairs. Moreover, since significant group differences were only evident in delay conditions, it appears that abnormal

auditory sensory memory processes in schizophrenia are most apparent when preservation of a memory trace is required over a silent ITI (Strous et al., 1995).

Two processes are central to the formation of memory traces. Firstly, extracted sensory information must be encoded in a precise manner in a sensory buffer for subsequent use (i.e., integrity factor) and secondly, this stored sensory information must be maintained over the duration of the task (i.e., decay factor) (Javitt et al., 1999). In a subsequent study in the same laboratory, Javitt and colleagues (1997) specifically sought to determine whether mechanisms underlying aberrant auditory sensory memory processes in schizophrenia are reflective of an encoding and/or retrieval impairment of sensory memory information or whether these deficits are due to a faster decay of the information stored in the memory trace from its initial encoding to its subsequent application.

In this study, Javitt et al. (1997) reported tone-matching abnormalities in schizophrenia across a range of ITIs (1-20 seconds) using 5% Δf and 20% Δf (Expt. 1), and nine pitch changes (0-20% Δf : no delay condition) (Expt.2). Data from the first experiment revealed that performance in the group of schizophrenics was reduced relative to controls at 5% Δf and 20% Δf and over varied ITIs. When performance ability was equated at one-second ITIs across the schizophrenic group and the control group, tone-matching ability to the easier 20% Δf and to the more difficult 5% Δf declined at similar rates across the groups with systematic increases in the ITI. This finding supports the notion that auditory sensory memory dysfunction in schizophrenia is associated with deficient encoding/consolidation and /or utilization of sensory information stored in

memory traces, rather than to a faster decay of these traces. Moreover, lack of differential performance effects of task difficulty over time (ITI) suggests that attentional factors related to task difficulty (i.e., fatigue or reduction of attention resources) could not exclusively account for poor performance in the schizophrenics relative to controls.

Javitt et al.'s second, "no-delay" experiment, where tone-matching performance to a range of pitch changes was examined, a significant group difference was revealed when the analysis was restricted to the frequency change range of 2.5% to 10%. This finding suggests, in contrast to the findings of their previous study, that schizophrenics demonstrate tone-matching deficits even in no delay conditions. This additional finding may reflect enhanced sensitivity of detecting abnormalities secondary to employment of smaller frequency changes. The hypothesis that abnormalities exist in the precision in which sensory information extraction, encoding and/or retrieval occurs is supported by this study. The hypothesis that tone-matching ability in schizophrenia is reduced was further supported by findings from another tone-matching study (Javitt et al., 1999) where the ITI was reduced to 250ms and systematically increased to 20 seconds. When schizophrenics and controls were matched for performance at one-second delays, altering the length of the ITI did not differentially affect performance between groups.

Tone-matching task demands require execution of a behavioural response, namely a verbal or motor response indicating whether the tone pairs are the same or different. Thus, abnormal tone discrimination thresholds revealed in schizophrenia may be accounted for in part by disordered processes, such as impaired response execution, rather than impaired sensory memory traces. In an effort to determine whether tone-

matching deficits are specifically related to dysfunction within the auditory cortex rather than to a deficit in prefrontal functioning, Rabinowicz and colleagues (2000) evaluated tone discrimination performance in the presence and absence of same modality distractors. The rationale for this approach was derived from animal lesion studies that found differential tone-matching performance deficits contingent on lesion location. For example, bilateral lesions of the superior temporal plane in monkeys result in elevated tone discrimination thresholds (Massopust, Wolin, & Frost, 1971), whereas lesions to the prefrontal cortex only affects tone discrimination when distractors are interspersed within tone pairs (Iversen & Mishkin, 1973). Thus, based on these findings, Rabinowicz et al. predicted that if prefrontal mechanisms, rather than neural processes in the auditory cortex, mediate apparent deficits in auditory sensory memory in schizophrenia, tone-matching ability would be more impaired in the presence, compared to the absence of distractors. Rabinowicz and colleagues reported that although tone-matching thresholds in schizophrenia were increased in the presence/absence of distractors compared to controls, threshold changes were not significantly elevated in the distraction condition. Thus based on these findings, it does not appear that impaired attentional processes mediated by prefrontal brain regions can account for the apparent abnormal auditory sensory memory observed in schizophrenia.

In summary, simple tone-matching studies have revealed that echoic or auditory sensory memory is dysfunctional in schizophrenia. The main finding of these investigations was that individuals with schizophrenia demonstrated significant deficits in their ability to match tone pairs following a brief delay (i.e., 300 ms) and, even when no

delay was presented between tone pairs. The observation that schizophrenics, when equated for performance ability relative to controls, were no more affected by increases in the intertone interval, suggests that the underlying mechanism of this dysfunction is not due to a time decay factor of sensory memory information. Rather, the particular pattern of findings as a function of time and task difficulty suggests that individuals with schizophrenia are unable to efficiently extract, store and/or utilize precise sensory auditory information (Javitt et al., 1997; 1999).

1.7 Event-Related Potentials

Given that the human ability to process sensory information and to generate integrated perceptual experiences occurs in the brain, it seems justified to examine neurophysiological correlates to pursue a greater understanding of the nature of information-processing. ERPs can be recorded concomitantly with behavioural task performance, and thus aid in the investigation of active brain functions during cognitive tasks. Since the initial discovery that electrical activity in the brain could be recorded through electrodes placed on the scalp (Berger, 1929), the relationship between scalp derived electrical recordings and psychological processes has drawn considerable interest in cognitive science.

ERPs are neuroelectrophysiological correlates of specific cognitive processes and provide an electrophysiological temporal window into brain functions during cognitive processes. The waveform itself is interpreted as an aggregate of several components. In comparison to behavioural measures (i.e., measures of reaction time, hits & false alarms),

ERPs provide a more complete description of brain functioning during cognition as they reflect brain activity elicited at various stages in sensory information processing (i.e., earlier versus later ERP components). For example, short-latency ERPs are believed to offer an index of neuronal activity occurring at the earliest stages of sensory nerve stimulation, reflecting activity at relay stages in the ascending pathways (Hillyard, 1993). Furthermore in the study of attention, ERPs are advantageous in that they provide a measure of stimulus response in the absence of any requirement that the subject actively attend to or behaviourally respond to the stimuli. High temporal resolution of ERPs (in the range of milliseconds) provides insight into the absolute and relative timing of neural based cognitive processes that is difficult to abstract from purely behavioural measures (Mangun & Hillyard, 1987). Fast temporal resolution is most optimal for investigating fast-acting processes underlying rapid processing, identification and categorization of stimuli. Moreover, the millisecond (ms) time resolution of ERPs at speeds of cognitive processing permits coupling of ERPs with particular cognitive tasks. Cognitive tasks can then be tailored to probe specific areas of interest. The non-invasive nature of ERP recordings encourages their use in clinical settings as little, if any distress is caused to the individual. Another advantage of ERPs is that they are obtained with small financial cost. The main disadvantage of ERPs is that they do not provide clear information concerning localization of their brain sources. ERPs may be combined with information obtained from other techniques, such as CT (Computerized Tomography) or MRI (Magnetic Resonance Imaging) scans to allow for inferences about brain sources.

ERPs are voltage changes in brief segments (< 1 s) of electroencephalographic (EEG)

activity that are typically time locked to the presentation of a sensory stimulus. These time-locked voltage variations reflect the brain's activity in response to sensory input. As voltage variations evoked by the individual stimuli are notably small in contrast to background EEG activity, signal averaging is a commonly used technique to extract the signal (i.e., time-locked ERP) from the noise (i.e., background EEG). Signal averaging enhances the signal-to-noise ratio by averaging values of identical time points across multiple ERP epochs. As background EEG varies randomly, when averaged, it will sum to zero. The residual waveform represents non-random stimulus-locked neural activity.

Recordable brain activity at the scalp is dependent on the orientation and synchronous activity of groups of neurons (Rugg & Coles, 1995). Electrical fields generated by populations of neurons must possess "open fields" rather than "closed ones". In open field populations, neurons are oriented in a similar fashion (i.e., dendritic trees are all oriented on one side while their axons all depart from the other side) (Fabiani, Gratton & Coles, 2000). Open fields are common in brain regions such as the cortex and cerebellum and other structures where neurons are organized in layers. There are areas of the brain where neurons are configured in such a way that they constitute "closed fields", such as midbrain nuclei (Fabiani, Gratton & Coles, 2000). Their dissimilar orientation and/or asynchronous activity prevent summated potentials. Thus, electrical fields generated by these neurons are different and are often in opposite directions, thus canceling out their individual electrical activity.

Individual components of the ERP waveform represent the integrated activity of a large number of neurons in various regions of the brain. The most likely source of ERPs

is the summated activity of postsynaptic potentials (Allison, Wood, & McCarthy, 1986). In contrast to presynaptic potentials, the activity of post-synaptic potentials is temporally slower, which renders them more likely to be synchronously active and to summate at the scalp, generating recordable potentials (Allison et al., 1986). An exception to this is the activity of very-short latency auditory ERPs (< 10 ms) which is derived from synchronous volleys of action potentials (Allison et al., 1986).

From a sensory-cognitive perspective, individual positive (P) and negative (N) voltage components of the ERP are typically described in terms of their functional stages in information processing. The functional approach classifies ERPs into two general categories: exogenous and endogenous components. The amplitudes (μV) and latencies (ms) of the early components of the ERP, generating a poststimulus latency of < 100 milliseconds, reflect the initial sensory processing during which the feature extraction process takes place. Amplitudes and latencies of these components are mostly functions of the physical properties of the stimulus, including variables such as modality, intensity and rate (i.e., inter-stimulus interval) (Friedman & Squires-Wheeler, 1994), and thus are termed “exogenous”. These short latency ERP components are reflective of early brainstem/midbrain processes involving transmission and arrival of sensory information from the peripheral sensory system to the cortex (McCarley et al., 1991). Exogenous ERP components are relatively insensitive to internal psychological variables such as attention and memory; their waveforms remain fairly constant across various types of cognitive information processing (Roth, 1977).

Longer latency (> 100 ms) ERP components are endogenous in nature in that their waveforms are relatively independent of the physical parameters of the stimuli (Pritchard et al., 1986; McCarley et al., 1991), but are highly influenced by cognitive and psychological variables such as attention, task complexity and decision-making, as well as by experimental parameters such as probability. Endogenous ERP components are directly modulated by the characterization (i.e., significance) and/or interpretation of the stimulus as established by the task or by the perception of the subject (Sutton, Braren, Zubin, & John, 1965).

The long latency P300 (P3) component has received particular interest in information processing research (Pritchard, 1986; Friedman & Squires-Wheeler, 1994). It has been described as a correlate of elementary cognitive information processing, also possibly involving aspects of attention (Morstyn, Duffy & McCarley, 1983). To date, the P3 is the most extensively studied ERP component and is typically elicited during an auditory two-tone oddball paradigm, where participants are required to attend, detect and respond to unexpected, low probability target stimuli randomly presented among frequent, non-target standard stimuli. It is composed of multiple components, including the P3a and P3b (Squires, Squires & Hillyard, 1975) and its generators have been localized to the frontal and temporal lobes, respectively. P3b responses are consistently and reliably altered by variables such as stimulus probability, stimulus meaning (i.e., task/stimulus complexity, and stimulus value) and subjective information transmission (Johnson, 1986). The amplitude of the P3b component elicited by detected target stimuli, which is largest at parietal sites, appears to reflect the allocation of attentional resources to task-

relevant signals, higher amplitudes being elicited by attended than unattended stimuli (Picton, 1992). The latency of the P3b is interpreted as a sensitive measure of stimulus evaluation time, which is independent of response selection/execution processes (Polich & Kok, 1995). In a three-tone paradigm, where low probability, non-target or novel stimuli are interspersed in a typical two-tone oddball discrimination task, an earlier latency component, the P3a, is revealed which is maximal at anterior-central frontal areas (Squires et al., 1975). The P3a is linked to an early stage in the conscious detection of deviant, unexpected events (Roth & Kopell, 1973) and, accordingly, is used to probe at an electrophysiological level the phenomenon of distractibility. In a typical oddball paradigm, P3 components are preceded by several components that reflect discrete stages of information processing including the MMN and N2.

The MMN, N2 and P3 ERPs are superimposed on a sequence of “obligatory” sensory components including the N1, a frontal negativity with peak latency of approximately 100 ms and the P2, a fronto-central positivity with peak latency of approximately 200 ms. Obligatory potentials, unlike cognitive ones, are elicited to both standard and rare stimuli, and the amplitude of these components is determined foremost by the physical nature of the stimuli, for example, pitch and intensity. The amplitude of cognitive components depends primarily on the relationship between the stimuli as defined by the stimulus sequence and behavioural paradigm. The P3, N2 and MMN ERPs are elicited by rare, deviant stimuli and not by frequent standard stimuli, and therefore, they reflect higher order information processing. The latencies of the MMN, N2 and P3 covary which

suggests that they index sequentially, organized events in the processing of unexpected stimulus change (Novak, Ritter, & Vaughan, 1992).

The P3b ERP has been comprehensively studied in schizophrenia and robust findings of diminished P3b responses have been repeatedly documented (Levit, Sutton, & Zubin, 1973; Steinhauer & Zubin, 1982; Pritchard, 1986; McCarley, Faux, Shenton, Nestor, & Adams, 1991). Abnormal P3b appears to reflect a vulnerability marker for this disease (Kutcher, Blackwood, St.Clair, Gaskell, & Muir, 1987) as P3b deficits have been reported in non-medicated schizophrenics (Faux et al., 1993; Ford et al., 1994), offspring (Friedman, Vaughan, & Erlenmeyer-Kimling, 1982), first-degree relatives (Saitoh, Niwa, Hiramatsu, Kameyama, Rymar, & Itoh, 1984) and remitted clinical states (Blackwood, St-Clair, & Kutcher, 1986). Other ERP components, although they have been less extensively studied, have also been shown to be attenuated in schizophrenia. These potentials include the P3a (Grillon et al., 1991), the N2 (Pfefferbaum, Ford, White, & Roth, 1989), the N1 (Roth, Horvath, Pfefferbaum & Kopell, 1980), the P200 (Jones & Callaway, 1970) and the P50 (Freedman, Alder, Waldo, Pachtman, & Franks, 1983). In the early nineties, a group of investigators (Shelley, Ward, Catts, Mitchie, Andrews, & McConaghy, 1991) provided the first report of attenuated MMN amplitude in schizophrenia.

1.9 The Mismatch Negativity

The MMN is a neurophysiological index of auditory sensory change detection based on information stored in auditory memory traces (Näätänen, 1992). It is the first

measurable ERP-neurophysiological response that differentiates between standard and deviant auditory events (Näätänen, 1992).

The MMN is typically studied using a passive auditory oddball design where a train of repetitive, homogenous tones, termed “standards” is rapidly presented. These standard tones are occasionally and unpredictably substituted with a deviant tone that differs physically in some way (i.e. Bernoulli sequence). The MMN is usually recorded while the subject’s attention is directed away from the auditory stimuli, such as while reading a book or watching a video. The MMN response is dependent on the brain’s ability, specifically the auditory cortex, to generate and maintain a short-duration representation of auditory input (Näätänen, 1992) occurring within an approximate ten-second time window (Cowan, 1984). These auditory representations are automatically updated and compared, and when the features of a sound differ (e.g., deviant stimuli) from those of an existing neural memory trace created by a series of repetitive stimuli (e.g., standard stimuli with identical features), a negative potential is elicited following the presentation of the mismatched tone, hence the name “mismatch negativity”. The MMN is most visible through a subtraction process, where digitized values of the averaged waveform elicited by the standard stimuli are subtracted from those of the deviant stimuli. This subtraction process uncovers the MMN, which has a latency of approximately 100-200 ms (Näätänen, 1992).

Näätänen, Gaillard & Mantysalo (1978) provided the first account of the MMN. Using a dichotic listening paradigm, subjects were instructed to detect infrequently occurring deviant stimuli presented in a train of repetitive standard stimuli in the attended

channel while ignoring an identical stimulus sequence, presented in the unattended channel. In the first of two experiments, the deviant stimuli were of a slightly higher intensity than the standard stimuli (standard = 70 dB, deviant = 80 dB). In the second experiment, the stimuli sequence varied with respect to the pitch (but not intensity), with the deviants being of a higher frequency (1140 Hz) than the standard stimuli (1000 Hz). All stimuli in the second experiment were 70 db in intensity. Näätänen and colleagues (1978) found that the N100 waveform was consistently larger to the deviant stimuli compared to the standard stimuli across both conditions and its morphology in the attended and the non-attended channels was similar. The only difference noted between ERP signals in the attended versus the unattended channels was the late positivity (i.e., P300) elicited only in the attended channel to the target stimuli. Their most interesting finding was an enhanced negativity to the deviant stimuli elicited 100-200 ms post stimulus presentation, superimposed on the N100 waveform. Standard tones did not elicit this change. This negativity was revealed by a difference wave, computed by subtracting the deviant from the standard waveform and was labeled the mismatch negativity. Through this subtraction process, ERP components common to both types of stimuli such as the N1 and P2 were removed. Näätänen et al (1978) concluded that the MMN reflected “specific auditory stimulus discrimination processes taking place in the auditory primary and association areas”.

This discovery of the MMN set in motion a series of subsequent studies that sought to identify which features of acoustic change reliably and consistently generated a brain deviance detection response indexed by the MMN. MMN feature manipulation studies

ranged from conditions where basic acoustic stimulus parameters were varied, to situations where complex feature changes were examined. It has been well established that any detectable change in the physical characteristics in an otherwise standard auditory environment evokes the MMN (Näätänen, 1992). For example, MMN is elicited to changes in either an increment or decrement in intensity (Näätänen, Paavilainen, Alho, Reinikainen & Sams, 1989; Lounasmaa, Hari, Joutsiniemie, & Hamalainen, 1989), duration (Näätänen, Paavilainen, Alho, & Reinikainen, 1989; Kaukoranta, Sams, Hari, Hämäläinen, & Näätänen, 1989), frequency (Sams, Paavilainen, Alho, & Näätänen, 1985; Tiitinen, May, Reinikainen, & Näätänen, 1994) and spatial location of a sound (Paavilainen, Karlesson, Reinikainen, & Näätänen, 1989; Schroger & Wolff, 1996), as well as to more complex stimulus changes such as phonemes (Aaltonen, Niemi, Nyrke, & Tuhkanen, 1987; Krauss, McGee, Carrell, & Sharma, 1995), omissions (Sabri & Campbell, 2000) and noise (Marcoux, Muller-Grass, Logan, & Campbell, 1999).

The amplitude and latency of the MMN is influenced by a number of stimulus parameters including degree of deviance, strength of standard-stimulus trace and stimulus probability (Näätänen, Hukkanen & Jarvilehto, 1980). Näätänen et al. (1980) observed that the amplitude and latency of the MMN in normal controls progressively increases and decreases, respectively, as the degree of deviance between standard and deviant stimuli increases and as deviance probability progressively declines. According to Näätänen's (1992) "memory trace" theory of the MMN, as the number of standard stimuli between each deviant in the stimulus sequence increases (i.e., the probability of deviance is reduced), the strength of the standard memory trace is enhanced. Therefore,

when a deviant stimulus is presented infrequently in a repetitive series of rapidly presented standards, the comparison process of the deviant input to that of the memory trace generated by the standards is strengthened, generating a stronger neuronal mismatch detection, and thus larger MMN amplitude.

The clinical utility of the MMN is in part determined by its replicability over a short period of time. Escera and Grau (1996) demonstrated short-term replicability of the MMN (amplitude and latency) at the group level using frequency deviants in two recording sessions spaced two hours apart ($r = 0.598$, $p = 0.04$). In a previous study (Pekkonen, Rinne, & Näätänen, 1995), with a one-month interval between MMN recording sessions, MMN to frequency and intensity changes were found to be stable across sessions at the group level (r values were not provided in the original text). The MMN to duration only revealed significant individual test-retest stability ($r = 0.5631$, $p < 0.05$). Tervaniemi and colleagues (1999) reported that MMN to duration decrements elicited the most replicable MMN ($r = 0.78$, $p < 0.05$). Using test-retest measures over an approximate one-week interval, it was reported that duration decrements, where the duration of the deviant stimulus was 66% shorter than the standard stimuli (i.e. 25 ms deviants interspersed among 75 ms standards) generated the most replicable MMN response.

Localization of MMN generators may aid in identifying neurophysiological correlates of auditory sensory memory, and therefore may be useful in making inferences concerning the integrity of brain processes in individuals with auditory sensory processing dysfunction. A number of different techniques have been used to localize

MMN generators including animal and human intracranial MMN recordings (Csepe, Karnos, Molnar, 1989; Woods, Knight, & Scabini, 1993), magnetoencephalographic (MEG) recordings (Hari, Hamalainen, Ilmoniemi, Kaukoranta, et al., 1984), dipole modeling (Scherg, Vajsar & Picton, 1989) and lesioning studies (Aaltonen, Tuomainen, Laine, & Niemi, 1993). The results of these studies suggest that MMN generators are localized bilaterally in the temporal lobes, specifically within the auditory cortex.

Brain activity in areas outside the auditory cortex also contributes to the generation of the MMN, specifically the prefrontal cortex. Whereas temporal lobe generators are responsible for detection of deviance, according to Giard and colleagues (1990), neural MMN generators in the frontal cortex may trigger an automatic attention-switching mechanism to deviant events (Giard, Perrin, & Bouchet, 1990). Support for a frontal MMN generator was initially provided by observations that individuals with prefrontal dorsolateral cortex lesions exhibit significant reductions in MMN amplitude (Alho, Woods, Knight, & Näätänen, 1994).

Two theories, the new afferent element and echoic memory trace hypotheses have been proposed in the literature to account for the nature of the MMN (Näätänen, 1992). The new afferent hypothesis suggests that a group of neurons sensitive to the features of the deviant stimuli but not to that of the standard stimuli activate a new afferent element which gives rise to the MMN. These feature specific neurons remain responsive due to long intervals between deviant stimuli. The viability of this theory is questionable as there are several inconsistent observations. For example, the MMN is no longer elicited when the duration of the ISI is increased past a certain point, approximately 10 seconds

(Sams, Hari, Rif, & Knuuttila, 1993; Bottcher-Gandor & Ullsperger, 1992). Moreover, the new afferent explanation cannot account for the observation that a MMN is also elicited by stimulus omission in a rapid rate stimulus sequence (Hari, Hamalainen, Ilmoniemi, Reinikainen, Alho, Näätänen, & Sams, 1984). Furthermore, this account cannot explain a MMN response elicited by an occasional too early stimulus in a stimulus sequence (Ford & Hillyard, 1981; Norby, Hammerborg, Roth, & Hugdahl, 1988). Also, no MMN response is elicited to a deviant stimulus presented at the beginning of a stimulus sequence (Näätänen, 1992; Sams, Paavilainen, Alho & Näätänen, 1985). Lastly, Näätänen, Paavilainen, Alho, Reinikainen and Sams, (1989) argued that prolonged duration and latency of the MMN for slight stimulus changes is an uncommon observation for a new afferent response.

The evidence reviewed suggests that the MMN is not simply the manifestation of neural activity generated by a new afferent activation. Rather, brain processes underlying the MMN appear to reflect a “mismatch” automatic comparison process between a neural trace formed by deviant sensory input, to that of stimulus memory traces formed by the physical features of the preceding, repetitive auditory stimuli (Näätänen, 1992). According to Näätänen’s theory, the presentation of deviant stimuli generates a memory trace of its own in the auditory sensory memory system, which is automatically compared to the existing (standard) memory trace. Näätänen (1992) argued that this change detection process reflects a higher order response of a dynamic discriminative process and that the memory traces underlying the MMN reflect auditory sensory memory traces, more specifically echoic memory. Although the MMN is not a direct measure of echoic

memory, it can be used to probe the integrity and duration of these traces.

Echoic memory and the MMN have multiple features in common. Both occur automatically, are attention-independent in their formation, and last for approximately 5-10 seconds. Each of these processes contains extensively processed information (Näätänen, 1992).

The change detection processes reflected by the MMN relies on the existence of extracted sensory information stored in auditory traces that is subsequently available to higher order processes, such as conscious perception and voluntary actions. Thus, the primary functional attribute of the MMN appears to be associated with the transient storage of repetitive features, and detection of deviant sounds that differ from the existing standard acoustic environment.

Näätänen's functional account of the MMN allows for the MMN to be used indirectly to measure the duration and decay of the neuronal sensory memory trace. Varying the ISI offers a means of determining the strength of the memory trace, in terms of decay from initial stimulus trace formation, to subsequent use of extracted information.

Mantysalo and Näätänen (1987) undertook one of the earliest studies that measured the duration of auditory sensory memory traces inferred indirectly by time decay of the MMN. Their findings suggested that the MMN was only elicited under conditions with ISIs of 1-2 seconds (MMNs were extinct at ISIs of 4 and 8 seconds). Performance data revealed that behavioural deviance detection was reduced in conditions where the ISIs were larger (i.e., 4 & 8 seconds) relative to conditions where shorter ISIs were used. Based on their findings, these investigators proposed that the duration of sensory memory

traces was approximately 2-4 seconds.

A subsequent study undertaken by Bottcher-Gandor and Ullsperger (1992) found that a MMN response is elicited even at ISIs up to 10 seconds. Inconsistent time decay estimates of the MMN between these two studies may be due to the type of deviant employed. In the latter study, the frequency of the deviant stimuli was 500 Hz higher than the standard stimuli compared to the former study, where the frequency difference between the standard and deviant stimuli was only 200 Hz. According to Näätänen (1992), greater deviance generates larger MMN amplitude, which may in turn prolong the time necessary for extinction of the MMN. Thus, based on these findings, Bottcher-Gandor and Ullsperger (1992) argued that the neuronal representation of the auditory sensory trace persists up to 10 seconds, which is consistent with Cowan's (1984) estimate of the duration of auditory sensory memory. Duration of sensory memory appears to be age related: memory traces in elderly individuals decay faster than younger persons (Pekkonen, Jousmäki, Partanen, & Karhu, 1993), as is observed in cases of Alzheimer's disease (Pekkonen, Jousmäki, Konomien, Reinikainen, & Partanen, 1994).

Based on the close association between MMN and sensory change detection, the MMN can be used to determine and monitor pathologies in the auditory modality (Näätänen & Alho, 1997). Indeed, several studies have used the MMN to investigate the normal development of auditory system in older children (Leppanen, Laukkonen & Lyytinen, 1992), as well as in developmental dysphasia (Korpilahti & Lang, 1994), Parkinson's disease (Pekkonen, Jousmaki, Reinikainen, & Partanen, 1995), and Alzheimer's disease (Pekkonen et al., 1994). The MMN has also been used to predict

recovery of coma patients (Kane, Curry, Rowlands, Manara, Lewis, Moss, Cummins, & Bulter, 1996).

1.10 MMN and Schizophrenia

Monitoring MMN response in schizophrenia may provide answers to basic questions concerning whether neurocognitive dysfunction is so pervasive that it extends to a lower level where preperceptual, inherently automatic, sensory processing of auditory events occurs.

Shelley, Ward, Catts, Mitchie, Andrews and McConaghy (1991) provided the first published account of reduced MMN to duration deviants in schizophrenia within an auditory oddball paradigm. The intensity and frequency of the auditory tones were 80dB and 633 Hz respectively, with a rise and fall time of 10 ms. Ninety percent of auditory tones presented in the first half of the 12 blocks were short (50 ms) duration (i.e., standards) while the remaining 10% of tones were long (100 ms) duration (i.e., deviant stimuli). In the remaining blocks, the duration of the stimuli was reversed, where 90% of the tones were long duration and the remaining 10% were short duration. Control and schizophrenic groups performed a simple visual discrimination task during presentation of the auditory tones so as to direct their attention away from the tones.

MMN amplitude to long duration deviants was significantly reduced in the schizophrenic group compared to control group, while in the short deviant condition, a trend towards smaller MMN amplitude was noted in the schizophrenics, but group differences did not achieve statistical significance. Shelley and colleagues suggested that

short duration deviants may have been more “attention capturing” and artificially reduced MMN amplitude by the elicitation of attention-dependent ERP components, such as the P3a. An alternate explanation for these findings may be linked to reports of smaller MMN amplitude to duration decrements than to duration increments in normal participants (Näätänen, 1992). Thus, floor effects may have dampened identification of group differences. MMN latency did not differ between groups. Correlational analysis revealed no relationships between MMN amplitude and medication dose levels and scores on psychiatric ratings scales. Shelley and colleagues noted that MMN dysfunction could potentially contribute to, or underlie deficits in controlled processing.

Shelley et al.’s (1991) initial report of reduced MMN amplitude to duration deviants in medicated schizophrenics was subsequently replicated by a number of studies (See Table 1 for a summary) (Lembregts & Timsit-Berthier, 1993; Kasai et al., 1999; Michie et al., 2000; Todd et al., 2000). Abnormal MMN has also been identified in non-medicated schizophrenics (Javitt et al., 1995; Catts, Shelley & Ward, 1995; Brockhaus-Dumke et al., 2005) and in prodromal subjects (Brockhaus-Dumke et al., 2005). Findings from these studies suggest abnormal pre-attentive temporal processing of auditory events.

Table 1. MMN-Duration Studies in Schizophrenia

Author	Sample	Standard (ms)	Deviant (ms)	Dvt. Prob (%)	ISI (ms)	Outcome
Shelley et al. (1991)	Chronic med	50 100	100 50	10	510	p<.02 N.S.
Catts et al. (1995)	Chronic med, med -free vs. Bipolar	50 100	100 50	10	510	p<0.001 p<0.03
Kasai et al. (1999)	Chronic med.	100	50	25	600	p<0.044
Michie et al. (2000)	Medicated	50	100	9	510	p<0.003
Todd et al. (2000)	Medicated	50	100	10	510	p<0.034
Michie et al. (2002)	1 st degree Relatives, Schizo- Spectrum	50	100	10	510	p<.044 p<.005
Umbricht et al. (2003)	Medicated vs. Bipolar; Medicated vs. MDD Medicated vs. Controls	100	250	10	300	p<0.056 p<0.005 p<0.005
Bramon et al. (2004)	Medicated	25	50	15	333	p<0.01
Brockhaus-Dumke (2005)	Med-free, Prodromal	80	40	10	500	p<0.046
Light & Braff (2005)	Chronic med.	50	100	10	500	p<0.001
Light & Braff (2005)	Chronic med.	50	100	15	500	p<0.001

A very recent study examined the stability of abnormal MMN to duration deviants over a 1-2 year period in a sample of medicated schizophrenics. Significantly lower MMN amplitude was reported in the schizophrenic group compared to controls at the initial test session and at the 1-2 year follow-up session (Light & Braff, 2005b).

Abnormal MMN appears to be a stable deficit; no progression of MMN impairment was reported. Light and Braff (2005b) also examined the relationship between abnormal MMN and functional status. A significant negative correlation was found between MMN

amplitude and functional status, while MMN was not correlated with positive or negative symptoms at either test session.

In another study, Light and Braff (2005a) provided further support of a negative association between MMN deficit and functional status. Using a regression model they found that 42% of the variance in global functional status was accounted for by abnormal MMN. Moreover, they observed that schizophrenics with greater MMN impairment were more likely to live in a structured, supportive environment rather than in the community independently.

Michie et al. (2002) provided the first published report of reduced MMN to duration increments in first-degree relatives of schizophrenics; the severity of dysfunction was similar to that observed in affected family members. The specificity of MMN dysfunction was recently tested in a study that looked at MMN generation in individuals with schizophrenia, bipolar disorder, major depressive disorder and healthy controls (Umbricht et al., 2003). A significant reduction in MMN amplitude to frequency and duration deviants compared to normal controls was only observed in the schizophrenic group; MMN amplitude did not significantly differ in the other two clinical samples compared to controls. Compared to the major depressive group, the schizophrenics showed significantly lower amplitude to duration and frequency MMN, while only a marginally significant difference to both types of deviants was found compared to the sample of individuals with bipolar disorder. An earlier study (Catts et al., 1995) reported non-significant MMN group differences between control participants and groups of individuals with bipolar disorder (Catts et al., 1995).

Javitt and colleagues provided the first report of attenuated MMN-frequency (Javitt, Doneshka, Zylberman, Ritter, & Vaughan, 1993). Javitt et al., (1993) studied MMN in chronic, medicated schizophrenics relative to controls to very small frequency deviants (i.e. 1000 Hz Standard, 1024 Hz deviant). A subsequent study in the same laboratory using a similar paradigm (see table 2) (Javitt, Doneshka, Grochowski, & Ritter, 1995), found reduced MMN amplitude to frequency in both medicated and non-medicated schizophrenics compared to controls during both active and passive recording conditions. No MMN latency differences were observed across groups. A significant relationship was reported between MMN and P300 across groups ($r = -0.38$ $p = <0.02$), which suggested that pre-attentive information processing dysfunction was associated with subsequent deficits in controlled, attention-dependent processing (i.e., impaired P300 generation).

Attenuated frequency MMN was subsequently replicated by a large number of studies (see table 2 for a summary) (Javitt et al., 1995; Shutara et al., 1996; Hirayasu et al., 1998; Alain, Hargrave, & Woods, 1998; Shelley, Silipo, & Javitt, 1999; Javitt et al., 2000), and has been observed in first-degree relatives (Jensen et al., 2001), across schizophrenia subtypes including paranoid and non-paranoid (Oades, Dittmann-Balcar, Zerbin, & Grzella, 1997), and in acute and post acute psychotic episodes (Shinozaki et al., 2002).

Table 2. MMN-Frequency Studies in Schizophrenia

Author	Sample	Standard (Hz)	Deviant (Hz)	Dev. Prob. (%)	ISI (ms)	Outcome
Javitt et al. (1993)	Chronic-Med.	1000	1024	6	50	p=0.031
O'Donnell et al. (1994)	Chronic-Med.	1500	1000	15	1250	N.S.
Javitt et al. (1995)	Med. & Med. Withdrawn	1000	1024	15	1300	p=.006
Kathmann et al. (1995)	Chronic-Med.	600	1000	20	580	N.S.
Shutara et al. (1996)	Chronic-Med.	1000	1100 1050	10	600	Sig ^a p<0.001
Oades et al. (1997)	Paranoid, Non-paranoid	800	2000	10	1200	p<0.009
Alain et al. (1998)	Medicated	1000	1122 1414	3	300	p<0.01
Hirayasu et al. (1998)	Medicated	1000	1200	5	300	p<0.002
Umbricht et al. (1998)	Medicated	1000	1200	14	800	p<0.05 ^b
Javitt et al. (2000)	Chronic-Med.	1000	1050	5	300	p<0.03
Michie et al. (2000)	Medicated	633	700 1000	10	510	N.S. p=0.07
Jessen et al. (2001)	1 st degree relatives	1000	1100	15	1250	p=0.045
Shinozaki et al. (2002)	Repeated Measures Acute & Post-Acute	1000	2000	10	500	p=0.02 ^c
Umbricht et al. (2003)	Med., Bipolar MDD	1000	1500	fixed order	300	p<0.05
Brockhaus-Dumke et al. (2005)	Med-free, Prodromal	1000	1200	10	500	N.S.
Korostenskaja et al. (2005)	Medicated	1000	2000	20	1500	N.S.

^a P value was not reported in text

^b Olanzapine and Risperidone treated patients compared to controls (MMN amplitude did not differ significantly between patient groups).

^c The same sample of patients during acute and post-acute phases (MMN amplitude did not differ significantly between illness phases).

The pharmacological effects of antipsychotic treatment do not alter the severity of MMN attenuation; risperidone and olanzapine elicit similar MMNs to frequency deviants (Umbricht, Javitt, Novak, Bates, Pollack, Lieberman, & Kane, 1998; Schall, Catts, Chaturvedi, Redenbach, Karayanidis, & Ward, 1995). Moreover, MMN frequency reductions are independent of clinical symptomatology, as Shutara et al., (1996) reported non-significant correlations between MMN parameters and total scores on a brief psychiatric rating scale.

A very recent study took a different approach to examine abnormal MMN response to frequency deviants in schizophrenics. Rather than recording MMN during a purely passive auditory oddball paradigm, MMN was also examined during an active condition while participants counted deviant tones (Korostenskaja, Dapsys, Siurkute, Maciulis, Ruksenas, & Kahkonen, 2005). Employing a recording condition where deviant tones were actively attended to provides information about auditory dysfunction at different stages of information-processing. Although the amplitude of the P3 was significantly lower in the patient group, MMN amplitude did not differ statistically between schizophrenics and normal controls. Individuals with less severe schizophrenia spectrum disorders were included in this study which may of accounted for the lack of significant group differences in MMN.

Attenuated MMN amplitude to duration deviants in schizophrenia is a robust finding. Reports of abnormal MMN to frequency deviants are less conclusive as non-significant group differences between schizophrenics and controls have been documented. A notable difference between MMN-frequency studies that reported significant group

differences and those that did not was the degree of pitch changes employed to elicit the MMN. O'Donnell, Hokama, McCarley, Smith, Salisbury et al. (1994) and Kathmann, Wagner, Rendtorff and Engel (1995) utilized large frequency changes between standard and deviant stimuli of 50% and 60%, and did not reveal significant group MMN frequency differences. In general, studies that reported significant amplitude attenuation employed small frequency changes to elicit the MMN, such as 2.5% (Javitt et al., 1993) and 5% or 10% (Shutara et al., 1996). MMN-frequency in schizophrenia may be a rather subtle effect that is only evident for relatively small frequency changes in the auditory stimulus properties (Mitchie et al., 2000). An alternate explanation may be that given the MMN is extracted by subtracting the standard from deviant waveform, in conditions where large frequency differences were utilized the amplitude of the MMN may have been artificially reduced due to large N100 amplitude generated by a large frequency change. Differential frequency-specificity refractory of the N100 to standard and deviant stimuli has been documented (Picton & Hillyard, 1974). Thus, overlap with N100 may have obfuscated the MMN thus rendering non-significant group differences. Although neither of these explanations can account for the findings reported by Oades et al. (1997) who, despite using a very large frequency change of 150% (i.e. 800 Hz vs. 2000 Hz), reported a significant reduction in MMN-frequency in schizophrenics compared to controls. It is also possible that inconsistencies in the frequency- MMN literature may be simply accounted for by variables such as sample size, experimental parameters (i.e., deviant probability and ISI), the heterogeneity of schizophrenia and differences in diagnostic criteria used by different research groups

(Mitchie, Budd, Todd, Rock, Wichmann, Box, & Jablensky, 2000).

Most MMN experimental paradigms employed in schizophrenia research only used single combinations of pitch change, deviant probability and ISI, and thus the effect of these variables on MMN generation in schizophrenics has not been adequately investigated. It has been well established that in normal controls, experimental factors such as degree of deviance, probability of deviance and ISI impact MMN response (Näätänen, 1990). Javitt, Grochowski, Shelley, & Ritter (1998) evaluated MMN generation in schizophrenia specifically as a function of these variables. In their first experiment, data was collected across a range of deviant probabilities (15%, 5%, 1.67% & 0.56%) and ISIs (50 ms, 150 ms, 450 ms & 1300 ms) at a fixed pitch change between standard and deviant stimuli (standard and deviant frequencies were not specified in the original text). The stimuli were 75dB in intensity and 100ms in duration. Their objective was to establish optimal conditions for detecting attenuated MMN in schizophrenics at a fixed pitch change. In a second experiment, pitch change between standard and deviant stimuli was systematically increased (2%, 5%, 20%, 200% & 300% Δf) at a fixed level of deviant probability (10%) and ISI (260ms). The aim of this study was to determine at what frequency change similar MMN amplitudes were elicited in schizophrenics and controls.

Multiple regression analysis revealed that deviant probability and degree of pitch change were significant predictors of MMN amplitude. MMN amplitude was reduced in the schizophrenic group across all levels of deviant probability and ISIs at a fixed pitch change (not specified) compared to controls. Although the schizophrenics, like the

controls, demonstrated progressive increases in MMN amplitude as deviance probability was reduced from 15% to 0.56%, a significant group by condition interaction revealed a differential response between groups with respect to alterations in probability. Follow-up analysis revealed that enhancement of MMN amplitude as a function of reduced deviance probability was significantly lower in the patient group compared to controls. MMN latency across groups was not responsive to changes in deviant probability or ISI. Across conditions, there was a significant increase in MMN latency in the schizophrenic group relative to controls.

Shelley et al. (1999) further examined the effect of deviant probability on MMN-frequency generation in schizophrenia (See Table 3). Deviant probabilities utilized ranged from 25%, 10%, 5% & 2.5% (std = 1000 Hz, deviant = 1200 Hz). MMN amplitude progressively increased in both groups as deviant probability was reduced from 25% to 2.5%. Consistent with the findings of Javitt et al. (1998), Shelley and

Table 3. MMN in Schizophrenics (relative to controls) at Varied Levels of Deviant Probability and ISI

Author	Sample	Standard (Hz)	Deviant (Hz)	Dev. Prob. (%)	ISI (ms)	Outcome
Shelley et al. (1999)	Medicated	1000	1200	25 10 5 2.5	250	N.S. p<0.05 p<0.001 p<0.05

colleagues (1999) reported that MMN amplitude enhancement, as a function of decreases in deviant probability was most evident in the control group. In both groups, peak MMN amplitude was observed at a 5% deviance probability level. No further increases in

MMN amplitude across groups were noted when deviance probability was reduced to 2.5%. MMN amplitude in the schizophrenic group was reduced overall across all conditions. Statistically larger between group differences occurred when the probability of presentation of a deviant stimulus was reduced from 10% to 2.5%. No between group differences were reported when deviance probability was further increased to 25%. Although MMN latency was prolonged across groups to increases in deviant probability, MMN latency did not statistically differ between schizophrenic and control groups.

Compared to control subjects, no differential effect of ISI on MMN generation in schizophrenics was reported, within intervals ranging from 50 ms to 3 seconds at fixed pitch deviance (Javitt et al., 1998). These findings were consistent with those from an earlier study (Shelley, Javitt, & Vaughan, 1996) that also reported no differential effect within the range of ISIs tested (up to 3 seconds) in schizophrenics relative to controls. Investigators from both studies noted that the maximum ISI utilized might not have been sufficiently long to elicit a significant group difference. Shelley et al. (1999) extended the ISI interval up to 4 seconds (ISI ranges: 250, 500, 1000, 4500 ms). Deviance probability was held constant at 10% and deviance pitch change was 1200Hz. Again, schizophrenics were no more affected than controls by variations in the ISI (250 ms to 4.5 seconds). Since the longest interval tested was 4.5 seconds, the possibility was not ruled out that premature decay of sensory information in schizophrenia might occur with larger ISIs. The main findings of these three studies were similar: schizophrenics elicited significantly smaller MMN amplitudes across ISI variations but were not differentially affected by ISI changes. Moreover, ISI was not significantly correlated with MMN

amplitude in the schizophrenic group. In both groups, MMN amplitude was reduced as a function of longer ISIs. Non-significant group differences in response to change in ISIs within intervals ranging from 50 ms to 4.5 seconds, supports the contention that MMN reduction to frequency deviants in schizophrenia is not the result of a faster decay of sensory information stored in memory traces underlying the elicitation of the MMN. This conclusion is consistent with that drawn from tone-matching behavioural performance in schizophrenia (Javitt et al., 1997; 1999).

In Javitt et al.'s (1998) second experiment, where MMN was evaluated as a function of systematic increases in pitch change, MMN amplitude increased progressively in both groups within a 2%-100% pitch change range (10% fixed deviant probability) (See Table 4). This enhancement was by far most evident in the control group; MMN amplitude in the schizophrenic group was only slightly enhanced to increases in pitch change. Larger pitch change (i.e. 300%) resulted in a plateau or a slight decline in MMN amplitude across groups (Javitt et al., 1998). MMN amplitude was attenuated across all pitch conditions in the schizophrenic group compared to controls; however only pitch changes of 20%, 100%, and 300% resulted in statistically significant group differences.

Table 4. MMN in Schizophrenics as a Function of Pitch Change

Author	Sample	Standard (Hz)	Deviant (Hz)	Dev. Prob. (%)	ISI (ms)	Outcome
Javitt et al. 1998	Medicated	1000	1020 1050 1200 2000 3000	10	260	N.S. N.S. p<0.05 p<0.05 p<0.005

This pattern of statistically significant effects suggests that the severity of MMN amplitude reduction in schizophrenia is most evident when the pitch change between standard and deviant stimuli is relatively large. This effect is not attributed to a large decline of MMN amplitude within the schizophrenic group across increases in pitch change, but rather, this effect appears in most part to be due to progressive enhancement of MMN amplitude within the control group with systematic increases in frequency change. Thus, as MMN amplitude increases in the normal controls as a function of larger pitch deviance, group differences in MMN amplitude become more apparent. Although no latency differences between groups were reported, it was noted that latency across groups declined significantly with larger frequency deviance. A correlation between MMN amplitude and deviance probability was observed in both groups.

Overall, results of these studies support previous findings of attenuated MMN-frequency amplitude across a broad range of conditions in schizophrenia and in addition, demonstrate that MMN response varies significantly as a function of stimulus probability and pitch deviance. It appears from these experiments which sought to characterize the pattern of MMN-frequency dysfunction, that schizophrenics are sensitive to the same stimulus parameters that impact on MMN response in normal controls (i.e. reduced deviance probability and increased pitch differences), however the degree of amplitude increase observed as a function of variation in these variables, is considerably smaller in patients than controls. In other words, MMN-frequency dysfunction in schizophrenia is most apparent in conditions where MMN amplitude is normally largest in healthy controls.

ISI manipulations provide further clues to uncovering the underlying pattern of MMN dysfunction in schizophrenia. These studies suggest that deficient MMN reflects a deficit in the precision in which auditory sensory information is stored or encoded, rather than to an abnormal decay of sensory memory traces over larger ISIs. This interpretation implies that schizophrenics are able to maintain the integrity of the information stored in their auditory sensory memory traces but the maximum strength or precision to which they are formed is reduced.

Javitt, Shelley and Ritter (2000) recently provided evidence to suggest that abnormal MMN in schizophrenics is directly related to impaired behavioural tone discrimination. Upon examining the relationship between tone- matching performance and MMN-frequency (Δf 5%), correlational analysis revealed a significant positive relationship between attenuated MMN amplitude and impaired tone-matching performance in a sample of schizophrenics. Furthermore, Javitt et al. reported that MMN-frequency amplitude, tone matching performance, and severity of negative symptoms were also related. These correlational findings suggested that early, automatic sensory processing deficits evidenced by attenuated MMN may impair the ability to successfully match simple tones and are associated with the severity of negative symptoms rather than positive ones.

The present literature review comprehensively reviewed the current MMN literature in schizophrenia and showed that schizophrenics suffer from pervasive sensory-memory based information-processing dysfunction. This review also described various attention-based and higher-ordered information-processing deficits apparent in this clinical

population. The link between dysfunction at very low levels of sensory information processing and higher-ordered cognitively based processes in schizophrenia is unclear. It has yet to be determined whether elementary sensory memory processing deficits have a sequential impact on a chain of processes that lead to higher-ordered cognitive abilities or whether these deficits represent distinct entities. Thus, the purpose of the present dissertation was three-fold: the first objective was to replicate previous findings in the schizophrenia literature of abnormal MMNs elicited by duration and frequency deviants in a passive paradigm (Experiment 1), while the second and third objectives were to examine behavioral and electrophysiological indices of distractibility and task performance to frequency deviants (Experiment 2) and to duration deviants (Experiment 3).

1.11 Rationale and Hypotheses for Experiment #1

Abnormal auditory sensory memory has profound consequences for information processing and perceptual functioning at the most basic level. An important step in determining what abnormal MMN amplitude reveals about the auditory sensory memory processing system in schizophrenia is to establish whether MMN amplitude is abnormally altered with respect to varied types of deviants. As discussed in the review of the MMN schizophrenia literature, MMN amplitude reduction to duration deviants, specifically to long duration deviants, has been successfully replicated without any inconsistent reports in the literature; however findings of diminished MMN amplitude to frequency deviants have been less consistently documented. To ascertain whether

abnormal MMN reflects a generalized sensory memory dysfunction, the MMN to frequency deviants requires further study. Thus, the primary goal of Experiment #1 was to further explore MMN-frequency in schizophrenia.

In the present study, pitch changes of 5%, 10% and 20% were employed, and were chosen specifically because at this pitch range, schizophrenic tone discrimination performance is beyond chance and is characterized by a wide range of performance abilities (Javitt et al., 1997; Strous et al., 1995). Previous research showed that small frequency changes incur floor effects in schizophrenics and control subjects (Mitchie et al., 2000). Thus, in order to avoid the possibility of floor effects in the current study, a 5% probability of deviant presentation and an inter-stimulus interval of 300 ms were employed. It was expected that these parameters would enhance the strength of the underlying memory traces and subsequent MMN amplitude and therefore improve the power to detect significant group differences. As illustrated in Table 2 (see page 36), previous studies have found statistically significant group differences in MMN amplitude using these stimulus parameters. A unique feature of the present study was that three frequency deviants as well as two duration deviants were examined in the same sample of individuals with schizophrenia.

The secondary objective of Experiment 1 was to replicate previous findings of attenuated MMN amplitude to duration deviants in schizophrenics compared to control subjects. A short duration deviant condition (deviant = 50 ms; standard = 100 ms) was employed in addition to a long duration deviant condition (deviant = 100 ms; standard = 50 ms).

Impairment of automatic, pre-attentive processing of sensory-based information as indexed by abnormal MMN has become an increasingly familiar finding in the schizophrenia literature. As previously mentioned, a unique feature of Experiment 1 was that both frequency and duration deviants were examined in the same sample of patients. It was expected that the amplitude of the MMN elicited by the schizophrenics would be reduced across three frequency deviants compared to the controls. Moreover, larger differences in MMN amplitude between schizophrenics and controls were predicted with greater pitch change. It was unlikely, however, based on the existing MMN-frequency literature that significant group differences with respect to MMN latency would be observed.

With respect to duration deviants, it was expected that the schizophrenic group would show reduced MMN amplitude to the long and short duration deviant conditions compared to the control group.

2.0 *Experiment 1: MMNs to frequency and duration deviants in schizophrenics and controls*

2.1 Method

2.1.2 Participants

Twenty-one ambulatory, community-dwelling outpatients from the Schizophrenia Clinic of the Royal Ottawa Hospital (males=18; mean age = 40), as well as 19 healthy individuals (males =14; mean age = 32) without a history of psychiatric illness participated in this study. Informed consent was obtained for all participants. Only patients who met DSM-IV diagnostic criteria for chronic schizophrenia and who were clinically judged to be in a non-acute, stable phase of their illness, over a minimum of 4 weeks prior to study enrollment, were included in this study. Symptoms of schizophrenia were rated using a 30-item scale with 16 general psychopathology symptoms items, seven positive-symptoms and seven negative symptom items (The Positive and Negative Syndrome Scale: PANSS; Kay, Fiszbein & Opler, 1987) which was administered by their primary physician. To rule out any variability in MMNs associated with different medications, only patients who had been receiving clozapine as their primary treatment for schizophrenia were included in the study. Adjunct medications such as anticholinergics, antidepressants and anxiolytics were documented. Considerable efforts were made to match the patient group and control group on age and sex. Nineteen non-patient volunteers who were not receiving any medications and who did not have a history of psychiatric illness participated in this study as normal controls. For inclusion in the study, all participants were required to detect each test frequency (5%, 10%, 20%

Δf) used in experimental conditions at an intensity of 20dB sound pressure level (SPL) or lower, indicating normal hearing. Participants with a history of major head injuries, serious medical problems, neurological disorders and alcohol or substance abuse/dependencies were excluded. Intellectual functioning was estimated using the Weschler Test of Adult Reading (WTAR: The Psychological Corporation, 2001) and the Information subtest of the Weschler Adult Intelligence Scale-III (WAIS-III: Wechsler, 1997). Immediate auditory attention was evaluated using the Digit Span subtest of the Weschler Adult Intelligence Scale-III (WAIS-III: Wechsler, 1997).

2.1.3 Stimuli

Auditory stimuli (75dB) were presented binaurally through headphones while participants watched a pre-selected movie. Each deviant (i.e. 5%, 10%, 20% Δf ; 50 ms and 100 ms) was incorporated into a separate auditory oddball sequence. Each of the three pitches in the oddball sequences were comprised of 3 separate blocks, with standard and deviant tones in each block being presented in random order. Each block consisted of 560 stimulus trials: 95% probability of standard tones (532 standard tones) and 5% probability of deviant tones (28 deviant tones). A total of 1680 stimulus trials per deviant condition (i.e., 1596 standards and 84 deviants) were presented. Stimuli were presented at an inter-stimulus interval of 300 ms.

For the frequency deviant conditions, all tones were 50 ms in duration (10 ms rise and decay). Standard tones were 1000 Hz and deviant tones were 1050 Hz in 3 blocks (5% Δf), 1100 Hz (10% Δf) in 3 blocks and 1200 Hz (20% Δf) in 3 blocks.

For the duration deviant conditions, all stimuli were 1000 Hz. Standard tones were 100 ms and deviant tones were 50 ms in 3 blocks. The reverse order was presented in an additional 3 blocks (i.e., standard = 50 ms; deviant = 100 ms).

2.1.4 Procedure

Testing was carried out in the morning following over-night abstinence of aspirin, anti-histamines, herbal drugs, alcohol, caffeine-containing substances and cigarettes. Prior to the formal recording session, a descending method of limits was used to establish normal hearing thresholds for each participant. This involved presenting tones (50 ms and 100 ms in duration) at a descending intensity of 5 dB beginning at 90 dB and ending at 20 dB for each of the test frequencies (i.e., 1000 Hz, 1050 Hz, 1100 Hz & 1200 Hz). Participants were instructed to respond verbally to each tone. It was a necessary requirement that participants were able to identify the tones. Upon confirmation of adequate hearing, each participant was seated in a sound attenuated, electrically shielded room where they were acclimated to the testing apparatus and procedures. Electrodes were then applied. Once acceptable impedance levels for all electrodes were established, headphones were placed on the participant's head. Participants were specifically instructed to watch the movie and to ignore all tones. Participants were given a 2-3 minute break period in between stimulus blocks. It took approximately 12-15 minutes to complete all 3 blocks per deviant condition. The entire recording session for Experiment 1 took approximately 1 hour and 15 minutes. Block sequence (Latin Square) was randomized for all participants.

2.1.5 Recording

EEG was recorded from tin electrodes applied to 3 midline sites (Fz, Cz and Pz), and referenced to linked electrodes on left and right earlobes. A ground electrode was attached to the forehead. Vertical (VEOG) and horizontal (HEOG) electro-oculographic activity was recorded with electrodes placed on supra orbital ridge and outer cantus of the right eye. All electrode impedances were kept below 5 k Ohms. EEG was recorded with a band-pass filter of 0.1 – 30.0 Hz and analog-to-digital sampling (512 Hz) was carried out on-line for an 800 ms sweep beginning 50 ms before stimulus onset. Digital data was stored on disk for later off-line ERP processing and analysis. A computer program statistically corrected EEG epochs for eye movement and blink artifact using an algorithm operating in the time and frequency domains (Woestenburg, Verhaten & Slangent, 1983), and excluded individual corrected sweeps from any site that displayed EEG voltage in excess of $\pm 50 \mu\text{V}$ from further analyses. A minimum of 40 artifact-free correctly detected deviant stimulus sweeps per condition was required to retain a participant's ERP averages in the final analysis (see Tables 6 and 7 for means and standard deviations of sweeps for each group across each condition). The MMN at each scalp site was obtained by digital point-by-point subtraction of the averaged ERP waveform to standard tones from the averaged ERP waveform to deviant tones (Figure 1). Based on inspection of the grand averaged waveforms, MMN amplitude and latency for all conditions was defined as the peak negativity occurring during the 80-220 ms latency range in the difference waveform (i.e. deviant minus standard waveform), post

stimulus onset. Only data (i.e., latency and amplitude) derived from Fz, the site of maximum amplitude, were subjected to statistical analyses.

2.1.6 Analysis

All statistical analyses were performed using SPSS (Statistical Package for Social Sciences, 14th Edition). A Mixed Analysis of Variance was used to determine whether there were between-group or across-condition differences in the number of sweeps obtained. Diagnostic group served as the between group factor, while frequency deviants (5%, 10% & 20% Δf) or duration deviants (50 & 100 ms) served as the within group factor.

The amplitude and latency of the MMN were analyzed together using Doubly Multivariate Analysis of Variance (dMANOVA), with diagnostic group (schizophrenic vs. control) serving as the between group factor and frequency deviants (5% Δf , 10% Δf & 20% Δf) or duration deviants (50 ms, 100 ms) as the within group factor. The term “Doubly” multivariate refers to a repeated measures variable(s) in addition to multiple dependent variables. Significant effects ($p < .05$) were followed up with univariate analysis of variance (ANOVA) and pairwise t-tests.

Independent sample t-tests were used to test whether there were significant group differences on demographic variables such as age and education, and on two measures of intellectual functioning (i.e., reading and factual knowledge) and digit span performance.

Pearson Product Moment Correlation (Pearson's r) coefficients were used to assess the relationship between MMNs, medication dosage, psychopathology ratings and digit span performance.

2.2 Results

2.2.3 Participant Characteristics

Demographic and clinical characteristics of the participants are presented in Table 5. An independent t-test revealed a significant age difference between the patient group and the control group [$t(38) = -3.6, p = .001$]. While the patient group was significantly older than the control group, there were no significant correlations between age and MMN latency or MMN amplitude across all conditions in either group. In addition, age was not a significant covariate in the frequency deviant dMANOVA [$F(2,36) = 1.45, p = .409$] or in the duration deviant dMANOVA [$F(2,36) = 1.367, p = .268$]. The group x age interaction was also non-significant in both dMANOVAs. Given these non-significant findings of age, it was excluded from any further analyses.

There were no significant differences between the groups in years of education ($[t(38) = -.782, p = .440]$), reading ability [$t(38) = -1.804, p = .08$] and factual knowledge [$t(38) = 1.977, p = .056$].

Table 5. Mean ($\pm$ SD) Characteristics of Schizophrenic Patients and Control Participants

Variable	Patients (n=21)	Controls (n=19)
Age	40 (8.0)	32 (7.0)
Yrs. of Education	13 (2.2)	13 (1.5)
WTAR total score	43 (4.5)	40 (4.5)
Info. total score	19 (4.2)	16 (4.8)
Digit Span (forward)	11 (2.2)	11 (2.3)
Digit Span (backward)	6 (2.8)	7 (2.2)
Digit Span (total score)	17 (4.3)	18 (3.7)
Clozapine (mg)	281 (153.1)	
PANSS (positive)	16 (4.9)	
PANSS (negative)	14 (3.6)	
PANSS ^a	27 (6.1)	

^a PANSS General Psychopathology total score

2.2.4 Frequency Deviant Conditions

Table 6 displays the number of standard and deviant EEG sweeps comprising each deviant condition for both patient and control groups. There was no significant difference between patients and controls in the number of EEG sweeps [$F(1,38)=1.922$, $p=.174$], furthermore, there was no significant effect of deviant condition/frequency (i.e. $\% \Delta f$) on the number of sweeps obtained [$F(2,36)=.284$, $p=.754$].

Table 6. Means ($\pm$ SD) of Averaged EEG Sweeps to Frequency Deviants

		Standard	Deviant
Patients	20% Δ f	1204 (372.92)	64 (19.80)
	10% Δ f	1203 (337.79)	63 (18.89)
	5% Δ f	1185 (324.72)	60 (18.10)
Controls	20% Δ f	1330 (361.25)	71 (18.73)
	10% Δ f	1319 (329.46)	70 (16.59)
	5% Δ f	1380 (264.33)	73 (15.46)

A dMANOVA revealed a significant main effect of group [$F(2,37)=10.02, p=.000$]. A follow-up ANOVA revealed that the latency [$F(1,38)=8.361, p=.006$] and the amplitude [$F(1,38)=13.66, p=.001$] of the MMN differed significantly between schizophrenics and controls. As shown in Table 7 and Figure 1, MMN latency was significantly shorter in the patient group compared to the control group, while MMN amplitude was significantly larger in the controls compared to the patients.

While the group x deviant interaction in the dMANOVA was not significant [$F(4,150)=1.305, p=.339$], contrasts analysis revealed a marginally non-significant group x deviant linear trend for MMN amplitude [$F(1,38)=3.81, p=.058$], which suggested that the slopes for amplitude at the end points were different between the patients and the controls.

The within-subjects effect of deviant was significant in the dMANOVA [$F(4,150)=5.627, p=.000$]. ANOVA showed that MMN latency [$F(2,76)=7.13, p=.002$] and MMN amplitude [$F(2,76)=3.443, p=.038$] were significantly different across the

frequency-change deviants. Bonferroni-corrected pairwise comparisons for latency [$p=.001$] and for amplitude [$p=.04$] showed a significant difference between 20% Δf and 5% Δf .

Table 7. Mean ($\pm$ SD) Peak MMN Amplitudes and Latencies at Fz to Frequency Deviants

	Amplitude (μ V)	Latency (ms)
Patients (n=21)		
20% Δf (1200 Hz)	-2.02 (1.8)	138.29 (40.0)
10% Δf (1100 Hz)	-2.14 (1.6)	159.30 (37.6)
5% Δf (1050 Hz)	-1.83 (1.2)	159.48 (36.2)
Controls (n=19)		
20% Δf (1200 Hz)	-4.65 (2.6)	156.17 (34.3)
10% Δf (1100 Hz)	-4.13 (2.8)	172.00 (25.0)
5% Δf (1050 Hz)	-3.30 (2.1)	187.62 (24.7)

Figure 1. Grand-averaged Fz-derived MMNs to a) 20% Δf , b) 10% Δf , c) 5% Δf at FZ in Controls and Patients

2.2.5 Duration Deviant Conditions

Table 8 displays the number of EEG sweeps per ERP average for short and long duration deviant conditions in the patient and control group. There was no significant difference between patients and controls in the number of EEG sweeps [$F(1,38)=1.876$, $p=.180$], furthermore, there was no significant effect of deviant condition (i.e. duration change) on the number of sweeps obtained [$F(2,36)=.750$, $p=.392$].

Table 8. Means ($\pm$ SD) of Averaged EEG Sweeps to Duration Deviants

		Standard	Deviant
Patients	short	1254 (295.07)	64 (17.38)
	long	1236 (310.53)	64 (16.13)
Controls	short	1385 (239.18)	72 (15.00)
	long	1364 (330.13)	71 (17.08)

As illustrated in Table 9 and Figure 2, A dMANOVA revealed a significant main effect of group [$F(2,37)=11.64$, $p=.000$]. A follow-up ANOVA revealed that the amplitude [$F(1,38)=94.58$, $p=.0001$] of the MMN differed significantly between schizophrenics and controls. MMN amplitude was significantly larger in the control group compared to the patient group. Although MMN latency was shorter in schizophrenics compared to controls, group differences did not achieve statistical significance [$F(1,38)=3.36$, $p=.074$]. Although a significant main effect of deviant was demonstrated in the dMANOVA [$F(2,37)=4.09$, $p=.025$], follow-up univariate tests for

amplitude [$F(1,38)=2.69, p=.109$] and latency [$F(1,38)=3.57, p=.067$] were non-significant.

Table 9. Mean ($\pm$ SD) Peak MMN Amplitudes and Latencies at FZ to Duration Deviants

	Amplitude (μ V)	Latency (ms)
Patients (n=21)		
Short (50 ms)	-1.09 (1.7)	169.86 (32.2)
Long (100 ms)	-2.19 (2.1)	158.55 (39.1)
Controls (n=19)		
Short (50 ms)	-3.72 (1.8)	184.74 (30.7)
Long (100 ms)	-3.92 (1.9)	169.54 (19.4)

2.2.6 MMN and Clozapine

The Pearson Product Moment Correlation analysis performed between MMN amplitude to the 20% Δ f, 10% Δ f and 5% Δ f, and clozapine dose yielded significant correlations between clozapine and MMN amplitude to the 20% frequency deviant ($r=.59, p=.01$) and between clozapine and MMN amplitude to the 10% frequency deviant ($r=.58, p=.01$). No significant correlations were observed between MMN latency to the 3 pitch changes and clozapine dose.

A significant correlation was found between clozapine dose and MMN amplitude to the long duration deviant ($r=-.51, p=.032$). Similarly, a significant association between MMN latency to the short duration deviant and clozapine dose ($r=-.58, p=.011$) was also uncovered.

Figure 2. Grand-average Fz-derived MMNs to a) short duration (50 ms), and b) long duration (100 ms) deviants in patient and control groups.

a)

b)

2.2.7 MMN and Psychopathology Ratings

Correlational analyses were performed comparing MMN amplitude and latency to the total score for the positive symptoms scale, the total score for the negative symptoms scale and the general psychopathology total score.

No significant correlations were revealed between MMN amplitude or MMN latency and psychopathology ratings in any of the deviant stimulus conditions.

2.2.8 Intellectual and Digit Span Performance

Independent t-tests were used to establish whether the patients and the controls differed on two measures of intellectual performance (i.e., a test of adult reading recognition and a test of factual knowledge) and on a digit span test. No significant differences were obtained between the groups on any of these measures.

Correlational analyses yielded only a few significant associations between MMN and intellectual and digit span performance (MMN latency 10% Δ f and digit span total score $r=-.57$, $p=.007$). Only a few significant correlations were obtained between MMN and reading ability (MMN latency 5% Δ f and WTAR). There were no significant correlations between MMN amplitude and latency, and age and years of education.

2.3 Discussion

The purpose of the present study was to replicate previous reports of aberrant acoustic sensory memory impairment in schizophrenia as indexed by abnormal frequency and duration MMNs in schizophrenia. A comprehensive literature review of the MMN-schizophrenia research to date revealed that the vast majority of studies examined MMN response to only one type of deviant (i.e., one frequency or one duration deviant). Three studies were identified that employed more than one MMN-eliciting deviant condition in their experimental design: Javitt et al. (2000) and Umbricht et al. (2003) examined a single frequency and a single duration deviant, while Michie et al. (2000) examined one duration deviant and two frequency deviants. Thus, a unique feature of the current study was that MMN response to multiple types of deviants, three frequency deviants and two duration deviants, were examined in the same sample of schizophrenic patients.

Examination of MMN response to multiple types of duration and frequency deviants speaks to a central issue in the MMN-schizophrenia literature of whether abnormal MMN response to duration deviants is more robust than abnormal MMN response to frequency deviants (Mitchie et al., 2000). Creating novel experimental designs that allow for multiple deviants to be examined (rather than typical single-deviant paradigms) in the same sample of individuals is advantageous not only from a statistical perspective in that error variances due to individual differences are statistically minimized, but also in that these types of paradigms may better elucidate whether abnormal MMN in schizophrenia is a generalized vs. focal impairment in auditory sensory memory change detection.

The current mass of empirical literature suggests that abnormal MMN to frequency deviants is a less robust finding than abnormal MMN response to duration deviants. This contention is supported by a recent meta-analysis of MMN studies in schizophrenia. Umbricht and Krljes (2005) reported an overall effect size of 0.99 for differences in MMN amplitude between schizophrenic patients and normal controls, but a smaller mean effect size for frequency MMN than for duration MMN. The effect size difference between MMN frequency and MMN duration was not statistically significant. They also reported that in three studies that examined MMN frequency and MMN duration in the same sample of schizophrenics (Javitt et al., 2000, Mitchie et al., 2000, Umbricht et al., 2003), the mean effect size for duration deviant MMN amplitude was more than twice as large than for the mean effect size for frequency deviant MMN amplitude. Despite this apparent inequality in effect size between MMN frequency and duration deviants, the reported differences did not achieve statistical significance. This meta-analysis also revealed that the largest effect sizes for frequency MMN were observed in studies that utilized deviants that were 10% or less of that of the standard. In contrast, duration-MMN effect sizes were largest when larger duration deviants were employed.

Effect sizes obtained in the current study (Table 10) appear much smaller than those reported in Umbricht and Krljes's (2005) meta-analysis, although the pattern of effect size across frequency and duration deviants is similar in some respects. The extent of differences in effect sizes obtained in the present study compared to those reported in Umbricht and Krljes's meta-analysis may reflect differences in calculations used to obtain effect sizes. Effect sizes derived by Umbricht and Krljes were derived using

modified variance formulas. Also, a random effects model was used to calculate the overall effect size and in studies where means and standard deviations were not available, they were replaced with alternate values (see Umbrecht and Krljes's original text for details). Effect sizes in the current study were obtained using the GLM function in SPSS.

Table 10. Estimates of effect size

	Effect size
Overall	.38
Frequency	.26
Duration	.38
20% Δf	.27
10% Δf	.17
5% Δf	.17
Short duration Δ	.37
Long duration Δ	.16

The overall effect size (i.e., MMN to all 5 deviant stimuli) obtained in the present study was .38. According to Cohen's (1988) effect size conventions, this value suggests a moderate separation between schizophrenics and controls in MMN amplitude across 5 types of deviant stimuli. Statistically, it represents the extent that the group distributions do not overlap. When effect sizes were generated for combined frequency deviant conditions and combined duration deviant conditions separately, a larger effect size was obtained for duration (.38) than for frequency (.26). This pattern is in line with findings from Umbrecht and Krljes's meta-analysis and suggests that the magnitude of MMN

amplitude difference between schizophrenics and control subjects is larger for duration MMN than for frequency MMN. Effect sizes obtained for each deviant condition individually revealed that of the 5 deviants employed in the present study to elicit the MMN, the short duration deviant (i.e., 50 ms) produced the largest effect size (.37), while the 10% Δf and the 5% Δf conditions generated the smallest effect size (.17).

The findings from the current study replicated previous reports of abnormal MMN in schizophrenia. MMN amplitude to frequency and duration deviants was significantly reduced across the 20% Δf , 10% Δf and 5% Δf conditions and in the short and long duration deviant conditions in schizophrenics compared to the controls. Although the group by deviant interaction was not significant, a marginally non-significant group by deviant linear trend ($p=.58$) was noted in the frequency analysis. This finding suggests differences in the linear slope between the groups as a function of changes in MMN amplitude to frequency deviants. Contrary to the original hypotheses, a significant group effect of MMN latency was observed. MMN latency was significantly shorter in the schizophrenic group compared to the control group across the frequency deviant conditions. Although, the schizophrenics also displayed shorter MMN latency in the duration deviant conditions compared to controls, differences did not achieve statistical significance.

The results obtained from the present study do not support an exclusive deficit in the processing of temporal features of auditory events. Rather, the present results suggest a more generalized deficit affecting both pitch and duration processing of acoustic change detection. This notion is supported by the observation that similar (i.e., non-significant t-

tests) MMN amplitudes were elicited to frequency and duration deviants in schizophrenics. Moreover, although the mean difference in MMN amplitude between schizophrenics and controls was marginally greater for MMN to duration deviants than MMN to frequency deviants, this difference was not statistically significant.

Thus overall, similar attenuation of MMN amplitude to frequency and duration suggest the presence of a more generalized rather than a focal impairment in pre-attentive auditory information processing in schizophrenia. Findings from the present study suggest that individuals with schizophrenia do not experience the same level of automatic cortical activation in response to new or unexpected changes in temporal and pitch processing.

The expected pattern of increasingly larger MMN amplitude with greater deviant frequency change was observed in the control group: MMN amplitude to frequency deviants increased in a linear fashion as the pitch separation between the standard stimuli and deviant stimuli increased (i.e., $20\%\Delta f > 10\%\Delta f > 5\%\Delta f$). This pattern of amplitude change is consistent with Näätänen's (1990) "memory trace hypothesis" of the MMN. According to this theory, the discharge of neural activity generated by the detection of a mismatch between the memory trace of the repetitive standard and irregularities in the incoming stimuli is enhanced as the degree of deviance is increased. Increasingly discrepant changes detected in the comparison process of sensory information creates a larger signal that results in a stronger mismatch detection, which subsequently results in larger MMN amplitude.

Unlike the linear effect observed in the control data, the patient group did not demonstrate this typical pattern of MMN response to frequency deviants. Rather, the schizophrenics showed a flat response across the three frequency change conditions. This observation speaks to the profile of MMN dysfunction in schizophrenia. It suggests that not only do MMN deficiencies manifest themselves in an overall reduction in mismatch amplitude, but also, that the mismatch process itself is insensitive to changes in the magnitude of the deviant stimuli. The schizophrenics' mismatch system does not differentially respond to auditory change as it does in normal controls. Findings from Javitt et al. (1998) which were subsequently confirmed by Shelley et al. (1999) further suggest that although schizophrenics differentially respond to changes in deviance probability they are responsive to a lower degree and they are no more affected than controls by alterations in the inter-stimulus interval.

In sum, the profile of MMN dysfunction in schizophrenia appears to reflect a pre-attentive sensory information processing system that performs at an attenuated level of functioning, that is not differentially impacted by changes in degree of deviance, and that responds at a lower rate of maximal MMN amplitude to changes in deviance probability.

There are several possible explanations for why the mismatch system in schizophrenia seems unable to generate appropriate mismatch signals. The answer to this question may lie in the hardware of the mismatch generator itself in that the maximum signal capable of being emitted from the mismatch signal generator may be inherently attenuated due to abnormalities in the underlying neuronal activity. The MMN neural generator process may be defective due to some unknown neuronal mechanism that renders it unable to

elicit signals of sufficient magnitude, resulting in attenuated MMN amplitude.

Alternately, a dysfunction may lie in the comparator process itself, which detects the MMN. Perhaps the “information (irregular sensory change)” collected during the mismatch process is not sufficiently retrieved or processed in an efficient manner.

Abnormal MMN may be related to the underlying processes on which its generation is dependent on, rather than to deficient signal transmission during the mismatch detection process. It has been argued that deficient sensory memory processes underlie MMN abnormalities. Sensory information extracted during the encoding phase of sensory registration may be organized in such a disordered and/or in a loosely way that it compromises the integrity of the mismatch response (Javitt et al., 1995).

The question of what abnormal MMN in schizophrenia suggests for pre-attentive auditory information processing and its functional significance to attention-controlled cognitive functions is obviously quite complicated. From a very general perspective, MMN impairment suggests that schizophrenics do not experience the same level of automatic cortical activation in response to new or unexpected events. There appears to be dysfunction during the early stages of cortical information processing, at the level of the auditory sensory cortex, perhaps extending to the cellular level. Impairment in this area of the brain is consistent with MRI evidence of reduced superior temporal gyrus volume (Barta, Pearson, Powers, Richards & Tune, 1990) as well as volume reduction in the middle and inferior gyri (Onitsuka et al., 2004).

From another general perspective, abnormal MMN suggests deficient auditory sensory memory processes. Schizophrenics may not be able to efficiently extract, encode and

retrieve sensory information, which in turn compromises the integrity of the mismatch detection system. The transient memory traces of sensory information may be encoded in a disorganized or in a loosely organized way such that when the automatic deviance detector system responds to an irregularity (in an otherwise repetitive standard environment); the signals emitted are also abnormal. However, the ability to maintain sensory memory traces once they are formed appears to be intact since various studies have demonstrated that schizophrenics are no more affected than controls by changes in the interstimulus interval between standard and deviant stimuli (Javitt et al., 1998; Shelley et al., 1999). From a functional perspective, deficient MMN may underlie some of the negative features of schizophrenia including lack of goal-directed behaviour, social isolation and lack of interest (Javitt et al., 1995). In normal conditions, as the auditory cortex maintains transient neural representations of background environment auditory events and change is detected, and a series of neuronal events occurs that leads to a shift in attention toward the source of novel events, causing a distraction effect (Schröger, 1996). This process may ultimately relate to a wide range of behavioural functions. Abnormal MMN may signify that schizophrenics are at a disadvantage to respond appropriately to auditory environmental changes.

As discussed in the introduction of this paper, abnormal auditory sensory memory processes have also been demonstrated behaviourally using tone-matching paradigms. On average, a difference of 20% between test and reference tones is required for schizophrenics to perform equally as well controls at a 5% difference between tones (Javitt et al., 1998; Strous et al., 1995). Javitt et al. (1998) observed that similar MMN

amplitudes were generated by schizophrenics at a 20% Δf tone-matching rate relative to controls at a 5% Δf level of tone-matching performance. They suggested that abnormal tone-matching performance parallels deficits in MMN generation. Increased threshold for tone discrimination in schizophrenics lends support to the contention that information in underlying transient neural memory traces is extracted and encoded in an imprecise way. Subsequently, additional information (i.e. easier task demands) is needed for schizophrenics to accurately identify differences in rapidly presented auditory stimuli. In another type of fast-paced auditory discrimination task, the AX-Continuous Performance Task (AX-CPT), schizophrenics repeatedly perform significantly poorer than control subjects. Although accurate performance on this task relies mainly on activation of the prefrontal cortex, brief memory stores of sensory information are required to correctly identify differences in transiently presented tones (Javitt, Shelley, Silipo, & Lieberman, 2000).

The schizophrenic group showed significantly shorter MMN latency in the frequency deviant conditions compared to controls and demonstrated a trend towards faster latency in the duration deviant conditions as well. MMN latency has not played a significant role in the schizophrenia-related MMN studies. A review of the literature revealed a minority of studies that commented on MMN latency and the findings of these studies were inconsistent. For example, MMN latency to frequency deviants was reported to be significantly longer (Shutara et al., 1996), significantly shorter (Umbricht et al., 2000) and no different from controls (Javitt et al., 2000). The latency of the MMN provides an index of the speed from stimulus onset at which the mismatch detection process occurs.

Shorter latencies in the schizophrenic group suggest that irregularities in an otherwise repetitive standard environment were detected more quickly than in the control group. It is unclear why the schizophrenics processed auditory deviance more quickly than the controls in the current study. In an effort to speculate, shorter MMN latencies may reflect deficiencies in the depth of automatic information-processing processes. Shorter latencies are typically interpreted as reflecting faster, more efficient stimulus detection, however in the present context, shorter latencies may be indicative of a processing system that is superficial, where information is scanned rather than extensively processed. Thus, information processing occurs only on a very “surface” level, rather than being subjected to in-depth, prolonged processing that would subsequently result in longer latencies. This deficient evaluation process may also render the system apt to potentially “skip” stages involved in the stimulus evaluation process.

An entirely different approach to understanding the present finding of shorter MMN latencies may be related to the “informational overload” hypothesis of schizophrenia. This theory suggests that abnormal selective filtering of sensory information leads to an influx of both relevant and superfluous information that is poorly filtered which creates a state of information overload. A potential compensatory mechanism to cope with excessive amounts of sensory information may be in place that processes sensory information at a much faster rate, which consequently, may account for shorter MMN latencies observed in the present sample of schizophrenics.

Schizophrenia-related deficits in MMN may be attributable to disturbances in NMDA (N-methyl-D-aspartate) glutamatergic neurotransmission within the auditory sensory

cortex (Javitt & Zukin, 1991). NMDA receptor activation is fundamental to learning and long-term memory formation. There is evidence from animal and human studies implicating deficient NMDA receptor functioning in MMN deficits. For example, ketamine and other antagonists of the NMDA- type glutamate receptors induce psychotic behaviours in humans that resemble symptoms of schizophrenia. Javitt, Steinschneider, Schroeder and Arezzo (1996) reported that local infusion of NMDA antagonists directly into the auditory cortex markedly reduced MMN generation in awake monkeys. In healthy volunteers, Umbricht and colleagues (2000) reported that subanesthetic doses of ketamine significantly reduced MMN amplitude to frequency and duration deviants. In addition, the effects of ketamine on MMN amplitude were selective; the amplitude of other ERP potentials (i.e., N100 and P200) was unaffected. It has been noted that dendritic spines are the primary location of NMDA receptors (Nimchinsky, Sabatini, & Svoboda, 2002). Dendritic abnormalities including loss of spines (Umbricht & Krljes, 2005) have been identified in schizophrenia, thus the interaction of these two variables may result in deficient signal transmission through NMDA receptors which results in abnormal sensory memory process, manifested electrophysiologically by MMN deficits (Umbricht & Krljes, 2005).

Identification of moderator variables that may impact on the expression of MMN deficits in schizophrenia is an active area of research. According to the meta-analysis undertaken by Umbricht and Krljes (2005), a multiple regression model with various independent variables including type of deviant stimulus (i.e. frequency vs. duration), deviant stimulus probability, degree of standard-deviant differences, sex ratio and

duration of illness, and with effect size as the dependent variable, was not significant.

This observation suggests that these independent variables do not significantly contribute to differences in MMN amplitudes between schizophrenics and controls. Further to the impact of moderator variables on MMN response in schizophrenia, there is little evidence in the literature to support a relationship between medication status and MMN amplitude. Studies have shown that clozapine and haloperidol have no impact on abnormal MMN (Umbricht et al., 1998); this study, as with other similar studies (Umbricht et al., 1999) which commented on the relationship between MMN and anti-psychotic medications utilized pre-post designs and reported on differences before and after treatment rather than reporting correlational statistics. The present study revealed a positive correlation between clozapine dose and MMN amplitude to the 20% and 10% frequency deviants. These findings may suggest that larger doses of clozapine enhance MMN amplitude, however replication studies are needed and the functional significance remains to be determined through future behavioural studies. With respect to age, there is no evidence to support a relationship between age and MMN amplitude or latency in adult samples of schizophrenics (Umbricht & Krljes, 2005). In their meta-analysis, Umbricht and Krljes (2005) reported that in 34 studies, the mean effect size was almost equal in patients above and below a mean age of 36 years. There were no correlations found between MMN indices and age in the present study.

There is little evidence to support a relationship between MMN and positive symptom scales of schizophrenia. There is considerable support however in favor of an association between MMN and negative symptoms. Umbricht and Krljes (2005) reported six studies

that revealed significant inverse correlations between MMN and negative symptom scores. The present study did not find any significant correlations between MMN and ratings of positive and negative symptoms.

There are several limitations of the present study that should be noted. There was a significant age effect between the groups; the patients were significantly older than the controls. Statistical measures were taken to ensure that age was not a significant covariate (see results section). As previously mentioned, Umbricht and Krljes (2005) reported no effect of age on MMN amplitudes in adult samples of schizophrenics. There were significantly more male schizophrenics in the present study. Gender has been shown to have no impact on MMN (Kasai et al., 2002). Moreover, it is not uncommon for studies in schizophrenia to have a preponderance of male participants given that schizophrenia is more common in males than females (Nicole, Lesage, & Lalonde, 1992). Given that only community dwelling, stable chronic schizophrenics were included in the present study; the generalizability of the current findings is questionable. However, given that many other studies have been undertaken with several different samples of schizophrenics, including first-episode patients, prodromal and chronic patients, as well as with samples at genetic risk, it seems that MMN deficits extend to all variants of schizophrenia. All patients who participated in this study received clozapine as their primary treatment for schizophrenia. Most clinical research is plagued with issues regarding the effects of medication. Umbricht and colleagues showed that clozapine had no effect on MMN amplitude in chronically-medicated schizophrenics (Umbricht, Javitt, Novak, Pollack, Liberman, & Kane, 1998). Other studies have also demonstrated that

other anti-psychotic medications such as haloperidol (Umbricht et al., 1998), risperidone (Umbricht et al., 1999), and olanzapine (Korostenskaja et al., 2005) have no impact on MMN amplitude generated in schizophrenics. In addition, MMN deficits have been identified in medication-free schizophrenics (Catts et al., 1995). In light of the correlational findings between MMN amplitude and clozapine revealed in the present study, further research may be necessary to better delineate the relationship between pre and post treatment with anti-psychotic medication on MMN amplitude as well as the relationship between varying medication dosages and MMN response.

Future MMN research in schizophrenia would benefit from several lines of investigation. MMN to multiple types of deviants needs more in-depth investigation. Experimental paradigms should be expanded and modified to include deviants other than frequency and duration, such as more complex auditory change and language functions. Studies should strive to obtain a more precise understanding of deficits in early cortical stages of information-processing, as indexed by the MMN in schizophrenia. However, a significant limitation to studying MMN to multiple deviants is that recording conditions become quite lengthy using the traditional “oddball” paradigm, which only incorporates a single type of auditory change. Thus, measurement of multiple deviants may not be feasible in many different clinical populations, especially those with motivational or attentional deficiencies. Recently, Näätänen, Pakarinen, Rinne, & Takegata (2004) developed a new recording paradigm where MMN to multiple types of deviants (5 different sound changes) can be evaluated in the same sequence, thus substantially reducing the recording time. Empirical testing of this new paradigm showed that it is just

as effective as the original, one deviant paradigm in eliciting the MMN and in addition, produces MMN amplitudes comparable to those yielded with the traditional paradigm. Näätänen and colleagues remarked that this new paradigm is suited to providing “multi-attribute profiles” of sound discrimination. Further research in this area would also benefit from additional efforts to better understand the relationship between everyday functional relationship and clinical presentation and abnormal auditory sensory memory processes. To date, only two studies have commented on the relationship between everyday functionality and the MMN.

It has yet to be determined what impact aberrant MMNs have on higher-ordered information processing in schizophrenia. Investigations into the relationship between abnormal, early stage sensory memory processing deficits and, task efficiency and attention are an interesting new area of research. A better understanding of the contribution of dysfunctional elementary sensory processes to disordered complex cognitive processes may be beneficial in elucidating novel mechanisms involved in the pathological clinical presentation of schizophrenia. Thus, the objective of the next two experiments was to investigate a possible relationship between aberrant MMNs to frequency (Experiment 2) and duration (Experiment 3) deviants, and behaviour (i.e., task proficiency and ERP deviance-related effects) in schizophrenics using a novel distraction paradigm.

3.0 Distraction

Switches in attention can occur automatically, drawn by external cues in the environment or they can be intentionally driven. Involuntary shifts in attention are a fundamental biological mechanism in that they direct attentional resources to potentially important events that are not currently in the realm of attention. In experimental settings, involuntary attentional switching is most frequently examined by investigating the processes underlying distraction and is indicated both behaviourally and in deviance-related electrophysiological measures.

Distraction in the auditory modality can be initiated at the level of pre-attentive sensory memory by evoking involuntary shifts in attention triggered by acoustic change in an otherwise repetitive, standard background. Neural detection of acoustic change based on an automatic, sensory memory based mismatch processes disrupts ongoing task relevant processing, thus giving rise to observable distraction effects (Berti & Schröger, 2001). The MMN ERP is the first stage in a series of brain processes that give rise to involuntary attention switches and to the conscious detection of auditory deviance. Frontal brain regions involved in MMN generation receive information from the sensory-specific, temporal brain regions of the MMN generator mechanism eliciting a call to involuntarily orient to a potentially significant background event that is currently outside the focus of attention (Schröger, 1997). Schröger's (1997) novel distraction paradigm allows examination of a sequence of neuroelectrophysiological measures of deviance processing including the MMN, P3a and RON in order to investigate in detail the response to unattended, task-irrelevant acoustic features. The neural processes

underlying these ERP components are assumed to reflect the processing stages involved in involuntary attention switching. Specifically, in a task where volunteers are required to respond to task-relevant auditory features, the MMN is a correlate of an automatic, pre-conscious detection of task-irrelevant auditory deviance, while the P3a is interpreted as reflecting a conscious attentional shift towards auditory deviance, and the RON is proposed to index the subsequent re-orienting of attention following deviance-induced distraction.

3.1.1 The P3a ERP

The event-related P3a component, frequently captured during auditory oddball detection task paradigms has been used to tap distraction vulnerability in schizophrenia. The P3a ERP sometimes referred to as the “novelty P3a” (Friedman, Cycowicz, & Gaeta, 2001), is an electrophysiological index of involuntary attention shifting. It is typically elicited in a three-tone auditory oddball paradigm where low-probability target stimuli are presented against a background of high probability standard stimuli and occasional, unexpected and unusual novel stimuli (e.g., dog barks, whistles, bells). Elicitation occurs when the attentional focus required for the primary discrimination task is interrupted by an infrequent non-target stimulus event, generating activation of an attentional switching mechanism. Its amplitude is an index of the amount of resources directed to stimulus processing and its latency is a measure of stimulus evaluation time.

The P3a has been described in relation to the orienting response (OR) initially described by Sokolov (1963). The OR is a biological survival mechanism that brings

unanticipated or unpredictable stimuli into perceptual awareness and is measured neuroelectrophysiologically by the P3a (Friedman, Cycoxicz, & Gaeta, 2001). A hallmark feature of the OR is its rapid habituation (Lynn, 1966); the P3a has also shown to be highly habituated (Courchesne, 1978). The earlier, central maximum “novelty” processing P3a is differentiated from the later, parietal maximum “target” processing P3b; although the P3b is evoked by infrequently occurring events, these events unlike the P3a, are task-relevant or involve a decision in order to elicit this component (Friedman, Cycoxicz, & Gaeta, 2001).

Initial conceptualization of the P300 waveform was that of a unitary neural process mediated by conditions of active attention to anticipated, pre-determined infrequently occurring target signals (Sutton, Braren, Zubin, & John, 1965). The psychological correlates were related to attentional resource allocation to task-relevant stimuli, decision-making and updating of working memory. Subsequent studies showed however that a P3 was also elicited by unpredictable changes in a repetitive series of auditory stimuli where the sounds were not designated as targets and were seemingly ignored (Ritter, Vaughan & Costa, 1968; Roth, 1973). These observations led to the notion that the neural processes underlying the orienting response may be involved in P3 generation (Roth, 1973).

To better understand the cerebral processes underlying the P3, Squires, Squires and Hillyard (1975) employed a two-tone paradigm with varying probability intensity and frequency deviants in active (counted target tones) and ignore (reading) conditions.

In the ignore condition, when the stimulus probability was reduced ($p=0.1$), a sharp, late positivity wave occurred between 220 and 280 ms. It was distinguished from a longer latency positive wave that was apparent in active attention conditions only with a peak latency between 310-380 ms. The amplitude of both of these components increased as a function of reduced stimulus probability, particularly with respect to the latter P3. The scalp distribution of the P3a peak amplitude in the ignore condition was largest at the frontal sites, while peak P3b amplitude in the attend condition was maximal at parietal sites. A principal components analysis to determine the extent to which the peaks represented separate underlying cerebral generators showed that the P3a factor was not significantly affected by the attentional task requirements, while the impact of attentional demand was marked for the P3b. Thus the findings of this study supported the existence of two distinct components of the P3 waveforms, the P3a to irrelevant, seemingly ignored stimuli and the P3b to decision-based task-relevant stimuli, which differ in latency, scalp topography and psychological correlates (Squires, Squires & Hillyard, 1975).

In another study designed to disentangle the P3 waveform (Courchesne, Hillyard & Galambos, 1975), complex visual patterns, which were difficult to label, were unexpectedly interspersed within a series of infrequent targets and frequent standards composed of single digits or letters. These authors found that unexpected, novel events were processed differently in the brain compared to pre-determined targets as evidenced by observations that novel stimuli elicited a late positive waveform that peaked at approximately 300 ms and was frontally oriented, and that another late positivity was also identified, however it was elicited by targets and was more parietal in orientation. In

addition, they noted that when a novel stimulus became familiar and predictable, smaller and more posterior P3 waves were elicited. P3a is produced when a demanding stimulus commands frontal lobe attention; P3b is produced when attention resources are allocated for memory updating in association cortex (Fabiani & Friedman, 1995). The amplitude of the P3a elicited by novel, environmental sounds are larger than their P3b target counterparts, and amplitude differences between the P3a and P3b are far more discernable over frontal areas and less obvious across posterior scalp regions (Fabiani & Friedman, 1995).

The neural generators underlying the P3a appear to be located in the frontal lobes (Friedman, Cycowicz, & Gaeta, 2001). Individuals with pre-frontal dorsolateral lesions show significant reductions in P3a amplitude (Knight, 1984). Other brain regions, including the auditory cortex, posterior hippocampus, temporoparietal junction, medial frontal gyrus and anterior cingulate gyrus (Friedman, Cycowicz, & Gaeta, 2001) have also been implicated in generation of the P3a.

P3a and Schizophrenia

The vast majority of P3 studies in schizophrenia report a reduction in P3a amplitude compared to controls (Devrim-Ucok, Keskin-Ergen, & Ucok, 2006; van der Stelt, Frye, Lieberman, & Belger, 2004; Alain, Bernstein, Cortese, Yu, & Zipursky, 2002; Merrin & Floyd, 1994; Grillon, Courchesne, Ameli, Geyer, & Braff, 1990) and some report prolonged latency (Grzell et al., 2000; Merrin & Floyd, 1994). However, one study reported increased P3a amplitude in patients compared to controls (Schall, Catts,

Karayanidis, & Ward, 1999) and a few have found no difference in P3a amplitude between schizophrenics and controls (Kogoj, Pirtosek, Tomori, & Vodusek, 2005; Frodl, Meisenzahl, Muller, Greiner, Juckel, Leinsinger, Hahn et al., 2001). Typically, reports of reduced P3a amplitude were derived from experimental procedures that incorporated very salient stimuli to elicit the P3a. These novel stimuli differed immensely from the background standard and target tones. Whereas background and target tones usually only differed from each other on a single stimulus dimension (i.e., frequency), these novel stimuli included intense noise bursts (Pfefferbaum, Ford, White, & Roth, 1989), environmental sounds (Devrim-Ucok, Keskin-Ergen, & Ucok, 2006), and sounds of varying pitch and dynamic characteristics (Merrin & Floyd, 1994). Multiple hypotheses have been put forth to explain attenuated P3a amplitude in schizophrenia including less efficient reorienting of processing resources from the ongoing task of target detection to auditory change (Mitchie et al., 2002), and an overall reduction in attentional processing resources (Grillon, Courchesne, Ameli, Geyer, & Braff, 1990; Pfefferbaum, Ford, White, & Roth, 1989). Studies that reported normal P3a amplitude in schizophrenia utilized less novel stimuli, including tones that differed on a single feature dimension including pitch (Kogoj, Pirtosek, Tomori, & Vodusek, 2005; Frodl et al, 2001) and duration (Mitchie, Innes-Brown, Todd, & Jablensky, 2002).

One approach not yet employed in the schizophrenia literature is to examine distractibility initiated by auditory mismatch detection based on sensory memory. To measure distraction based exclusively on the MMN, small deviants are needed, which is problematic because with most traditional paradigms, large deviance is needed to elicit

measurable distraction effects. A new paradigm was developed to yield reliable distraction effects with small differences between standard and deviant tones.

3.1.2 ERP Distraction Paradigms

Several ERP paradigms have been developed to investigate the nature of auditory distraction. Typically, these paradigms require fast discrimination of pre-selected targets interspersed amongst a series of high probability standard events, occasionally substituted with a deviant one (i.e., the distracting event). The main measures of interest are performance measures and ERPs to target stimuli preceded either by standard or deviant events. These paradigms are successful in eliciting behavioral effects of distraction including prolonged reaction time and deviance-related ERP effects, including the MMN and the P3a (Schröger, 1996). Typically, ERP/behavioural distraction paradigms utilize targets and distractors that represent discrete, individual events. The type of deviants used to elicit distraction effects range from different modality distractors (Escera, Alho, Winkler, & Näätänen, 1998; Alho, Escera, Diaz, Yago, & Serra, 1997) to same modality distractors (Schröger, 1996). These studies report reaction time increases of approximately 20 ms to targets immediately preceded by a deviant event (compared to targets preceded by a standard event).

3.1.3 Schröger's Auditory Distraction Paradigm

Schröger (1997) developed a novel type of auditory distraction paradigm whereby distractors are embedded directly in target events such that both events (i.e., target and distractors) occur in the same auditory stimulus. In the standard version of this paradigm,

participants are required to discriminate between equal probability auditory tones that differ in duration (i.e. short tones vs. long tones). These equal probability short and long duration tones are embedded with either a high probability standard feature (i.e., standard frequency) or a low probability deviant feature (i.e., deviant frequency). This physical change embedded directly in the task stimuli represents the distractor and has no task relevance (Schröger, 1997). This paradigm has proven successful in evoking consistent behavioral indices of distraction using relatively small changes in the acoustic environment (i.e. $< 10\% \Delta f$) (Schröger & Wolfe, 1998 a,b), and thus is particularly suited to the investigation of distraction initiated by MMN-related processes.

3.1.4 Pre-attentive Activation Model

The pre-attentive activation model (Schröger, 1997) proposes that the MMN is involved in a series of processes that lead to the conscious detection of auditory deviance (see Figure 3, next page). It has been conceptualized as the initial stage in a chain of brain processes leading to involuntary orienting of attention to acoustic environmental changes; a basic system designed to initiate conscious awareness of potentially significant stimulus deviance. The pre-attentive deviance detection system as indexed by the MMN scans the environment for acoustic change in a repetitive background. The activation of the MMN may contribute to the orienting of attention away from the standard environment toward the deviant stimulus (Schröger, 1997).

Figure 3

Schröger's Auditory Distraction Paradigm Task: Duration Discrimination

According to this model, this system extracts information from incoming sensory inputs, compares sensory information representations, detects potential discrepancies, creates proportional mismatch signals and if a variable threshold is surpassed, subsequent neural processes become activated that lead to a switch of attentional focus and to the conscious detection of deviance (Schröger, 1997). The final stage of this model involves a re-orienting of attention from the deviant event back to the primary task (Schröger, Giard, & Wolff, 2000).

This model makes multiple assumptions with regard to the series of stages involved in the elicitation of the MMN (Schröger, 1997) (see Figure 4, p. 87). Firstly, features of the actual auditory sensory input are extracted and encoded into transient sensory

memory representations, referred to by Schröger as “R”. Secondly, a neural representation of the upcoming sensory input is also generated and referred to as “R’”. R’ is based on sensory memory expectations about upcoming auditory events. Schröger describes R’ as “encoding of invariants inherent in the recent stimulation” (Schröger, 1997). Thus a neural model of the to be expected acoustic event is generated. Thirdly, there is a putative, automatic comparison process that continuously compares R and R’, and if a discrepancy is detected (between these two neural representations); mismatch signals proportional to the amount of deviance detected are elicited. And lastly, if the mismatch signals generated are sufficient to exceed a variable threshold, an involuntary shift in attention occurs and the deviant event is consciously detected. The processes underlying the MMN and its elicitation have been conceptualized as the automatic updating of the “acoustic neural model” (Winkler, Karmos & Näätänen, 1996).

According to this model, the sensory memory trace “R” is part of the short auditory store which lasts for approximately 100-200ms, while “R’” is part of the large auditory store maintaining information for about 10-20 seconds (Cowan, 1984). The R and R’ representations of sensory memory are compared on a feature-specific basis (Schröger, 1997), such that two or more features (for example, frequency and location) can be compared in parallel. According to Schröger, outputs from the feature-specific comparisons converge into an integrated mismatch signal.

Figure 4

A Model of Conscious Detection of Deviant Sounds

This model assumes that for an involuntary shift in attention to occur, a variable threshold must be exceeded by integrated mismatch signals. The variable nature of the putative threshold is a function of the attentional demands required for the primary task and the channel separation of task-relevant and task-irrelevant stimuli (Schröger, 1997).

With regard to the primary task burden, in conditions where the attentional demands are low, for example in conditions where the primary task is very simple or where the deviants are consciously attended, the threshold is reduced. Thus, even very small deviants will be able to surpass the threshold. On the other hand, in conditions where heavy demands are placed on the processing resources, for example by a difficult

selective attention task, attentional resources will be more resilient to distraction. In these situations, the threshold to be surpassed to elicit a switch in attention is higher.

Channel separation refers to the degree of physical and/or psychological similarity or difference between targets and distractors (Schröger, 1997). For example, if targets and distractors have similar features (e.g., same modality), they will be processed in the brain by similar attentional/processing filters, thus ending up in the same channel of processing. Engaging the same filters that are activated for processing of target stimuli will interfere with the processing of targets since the distractor will also undergo additional processing. According to Schröger and Wolfe (1998a), these types of stimuli will serve as powerful distractors. In situations where the channel separation between targets and distractors is high, for example, when the features of the deviant are highly divergent than those of the target, (e.g., different modalities), deviant stimuli are more apt to fall outside of the attentional filter that is active for the processing of targets. These types of deviants are more readily dismissed and thus are less likely to trigger an involuntary switch of attention and elicit distraction effects.

3.1.5 MMN and Conscious Detection of Auditory Deviance

There is behavioural and neuroelectrophysiological evidence to support a causal role of the MMN in the involuntary shift of attention and the conscious detection of deviance. Several lines of research support the functional relationship between MMN, attention switches and distraction. For example, in addition to neural activity generated in the supra-temporal cortex, MMN generators receive an additional, secondary contribution

localized to the frontal areas, in particular the prefrontal cortex (Giard, Perrin, & Boucher, 1990). Neural activity localized to the prefrontal cortex is linked to attention (Stuss & Benson, 1985). Moreover, the MMN is often followed by the P3a component, an ERP that is associated with the involuntary orienting of attention to novel external events (Squires, Squires, & Hillyard, 1975) during either passive or active conditions (Courchesne, 1977). Increases in reaction time following a task-irrelevant P3a eliciting tone have been reported (Grillon, Courchesne, Ameli, Geyer, & Braff, 1990). Thus, it appears that the MMN and P3a ERP components reflect different stages in the capture of involuntary attention to distracting events (Escera, Alho, Schröger, & Winkler, 2000). Moreover, the amplitude of the MMN and the behavioural distraction effects induced by task-irrelevant deviants (i.e., slowed reaction time and reduced hit rate in the primary task), increase with larger differences between standard and deviant stimuli (Schröger, 1996; Schröger, Wolff & Giard, 2000).

Additional support for a causal link between MMN and involuntary shifting of attention is derived from observations that the P3a is followed by a fronto-central negative deflection 400 – 600 ms post-stimulus onset in the ERP. This negative deflection, termed the re-orienting negativity (i.e., RON) is proposed to be a neuroelectrophysiological index of re-orienting of attention from distraction back to the primary task. Initial documentation of the RON was provided by Schröger and Wolff (1998b) using Schröger's (1997) auditory discrimination paradigm. The RON was identified exclusively in conditions of distraction: the RON waveform was not present in conditions where the deviancy was task-relevant or when the deviants were ignored

(Schröger & Wolff, 1998b). Schröger et al. (2000) speculated that the underlying mechanisms of the RON might involve prioritizing of task-relevant features as compared to other features of the sensory neural representation. An alternate suggestion is that the RON reflects an inhibition process of distraction.

The amplitude of the RON also increases as a function of the magnitude of stimulus deviance (Berti, Roeber, & Schröger, 2004). Taken together, the involvement of these processes, enhanced RT, and amplitude of the MMN, P3a and RON as related to the size of the distractor supports the existence of a pre-attentive deviance detection system that causes an involuntary attention shift, and the re-orienting away from the distractor back to the primary task (Yago, Corral, & Escera, 2001).

3.1.6 Application of Schröger's Paradigm

Deviance-related performance decrements achieved in this newer paradigm are almost twice as large (approximately 30-50 ms) (Schröger, 1988a,b) as those reported using other distraction tasks (Escera, Alho, Winkler, & Näätänen, 1998; 5-20 ms, Schröger, 1996; 25ms). This is in line with other visual and auditory discrimination studies that reported more pronounced performance decrements to distractors embedded in the same object as the target stimulus, than to distractors presented as distinct entities (Jones & Macken, 1993).

Although the magnitude of deviants employed in this novel paradigm are similar to those used in another distraction conditions (i.e. Schröger, 1996 – 5% & 20% Δf ; Escera et al., 1998 – 10% Δf), it appears that enhanced deviance-related effects are to some

extent mediated by the channel separation between targets and distractors (Schröger & Wolfe, 1998a). By embedding the distractor directly into the target stimulus in this novel paradigm, channel separation is markedly reduced thus evoking large behavioral effects even with small deviants. Behavioural distraction effects elicited by this novel paradigm extended to the individual level (Schröger & Wolfe, 1998a,b; Schröger et al., 2000). In more typical paradigms, which utilized targets and distractors that represented discrete, individual events, reaction time increases of approximately 20 ms to targets immediately preceded by a deviant stimulus were found (Escera et al., 1998; Alho, Escera, Diaz, Yago & Serra, 1997).

In their first published report utilizing this paradigm, Schröger and Wolfe (1998a) documented distraction effects across a range of pitch changes (i.e., 7%, 20% & 40%) in normal subjects. Reaction time was prolonged on average by 50 ms to target stimuli embedded with deviant frequencies relative to targets embedded with the standard frequency. Increases in reaction time were most pronounced to targets embedded with the largest pitch change (i.e. 40%). Hit rate was reduced by approximately 8% and false alarms rate increased on average by 4% when targets were of a deviant frequency. Although false alarms rates were similar in conditions where targets were embedded with standard and small deviant frequencies, the rate of false alarms increased substantially with medium and large deviants. MMN response was elicited to each pitch change indicating that they were sufficiently different from the background environment to elicit mismatch detection. An enhanced P3a response was also elicited to targets embedded with a deviant frequency, however its presence was restricted to the medium (20% Δf)

and large (40% Δf) deviant tones. The N2 ERP component, a negative deflection occurring 100-200 ms post stimulus presentation which is closely coupled to active stimulus evaluation processes (Hillyard & Kutas, 1983), was also only elicited to the medium and large pitch changes. Lack of a P3a response to small deviant tones (7% Δf) suggests that a 7% pitch change was not sufficient to trigger a shift in attention and thus did not undergo further processing as indicated by absence of the N2 waveform.

In an other study, Schröger and Wolfe (1998b) reported that a low probability 10% pitch change embedded in long and short duration target stimuli prolonged reaction time by 36 ms (233 ms vs. 397 ms), across all subjects individually. In this study, participants were subjected to three different experimental conditions: distraction (i.e., original condition; frequency changes were task irrelevant, sound durations were task relevant), attend (i.e., Δf distractors were task relevant) and ignore (i.e., auditory stimuli were completely ignored). In the distraction condition, subjects were required to respond to short duration tones with one index finger while responding to long duration tones with the other index finger. In the attend condition, subjects were required to discriminate between standard and deviant frequencies; while in the ignore condition, participants read a book. MMN was elicited in all conditions, while the N2 and P3a ERPs were only visible in the distraction and attend conditions. This pattern of findings suggest that a 10% frequency change was not sufficient to exceed the threshold required to elicit a shift in attention to the deviant frequency tone in the ignore condition. The RON was observed in the distraction condition only.

The effects of same modality distraction during visual and auditory discrimination performance were examined using this paradigm (Berti & Schröger, 2001). In both conditions, subjects were presented with either equal probability visual and auditory events and were instructed to respond with a button press to long duration targets only. The auditory and visual stimuli were either a standard version or two deviant versions (i.e., standard auditory = 1000 Hz, frequency increment = 1050Hz, frequency decrement = 950Hz; standard visual = triangle in the center of the stimuli, visual deviant = lower left corner, visual deviant = rotated triangle). Behavioral analysis revealed that reaction time to auditory and visual duration discrimination was increased by 22 ms and 16 ms respectively, to target stimuli embedded with distractors (visual or auditory) relative to targets embedded with standard features. These findings indicate that the behavioral effects of distraction are larger in the auditory modality. ERPs to distractors elicited in both modalities produced comparable effects. In both modalities, P3a amplitude was larger to target stimuli embedded with deviant features than to targets embedded with standard features. In the visual modality, an occipital N200 effect was reported, which was deemed equivalent to the MMN recorded in the auditory modality and these potentials were elicited only to stimuli embedded with deviant features. The RON was elicited to both visual and auditory distractors.

The stability of distraction effects obtained using this novel paradigm was recently examined (Schroger, Giard, & Wolfe, 2000). Behavioral and ERP deviance-related effects were reported to be highly stable across two sessions spaced 25 days apart ($r=0.76-0.90$). Clinically, this paradigm has been successfully applied to the study of the

effect of chronic alcohol use on auditory distraction (Jääskeläinen, Schröger, & Näätänen, 1999) and has also been used to examine distractibility in abstinent alcoholics (Ahveninen, Jääskeläinen, Pekkonen, Halberg, Hietanen, Näätänen, Schröger, & Sillanaukea, 2000).

3.1.7 Summary

Attentive processes that result in the conscious experience of an irregular, deviant event may utilize the output of the pre-attentive, memory-based deviance detection system indexed by the MMN. Schröger (1996; 1997) proposed a model for the conscious detection of deviants occurring in discrete repetitive stimulation. This model can be utilized to examine the chain of processes underlying behavioural distraction. A potentially important step in advancing knowledge of the relationship between information processing dysfunction and the psychopathology of schizophrenia is to examine how deficits in early, pre-attentive sensory information processing that are reflected in the MMN impact upon task proficiency and distraction vulnerability in schizophrenia.

Conventional distraction paradigms where task and distracting stimuli represent distinct sensory events (i.e., selective attention tasks), generally require relatively large deviants to elicit clear distraction behavioral effects. However, the use of large deviants introduces the likelihood that other neuronal deviant detection mechanisms, such as a new afferent activation, or a match mechanism based on information stored in long-term memory stores, may underlie switches in attention resulting in distraction effects

(Schröger, 1997). A newly developed auditory distraction paradigm has proven to be successful in eliciting clear behavioral and ERP deviance-related effects even to small changes in the acoustic environment.

5.8 Experiment 2 and Experiment 3: Rationale and Hypotheses

A relevant area of study for schizophrenic cognition is the attentional distraction effects induced by changes in the acoustic environment. Examining the relationship between abnormal, pre-attentive sensory deviance detection and behavioral and ERP measures of task proficiency in schizophrenic patients may yield important clues into the psychopathology of schizophrenia. With the exception of one study (Javitt, Shelley, & Ritter, 2000) that reported on the relationship between reduced MMN amplitude and behavioral performance in a tone discrimination task, the impact of aberrant automatic acoustic change detection processes reflected in attenuated MMNs on higher-order cognitive functions has yet to be investigated.

Schröger's (1997) auditory distraction paradigm has not been applied to the study of schizophrenia and thus the main objective of Experiments 2 and 3 was to use this paradigm to establish to what extent abnormal auditory MMN processes affect distraction vulnerability and task efficiency in schizophrenia. Experimental 2 utilized the traditional version of Schröger's paradigm; employing frequency deviants embedded in short and long equal probability duration tones. A modified version of Schröger's paradigm was used in Experiment 3, wherein long and short duration deviants were embedded in a high vs. low frequency discrimination task.

Using Schröger's auditory discrimination paradigm (1997), distraction effects evidenced both behaviourally and electrophysiologically, and a subsequent re-orienting following distraction, were expected to be observed in Experiment 2 and 3 across both control and patient samples. Specifically, behavioural distraction effects indicated by prolonged reaction time and reduced hit rate to targets embedded with deviants as compared to targets embedded with standards and, electrophysiological indices of distraction, the P3a, and subsequent re-orienting of attention following distraction (the RON) were expected to be observed in the patients' and controls' ERP waveforms.

With respect to the primary hypotheses of Experiments 2 and 3, it was expected that the amplitude of the MMNs would be significantly reduced in the schizophrenic group compared to the control group, suggestive of a deficit in early auditory sensory memory based change detection. As described earlier, Schröger's model (1997) proposes that MMN signals must be of sufficient magnitude to surpass a specific threshold for an involuntary shift in attention to occur. Thus, based on Schröger's model, it was further expected that the amplitude of the P3a and the subsequent RON would be reduced in patients compared to controls, due to low magnitude MMN signals. Low magnitude MMN signals would subsequently lead to reductions in the neural activity of other processes indicated in this model. Moreover, the behavioral distraction effects were also expected to be reduced in patients compared to controls, again as a result of low magnitude MMN signals that minimize the impact of deviance on behavioral distractibility.

4.0 *Experiment 2: ERP and behavioural correlates of auditory distraction induced by frequency deviants in schizophrenics and controls*

4.1 Method

4.1.2 Participants

Twelve controls (10 males) and 11 patients (11 males) from the Experiment #1 participant pool took part in Experiment 2. Informed consent was obtained from each participant. The inclusion/exclusion criteria (for patients and controls), symptoms ratings and auditory screening were the same as in Experiment 1. All patients received clozapine as their primary treatment. Considerable efforts were made to match the patient group and control group on age and sex. Intellectual functioning was estimated using the Wechsler Test of Adult Reading (WTAR: The Psychological Corporation, 2001) and the Information subtest of the Wechsler Adult Intelligence Scale-III (WAIS-III: Wechsler, 1997). Multiple neuropsychological tests were also administered, including a digit span (test of immediate auditory memory), letter-number sequencing (a measure of auditory working memory), the Trail Making Test A (Army Individual Test Battery, 1964), an index of processing speed and lastly, the modified version of the Wisconsin Card Sorting Test (Nelson, 1976), a test of frontal lobe functioning. These tests were administered with the intent of determining firstly, whether there were performance differences between the groups and secondly, to establish whether any of these measures correlated with behavioural (i.e., accuracy or reaction time) and/or electrophysiological indices (i.e., MMN, P3a and RON) of distractibility.

4.1.3 Stimulus Paradigm

Participants were asked to discriminate between two equal probability short (50 ms) and long (100 ms) 1000 Hz (standard) tones. Ten percent of the short and long duration standard tones were replaced by frequency deviants. In three separate frequency deviant conditions (i.e., 20% Δ f: 1200Hz; 10% Δ f: 1100 Hz; 5% Δ f: 1050 Hz) deviants were randomly intermixed with standard tones in 3 recording blocks, each consisting of 300 stimulus trials: 270 standard tones (135 long, 135 short) and 30 deviant (15 long, 15 short) tones. There were a total of 900 stimulus trials per deviant condition (i.e., 810 standards and 90 deviants) and in each of the 3 conditions; these infrequent changes in pitch were irrelevant for the duration discrimination task. Participants were required to respond as quickly and as accurately as possible with a left mouse button press to the short duration tones and with a right mouse button press to the long duration tones. Stimuli (75dB SPL) were presented binaurally via headphones at an inter-stimulus interval of 1300 ms. For each recording session, the 20% frequency deviant condition was presented first, followed by the 10% frequency deviant condition and then by the 5% frequency deviant condition. The rationale for ordering of deviant conditions was the accuracy of discriminability (i.e., high vs. low tones) was considerably enhanced by practice trials that began with the 20% deviant condition rather than with the 10% or 5% deviant conditions. For each practice trial, 50% of the stimuli were embedded with the deviant frequency deviant; with the 20% condition, the largest frequency change, participants were better able to detect the high from the low tones.

4.1.4 Study Procedure

Testing was carried out in the morning following over-night abstinence of aspirin, anti-histamines, herbal drugs, alcohol, caffeine-containing substances and cigarettes. Participants were seated in a sound attenuated, electrically shielded room where they were acclimatized to the testing apparatus and procedures prior to testing. Before the formal recordings, participants were introduced to the study stimuli and were required to perform a practice trial of the discrimination task for each of the 3 experimental conditions. A 60% accuracy rate for each condition was required for study inclusion. Upon successful completion of the first practice trial, electrodes were applied and formal testing commenced.

Participants were given short resting periods of about 2-3 minutes between the blocks and the entire recording session took approximately 90 minutes to complete. Participants were instructed to remain as still as possible and to avoid unnecessary body, head and eye movement during the recording sessions. Upon completion of the recording session, the electrodes were removed and the neuropsychological tests were administered.

4.1.5 ERP Recordings

EEG placement and recording followed the same procedures as outlined in Experiment 1. A minimum of 30 artifact-free correctly detected target stimulus sweeps per time block was required to retain a subject's ERP data in the final analyses (see Tables 13 means and standard deviations of sweeps for each group across each condition). ERPs at each scalp site were obtained by digital point-by-point subtraction of

the averaged ERP waveform to standard tones from the averaged ERP waveform to the deviant tones. Based on inspection of the grand averaged difference waveforms, latency windows were determined for each ERP component (i.e., MMN, P3a and RON) for each group separately. ERP measurement was carried out manually using a computer cursor to extract amplitude (μV) and latency (ms) values for each ERP component.

Based on the grand averaged difference waveforms for controls, the amplitude and latency of the MMN were derived from Fz, the site of maximal amplitude, and were defined as the peak negativity occurring in the 80-220ms latency range, post-stimulus onset for each condition. For the P3a, the amplitude and latency were derived from Cz, the site of maximal amplitude, and were defined as the peak positivity occurring in the 250-305 ms latency range. Finally, for the RON, amplitude and latency measures were taken from Fz, the site of maximum amplitude, and were defined as the peak negativity occurring in the 370-500 ms latency range.

Based on the grand averaged waveforms for patients, the amplitude and latency of the MMN were defined as the peak negativity occurring in the 70-120 ms (20% Δf), 95-150 ms (10% Δf) and 145-195 ms (5% Δf) latency ranges. The amplitude and latency of the P3a were defined as the peak positivity that occurred in the 185-280 ms (10% Δf), 250-350 ms (20% Δf) and 220-300 ms (5% Δf) latency ranges. The amplitude and latency of the RON were defined as the peak negativity that occurred in the 375-400 ms (5 % & 10% Δf) and 375-520 ms (20% Δf) latency ranges. Only data derived from Fz (MMN and RON) and Cz (P3a), the sites of maximal amplitude for each respective peak, were subjected to peak detection measurement and statistical analyses.

4.1.6 Behavioral Measures

Correct button press responses to stimuli in the interval from 100-1000 ms relative to stimulus onset were considered hits. Reaction times (ms), hit rates (%) and non-responses (%) were determined separately for the standard and deviant tones in each of the 3 conditions.

4.1.7 Statistical Analyses

All statistical analyses were performed using SPSS (Statistical Package for Social Sciences, 14th edition).

4.1.7.1. ERP Measures

A Mixed Analysis of Variance was used to determine whether there were between-group or across-condition differences in the number of sweeps obtained. Diagnostic group served as the between-group factor, while frequency deviants served as the within-group factor.

Doubly Multivariate Analysis of Variance (dMANOVA) with amplitudes and latencies as dependent variables were performed separately for the MMN, P3a and RON, with diagnostic group (schizophrenic vs. control) serving as the between-group factor and frequency deviants (5% Δ f, 10% Δ f & 20% Δ f) as the within-group factor. Significant effects ($p < .05$) were followed up with Univariate Analysis of Variance (ANOVA) and with pairwise t-tests.

Independent sample t-tests were used to test whether there were significant group differences on demographic variables such as age and education, and on two measures of intellectual functioning (i.e., reading and factual knowledge), and performance on the digit span, letter-number sequencing, Trails A and the mWCST.

4.1.7.2 Behavioural Measures

Tone duration (i.e., primary task: short vs. long tones) was not incorporated into the statistical design; data were pooled over the short and long duration tones. This is in line with studies by Schröger and colleagues who reported no difference in distraction effects with short vs. long duration tones. Since the pitch used for the standard tone (1000 Hz) was the same for all 3 deviant conditions, it was collapsed across all 9 test blocks.

Reaction time (ms) was analyzed using mixed ANOVA with diagnostic group (i.e., schizophrenics vs. controls) serving as the between-group factor and frequency (i.e., 1200 Hz, 1100 Hz, 1050 Hz & 1000 Hz) serving as the within-group factor.

Hit rate (%) and no-responses (%) were analyzed using dMANOVA with diagnostic group serving as the between-group factor and frequency serving as the within-group factor. Significant effects ($p < .05$) were followed up with ANOVAs and pair-wise t-tests.

Pearson Product Moment Correlation (Pearson's r) coefficients were used to assess the relationship between behavioral and electrophysiological measures of distraction and medication dosage, psychopathology ratings and neuropsychological performance.

4.2 Results

4.2.1 Participant Characteristics

Demographic and clinical characteristics of the participants are presented in Table 11. Independent t-tests did not yield significant group differences in age ($t(20)=-1.81, p=.250$), years of education ($t(20)=-.079, p=.938$), reading ability [$t(20)=-1.38, p=.181$] or factual knowledge [$t(20)=-1.977, p=.057$]. Independent t-tests revealed that the patient group was slower on Trails A [$t(20)=-3.353, p=.002$] and produced fewer card sorts on the mWCST [$t(20)=2.14, p=.044$] than the control group. There were no significant group differences on the digit span test or on the test of letter-numbering sequencing.

Table 11. Mean ($\pm$ SD) Demographic, Intellectual and Clinical Characteristics of Patients and Controls

Variable	Patients	Controls
Age	37 (8.2)	34 (5.5)
Yrs. of Education	13 (1.9)	13 (1.5)
WTAR	42 (4.6)	40 (3.8)
Information	21 (4.5)	17 (4.5)
Trails A	30 (8.6)	21 (3.7)
Letter-Number Sequencing	10 (3.0)	12 (2.2)
mWCST (# categories)	5 (1.5)	6 (1.1)
Clozapine (mg)	314 (154)	
PANSS (positive)	14 (5.6)	
PANSS (negative)	13 (2.9)	
PANSS ^a	26 (5.4)	

^a PANSS General Psychopathology total score

4.2.2 Behavioural Measures

4.2.2.1 Reaction Time

Table 12 presents reaction times for each group in each of the deviant conditions. An ANOVA failed to reveal a significant main effect of group [$F(1,20)=.037, p=.849$]. A main effect of frequency was revealed [$F(3,62)=6.717, p=.001$]; pairwise t-tests showed significantly longer reaction time to the deviant 10% Δf ($p=.000$) and to the deviant 20% Δf ($p=.001$) compared to reaction time to the standard. The group x frequency interaction was not significant.

4.2.2.2 Response Accuracy

Table 12 presents percentages of correct responses and non-responses for both groups across each condition. A dMANOVA did not yield a significant main effect of group [$F(2,20)=1.041, p=.372$]. A significant main effect of frequency was revealed [$F(6,124)=3.766, p=.002$]; univariate tests showed a significant effect with respect to correct responses [$F(3,62)=7.141, p=.001$]. Pairwise t-tests revealed a higher percentage of correct responses to the standard frequency compared to the deviant 10% ($p=.004$) and 20% ($p=.001$) frequency changes. The group x frequency interaction was not statistically significant. No significant group or frequency effects were observed for non-responses.

Table 12. Mean ($\pm$ SD) Reaction Times (ms), Correct Responses (%) and Non Responses (%) in Patients and Controls

	RT	CR	NR
Patients			
1200 Hz (20% Δ f)	541 (73.8)	72 (19)	02 (03)
1100 Hz (10% Δ f)	545 (42.1)	77 (14)	03 (04)
1050 Hz (5% Δ f)	524 (41.0)	82 (13)	02 (03)
1000 Hz (Std.)	501 (47.6)	85 (08)	01 (02)
Controls			
1200 Hz (20% Δ f)	548 (64.8)	78 (12)	03 (06)
1100 Hz (10% Δ f)	532 (79.2)	80 (17)	03 (04)
1050 Hz (5% Δ f)	517 (82.2)	75 (19)	05 (06)
1000 Hz (Std.)	497 (67.8)	88 (10)	03 (04)

4.2.3 ERP Measures

Table 13 displays the number of standard and deviant EEG sweeps comprising each deviant condition for both patient and control groups. There was no significant difference between patients and controls in the number of EEG sweeps [$F(1,19)=.037$, $p=.849$]. Furthermore, there was no significant effect of frequency (i.e. % Δ f) on the number of sweeps obtained [$F(2,21)=1.24$, $p=.295$].

Table 13. Means ($\pm$ SD) Number of Averaged EEG Sweeps to Frequency Deviants in Patients and Controls

		Standard	Deviant
Patients	20% Δ f	546 (117.0)	51 (15.7)
	10% Δ f	568 (149.0)	59 (17.0)
	5% Δ f	542 (184.5)	56 (14.1)
Controls	20% Δ f	561 (152.2)	59 (16.7)
	10% Δ f	585 (185.8)	60 (20.1)
	5% Δ f	547 (238.6)	55 (22.7)

4.2.3.1 MMN

A dMANOVA revealed a significant main effect of group [$F(2,18)=4.26, p=.031$]. As shown in Table 14 and Figure 5, a follow-up ANOVA revealed that MMN amplitude was significantly lower in the patient group compared to the control group [$F(1,19)=7.579, p=.013$]. There were no significant differences with respect to latency. The main effect of frequency and the group x frequency interaction were not statistically significant.

Table 14. Mean ($\pm$ SD) Peak MMN Amplitudes and Latencies at Fz to Frequency Deviants in Patients and Controls

	Amplitude (μ V)	Latency (ms)
Patients		
20% Δ f (1200 Hz)	-1.14 (1.3)	136.33 (37.8)
10% Δ f (1100 Hz)	-1.87 (1.8)	124.21 (26.1)
5% Δ f (1050 Hz)	-2.07 (1.2)	144.56 (36.9)
Controls		
20% Δ f (1200 Hz)	-3.11 (1.6)	141.47 (17.6)
10% Δ f (1100 Hz)	-2.88 (1.7)	145.74 (29.4)
5% Δ f (1050 Hz)	-2.93 (1.7)	148.65 (23.5)

4.2.3.2 P3a

A dMANOVA failed to find a significant main effect of group for P3a amplitude or P3a latency. A group X frequency interaction was significant [$F(4,17)=4.26, p=0.02$]. Follow-up univariate analysis revealed significant effects for amplitude [$F(2,40)=4.22, p=.02$] and for latency [$F(2,40)=6.71, p=.004$]. Pairwise comparisons revealed significantly larger P3a amplitude in schizophrenics compared to controls to the 5% Δf deviant and significantly shorter P3a latency in schizophrenics compared to controls to the 10% Δf deviant. A main effect of frequency was also revealed [$F(4,17)=3.55, p=.028$]; follow-up univariate revealed a significant effect for both amplitude [$F(2,40)=5.13, p=.012$] and latency [$F(2,40)=4.158, p=.023$]. Pairwise comparisons showed that P3a latency was significantly longer to the 20% Δf compared to the 10% Δf ($p=.075$) and compared to the 5% Δf ($p=.027$), and that P3a amplitude was significantly larger to the 20% Δf than to the 5% Δf .

Table 15. Mean ($\pm$ SD) Peak P3a Amplitude and Latencies at Cz to Frequency Deviants in Patients and Controls

	Amplitude (μV)	Latency (ms)
Patients		
20% Δf (1200 Hz)	3.58 (1.7)	300.9 (39.8)
10% Δf (1100 Hz)	3.04 (1.8)	254.7 (45.6)
5% Δf (1050 Hz)	3.79 (2.7)	293.8 (42.4)
Controls		
20% Δf (1200 Hz)	4.21 (2.6)	306.9 (29.3)
10% Δf (1100 Hz)	3.46 (1.5)	300.9 (39.8)
5% Δf (1050 Hz)	1.35 (1.8)	267.1 (40.4)

4.2.3.3 RON

Mean peak RON amplitudes and latencies are presented in Table 16. A dMANOVA failed to reveal any significant between-group, within-group or interaction effects for RON amplitude or latency.

Table 16. Mean ($\pm$ SD) Peak RON Amplitudes and Latencies at Fz to Frequency Deviants in Patients and Controls

	Amplitude (μ V)	Latency (ms)
Patients		
20% Δ f (1200 Hz)	-1.70 (1.5)	442.44 (29.8)
10% Δ f (1100 Hz)	-2.11 (1.5)	431.86 (30.8)
5% Δ f (1050 Hz)	-2.48 (2.3)	429.25 (30.7)
Controls		
20% Δ f (1200 Hz)	-3.52 (2.9)	423.04 (31.1)
10% Δ f (1100 Hz)	-3.69 (3.1)	439.54 (35.2)
5% Δ f (1050 Hz)	-2.83 (1.8)	438.07 (34.0)

Figure 5: Grand average ERP waveforms for controls and patients for a) 20%Δf, b) 10%Δf, and c) 5%Δf deviant conditions

4.2.4 Correlations

Given the small sample sizes, the following correlation analyses are exploratory at best and they may just reflect chance findings.

4.2.4.1 Reaction Time and ERPs

Controls

There were no significant correlations between reaction time and MMN or RON. A significant correlation was found between P3a latency and reaction time to the 10% deviant ($r=.722, p=.012$). A significant correlation was also found between P3a latency and reaction time to the 20% deviant ($r=.763, p=.006$).

Patients

Significant correlations were found between MMN amplitude to the 10% deviant and reaction time to the 10% standard ($r=.781, p=.005$), between MMN amplitude to the 10% deviant and reaction time to the 20% standard ($r=.686, p=.020$), and between MMN amplitude to the 5% deviant and reaction time to the 5% standard ($r=.832, p=.001$). A significant correlation was found between P3a latency to the 5% deviant and reaction time to the 5% standard ($r=-.694, p=.018$). Significant correlations were observed between RON amplitude to the 20% deviant and reaction time to the 5% standard ($r=.667, p=.035$), between RON amplitude to the 20% deviant and reaction time to the 5% deviant ($r=.657, p=.039$), and between RON amplitude to the 20% deviant and reaction time to the 10% deviant ($r=-.659, p=.038$).

4.2.4.2 Clozapine

The Pearson Product Moment Correlation analysis performed between behavioral measures (i.e., response accuracy and reaction time) and clozapine dosage did not yield any significant correlations. In addition, no significant correlations were found between clozapine dosage and ERPs (i.e., MMN, P3a, RON).

A significant correlation was found between clozapine dosage and the total score for the negative symptoms scale ($r=.811, p=.002$). Also, a significant correlation was observed between clozapine dosage and performance on the letter-number sequencing test ($r=-.664, p=.026$).

4.2.4.3 Psychopathology Ratings

There were no significant correlations between the PANSS (i.e., total scores for general psychopathology, positive symptoms and negative symptoms) and behavioural measures (i.e., response accuracy and reaction time).

A significant correlation was observed between the total score for negative symptoms and P3a latency to the 20% deviant ($r=.627, p=.039$) and P3a amplitude to the 20% deviant ($r=.622, p=.041$). No other significant correlations were observed between psychopathology rating and ERPs.

4.2.4.4 Neuropsychological Performance

Controls

A significant correlation was observed between letter-number sequencing span and reaction time to the 20% deviant ($r=.604, p=.029$). No other correlations were observed

between reaction time and neuropsychological performance. Other than one significant correlation between the number of categories of the mWCST and the percentage of correct responses to the 5% standard frequency ($r=.684, p=.010$), no other significant correlations between accuracy performance and neuropsychological performance were found.

A significant correlation was found between MMN amplitude to the 20% frequency deviant and performance on Trails A ($r=.701, p=.016$). In addition a significant correlation was observed between P3a latency to the 20% frequency deviant and performance on Trails A ($r=.698, p=.017$). No significant correlations were observed with respect to the RON.

Patients

A significant correlation was found between performance on Trails A and reaction time to the 5% standard frequency ($r=.660, p=.027$). No other significant correlations were observed between neuropsychological performance and behavioural measures.

There were no significant correlations between MMN or RON and neuropsychological performance. A significant correlation was found between performance on Trails A and P3a latency to the 5% deviant ($r=-.658, p=.028$).

5.0 Experiment 3: *ERP and behavioural correlates of auditory distraction induced by duration deviants in schizophrenics and controls*

5.1 Method

5.1.2 Participants

Seventeen patients (16 males) and 14 controls (12 males) from the Experiment 1 participant pool took part in Experiment 3. Three additional patients were recruited to participate in this experiment, which increased the patient sample size to 20. Informed consent was obtained from each participant. Inclusion and exclusion criteria were the same as in Experiment 2, as were the neuropsychological tests administered to patients and controls. Adjunct medications were documented in patients. All patients received clozapine as their primary treatment; three patients were also receiving small doses of risperidone.

8.2 Stimulus Paradigm

Participants were asked to discriminate between two equal probability high (1500 Hz) and low (1000 Hz) frequency standard tones. In 3 blocks, the duration of the standard tones was 100 ms and in another 3 blocks the duration of the standard tones was 50 ms. In each of these two deviant task conditions, 10% of the standards were randomly replaced by duration deviants, i.e., the 50 ms standard tones were replaced by 100 ms tones and the 100 ms standards were replaced by 50 ms tones. Each of the 3 recording blocks in each of the two tasks consisted of 300 stimulus trials: 270 standard (135 high, 135 low) and 30 deviant (15 high, 15 low) tones. There were a total of 900 stimulus trials

per deviant task condition (i.e., 810 standards and 90 deviants), and in each of these two deviant task conditions these infrequent changes in duration were irrelevant for the frequency discrimination task. Thus, participants were required to respond as quickly and as accurately as possible with a left mouse button press to the low frequency tones and with a right mouse button press to the high frequency tones. Stimuli (75 dB SPL) were presented binaurally via headphones at an inter-stimulus interval of 1300 ms. For half of the participants in each group, the presentation of the short duration tone deviant condition was presented before the long duration tone deviant condition, and for the remaining half of the participants in each group the duration deviants were presented in the reverse order.

5.1.4 Study Procedure

The same testing procedure as Experiment 2 was used. Prior to the formal recording sessions, participants were introduced to the study stimuli and were required to perform a practice trial of the discrimination task for each of the 2 experimental conditions. A 60% accuracy rate for each condition was required for study inclusion.

Participants were given short resting periods of about 2-3 minutes between the blocks and the recording session took approximately 60 minutes to complete. Participants were instructed to remain as still as possible and to avoid unnecessary body, head and eye movement during the recording sessions.

5.1.5 ERP Recordings

The same EEG placement and recording techniques were used as in Experiments 1 and 2. A minimum of 30 artifact-free correctly detected target stimulus sweeps per time block was required to retain a subject's ERP data in the final analyses (see Table 19 for means and standard deviations of sweeps for each group across each condition). ERPs at each scalp site were obtained by digital point-by-point subtraction of the averaged ERP waveform to standard tones from the averaged ERP waveform to the deviant tones. Based on inspection of the grand averaged difference waveforms, latency windows were determined for each ERP component (i.e., MMN, P3a and RON) for each group separately. ERP amplitude and latency measurement was carried out manually using a computer cursor.

Based on the grand-averaged difference waveforms for controls, the amplitude and latency of the MMN were defined as the Fz-derived peak negativity occurring in the 110-205 ms latency range for the long duration deviant condition and in the 105-190 ms latency range for the short duration deviant condition, post-stimulus onset, for each condition. For the P3a, the amplitude and latency were defined as the Cz-derived peak positivity occurring in the 250-350 ms latency range for the long duration deviant condition and in the 180-300 ms latency range for the short duration deviant condition. Finally, for the RON, the amplitude and latency were defined as the Fz-derived peak negativity occurring in the 390-490 ms latency range for both duration deviant conditions.

Based on the grand-averaged waveforms for patients, the amplitude and latency of the MMN were defined as the Fz-derived peak negativity occurring in the 175-250 ms (long duration deviant) and 100-200 ms (short duration deviant) latency ranges. The amplitude and latency of the P3a were defined as the Cz-derived peak positivity that occurred in the 230-340 ms (long duration deviant) and 150-250 ms (short duration deviant) latency ranges. The amplitude and latency of the RON were defined as the Fz-derived peak negativity that occurred in the 380-490 ms (long duration deviant) and 350-450 ms (short duration deviant) latency ranges. Only data derived from Fz (MMN and RON) and Cz (P3a), the sites of maximum amplitude for each respective peak, were subjected to peak detection and statistical analyses.

5.1.6 Behavioral Measures

Correct button press responses to stimuli in the interval from 100-1000 ms relative to stimulus onset were considered hits. Reaction times (ms), hit rates (%) and non-responses (%) were determined separately for the standard tones (i.e., 100 ms: short condition; 50 ms: long condition) and for the deviant tones (i.e., 100 ms: long condition; 50 ms: short condition).

5.1.7 Statistical Analyses

All statistical analyses were performed using SPSS (Statistical Package for Social Sciences, 14th edition).

5.1.7.1 ERP Measures

A Mixed Analysis of Variance was used to determine whether there were between-group or across-condition differences in the number of sweeps obtained. Diagnostic group served as the between-group factor, while duration deviants served as the within-group factor.

Doubly Multivariate Analysis of Variance (dMANOVA) with amplitudes and latencies as dependent variables were performed separately for the MMN, P3a and RON, with diagnostic group (schizophrenic vs. control) serving as the between-group factor and duration deviants (long & short) as the within-group factor. Significant effects ($p < .05$) were followed up with Univariate Analysis of Variance (ANOVA) and with pairwise t-tests.

Independent sample t-tests were used to test whether there were significant group differences on demographic variables such as age and education, and on two measures of intellectual functioning (i.e., reading and factual knowledge), letter-number sequencing, Trails A and the mWCST.

5.2.2 Behavioral Measures

Frequency (i.e., primary task: higher frequency vs. lower frequency) was not incorporated into the statistical design; data were pooled over the higher and lower frequency tones.

Reaction time (ms) was analyzed using mixed ANOVA with diagnostic group (i.e., schizophrenics vs. controls) serving as the between-group factor and duration (i.e., long standard, short standard, long deviant, short deviant) serving as the within-group factor.

Hit rate (%) and non-responses (%) were analyzed using dMANOVA with diagnostic group serving as the between-group factor and duration serving as the within-group factor. Significant effects ($p < .05$) were followed up with ANOVAs and pair-wise t-tests. Pearson Product Moment Correlation (Pearson's r) coefficients were used to assess the relationship between behavioral and electrophysiological measures of distraction and medication dosage, psychopathology ratings and neuropsychological performance.

5.2 Results

5.2.1 Participant Characteristics

Demographic and clinical characteristics are presented in Table 17. Independent t-tests did not yield significant group differences in age ($t(33) = -1.89$, $p = .067$), years of education ($[t(33) = .886$, $p = .382]$, reading ability [$t(33) = -1.33$, $p = .192]$ or factual knowledge [$t(33) = -1.48$, $p = .147]$. Independent t-tests revealed that the patient group was slower than the control group on Trails A [$t(33) = -4.42$, $p = .000$], had lower letter-number

sequence span [$t(33)=3.47$, $p=.002$] and produced fewer card sorts on the mWCST

[$t(33)=3.59$, $p=.001$].

Table 17. Mean ($\pm$ SD) Demographic, Intellectual and Clinical Characteristics of Patients and Controls

Variable	Patients (n=20)		Controls (n=14)	
Age	40	(10.0)	34.5	(6.2)
Yrs. of Education	12	(1.9)	13	(1.5)
WTAR	42	(4.7)	40	(4.5)
Information	19	(4.6)	17	(4.1)
Trails A	34.5	(10.1)	21	(4.3)
Letter-Number Sequencing	8.6	(3.2)	12	(2.0)
mWCST (# categories)	4	(2.0)	6	(1.1)
Clozapine (mg)	274	(134.8)		
PANSS (positive)	14	(4.5)		
PANSS (negative)	13	(3.0)		
PANSS ^a	25	(5.8)		

^a PANSS General Psychopathology total score

5.2.2 Behavioural Measures

5.2.2.1 Reaction Time

Table 18 presents reaction times for each group in each of the deviant conditions.

ANOVA failed to reveal a significant main effect of group [$F(1,32)=.960$, $p=.334$]. A main effect of duration was revealed [$F(3,98)=10.53$, $p=.000$]; pairwise t-tests showed significantly longer reaction time to the long deviant tone compared to the short standard tone ($p=.000$) and significantly longer reaction time to the short deviant tone compared to the long standard tone ($p=.000$). The group x duration interaction was not significant.

5.2.2.2 Response Accuracy

Table 18 presents percentages of correct responses and non-responses for both groups across each condition. dMANOVA yielded a significant main effect of group [$F(2,31)=2.37, p=.000$]; follow-up univariate tests revealed that the schizophrenics incurred more non-responses than controls [$F(1,32)=4.85, p=.035$]. dMANOVA also yielded a significant main effect of duration [$F(6,26)=5.132, p=.000$]; univariate tests showed a significant effect with respect to both correct responses [$F(3,96)=3.00, p=.048$] and non-responses [$F(3,96)=9.06, p=.000$]. Pairwise t-tests revealed a higher percentage of correct responses to the short standard tone compared to the short deviant tone ($p=.000$) and a higher percentage of non-responses to the short deviant tone compared to the long standard tone ($p=.012$). A higher percentage of non-responses to the short deviant tone than to the short standard tone ($p=.001$) was also found. The group x duration interaction was not statistically significant for correct or for non-responses.

Table 18. Mean ($\pm$ SD) Reaction Times (ms), Correct Responses (%) and Non-Responses (%) in Patients and Controls

	RT	CR	NR
Patients			
Long standard	444 (65.3)	89 (13)	03 (03)
Long deviant	465 (70.7)	85 (15)	03 (02)
Short standard	426 (57.3)	89 (12)	02 (02)
Short deviant	445 (61.4)	84 (16)	04 (04)
Controls			
Long standard	455 (67.2)	92 (13)	00 (00)
Long deviant	473 (67.4)	92 (06)	00 (01)
Short standard	449 (59.0)	96 (03)	00 (00)
Short deviant	482 (54.9)	92 (05)	02 (02)

5.2.3 ERP Measures

Table 19 displays the number of standard and deviant EEG sweeps comprising each deviant condition for both patient and control groups. There was no significant difference between patients and controls in the number of EEG sweeps [$F(1,26)=2.86$, $p=.103$], furthermore, there was no significant effect of duration (i.e. $\% \Delta f$) on the number of sweeps obtained [$F(1,26)=.007$, $p=.933$].

Table 19. Means ($\pm$ SD) Number of Averaged EEG sweeps to Duration Deviants in Patients and Controls

		Standard	Deviant
Patients	short	553 (113)	58 (13)
	long	562 (165)	61 (20)
Controls	short	644 (149)	70 (15)
	long	631 (138)	68 (15)

5.2.3.1 MMN

Table 20 and Figure 6 display the amplitudes and latencies of the MMN for both duration deviant conditions. Although dMANOVA failed to reveal a significant main effect of group [$F(2,29)=2.44$, $p=.105$], ANOVA yielded a significant main effect of group for amplitude [$F(1,30)=5.047$, $p=.032$], revealing lower MMN amplitude in the patient group compared to the control group. A significant group x duration interaction [$F(2,29)=6.65$, $p=.004$] was found; ANOVA showed a significant effect for amplitude, with pairwise t-tests revealing that the MMN amplitude in the patient group was lower to long deviant tones compared to the control group. dMANOVA also showed a significant main effect of duration [$F(2,29)=4.79$, $p=.016$]; follow-up ANOVA indicated that MMN

latency was significantly longer to the long deviant tone compared to the short deviant tone [$F(1,30)=6.83, p=.014$].

Table 20. Mean ($\pm$ SD) Peak MMN Amplitudes and Latencies at Fz to Duration Deviants in Patients and Controls

	Amplitude (μ V)	Latency (ms)
Patients		
Short	-2.05 (2.3)	149.78 (31.0)
Long	-0.26 (.41)	174.30 (34.4)
Controls		
Short	-1.38 (1.1)	152.79 (30.6)
Long	-2.36 (1.0)	176.29 (31.9)

5.2.3.2 P3a

Mean peak P3a amplitudes and latencies are presented in Table 21. A dMANOVA failed to find a significant main effect of group. A significant main effect of duration was revealed only for P3a latency [$F(2,31)=6.24, p=.005$]; ANOVA showed that P3a latency was significantly longer to the long deviant tone compared to the short duration tone [$F(1,32)=12.386, p=.001$]. No significant interactions were observed.

Table 21. Mean ($\pm$ SD) Peak P3a Amplitude and Latencies at Cz to Duration Deviants in Patients and Controls

	Amplitude (μ V)	Latency (ms)
Patients		
Short	2.31 (2.5)	239.1 (55.7)
Long	1.76 (2.2)	286.5 (38.7)
Controls		
Short	0.27 (2.4)	259.3 (53.5)
Long	2.18 (2.5)	294.6 (28.8)

5.2.3.3 RON

Mean peak RON amplitudes and latencies are presented in Table 22. A dMANOVA failed to reveal any significant between-group, within-group or interaction effects for RON amplitude and latency.

Table 22. Mean ($\pm$ SD) Peak RON Amplitudes and Latencies at Fz to Duration Deviants in Patients and Controls

	Amplitude (μ V)	Latency (ms)
Patients		
Short	-2.68 (2.2)	432.36 (41.6)
Long	-1.68 (1.5)	434.10 (41.7)
Controls		
Short	-2.18 (1.1)	435.96 (37.1)
Long	-1.52 (2.0)	427.35 (29.8)

Figure 6: Grand averaged ERP waveforms for control and patients for a) long duration (100 ms) and b) short duration (50 ms) deviants

5.2.4 Correlations

5.2.4.1 Reaction Time and ERPs

Controls

There were no significant correlations between reaction time and MMN or RON.

Significant correlations were found between P3a amplitude to the long deviant and reaction time to the long standard ($r=.583, p=.029$) as well as between P3a amplitude to the long deviant and reaction time to the long deviant ($r=.613, p=.020$) and between P3a amplitude to the long deviant and reaction time to the short deviant ($r=.605, p=.02$).

Patients

No significant correlations were found between reaction time and ERPs.

5.2.4.2 Clozapine

The Pearson Product Moment Correlation analysis performed between behavioral measures (i.e., response accuracy and reaction time) and clozapine dosage did not yield any significant correlations. In addition, no significant correlations were found between clozapine dosage and ERPs (i.e., MMN, P3a, RON).

A significant correlation was found between clozapine dosage and the total score for the negative symptoms scale ($r=.521, p=.02$).

5.2.4.3 Psychopathology Ratings

There were no significant correlations between the PANSS (i.e., total scores for general psychopathology, positive symptoms and negative symptoms) and behavioural measures (i.e., response accuracy and reaction time) or ERPs.

5.2.4.4 Neuropsychological Performance

Controls

There were no significant correlations found between accuracy performance and neuropsychological performance. In addition, there were no significant correlations observed between the P3a or RON and neuropsychological performance. A significant correlation was found between MMN amplitude to the short deviant and the mWCST ($r=-.657$, $p=.011$).

Patients

A significant correlation was found between performance on Trails A and the percentage of correct responses to the long deviant ($r=-.495$, $p=.037$). A significant correlation was also found between letter-number sequencing span and the percentage of correct responses to the long standard ($r=.559$, $p=.016$). In addition, a significant correlation was observed between the mWCST and the percentage of correct responses to the long standard ($r=.510$, $p=.031$).

There were no significant correlations between MMN or P3a and neuropsychological performance. A significant correlation was found between letter-number sequencing span and RON latency to the long deviant ($r=-.565$, $p=.023$).

6.0 Discussion

The purpose of Experiments 2 and 3 was to examine the role of abnormal pre-attentive auditory sensory memory, as indexed by the MMN, in distraction vulnerability and task proficiency in schizophrenia. Schröger's (1997) auditory ERP-based distractibility paradigm was specifically developed to enable investigation of involuntary changes in attention related to memory-based detection of very small acoustic changes in an otherwise standard acoustic environment. This paradigm yields distinct ERP and marked behavioural distraction effects with much smaller deviances (i.e., 10% Δf) than in other distraction paradigms. In this paradigm, task-irrelevant deviants give rise to distractibility indexed at both behavioural and electrophysiological levels; the former by deterioration in primary task performance (i.e., prolonged reaction time and lower hit rate to targets embedded with deviants) and the latter, by elicitation of the P3a component of the event-related potential. An additional fronto-central negativity in the 400-600ms range (post-stimulus onset) has also been documented using this paradigm. This ERP, termed the RON, is purported to reflect the re-orienting of attention back to the primary task following distraction (Berti & Schroger, 2001). The RON appears to be exclusively elicited in conditions where deviance is task-irrelevant and it is not evoked when deviants are task-relevant or when auditory input is ignored (Schröger & Wolff, 1998b).

The clinical utility of this paradigm is wide-ranging; it can be applied to any condition where aberrant attentional processes are considered to play a role in behavioral disorder. For example, using this paradigm, it has been shown that low doses of ethanol administered to healthy social drinkers attenuates behavioural distraction effects of

reaction time prolongation to deviance and diminishes the amplitude of the P3a ERP (Jaaskelainen, Schröger & Naatanen, 1999). These findings suggest that alcohol has a suppressing effect on involuntary attention shifting and acts to decrease the distracting effects of deviance.

Experiments 2 and 3 represent the first attempt at applying Schröger's distraction paradigm to a sample of individuals with chronic schizophrenia. The main predictions were that compared to controls, patients would show reduced behavioural and ERP-related effects of distraction. This prediction was based on Schröger's model that proposes that MMN signals must be of sufficient magnitude to surpass a variable threshold for an involuntary shift in attention to be triggered and for deviance-related effects to be manifested. It has been well established in the literature that MMN amplitude is attenuated in individuals with schizophrenia (Mitchie et al., 2000).

6.1 Experiment 2

Experiment 2 employed three frequency deviants; a 20% frequency change, a 10% frequency change and a 5 % frequency change. It appears from an extensive review of the literature that most other studies using Schröger's model employed only a single frequency deviant such as a 5% Δf (Berti & Schröger, 2003), a 12% Δf (Munka & Berti, 2006; Sussman, Winkler, & Schröger, 2003), or an increase/decrease of a 10% Δf (Schröger et al., 2000; Schröger & Wolff, 1998b). Only two other studies have incorporated multiple frequency deviants in the same study (Berti, Roeber, & Schröger, 2004: 1%, 3%, 5% & 10%; Schröger & Wolff, 1998a: 7%, 20% & 40%).

As predicted by Schröger's model, the presentation of and response to low-probability frequency changes embedded in a series of high-probability standard tones yielded the expected behavioral and electrophysiological distraction effects which were observed in both controls and patients. Behaviorally, reaction time was prolonged to all three frequency deviant conditions compared to the reaction time to the standard tones and, the percentage of correct responses was lower to the three frequency deviants as compared to the percentage of correct responses to the standard frequency tones. Across both groups, reaction time was delayed by 45 ms in the 20% Δf condition, by 35 ms in the 10% Δf condition and by 21.5 ms in the 5% Δf condition. The present results showed that reaction time to the 20% Δf and 10% Δf conditions but not the 5% Δf was significantly slower than reaction time to the standard tones. The reaction time prolongation found in the present study was similar to other studies which used Schröger's paradigm. For example, using a 10% Δf , reaction time prolongation in the range of 30-45 ms has been reported (Mager, Falkenstein, Stormer, Brand, Miller-Spahn & Bullinger, 2004; Roeber, Berti, & Schröger, 2003; Schröger et al., 2000; Schröger & Wolff, 1998b). Moreover, reaction time prolongation of 22 ms (Berti & Schröger, 2001) and 48 ms (Berti & Schröger, 2003) to 5% Δf has been documented.

As mentioned above, behavioral distraction effects were also indicated in the response accuracy measures; the percentage of correct responses, 75%, 78.5% and 78.5% for the 20% Δf , 10% Δf and 5% Δf conditions respectively, was lower than the percentage of correct responses to the standard frequency (86%). These results are also consistent with reports from previous studies that found significantly higher rates of correct responses to

standard frequency tones (96%) than to deviant frequency tones (92%) (Roeber et al., 2003; Schröger et al., 2000). Similar to the pattern of statistically significant effects observed in the reaction time data, the percentage of correct responses to the 20% Δf and 10% Δf conditions but not to the 5% Δf condition was significantly lower than the rate of correct responses to the standard frequency tone. Thus it appears that although deviance-related performance deterioration as measured by reaction time prolongation and lower correct responses were evident in the 5% Δf condition, this very small deviant was not sufficiently salient to induced statistically significant distraction effects when compared to the standard frequency tone. Behavioural distraction effects as measured by a higher percentage of non-responses to deviant frequencies were not evident in the data. Previous studies using Schröger's paradigm have not commented on this behavioural index.

Overall, these behavioural distraction effects suggest that ongoing cognitive processes were interrupted by the involuntary detection of auditory change in an otherwise standard environment. The detection of the changed frequency by the automatic sensory system disrupted the processing of task-relevant information which subsequently led to increased response speed and to less efficient detection of task-relevant events.

A linear increase in reaction time prolongation was observed in the data; reaction time increases were larger with greater stimulus deviance (20% Δf > 10% Δf > 5% Δf). In a recent study (Berti, Roeber, & Schröger, 2004) the effect of bottom-up processes (i.e., the magnitude of task-irrelevant deviances) on distractibility measures using Schröger's paradigm were examined. Bottom-up mechanisms are thought to operate on raw sensory input, rapidly and involuntarily shifting attention to salient features of potential

importance in the environment. Using four frequency deviants, a 1% Δf , a 3% Δf , a 5% Δf and a 10% Δf , they reported a statistically significant increase in reaction time prolongation to the 10% Δf compared to the smaller frequency deviants. The authors suggested that the magnitude of behavioural distractibility is not an all-or-none phenomenon, but rather, the degree of attentional capture is mediated by the degree of physical difference between standard and deviant pitches (Berti, et al., 2004). These findings may be understood in the context of Schröger's model which stipulates that there is a direct relationship between the magnitude of mismatch signal detection and the degree of involuntary attentional orienting. Thus, enhanced MMN signals generated by greater physical difference between standard and deviant tones elicits a stronger attention switching response that subsequently leads to greater processing disruptions of task-relevant information.

All three frequency change conditions elicited the expected deviance-related ERPs, namely the MMN, the P3a and the RON. The best representation of these ERPs is in the 20% Δf condition (see Figure 5). These components are related to different stages involved in the processing of deviant auditory events. Elicitation of the MMN indicates the pre-attentive registration and detection of a sound change based on the sensory representation of acoustic regularities extracted from the sound sequence, while the presence of the P3a suggests that activation of neural processes involved in involuntary attention orienting to a distracting event. The current observation that the P3a was present in the waveforms to all three frequency deviant conditions implies that even a 5% Δf elicited sufficient change detection signals to evoke an involuntary attention

switch. The presence of the RON reveals that, following distraction by deviant tones, a re-orienting of attention occurred that served to direct attentional resources back to the primary task. Thus, once attention has been diverted away from the primary task, resources have to be reoriented back to the primary task at hand in order to resume efficient task performance.

The impact of bottom-up processing was also present in the ERP-related distraction indices. The control data revealed that the largest frequency deviant, the 20% condition, generated the largest MMN and P3a amplitudes. The amplitude of the P3a progressively decreased with reduced deviance; it was almost nil in the 5% Δf condition and smaller in the 10% Δf condition compared to the 20% Δf condition. This decline is consistent with bottom-up processing effects (Berti et al., 2004). The amplitude of the RON was similar for the 20% and 10% frequency change conditions. Berti et al. (2004) reported a saturation of RON amplitude increase from a 3% to a 5% frequency deviance, and found no amplitude difference between the 5% and the 10% frequency changes. Thus, these findings suggest that the amplitude of the RON is less affected than the P3a by the magnitude of the distractor.

The main finding of Experiment 2 was that the schizophrenics displayed a significant reduction in MMN amplitude across all three frequency change condition compared to controls. Abnormally low MMN amplitude suggests a defect in pre-attentive deviance detection, a deficiency in early auditory change information-processing. MMN generation reflects context-dependent information processing at the level of the auditory sensory cortex (Näätänen & Alho, 1997). Deficits in the generation of the MMN are a

well-replicated finding in schizophrenia research and are consistent with the findings from Experiment 1. Abnormal MMN supports disturbed pre-attentive sensory processing and appears to be a stable trait maker of schizophrenia. Given that patients performed a difficult attention task, MMN deficits identified in schizophrenia do not appear to be the result of an overall generalized attentional failure (Javitt, Shelley, Silipo, & Lieberman, 2000), but rather, are suggestive of specific deficits in extracting relevant information from sensory stimuli and dysfunction in the very early stages of cerebral processes leading to a shift of overt attention. Reduced MMN generation in schizophrenia is consistent with the idea that these individuals do not experience the same degree of automatic cortical activation in response to new or unexpected events.

Given that the MMN plays a causal role in the elicitation of involuntary shifts in attention from the current focus of attention toward deviation, it was expected that a defect in this initial stage in the conscious detection of change would subsequently impact on behavioural and electrophysiological indices of distraction. The results from the present study did not support this assumption. Rather, to the contrary, behavioural measures of distraction and ERP indices of deviance processing were quite similar in the schizophrenics compared to the controls despite a significant reduction in MMN amplitude in the former. Thus it appears from these findings that although the schizophrenics demonstrated deficits in pre-attentive, sensory memory change detection as indicated by significantly lower MMN amplitude, this deficit did not appreciably impact on behavioural distractibility or electrophysiological measures of involuntary attention switching and re-orienting of attention. It may be worthwhile noting that

inspection of the grand-averaged waveforms (see Figure 5) especially to the 20% Δ f condition, suggests a possible overall reduction in amplitude in the patients compared to the controls. However, as previously mentioned only differences in MMN amplitude were statistically significant.

In general, the findings of similar behavioral proficiency between patients and controls, in addition to the non-significant group differences in P3a and RON amplitude, does not support the initial prediction that aberrant MMNs would significantly impact on these measures of deviance processing. There are multiple possible explanations to account for these findings.

One potential explanation involves the idea that top-down processes may have actively compensated for attention-independent, lower-level information-processing deficits. Recruitment of sufficient top-down resources may have successfully obfuscated the potential sequelae of disordered, higher level processing secondary to deficiencies in automatic, pre-attentive sensory processing. Thus, the impact of abnormal detection of auditory change on subsequent deviance-related processing and behavioral response may have been neutralized by the activation of attention. A recent study (Sussman, Winkler, & Schröger, 2003) showed that top-down control (where participants were able to predict the occurrence of task-irrelevant sound change) substantially reduced the amplitude of the P3a without impacting the responsiveness of the MMN. Moreover, the task demands of Schröger's paradigm required controlled attention, efficient allocation and maintenance of attentional resources. Thus, the paradigm itself may have provided a suitable context for a compensatory effect to occur. In Stroop interference studies which

have been used to probe distractibility in schizophrenia, schizophrenics perform more poorly than controls using the traditional card version of the Stroop task, but not when the more contemporary computerized version is employed. Normal (Barch, Carter, Hachten, Usher & Cohen, 1999) and even reduced (Peters et al, 2002) Stroop interference using the computerized version has been documented. In the card version, multiple stimulus trials (~100) are presented on a large card, while in the computerized version, a single trial methodology is employed, where a single, very brief stimulus (~100 ms) is rapidly presented on a screen. These differential Stroop findings have been explained by the inherent differences in the tasks and may be interpreted in the context of a compensatory process. The fast-paced, short intertrial intervals, single trial procedure in the computerized version of this task is much like the procedural features of the Schröger paradigm employed in the present study, where one stimulus is presented at a time. Both of them are in contrast to the card version of the Stroop where several stimuli are presented simultaneously. In a single-trial procedure, excessive interference may have been reduced providing a context for patients that may have enabled them to adequately apportion their cognitive resources to avoid becoming overly distracted by the deviant stimuli.

The notion that top-down processes can impact the processing of sensory memory based acoustic change related information was recently examined in normal controls using a visuo-spatial attention tracking task (Zhang, Chen, Yuan, Zhang, & He, 2006). In this study, varying “loads” or demands were placed on working memory in order to investigate how active cognitive control mechanisms (i.e., working memory) filter or

modify the processing of irrelevant, auditory distractors. By manipulating the complexity of the attention tracking task (i.e., additional targets), Zhang et al. (2006) were able to examine the impact of high vs. low demand on cognitive control functions at different stages of deviance processing (i.e., early sensory based and later attention-dependent). They found that the MMN and the P3a were elicited by task-irrelevant tones however their manifestation was dependent on the demand placed on active control mechanisms; MMN amplitude increased with increasing working memory load while the amplitude of the P3a was higher only in the low load condition. These findings suggest that pre-attentive change detection of irrelevant acoustic stimuli varies with the availability of controlled attentional resources and furthermore, in conditions of high demand of cognitive control mechanisms, distractor processing is enhanced due to a reduction in the availability of attention controlled processes. Thus this study provided neurophysiological support for an active mechanism of attentional control that actively impacts processing of task-irrelevant distractors (Zhang et al., 2006). Although this study did not use Schröger's paradigm, Zhang et al.'s results suggest that the MMN can be actively modified by attention and that further research is needed to better understand the relationship between active cognitive processes and the processing of auditory distractors.

Another potentially viable explanation for similar distractibility indices in patients and controls despite abnormal sensory change detection in the former group may be found in Schröger's model, particularly in regard to his concept of the "variable threshold". The underlying premise is that MMN signals, the initial stage in the conscious detection of

auditory change, must be of a certain, though undetermined magnitude to exceed the threshold. The present data may suggest that the “variable threshold” is not as variable as initially proposed by Schröger’s model; it may be that even very minimal MMN signals are sufficient to initiate an involuntary attention switch, and moreover that any MMN input, even MMN signals based on disordered or abnormal sensory memory traces are sufficient to trigger attentional switching. Thus, it remains unclear whether any magnitude (high or low signals) of MMN input may trigger an attention switch as indexed by the P3a and whether there is indeed a direct relationship between abnormal MMN and subsequent indices of attention and cognitive processing.

There are two main limitations of the present study that should also be explored as potential factors to account for the current findings.

Firstly, statistical issues relating to power may have been a contributing factor. The demanding nature of the primary task which required participants to behaviorally discriminate between two very similar tones; a 50 ms duration tone and a 100 ms duration tone proved to be quite arduous. More than half of the patients and even a few controls that were recruited for this experiment were not able to achieve the performance criterion in the practice trials to be eligible for inclusion in this study. Hence, the final sample size was relatively low. Low power may have had little impact on finding significant reductions in MMN amplitude, which appears to be quite a robust phenomenon in the literature (Mitchie, et al., 2000). In contrast, abnormal P3a amplitude in schizophrenia is a less consistent phenomenon (Frodl, Meisenzahl, Muller, Greiner, Juckel, Leinsinger et al., 2001) and that may require more power to be consistently

observed. To the author's knowledge, this study represents the first attempt at investigating the RON in schizophrenia, thus its profile has yet to be determined.

The second main limitation of the study relates to the nature of the experimental paradigm used to test Schröger's pre-attentive attention switching model. The paradigm itself requires fast active discrimination of tones that differ in duration but may be perceived as quite similar and difficult to distinguish. A specified level of performance proficiency was established in the practice trials and only the schizophrenics who exceed the performance criterion were included in the formal recordings. This is may be possible that more representative individuals of schizophrenia in general were excluded based on their performance during the practice trials and that the current sample is not a valid representation in that these individuals were more cognitively high-functioning than those not included in the study. For reasons unknown, these patients were better equipped to cope with the high demand for controlled attention facilitation and their vigilance and psychomotor speed were not significantly compromised. Thus, although all potential patient participants were stable, ambulatory out-patients with chronic schizophrenia, the actual sample generated for this experiment may have been higher functioning than the general population of schizophrenics and inherently less distractible and/or better able to compensate for low-level information processing abnormalities, thereby minimizing the impact on measures of task-proficiency and ERP deviance. Although schizophrenics typically perform one to two standard deviations below the general population on standardized neuropsychological tests (Bilder, 1997), there were no differences between patients and controls who participated in this study on

neuropsychological measures of immediate auditory attention (i.e., digit span) or auditory working memory (i.e., letter-number sequencing).

6.2 Experiment 3

Small deviations in the duration of a sound can successfully induce involuntary shifts in attention (Schröger, 1997). The objective of experiment 3 was to compare patients and controls with respect to behavioural and electrophysiological indices of distractibility due to irregularities in the duration of sounds when their frequencies (high and low) were to be actively discriminated (during a frequency discrimination task). Using a modified version of Schröger's auditory discrimination paradigm, two duration deviants were employed; a long (100 ms) duration sound change and a short (50 ms) duration sound change. Based on an extensive review of the literature, it appears that only one other study (Roeber, Widmann, & Schröger, 2003) has examined distractibility due to changes in sound duration using Schröger's paradigm.

As predicted by Schröger's model, low-probability duration deviant tones embedded in a series of high-probability standard duration tones caused an involuntary attention shift towards the deviant (Roeber et al., 2003). In the present study, distraction-related effects evoked by duration deviants were found in both the behavioral and electrophysiological data for patients and controls. Behavioral deterioration as measured by reaction time prolongation was most apparent in the long duration deviant condition (see Figure 6); reaction time was significantly prolonged by approximately 32 ms to the long duration deviant as compared to the short duration standard tones. There were no

significant behavioral distraction effects in terms of accuracy indices (i.e., % of correct responses or % of non-responses) in the long duration deviant condition.

Reaction time prolongation in the short duration deviant condition was minimal; reaction time to the short duration deviant tones was increased by 11 ms as compared to reaction time to the long standard duration tones. The percentage of correct responses to the short duration deviant was significantly lower than the percentage of correct responses to the short duration standard tone. In addition, the percentage of non-responses to the short duration deviant tones was significantly higher compared to the percentage of non-responses to the short duration standard tone.

For ERP indices of distractibility, only the long duration deviant condition elicited the expected deviance-related effects. As illustrated by Figure 6, the MMN, and the P3a and, to a lesser extent, the RON, were visible in the grand-averaged waveforms. These ERP deviance-related effects were negligible in the short duration deviant condition (see Figure 6).

Overall, these findings support the notion that deviations in a sound's duration evoke involuntary changes in attention and give rise to distractibility evidenced behaviorally and in ERP deviance-related effects. However, contrary to the main predictions of the present study, namely, that the schizophrenics would show less behavioral distractibility and lower P3a and RON amplitude as a result of abnormally low mismatch negativity input, measures of distractibility were quite similar across both schizophrenics and controls.

The main finding of Experiment 3 was that MMN amplitude was significantly reduced to the long duration deviant tones in the schizophrenics compared to the controls. There were no significant group effects with respect to P3a or RON amplitude. Similarly, from a behavioral perspective, reaction time prolongation and the percentage of correct responses were comparable across both groups. There was a significant difference with respect to the percentage of non-responses; the schizophrenics produced significantly more non-responses to deviant tones compared to controls.

In a recent study, using healthy control subjects, Roeber, Widmann and Schröger (2003) examined a duration increment deviant (i.e., 400 ms; deviant vs. 200 ms; standard) in a location discrimination task. This study showed that although the processing of a sound's duration can be distracted by low-probability, task-irrelevant changes in its duration, the behavioural distraction effects induced by detection of duration change were smaller than expected, and were considerably smaller than those observed to location and frequency deviants. Roeber et al. (2003) reported that reaction time to duration deviant tones was prolonged by approximately 15 ms compared to the reaction time to the standard duration tones; this is comparable to the estimates of reaction time prolongation obtained in the present study. In order to account for reduced behavioural distractibility using duration deviants relative to frequency or location deviants, Roeber et al. examined differences in the onset/offset of location and duration deviants. For example, in their location-task duration-deviant condition, primary discrimination of sound location (i.e., left or right speaker) can be made at the onset of the tone, and occurs much earlier than the detection of a duration change since this

change can only be detected with the offset of the shortest duration (i.e., 200 ms) tone. Thus, detection of duration deviance occurs relatively late in the processing of irrelevant sound change as compared to the processing of task-relevant (location or frequency, both of which can be determined at the onset of stimulus) information. Therefore, Roeber et al (2003) argued that task-relevant processing is well underway before a potential irregularity in duration occurs and is detected which subsequently minimizes the impact of deviance on task proficiency.

Reports of abnormal MMN amplitude to duration increments (i.e., long duration deviants) rather than to duration decrements (i.e., short duration deviants) in a typical passive paradigm is a robust finding in the schizophrenia literature (Mitchie, Innes-Brown, Todd, & Jablensky, 2002; Mitchie, 2001; Shelley et al., 1991). As previously mentioned, the main finding of the present experiment was that MMN amplitude was significantly reduced to long, but not to short duration deviant tones in patients compared to controls. To account for this discrepancy in MMN response to duration deviants, Mitchie (2001) proposed that ceiling/floor effects may be a contributing factor. Specifically, Mitchie (2001) argued that duration decrements produced a substantially smaller response in healthy controls, and thus, the lack of significant reduction in MMN amplitude to duration decrements may simply be attributed to floor effects. In contrast, long duration deviants may be more salient, given a larger separation between the sound properties of the standard and of the deviant tones, thus giving rise to an enhanced MMN response in control subjects and thereby increasing the sensitivity of detecting group differences.

The mismatch negativity has been conceptualized as the initial stage in a chain of brain processes that leads to involuntary orienting of attention to changes in the acoustic environment. Schröger's model supposes that this attentional shift will only occur if the magnitude of the MMN signals surpasses a certain threshold. Thus, this model predicts that the P3a and behavioral distraction elicited in patients (due to change detection) would be reduced as a result of a significant reduction in the amplitude of the MMN. This was clearly not evident in the data derived from either Experiment 2 or Experiment 3. Rather, the data showed that the patients responded in a fashion similar to controls, eliciting the predicted distraction effects.

One possible explanation for these findings which was not presented in the discussion of Experiment 2 relates to the specific neuronal generators of the MMN and how they may contribute to processes involved in the switching of attention. As discussed briefly in the introduction section of Experiment 1, recent evidence suggests that more than a single source may contribute to the scalp-recorded MMN (Giard, Perrin, Echallier, Thevenet, Froment, & Pernier, 1994). However, most MMN-schizophrenia studies have not focused on the discrimination of MMN generated by the multiple brain sources. Although MMN is mainly generated in the supratemporal auditory cortex (Scherg, Vajsar, & Picton, 1989), an additional contribution to the MMN generation has been localized to the frontal lobe (Molnar, Skinner, Csepe, Winkler, & Karmos, 1995). The supratemporal contribution is thought to reflect the activity of sensory memory, the establishment of sensory memory traces and upcoming irregularities and the detection of change, while the contribution of the frontal lobes to the MMN is thought to reflect the

switching of attention to change (Alho, Woods, Algazi, Knight & Näätänen, 1994).

The frontal MMN generator is activated later than the auditory cortex generator (Rinne, Alho, Ilmoniemi, Virtanen, & Naatanen, 2000). Studies that have differentiated between these generators have reported normal MMN amplitude at mastoids electrodes, but reduced MMN amplitude at frontal sites in schizophrenia (Baldeweg, Klugman, Gruzelier, & Hirsch, 2002; Shinozaki, Yabe, Sato, Hiruma, Sutoh, Nashida, Matsuoka, & Kaneko, 2002; Alain, Hargrave, & Woods, 1998). In the context of the present findings, if frontal generators are responsible for initiating the processes of involuntary attention switching and are dysfunctional in schizophrenics, perhaps the normal activation of the supratemporal generators is sufficient to evoke a frontal MMN subcomponent and thus giving rise to a normal P3a response (Mitchie, Innes-Brown, Todd, & Jablensky, 2003). Future studies should include a larger number of scalp recording sites and specifically record from both frontal and mastoid electrodes to determine whether temporal-related detection or frontal-related switching procedure are differentially involved in distractibility in patient with schizophrenia. The inclusion of mastoids recordings, a site at which MMN reverses polarity would also be useful in the identification of MMNs in patients with schizophrenia as their MMNs are typically smaller as compared to controls and are more variable with respect to peak latency.

A main limitation of Experiment 3, as in Experiment 2, was the level of difficulty associated with the task demands of the paradigm. Although the primary discrimination task in Experiment 3 (i.e., discrimination and response to high and low frequency tones)

was inherently easier than that of Experiment 2, some patients were still not able to successfully achieve the criterion level during practice trials required to participate in the study. Thus, the generalizability of the present results may be limited. One means to reduce the degree of difficulty may be to increase the interstimulus interval between stimulus presentations. In the present study, a 1.3 second interval was used. Roeber et al. (2003) demonstrated that the behavioural and electrophysiological effects of distractibility using Schröger's auditory discrimination paradigm are not contingent of the timing of the stimulus occurrence. Roeber et al. (2003) tested inter-stimulus-intervals in the range of 1300 ms to 3000 ms and found no differences in the magnitude of distractibility indices.

7.0 Overall Summary

The main finding across Experiments 1, 2 and 3 was a significant reduction in the amplitude of the MMN in patients compared to controls. This finding supports the robustness of a deficit in early, pre-attentive information-processing in schizophrenia. The MMN is generated by a sensory-memory based discriminatory process that registers and compares the difference between memory traces of previous input to present stimulation and detects change in a sequence of sounds. Thus, reduced MMN amplitude suggests a dysfunction in the automatic encoding/retrieval of neural representations of auditory input in sensory memory and/or in the detection of auditory change based on sensory memory processes. It remains unclear, however, what, if any impact abnormal MMN amplitude has on subsequent higher-ordered information-processing processes

such as involuntary attention switching and task proficiency, indexed behaviorally and with neuroelectrophysiological measures. The results from Experiments 2 and 3 suggest that abnormal MMN amplitude has no behavioural impact on task proficiency; patients and controls displayed very similar levels of performance in terms of speed and accuracy indices. In addition, the electrophysiological data also failed to support a clear relationship between abnormal MMN and deviance-related ERPs.

Multiple ideas were put forth to account for these findings including the contribution of a top-down compensatory effect, as well as methodological issues related to patient sample selection and power. Future research in this area may benefit from modifications to the paradigm such as increasing the inter-stimulus interval or the duration of the stimuli to ease the level of difficulty to promote recruitment of a more representative sample of individuals with schizophrenia. In addition, future attempts at applying Schröger's distraction model to schizophrenia may benefit from recording MMN from multiple brain regions for more accurate identification and separation of mismatch processes precipitating distraction in this attention deficient disorder.

8.0 References

- Aaltonen, O., Niemi, P., Nyrke, T., & Tuhkanen, J. (1987). Event-related brain potentials and the perception of a phonetic continuum. Biological Psychology, 24, 197-207.
- Aaltonen, O., Tuomainen, J., Laine, M., & Niemi, P. (1993). Cortical differences in tonal versus vowel processing as revealed by an ERP component called mismatch negativity (MMN). Brain Language, 44, 139-152.
- Abel, L., Friedman, L., Jasberger, J., Malki, A., & Meltzer, H. (1991). Quantitative assessment of smooth pursuit gain and catch-up saccades in schizophrenia and affective disorders. Biological Psychiatry, 29, 1063-72.
- Addington, J., Addington, D., & Gasbarre, L. (1997). Distractibility and Symptoms of Schizophrenia. Journal of Psychiatry Neuroscience, 22 (3), 180-184.
- Adler, L., Pachtman, E., Franks R., Pecevich, M., Waldo, M., & Freedman, R.. (1982) Neuropsychological evidence for a defect in neural mechanisms involved in sensory gating in schizophrenia. Biological Psychiatry, 17, 639-654.
- Ahveninen, J., Jaaskelainen, I., Pekkonen, E., Hallberg, A., Hietanen, M., Näätänen, R., & Schröger, E. (2000). Increased distractibility by task-irrelevant sound changes in abstinent alcoholics. Alcohol Clin Exp Res, 24, 1850-1854.
- Alain, C., Bernstein, L., Cortese, F., Yu, H., & Zipursky, R. (2002). Deficits in automatically detecting changes in conjunction of auditory features in patients with schizophrenia. Psychophysiology, 39, 599-606.
- Alain, C., Hargrave, R., & Woods, D. (1998) Processing of auditory, stimuli during visual attention in patients with schizophrenia. Biol. Psychiat, 44, 1151-1159.
- Alho, K., Woods, D., Algazi, A., Knight, R., & Naatanen, R. (1994b) Lesions of frontal cortex diminish the auditory mismatch negativity. Electroencephalography and Clinical Neurophysiology, 91, 353-362.
- Alho, K, Escera, C., Diaz, R., Yago, E., & Serra J. (1997) Effects of involuntary auditory attention on visual task performance and brain activity. Neuroreport, 8, 3233-3237.
- Allison, T., Wood, C., & McCarthy, G. (1986). The central nervous system. In M.G.H. Coles, E. Donchin, & S. Porges (Eds.), *Psychophysiology: Systems, Processes and Applications*, pp. 5-25. New York: Guilford.

American Psychiatric Association. (1994) Diagnostic and Statistical Manual of Mental Disorders. 4th Edition Washington, DC: The Association.

Army Individual Test Battery (1964). Manual of Directions and Scoring. War Department, Adjutant General's Office: Washington, DC.

Asarnow, R., & MacCrimmon, D. (1978). Residual performance deficit in clinically remitted schizophrenics: A marker of schizophrenia? Journal of Abnormal Psychology, 87, 597-608.

Baddeley, A. (1986). Working Memory. Oxford: Oxford University Press.

Baddeley, A. (2000). The episodic buffer: A new component of working memory. Trends in Cognitive Science, 4, 417-423.

Baldeweg, T., Klugman, A., Gruzelier J., & Hirsch, S. (2002). Impairment in frontal but not temporal components of mismatch negativity in schizophrenia. Int J Psychophysiology, 43, 111-122.

Barch, D., Carter, C., Hachten, P., Usher, M., & Cohen, J. (1999). The benefits of distractibility: mechanisms underlying increased Stroop effects in schizophrenia. Schizophrenia Bulletin, 25, 749-762.

Barta, P., Pearlson, G., Powers, R., Richards, S., & Tune, L. (1990). Auditory hallucinations and smaller superior temporal gyrus volume in schizophrenia. American Journal of Psychiatry, 147, (11), 1457-1462.

Berger, H. (1929). Über das elektroencephalogramm des menschen. Translated and reprinted in Pierre Gloor, Hans Berger on the electroencephalogram of man. Electroencephalography and Clinical Neurophysiology, (Supp. 28), Amsterdam: Elsevier.

Bernstein, A. (1987). Orienting response research in schizophrenia: where we have come and where we might go. Schizophrenia Bulletin, 13, 623-41.

Berti, S., & Schröger, E. (2001). A comparison of auditory and visual distraction effects: behavioral and event-related indices. Cognitive Brain Research, 10, 265-273

Berti, S., & Schröger, E. (2003). Working memory controls involuntary attention switching: evidence from an auditory distraction paradigm. Eur J Neurosci, 17, 1119-1122.

Berti, S., Roeber, U., & Schröger, E. (2004). Bottom-up influences on working memory: behavioral and electrophysiological distraction varies with distractor strength. Exp Psychol., 51, 249-57.

Bilder, R., Turkel, E., Lipschutz-Broch, L., & Lieberman, J. (1992) Antipsychotic medication effects on neuropsychological functions. Psychopharmacol Bull, 28, 353-66.

Bilder, R. (1997). Neurocognitive impairment in schizophrenia and how it affects treatment options. Can J Psychiatry, 153, 255-264.

Blackwood, D., St.Clair, D., & Kutcher, S. (1986). P300 event-related potential abnormalities in borderline personality disorder. Biol Psychiatry, 21, 560-4.

Bleuler, E: Dementia Praecox or the Group of Schizophrenias (1911). Translated by Zinklin. New York, International Sites Press, 1950.

Bottcher-Gandor, C., & Ullsperger, P. (1992). Mismatch negativity in event-related potentials to auditory stimuli as a function of varying interstimulus interval. Psychophysiology, 29, 546-550.

Braff, D. (1993). Information processing and attention dysfunction in schizophrenia. Schizophrenia Bulletin, 19, 233-259.

Bramon, E., Croft, R., McDonald, C., Virdi, G., Gruzelier, J., Baldeweg, T., Sham, P., Fangou, S., & Murray, R. (2004). Mismatch negativity in schizophrenia: a family study. Schizophrenia Research, 67, 1-10.

Broadbent, D. (1958). Perception and Communication. London: Pergamon Press.

Brockhaus-Dumke, A., Tendolkar, I., Pukrop, R., Schultze-Lutter, F., Klosterkötter, J., & Ruhrmann, S. (2005). Impaired mismatch negativity generation in prodromal subjects and patients with schizophrenia. Schizophrenia Research, 73, 297-310.

Catts, S., Shelley, A., & Ward, P. (1995) Brain potential evidence for an auditory sensory memory deficit in schizophrenia. Am. J. Psychiat. 152, 213-219.

Cohen, J. (1988). Statistical power analysis for the behavioural sciences. Hillsdale, NJ: Erlbaum.

Columbo, M., D'Amato, M., Rodman, H., & Gross, C. (1990) Auditory association cortex lesions impair auditory short-term memory in monkeys. Science. 247, 336-338.

Courchesne, E., Hillyard, S., & Galambos, R (1975). Stimulus novelty, task relevance, and the visual evoked potential in man. Electroencephalography Clinical Neurophysiology, 39, 131-143.

- Courchesne, E. (1977). Event-related brain potentials: comparison between children and adults. Science, 197, 589-592.
- Courchesne, E. (1978). Changes in P3 waves with event repetition: long-term effects on scalp distribution and amplitude. Electroencephalography and Clinical Neurophysiology, 45, 754-766.
- Cowan, N. (1984) On short and long auditory stores. Psychological Bulletin, 96, 341-370.
- Csepe, V., Karmos, G., & Molnar, M. (1989) Subcortical evoked potential correlates of early information processing: Mismatch negativity in cats. In E. Basar & T. H. Bullock (Eds.) Brain dynamics: Progress and perspectives, 279-289.
- Devrim-Ucok, M., Keskin-Ergen, Y., & Ucok, A. (2006). Novelty P3 and p3b in first-episode schizophrenia and chronic schizophrenia. Prog Neuro-Psychopharm Bio Psychiatry, 30, 1426-1434.
- Escera, C., & Grau, C. (1996) Short-term replicability of the mismatch negativity. Electroencephalography and Clinical Neurophysiology, 100, 549-554.
- Escera, C., Alho, K., Winkler, I., & Naatanen, R. (1998) Neural mechanisms of involuntary attention switching to novelty and change in the acoustic environment. J Cogn Neurosci, 10, 590-604.
- Escera, C., Alho, K., Schroger, E., & Winkler, I. (2000) Involuntary attention and distractibility as evaluated with event-related brain potentials. Audiol Neurotol, 5, 151-166.
- Fabiani, M., & Friedman, D. (1995). Changes in brain activity in aging: the novelty oddball. Psychophysiology, 32, 579-594.
- Fabiani, M., Gratton, G., & Coles, M. (2000). Event-related brain potentials. In J. Cacioppo, L. Tassinary & G. Berntson (Eds.), Handbook of Psychophysiology (2nd ed.) pp. 53-83. Cambridge University Press.
- Faux, S., McCarley, R., Nestor, P., Shenton, M., Pollack, S., Penhume, V., Mondrow, E., Marcy, B., Peterson, A., et al. (1993). P300 topographic asymmetries are present in unmedicated schizophrenics. Electroencephalogr Clin Neurophysiol., 88, 32-41.
- Ford, J., & Hillyard, S. A. (1981). Event related potentials (ERPs) to interruptions of steady rhythm. Psychophysiology, 18, 322-330.

Ford, J., White, P., Csemansky, J., Faustman, W., Roth, W., & Pfefferbaum, A. (1994). ERPs in schizophrenia: effects of antipsychotic medication. Biol Psychiatry, 36, 153-70.

Freedman, R., Waldo, M., Bickford-Wimer, P., & Nagamoto, H. (1991). Elementary neuronal dysfunction in schizophrenia. Schizophrenia Research, 4, 233-243.

Freedman, R., Adler, L., Waldo, M., Pachtman, E., & Franks, R.. (1983) Neurophysiological evidence for a defect in inhibitory pathways in schizophrenia: Comparison of medicated and drug-free patients. Biol Psychiatry, 18, 537-552.

Friedman, D., Vaughan, H., & Erlenmeyer-Kimling, L. (1982). Cognitive brain potentials in children at risk for schizophrenia: preliminary findings. Schizophrenia Bulletin, 8, 514-31.

Friedman, D., & Squires-Wheeler, E. (1994). Event-related potentials (ERPs) as indicators of risk for schizophrenia. Schizophrenia Bulletin, 11, 63-74.

Friedman, D., Cyciwicz, Y., & Gaeta, H. (2001). The novelty P3: an event-related brain potential (ERP) sign of the brain's evaluation of novelty. Neuroscience and Biobehav Review, 25, 355-373.

Frodl, T., Meisenzahl, E., Muller, D., Greiner, J., Juckel, G., Leinsinger, G., Hahn, H., & Hegerl, U. (2001). Corpus callosum and P300 in schizophrenia. Schizophrenia Research, 49, 107-120.

Giard, M., Perrin, J., & Bouchet, P. (1990) Brain generators implicated in the processing of auditory stimulus deviance: a topographic event-related potential study. Psychophysiology, 27, 627-640.

Giard, M., Perrin, F., Echallier, J., Thevenet, Froment, J., & Pernier, J. (1994). Dissociation of temporal and frontal components in the human auditory N1 wave: a scalp current density and dipole model analysis. Electroencephalography Clin Neurophysiology, 92, 238-252.

Goeree, R., O'Brien, B., Goering, P., Blackhouse, G., Agro, K., Rhodes, A., & Watson, J. (1999). The economic burden of schizophrenia in Canada. Can J Psychiatry, 44, 464-472.

Goldberg, T., Saint-Cry, J., & Weinberger, D. (1990). Assessment of procedural learning and problem solving in schizophrenic patients by Tower of Hanoi type tasks. J Neuropsychiatry Clin Neurosci., 2, 165-73.

- Goldman-Rakic, P. (1994). Working memory dysfunction in schizophrenia. J Neuropsychiatry Clin Neurosci, 6, 348-357.
- Green, M. (1996). What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry, 153, 321-330.
- Grillon, C., Courchesne, E., Ameli, R., Geyer, M., & Braff, D. (1990) Increased distractibility in schizophrenic patients. Arch Gen Psychiatry, 47, 171-179.
- Grillon, C., Courchesne, E., Ameli, R., Elmasian, R., & Braff, D. (1990). Effects of rare non-target stimuli on brain electrical activity. International Journal of Psychophysiology, 9, (3), 257-67.
- Grillon, C., Ameli, R., Courchesne, E., & Braff, D. (1991). Effects of task relevance and attention on P3 in schizophrenic patients. Schizophr Res., 4, 11-21.
- Hafner, H., & der Heiden, W. (1997). Epidemiology of Schizophrenia. Canadian Journal of Psychiatry, 42, 139-51.
- Hagger, C., Buckley, P., Kenny, J., Friedman, L., Ubogy, D., & Meltzer, H. (1993). Improvement in cognitive functions and psychiatric symptoms in treatment-refractory schizophrenic patients receiving clozapine. Biol Psychiatry, 34, 702-12.
- Hari, R., Hamalainen M., Ilmoniemi, R., Kaukoranta, E., Reinkainen, K., Salminen, J., Alho, K., Naatanen, R., & Sams, M. (1984). Responses of the primary auditory cortex to pitch changes in a sequence of tone pips: Neuromagnetic recordings in man. Neuroscience Letters, 50, 127-132.
- Harvey, P., Howanitz, E., Parrella, M., White, L., Davidson, M., Mohs, R., Hoblyn, J., & Davis, K. (1998). Symptoms, cognitive functioning and adaptive skills in geriatric patients with lifelong schizophrenia: a comparison across treatment sites. Am J Psychiatry, 155, 1080-1086.
- Heaton, R., & Crowley, T. (1981) Effects of psychiatric disorders and their somatic treatment on neuropsychological test results. IN: Filskov SB, Boll, TJ, editors. Handbook of Clinical Neuropsychology. New York: J Wiley, pp481-525.
- Hillyard, S. (1993). Electrical and magnetic brain recordings: Contributions to cognitive neuroscience. Current Opinion in Neurobiology, 3, 217-214.
- Hillyard, S., & Kutas, M. (1983). Electrophysiology of cognitive processing. Annu Rev Psychol, 34, 33-61.

- Hiraysu, Y., Potts, G., O'Donnell, B.F. et al. (1998). Auditory mismatch negativity in schizophrenia: topographic evaluation with a high density recording montage. Am. J. Psychiat. 155, 1281-1284.
- Holzman, P. (1987). Recent studies of psychophysiology of schizophrenia. Schizophrenia Bulletin, 13, 49-75.
- Holzman, P., & Goldman-Rakic, P. (1995). Spatial working memory deficits in relatives of schizophrenics patients. Arch General Psychiatry, 52, 821-828.
- Imada, T., Hari, R., Loveless, N., McEvoy, L., & Sams, M. (1993). Determinants of the auditory mismatch response. Electroencephalogr Clin Neurophysiol. 87, 144-153.
- Iverson, S., & Mishkin, M. (1973). Comparison of superior temporal and inferior prefrontal lesions on auditory and non-auditory tasks in rhesus monkeys. Brain Research, 55, 355-367.
- Jaakelainen, I., Schroger, E., & Naatanen, R. (1999). Effects of ethanol on auditory distraction: An ERP and behavioral study. Psychopharmacology, 141, 16-21.
- Javitt, D., & Zukin, S. (1991). Recent advances in the phencyclidine model of schizophrenia. American Journal of psychiatry, 148, 1301-1308.
- Javitt, D., Steinschneider, M., Schroeder, C., & Arezzo, J. (1996). Role of cortical N-methyl-D-aspartate receptors in auditory sensory memory and mismatch negativity generation: implications for schizophrenia. Proc Natl. Acad. Sci, 93, 11962-11967.
- Javitt, D., Strous, D., Grochowski, S., Ritter, W., & Cowan, N. (1997) Impaired precision, but normal retention, of auditory sensory ("echoic") memory information in schizophrenia. J Abnorm Psychol, 106, 315-324.
- Javitt, D., Leiderman, E., Cienfuegos, A., & Shelley, A. (1999) Pan modal processing imprecision as a basis for dysfunction of transient memory storage systems in schizophrenia. Schizophr Bull, 25, 763-775.
- Javitt, D., Grochowski, S., Shelley, A., & Ritter, W. (1998). Impaired mismatch negativity (MMN) generation in schizophrenia as a function of stimulus deviance, probability, and interstimulus/interdeviant interval. Electroencephalogr Clin Neurophysiol. 108, 143-153.
- Javitt, D., Doneshka, P., & Zylberman, I., Ritter, W., & Vaughan, W. (1993). Impairment of early cortical processing in schizophrenia: an event-related potential confirmation study. Biol. Psychiatry, 33, 513-519.

- Javitt, D., Doneshka, P., Grochowski, S., & Ritter, W. (1995). Impaired mismatch negativity generation reflects wide-spread dysfunction of working memory in schizophrenia. Arch. Gen. Psychiatry, *52*, 550-558.
- Javitt, D., Shelley, A., & Ritter, W. (2000). Associated deficits in mismatch negativity in schizophrenia. Clinical Neurophysiology, *111*, 1733-1737.
- Javitt, D., Shelley, A., Silipo, G., & Lieberman, J. (2000). Deficits in auditory and visual context-dependent processing in schizophrenia: defining the pattern. Arch Gen Psychiatry, *57*, 1131-1137.
- Jessen, F., Fries, T., Kucharski, C., Nishimura, T., Hoeing, K., Maier, W., Falkai, P., & Heun, R. (2001). Amplitude reduction of the mismatch negativity in first-degree relatives of patients with schizophrenia. Neuroscience Letters, *309*, 185-188.
- Johnson, R. (1986). A triarchic model of P300 amplitude. Psychophysiology, *23*, 367-84.
- Jones, D., & Macken, W. (1993). Irrelevant tones produce an irrelevant speech effect: Implications for phonological coding in working memory. J Exp Psychol Learn Mem Cogn, *19*, 369-381.
- Jones, R., & Callaway, E. (1970). Auditory evoked responses in schizophrenia--a reassessment. Biol Psychiatry, *2*, 291-8.
- Kane, N., Curry S., Rowlands, C., Manara, A., Lewis, T., Moss, T., Cummins, S., & Butler, S. (1996). Event-related potentials- neuropsychological tools for predicting emergence and early outcome from traumatic coma. Intensive Care, *22*, 39-46
- Kasai, K., Okazawa, K., Nakagome, K. et al. (1999). Mismatch negativity and N2b attenuation as an indicator for dysfunction of the pre-attentive and controlled processing for deviance detection in schizophrenia: a topographic event-related potential study. Schiz. Res. *35*, 121-129.
- Kasai, K., Nakagome, K., Iwanami, A., Fukuda, M., Itoh, K., Koshida, I., & Kato, N. (2002). No effect of gender on tonal and phonetic mismatch negativity in normal adults assessed by a high-resolution EEG recording. Brain Res Cognitive Brain Res, *13 (3)* 3-5-312.
- Kathman, N., Wagner, M., Rendtorff, N., & Engel, R. (1995). Delayed peak latency of the mismatch negativity in schizophrenics and alcoholics. Biol Psychiatry. *37*, 754-757.
- Kahneman, D. (1973). Attention and Effort. New Jersey, Englewood Cliffs: Prentice Hall.

Kaukoranta, E., Sams, M., Hari, R., Hamalaolinen M., & Naatanen, R. (1989). Reactions of human cortex to a change in tone duration. Hearing Research 41, 15-22.

Kay, S., Fiszbein, A., & Opler, L. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia Bulletin, 13, 261-271.

Knight, R. (1984). Decreased response to novel stimuli after prefrontal lesions in man. Electroencephalography Clin Neurophysio, 59, 9-20.

Knight, R., et al. (1988) The effects of lesions of superior temporal gyrus and inferior parietal lobe on temporal and vertex components of the human AEP. Electroencephalogr. Clin. Neurophysiol. 70, 499-509.

Knott, V., Mahoney, C., Labelle, A., Ripley, C., Cavazzoni, P., & Jones, B. (1999). Event-related potentials in schizophrenic patients during a degraded stimulus version of the visual continuous performance task. Schizophrenia Research, 15, 263-78.

Kogoj, A., Pirtosek, Z., Tomori, M., & Vodusek, D. (2005). Event-related potentials elicited by distractors in an auditory oddball paradigm in schizophrenia. Psychiatry Research, 15, 49-59.

Korostenskaja, M., Dapsys, K., Siurkute, A., Maciulis, V., Ruksenas, O., & Kahkonen, S. (2005). Effects of Olanzapine on auditory P300 and mismatch negativity in schizophrenia spectrum disorders. Progress in Neuro-psychopharmacology & Biological Psychiatry, 29, 543-548.

Korpilahti, P. & Lang, H. (1994). Auditory ERP components and mismatch negativity in dysphasic children. Electroencephalography and Clinical Neurophysiology.

Kraepelin, E. (1919). Dementia Praecox and Paraphrenia. Translated by Barclay RM; edited by Robertson GM. New York Robert E Kreiger, 1971.

Kraus, N, McGee, T., Carrell, T., & Sharma, A. (1995) Neurophysiologic bases of speech discrimination. Ear Hear. 1, 19-37.

Kutcher, S., Blackwood, D., St.Clair, D., Gaskell, D., & Muir, W. (1987). Auditory P300 in borderline personality disorder and schizophrenia. Archives of General Psychiatry, 44, 645-650.

Lembregts, M., & Timsit-Berthier, M. (1993) The value of cognitive psychophysiological studies in a comprehensive approach to schizophrenia (treatment of information and attention capacities in acute-stage schizophrenia). Acta Psychiat. Belgica, 93, 322-342.

- Leppanen, P., Laukkonen, K., & Lyytinen, H. (1992). Mismatch negativity in children and adults. Abstracts of the 10th International Conference on the Event-Related Potentials of the Brain (EPIC X), Eger, Hungary, May31-June 5,.
- Levit, R., Sutton, S., & Zubin, J. (1973). Evoked potential correlates of information processing in psychiatric patients. Psychological Medicine, 3, 487-494.
- Light, G., & Braff, D. (2005a). Mismatch negativity deficits are associated with poor functioning in schizophrenic patients. Arch Gen Psychiatry, 62, 127-136.
- Light, G., & Braff, D. (2005b). Stability of mismatch negativity deficits and their relationship to functional impairments in chronic schizophrenia. Am J Psychiatry, 162, 9, 1741-1743.
- Lounasmaa, O., Hari, R., Joustiniemi, S., & Hamalainen, M. (1989). Multi-SQUID recordings of human cerebral magnetic fields may give information about memory processes. Europys. Lett.9, 603-608.
- Lynn, R. (1966). Attention, arousal and the orientation reaction. Vol 3. London: Pergamon.
- McCarley, R., Faux, S., Shenton, M., Nestor, P., & Adams, J. (1991). Event-related potentials in schizophrenia: their biological and clinical correlates and a new model of schizophrenic pathophysiology. Schizophrenia Research, 4, 209-231
- McGhie, A., Chapman, J., & Lawson, J. (1965) The effect of distraction of schizophrenic performance. 2. Perception and immediate memory. Br J Psychiatry, 3, 383-390.
- Mager, R., Falkenstein, M., Stormer, R., Brand, S., Muller-Spahn, F., & Bullinger, A. (2005). Auditory distraction in young and middle-aged adults: a behavioral and event-related potential study. J Neural Transmission, 112, 1165-1176.
- Mangun, G., & Hillyard, S. (1987). The spatial allocation of visual attention as indexed by event-related brain potentials. Human Factors, 29, 195-212.
- Mantysalo, S., & Naatanen, R. (1987). The duration of a neuronal trace of an auditory stimulus as indicated by event-related potentials. Biological Psychology, 24, 183-195.
- Marcoux, A., Muller-Grass, A., Logan, J., & Campbell, K. (1999) Mismatch negativity to inclusions of noise within complex spectrotemporal sound patterns. Neuroreport, 10, 2157-2163.

- Massopust, L., Wolin, L., & Frost, V. (1991) Frequency discrimination thresholds following auditory cortex ablations in the monkey. J Aud Res. 11, 227-233.
- McGhie, A., & Chapman, J. (1961). Disorders of attention and perception in early schizophrenia. Br J Med Psychol., 34, 103-116.
- Meltzer, H., & McGurk, S. (1999). The effects of clozapine, risperidone and olanzapine on cognitive function in schizophrenia. Schizophrenia Bulletin, 25, 233-255.
- Merrin, E., & Floyd, T. (1994). P300 responses to novel auditory stimuli in hospitalized schizophrenics patients. Biological Psychiatry, 36, 527-542.
- Michie, P., Budd, T., Todd, J., Rock, D., Wichmann, H., Box, J., & Jablensky, A. (2000). Duration and frequency mismatch negativity in schizophrenia. Clin. Neurophysiol. 111, 1054-1065.
- Michie, P. (2001). What has MMN revealed about the auditory system in schizophrenia? Int J Psychophysiology, 42 177-194.
- Michie, P., Innes-Brown, H., Todd, J., & Jablensky, A. (2002). Duration MMN in biological relatives of patients with schizophrenia spectrum disorders. Biological Psychiatry, 52, 749-758.
- Molnar, M., Skinner, J., Csepe, V., Winkler, I., & Karmos, G. (1995). Correlation dimension changes accompanying the occurrence of the mismatch negativity and the P3 event-related potential component. Electroencephalography Clinical Neurophysiology, 95, 118-126.
- Morstyn, R., Duffy, F., & McCarley, R. (1983). Altered P300 topography in schizophrenia. Arch Gen Psychiatry, 40, 729-34.
- Munka, L., & Berti, S. (2006). Examining task-dependencies of different attentional processes as reflected in the p3a and reorienting negativity components of the human event-related potential. Neurosci Letter, 396, 177-181.
- Näätänen, R., Pakarinen, S., Rinne, T., & Takegata, R. (2004). The mismatch negativity (MMN): towards the optimal paradigm. Clinical Neurophysiology, 115, 140-144.
- Näätänen, R., & Winkler, I. (1999) The Concept of Auditory Representation in Cognitive Neuroscience. Psychological Bulletin. 6, 826-859.
- Näätänen, R., & Alho, K. (1997). Mismatch Negativity-The Measure from Central Sound Representation Accuracy. Audiol Neurotol, 2, 341-353.

Näätänen, R., Paavilainen, P., Alho, K., Reinikainen, K., & Sams, M.. (1989). Do event related potentials reveal the mechanism of the auditory sensory memory in the human brain? Neuroscience Letters, 98, 217-221.

Näätänen, R., Paavilainen, P., Alho, K., & Reinikainen, K. (1989). Do event related potentials to infrequent decrements in duration of auditory stimuli demonstrate a memory trace in man? Neuroscience Letters, 107, 347-352.

Naatanen, R., Hukkanen, S., & Jarvilehto, T. (1980). Magnitude of stimulus deviance and brain potentials. Prog Brain Res., 54, 337-342.

Näätänen, R., Gaillard, A., & Mantysalo, S. (1978). Early selective attention effect on evoked potential reinterpreted. Acta Psychologica, 42, 313-329.

Näätänen, R. (1990). The role of attention in auditory information processing as revealed by event-related potentials and other measures of cognitive function. Behav Brain Sci. 13, 201-288.

Näätänen, R. (1992) Attention and brain function. Hillsdale, NJ: Erlbaum.

Nelson, H (1976). A modified card sorting sensitive to frontal lobe defects. Cortex, 12, 313-324.

Nicole, L., Lesage, A., & Lalonde, P. (1992). Lower incidence and increased male: female ratio in schizophrenia. British Journal of Psychiatry, 161, 556-557.

Nimchinsky, E., Sabatini, B., & Svoboda, K. (2002). Structure and function of dendritic spines. Annu. Rev. Physiol., 34, 313-353.

Nordgy, H., Hammerbourg, D., Roth, W., & Hugdahl, K. (1988). Event-related potentials to time-deviant and pitch deviant tones. Psychophysiology, 25, 249-261.

Novak, G., Ritter, W., & Vaughan, H. (1992). The chronometry of attention-modulated processing and automatic mismatch detection. Psychophysiology, 29, 412-30.

Nuechterlein, K., & Dawson, M. (1984). A heuristic vulnerability/stress model of schizophrenic episodes. Schizophrenia Bull, 10, 300-312.

O'Donnell, B., Hokama, E., McCarley, R., Smith, R., Salisbury, D., Mondrwo, E., Nestor, P., & Shenton, M. (1994). Auditory ERP's to non-target stimuli in schizophrenia: Relationship to probability, task-demands, and target ERP's. Int J Psychophysiol. 17, 219-231.

- Oades, R., Dittmann-Balcar, A., Zerbin, D., & Grzella, I. (1997). Impaired attention-dependent augmentation of MMN in non-paranoid vs. paranoid schizophrenic patients: a comparison with obsessive-compulsive disorder and healthy subjects. Biol. Psychiat. 41, 1196-1210.
- Onitsuka, T., Shenton, M., Salisbury, D., Dickey, C., Kasai, K., Toner, S., Frumin, M., Kikinis, R., Jolesz, F., & McCarley, R. (2004). Middle and inferior temporal gyrus gray matter volume abnormalities in chronic schizophrenia: an MRI study. Am J Psychiatry, 161, 9, 1603-11.
- Paavilainen, P., Alho, K., Reinikainen, K., Sams, M., & Naatanen, R. (1991) Right hemisphere dominance of different mismatch negativities. Electroenceph. Clin. Neurophysiol. 78, 466-479.
- Paavilainen, P., Karlsson, M., Reinikainen, K., & Naatanen, R. (1989). Mismatch negativity to change in the spatial location of an auditory stimulus. Electroencephalogr Clin. Neuroreport, 73, 129-141.
- Pekkonen, E., Rinne, T., & Naatanen, R. (1995) Variability and replicability of the mismatch negativity. Electroenceph. Clin. Neurophysiol., 96, 546-554.
- Pekkonen, E., Jousmaki, V., Partanen, J., & Karhu J. (1993) Mismatch negativity area and age-related auditory memory. Electroencephalography and Clinical Neurophysiology, 87, 321-325.
- Pekkonen, E., Jousmaki, V., Kononen, M., Reinikainen, K., & Partanen, J. (1994). Auditory sensory memory impairment in Alzheimer's disease: An event-related potential study. Neuroreport, 5, 2537-2540.
- Pekkonen, E., Jousmaki, V., Reinikainen, K., & Partanen, J. (1995). Automatic auditory discrimination is impaired in Parkinson's disease. Electroencephalography Clinical Neurophysiology, 1, 47-52.
- Peters, E., Nunn, J., Pickering, A., & Hemsley, D. (2002). Perceptual organization deficits in psychotic patients. Psychiatry Research, 110, 125-135.
- Pfefferbaum, A., Ford, J., White, P., & Roth, W. (1989). P3 in schizophrenia is affected by stimulus modality, response requirements, medication status and negative symptoms. Arch Gen Psychiatry, 46, 1035-1044.
- Picton, T., & Hillyard, S. (1974). Human auditory evoked potentials: II. Affects of attention. Electroencephalography Clinical Neurophysiology, 36, 191-199.

Picton, T. (1992). The P300 wave of the human event-related potential. Journal of Clinical Neurophysiology, 9, 456-479.

Polich, J., & Kok, A. (1995). Cognitive and biological determinants of P300; an integrative review. Biological Psychology, 41, 103-146.

Pritchard, W., Brandt, S., Shappel, A., O'Dell, T., & Barratt, E. (1986) No decrement in visual P300 amplitude during extended performance of the oddball task. International Journal of Neuroscience, 29, 199-204.

Pritchard, W. (1986). Cognitive event-related potential correlates of schizophrenia. Psychological Bulletin, 100, 43-66.

Rabinowicz, E., Silipo, G., Goldman, R., & Javitt, D. (2000). Auditory sensory dysfunction in schizophrenia. Arch gen Psychiatry, 57, 1149-1155.

Rinne, W., Alho, K., Ilmoniemi, R., Virtanen, J., & Naatanen, R. (2000). Separate time behaviours of the temporal and frontal mismatch negativity sources. Neuroimage, 12, 14-19.

Ritter, W., Vaughan, H., & Costa, L. (1968). Orienting and habituation to auditory stimuli: a study of short term changes in average evoked responses. Electroencephalography Clin Neurophysio, 25, 550-556.

Rodnick, E., & Shakow, D. (1940). Set in the schizophrenic as measured by a composite reaction time index. American Journal of Psychiatry, 97, 144-225.

Roeber, U., Widmann, A., & Schröger, E. (2003). Auditory distraction by duration and location deviants: a behavioural and event-related potential study. Brain Res Cogn Brain Res, 17, 347-357.

Roeber, U., Berti, S., & Schröger, E. (2003). Auditory distraction with different presentation rates: an event-related potential and behavioural study. Clin Neurophysio, 114, 341-349.

Romo, R., Brody, C., Herbabdez, A., & Lemus, L. (1999). Neuronal correlates of parametric working memory in the prefrontal cortex. Nature, 399, 470-473.

Roth, W. (1973). Auditory evoked responses to unpredictable stimuli. Psychophysiology, 10, 125-138.

Roth, W. (1977). Late event-rated potentials and psychopathology. Schizophrenia Bulletin, 3, 105-120.

- Roth, W., Horvath T., Pfefferbaum, A., & Kopell, B. (1980) Event-related potentials in schizophrenics. Electroencephalogr Clin Neurophysiol, 48, 12-139.
- Roth, W., & Kopell, B. (1973). P300: an orientating reaction in the human auditory evoked response in schizophrenics. Percept Mot Skills, 36, 219-225.
- Rugg, D., & Coles, M. (1995). *Electrophysiology of Mind: Event-related brain potentials and cognition*. Oxford University Press
- Rund, B. (1983). The effect of distraction on focal attention in paranoid and non-paranoid schizophrenic patients compared to normals and non-psychotic psychiatric patients. J. Psychiatric Res, 17, 241-250.
- Sabri, M., & Campbell, K. (2000). Mismatch negativity to inclusions and omissions of stimulus features. NeuroReport, 11 (7), 1503-1507.
- Saccuzzo, D., Hirt, M., & Spencer, T. (1974). Backward masking as a measure of attention in schizophrenia. J Abnormal Psychology. 83, 512-522.
- Saitoh, O., Niwa, S., Hiramatsu, K., Kameyama, T., Rymar, K., & Itoh, K. (1984). Abnormalities in late positive components of event-related potentials may reflect a genetic predisposition to schizophrenia. Biol Psychiatry, 19, 293-303.
- Sams, M., Paavilainen, P., Alho, K., & Naatanen, R. (1985b). Auditory frequency discrimination and event-related potentials. Electroencephalography and Clinical Neurophysiology, 62, 437-448.
- Sams, M., Hari, R., Rif, J., & Knuutila, J. (1993). The human auditory sensory memory trace persists about 10 sec: Neuromagnetic evidence. Journal of Cognitive Neuroscience, 5, 363-370.
- Schall, U., Catts, S., Karayanidis, F., & Ward, P. (1999). Auditor event-related potential indices of fronto-temporal information processing in schizophrenia syndromes: valid outcome prediction of clozapine therapy in a three-year follow-up. Int J Neuropsychopharmacology, 2, 83-93.
- Schall, U., Catts, S., Chaturvedi, S., Redenbach, J., Karayandis, F., & Ward, P. (1995) The effect of clozapine therapy on psychometric and event-related potential (ERP) measures on cognitive dysfunction in schizophrenia. Schizophr Res. 15, 164.
- Scherg, M., Vajsar, J., & Picton, T. (1989.) A source analysis of the late human auditory evoked potentials. Journal of Cognitive Neuroscience, L. 336-355.

- Schröger, E. (1996). A neural mechanism for involuntary attention shifts to changes in auditory stimulation. J Cogn Neurosci, 8, 527-539.
- Schröger, E., & Wolff, C. (1996) Mismatch response of the human brain to changes in sound location. Neuroreport, 7, 3005-3008.
- Schröger, E. (1997). On the detection of auditory deviants. A pre-attentive activation model. Psychophysiology, 34, 245-257.
- Schröger, E., & Wolff C. (1998a). Behavioral and electrophysiological effects of task-irrelevant sound change: A new distraction paradigm. Cogn Brain Res, 7, 71-87.
- Schröger, E., & Wolff, C. (1998b). Attentional orienting and reorienting is indicated by human event-related brain potentials. Neuroreport, 9, 3355-3358.
- Schröger, E., Giard, M. & Wolff, C. (2000). Auditory distraction: event-related potential and behavioral indices. Clinical Neurophysiology, 111, 1450-1460.
- Schwartz, B., Rosse, R., & Deutsch, S. (1992). Towards a neuropsychology of memory in schizophrenia. Psychopharmacology Bulletin, 28, 341-345.
- Shelley, A., Ward, P., Catts, S., Mitchie, P., Andrews, A., & McConaghy, N. (1991). Mismatch negativity: an index of a pre-attentive processing deficit in schizophrenia. Biol. Psychiat. 30, 1059-1062.
- Shelley, A., Javitt, D., & Vaughan, H. (1996). Mechanisms of auditory working memory dysfunction in schizophrenia. Biological Psychiatry, 39 655.
- Shelley, A., Silipo, G., & Javitt, D. (1999). Diminished responsiveness of ERP's in schizophrenic subjects to changes in auditory stimulation parameters: implications for theories of cortical dysfunction. Schiz. Res. 37, 65-79.
- Shinozaki, N., Yabe, H., Sato, Y., Hiruma, T., Sutoh, T., Nashida, T., Matsuoka, T., & Kaneko, S. (2002). The difference in Mismatch negativity between the acute and post-acute phase of schizophrenia. Biological Psychology, 59, 105-119.
- Shinozaki, N., Yabe, H., Sato, Y., Hiruma, T., Sutoh, T., Nashida, T. et al (2002). The difference in mismatch negativity between the acute and post-acute phase of schizophrenia. Biological Psychology, 59, 105-119.
- Shutara, Y., Koga, Y., Fujita K., Takeuchi, H., Mochida, M., & Takemasa, K. (1996) An event-related potential study on the impairment of automatic processing of auditory input in schizophrenia. Brain Topogr. 8, 285-289.

Sokolov, E. (1963). Perception and the conditioned reflex. Oxford, UK: Pergamon, Press.

Squires, N., Squires, K., & Hillyard, S. (1975). Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man. Electroencephalogr Clin Neurophysiol, 38, 387-401.

Steinhauer, S., & Zubin, J. (1982). Vulnerability to schizophrenia: Information processing in the pupil and event related potential. In Ilanin, I., and Usdin, E. (Eds.). Biological Markers in Psychiatry and Neurology. Pergamon Press, Oxford.

Strous, R., Cowan, N., Ritter, W., & Javitt, D. (1995) Auditory sensory ("echoic") memory dysfunction in schizophrenia. American Journal of Psychiatry, 152, 1517-1519.

Stuss, D., & Benson, D. (1985). The Frontal Lobes. New York Raven Press.

Sussman, E., Winkler, I., & Schorger, E. (2003). Top-down control over involuntary attention switching in the auditory modality. Psychonomic Bulletin & Review, 10, (3), 630-637.

Sutton, S., Braren, M., Zubin, J., & John, E. (1965). Evoked potential correlates of stimulus uncertainty. Science, 150, 1187-1188.

Tervaniemi, M., Lehtokoski, A., Sinkkonen, J., Virtanen, J., Ilmoniemi, R., & Näätänen, R. (1999). Test-retest reliability of mismatch negativity. Clin Neurophysiol, 110, (8), 1388-93.

The Psychological Corporation. (2001). Wechsler Test of Adult Reading. USA

Tiitinen, H., May, P., Reinikainen, K., & Naatanen, R. (1994). Attentive novelty detection in humans is governed by pre-attentive sensory memory. Nature, 370, 90-92.

Todd, J., Michie, P., Budd, T., Rock, D., & Jablensky, A. (2000). Auditory sensory memory in schizophrenia: inadequate trace formation? Psychiat. Res. 96, 99-115.

Umbricht, D., Javitt, D., Novak, G., Bates, J., Ollack, S., Lieberman, J., & Kane, J. (1998). Effects of clozapine on auditory event-related potentials in schizophrenia. Biol. Psychiat. 44, 716-725.

Umbricht, D., Koller, R., Schmid, L., Skrabo, A., Grubel, C., Huber, T., & Stassen, H. (2003). How specific are deficits in mismatch negativity generation to schizophrenia? Biol Psychiatry, 53, 1120-31.

Umbricht, D., Javitt, D., Novak, G., Bates, J., Pollack, S., Lieberman, J., & Kane, J. (1999). Effects of risperidone on auditory event-related potentials in schizophrenia. Int J Neuropsychopharmacology, 2, 299-304.

Umbricht, D., Schimd, L., Koller, R., Vollenweider, F., Hell, D., & Javitt, D. (2000). Ketamine-induced deficits in auditory and visual context-dependent processing in healthy volunteers. Arch Gen Psychiatry, 57, 1139-1147.

Umbricht, D., & Krljes, S. (2005). Mismatch negativity in schizophrenia: a meta-analysis. Schizophrenia Research, 76, 1-23.

Van der Stelt, O., Frye, J., Lieberman, J., & Belger, A. (2004). Impaired P3 generation reflects high-level and progressive neurocognitive dysfunction in schizophrenia. Arch Gen Psychiatry, 61, 237-248.

Walker, E. (1981) Attentional and neuromotor functions of schizophrenics, schizoaffectives and patients with other affective disorders. Archives of General Psychiatry, 38, 1355-1358.

Wang, X. (2001). Synaptic reverberation underlying mnemonic persistent activity. Trends in Neuroscience, 24, 455-463.

Wechsler, D. (1997). Wechsler Adult Intelligence Scale-III. The Psychological Corporation. USA.

Winkler, I., Karmos, G., & Naatanen, R. (1996). Adaptive modeling of the unattended acoustic environment reflected in the mismatch negativity event-related potential. Brain Res, 2, 239-52.

Woestenburg, J., Verhagen, M., & Slangen, J. (1983). The removal of the eye movement artifact from the EEG by regression analysis in the frequency domain. Biological Psychiatry, 16, 127-147.

Wohlberg, G., & Kornetsky, C. (1973). Sustained attention in remitted schizophrenics. Arch Gen Psych, 28 533-537.

Woods, D., Knight, R., & Scabini, D. (1993) Anatomical substrates of auditory selective attention: behavioral and electrophysiological effects of posterior association cortex lesions. Cogn. Brain Res., 1, 227-240.

Yago, E., Corral, M., & Escera, C. (2001). Activation of brain mechanisms of attention switching as a function of auditory frequency change. Neuroreport, 12, 4093-4097.

Zhang, P., Xiangchuan, C., Yuan, P., Zhang, D., & He, S. (2006). The effect of visuospatial attentional load on the processing of irrelevant acoustic distractors. Neuroimage, 33, 715-724.

ROYAL OTTAWA HEALTH CARE GROUP
SERVICES DE SANTÉ ROYAL OTTAWA

Royal Ottawa Hospital / Brockville Psychiatric Hospital

Hôpital Royal Ottawa / Hôpital Brockville Psychiatrique

INFORMATION SHEET AND INFORMED CONSENT FORM

Title of Study: Behavioral and Electrophysiological Indices of Acoustic Change Detection and Involuntary Attention Switches in Schizophrenia

Principal Investigator: Jemeen Horton, MSc (PhD Candidate, Carleton University)

Co-Investigator: Alain Labelle MD

Supervisors: Verner Knott PhD & John Logan PhD

Description of Study: Individuals who are diagnosed with schizophrenia have been shown to have difficulties with attention and concentration. Research studies have reported that individuals with schizophrenia are easily distracted and their ability to perform simple and complex tasks is seriously affected by unexpected noise and sounds. Studies which have examined this problem in the laboratory, have found that brain wave activity reported in the electroencephalogram (EEG) can be helpful in our understanding of attentional problems in schizophrenia. The purpose of this research is to use EEG measures to study how individuals with schizophrenia differ from non-patients in their response to unexpected sounds, which may act to reduce attention. It is hoped that this type of research will lead to a better understanding of how persons with schizophrenia handle the processing of information in their immediate environment.

Study Procedure: Demographic information including medical/psychiatric history, medication status and substance abuse will be collected. Participants will attend the laboratory for two recording/testing sessions. Each session will last approximately 90 minutes. Testing will be carried out in the morning or afternoon. Patients will be allowed to take their antipsychotic medication, but beginning at midnight prior to the test day, all participants will be required to abstain from illegal street drugs (e.g. marijuana, cocaine) and over-the-counter medications (e.g. aspirin, Tylenol antihistamines, muscle relaxants, alcohol, caffeine and cigarettes). Once you arrive at the laboratory you will have a hearing test to make sure your hearing is normal. To do this, a series of tones with different intensities and pitches will be presented through headphones and you will be required to detect these tones. If you are unable to detect these tones, you will not be allowed to participate in the study. After the hearing test, you will be asked to undergo four brief tests of cognitive functioning. These tests will be used to evaluate your reading

ROYAL OTTAWA HEALTH CARE GROUP
SERVICES DE SANTÉ ROYAL OTTAWA

Royal Ottawa Hospital / Brockville Psychiatric Hospital

Hôpital Royal Ottawa / Hôpital Brockville Psychiatrique

INFORMATION SHEET AND INFORMED CONSENT FORM

Title of Study: Behavioral and Electrophysiological Indices of Acoustic Change
Detection and Involuntary Attention Switches in Schizophrenia

Principal Investigator: Jemeen Horton, MSc (PhD Candidate, Carleton University)

Co-Investigator: Alain Labelle MD

Supervisors: Verner Knott PhD & John Logan PhD

Description of Study: Individuals who are diagnosed with schizophrenia have been shown to have difficulties with attention and concentration. Research studies have reported that individuals with schizophrenia are easily distracted and their ability to perform simple and complex tasks is seriously affected by unexpected noise and sounds. Studies, which have examined this problem in the laboratory, have found that brain wave activity reported in the electroencephalogram (EEG) can be helpful in our understanding of attentional problems in schizophrenia. The purpose of this research is to use EEG measures to study how individuals with schizophrenia differ from non-patients in their response to unexpected sounds, which may act to reduce attention. It is hoped that this type of research will lead to a better understanding of how persons with schizophrenia handle the processing of information in their immediate environment.

Study Procedure: Participants will attend the laboratory for two recording/testing sessions. Each session will last approximately 90 minutes. Testing will be carried out in the morning or afternoon. Patients will be allowed to take their antipsychotic medication, but beginning at midnight prior to the test day, all participants will be required to abstain from illegal street drugs (e.g. marijuana, cocaine) and over-the-counter medications (e.g. aspirin, Tylenol antihistamines, muscle relaxants, alcohol, caffeine and cigarettes). Once you arrive at the laboratory you will have a hearing test to make sure your hearing is normal. To do this, a series of tones with different intensities and pitches will be presented through headphones and you will be required to detect these tones. If you are unable to detect these tones, you will not be allowed to participate in the study. After the hearing test, you will be asked to undergo four brief tests of cognitive functioning. These tests will be used to evaluate your reading and reasoning abilities, speed of information-processing and attention. Sensors will then be placed on your scalp to record EEG and other sensors will be placed around your eyes, your forehead and on your ears. In the

Demo Sheet - Patients

Date: _____ Initials: _____ ID#: _____

DOB: _____ Age: _____ Sex: _____ G:

Contact Number: _____

Chart Reviewed: _____ Primary Diagnosis: _____
Secondary Diagnosis: _____

PANSS? _____

WTAR Score: _____ (raw) _____ (std)

Inclusion Criteria: Anti-Psychotic Meds: (**atypical**) _____ (dose) _____
Adjunct Meds: _____Length of Illness: (**> 1 year**) _____ Onset (1st visit Y): _____
Last In-Patient Admission: (**> 4 weeks**) _____Exclusion Criteria: Hearing Loss greater than 20DB: (**no**) (**yes**) _____
Major Head Injury: (**no**) (**yes**) _____Serious Medical Problems: (**no**) (**yes**) _____Neurological D/O: (**no**) (**yes**) _____ Substance Abuse: (**no**) _____2 SD below average on WTAR: (**no**) _____

Smoker: _____ Refrain 1 hour prior: _____

Information Sheet Provided and Study Reviewed: _____ Consent Signed: _____

Auditory Thresholds: Right Ear _____ @ 1000Hz Left Ear _____ @ 1000Hz
_____ @ 1500 Hz _____ @ 1500Hz

Digit Span: Forward _____ Backward _____ Info: _____

EXPT 2: _____

Coding: _____ Trails A: _____

MWCST: Cat _____ Perseverative Errors _____ Non-Perseverative _____

Demo Sheet - Controls

Date: _____ Initials: _____ ID#: _____

DOB: _____ Age: _____ Sex: _____ Gr

Contact Number: _____ WTAR Score: _____ (raw) _____ (std)

Inclusion Criteria: Psychiatric Meds _____ (no) _____ (yes) _____ (dose)

Other Meds: _____

History of Psychiatric Illness: _____ (no) _____ (yes)

Family History of Schizophrenia: _____ (no) _____ (yes)

Exclusion Criteria: Hearing Loss greater than 20DB: _____ (no) _____ (yes)

Major Head Injury: _____ (no) _____ (yes)

Serious Medical Problems: _____ (no) _____ (yes)

Neurological D/O: _____ (no) _____ Substance Abuse: _____ (no)

2 SD below average on WTAR: _____ (no)

Smoker: _____ Refrain 1 hour prior: _____

Information Sheet Provided and Study Reviewed: _____ Consent Signed: _____

Auditory Thresholds: Right Ear _____ @ 1000Hz Left Ear _____ @ 1000Hz
_____ @ 1500 Hz _____ @ 1500Hz

Digit Span: Forward _____ Backward _____ Info: _____

EXPT 2: _____

Coding: _____ Trails A: _____

MWCST: Cat _____ Perseverative Errors _____ Non-Perseverative _____

1. Again		26. Conscientious	
2. Address		27. Homily	
3. Cough		28. Malady	
4. Preview		29. Subtle	
5. Although		30. Fecund	
6. Most		31. Palatable	
7. Excitement		32. Menagerie	
8. Know		33. Obfuscate	
9. Plumb		34. Liasion	
10. Decorate		35. Exigency	
11. Fierce		36. Xenophobia	
12. Knead		37. Ogre	
13. Aisle		38. Scurrilous	
14. Vengeance		39. Ethereal	
15. Prestigious		40. Paradigm	
16. Wreath		41. Perspicuity	
17. Gnat		42. Plethora	
18. Amphitheater		43. Lugubrious	
19. Lieu		44. Treatise	
20. Grotesque		45. Dilettante	
21. Iridescent		46. Vertiginous	
22. Ballet		47. Ubiquitous	
23. Equestrian		48. Hyperbole	
24. Porpoise		49. Insouciant	
25. Aesthetic		50. Hegemony	

Participant Code =

Date =

Total Correct =

1. What day comes after Saturday?	
2. How old are you?	
3. What is the shape of a ball?	
4. How many months are there is a year?	
5. What is a thermometer?	
6. In what direction does the sun rise?	
7. How many weeks are there is a year?	
8. Who wrote Hamlet?	
9. On what continent is Brazil?	
10. Who was Martin Luther King Jr.?	
11. Who was the president of the United States during the civil war?	
12. Who was Cleopatra?	
13. What is the capital of Italy?	
14. Whose name is usually associated with the theory of relativity?	
15. In what country did the Olympic Games originate?	
16. On what continent is the Sahara Desert?	
17. What is the main theme of the Book of Genesis?	
18. Who painted the Sistine Chapel?	
19. Who was Mahatma Gandhi?	
20. What is the Koran?	
21. At what temperature does water boil?	
22. Name three knids of blood vessles in the human body?	
23. Who was Catherine the Great?	
24. Name all the continents?	
25. What was Marie Curie famous for?	
26. What is the world population?	
27. What is the speed of light?	
28. Who wrote Faust?	

1. <u>1-7</u> 6-3		1. <u>4-8</u> 2-9	
2. <u>8-5-2</u> 9-1-6		2. <u>5-3-8</u> 6-9-1	
3. <u>7-8-5-4</u> 2-6-8-1		3. <u>4-9-2-8</u> 7-5-9-3	
4. <u>8-1-5-3-6</u> 9-3-7-2-8		4. <u>7-2-6-4-5</u> 8-4-6-1-7	
5. <u>6-9-4-1-7-5</u> 1-8-5-3-6-9		5. <u>5-8-3-2-6-4</u> 2-7-6-4-8-1	
6. <u>6-8-4-7-3-1-9</u> 3-8-6-1-4-9-2		6. <u>5-9-3-8-2-1-7</u> 4-9-5-2-3-8-1	
7. <u>5-8-1-9-3-5-7-4</u> 8-2-5-9-4-3-1-6		7. <u>6-9-2-8-4-7-1-3</u> 9-1-6-8-4-3-2-7	
8. <u>7-2-8-6-9-1-4-5-3</u> 1-5-3-9-7-4-8-6-2		8. <u>8-2-7-9-6-3-4-5-1</u> 5-1-3-7-9-4-8-6-2	
Digit Span Forward TS		Digit Span Backward TS	

Total Score =

Participant Code =

Date =

Notes =

LNS

Date:

Participant Code:

1. L-2 (2-L) _____
6-P (6-P) _____
B-5 (5-B) _____
2. F-7-L (7-F-L) _____
R-4-D (4-D-R) _____
H-1-8 (1-8-H) _____
3. T-9-A-3 (3-9-A-T) _____
V-1-J-5 (1-5-J-V) _____
7-N-4-L (4-7-L-N) _____
4. 8-D-6-G-1 (1-6-8-D-G) _____
K-2-C-7-S (2-7-C-K-S) _____
5-P-3-Y-9 (3-5-9-P-Y) _____
5. M-4-E-7-Q-2 (2-4-7-E-M-Q) _____
W-8-H-5-F-3 (3-5-8-F-H-W) _____
6-G-9-A-2-S (2-6-9-A-G-S) _____
6. R-3-B-4-Z-1-C (1-3-4-B-C-R-Z) _____
5-T-9-J-2-X-7 (2-5-7-9-J-T-X) _____
E-1-H-8-R-4-D (1-4-8-D-E-H-R) _____
7. 5-H-9-S-2-N-6-A (2-5-6-9-A-H-N-S) _____
D-1-R-9-B-4-K-3 (1-3-4-9-B-D-K-R) _____
7-M-2-T-6-F-1-Z (1-2-6-7-F-M-T-Z) _____

Name: _____

Age: _____

Date: _____

Examiner: _____

MODIFIED WISCONSIN CARD SORT TASK (mWCST)

Trial	Rule	Score	Trial	Rule	Score	Trial	Rule	Score	Trial	Rule	Score
1			13			25			37		
2			14			26			38		
3			15			27			39		
4			16			28			40		
5			17			29			41		
6			18			30			42		
7			19			31			43		
8			20			32			44		
9			21			33			45		
10			22			34			46		
11			23			35			47		
12			24			36			48		

Categories

Non-Perseverative Errors

Perseverative Errors