Effects of Nicotine on Brain Event-related Potential and Behavioural Performance Indices of Auditory Distraction in Schizophrenia
EFFECTS OF NICOTINE ON
BRAIN EVENT-RELATED POTENTIAL AND BEHAVIOURAL
PERFORMANCE INDICES OF AUDITORY DISTRACTION
IN SCHIZOPHRENIA

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Abstract

Attention dysfunction is a hallmark of schizophrenia, a disorder in which smoking prevalence is double that of the general population. The main interest of this dissertation was in using behavioural performance (accuracy, reaction time or RT) and brain event-related potential (ERP) measures to examine the processing of distracting events in schizophrenic patients and control subjects, and to assess the effects of acute nicotine on this processing. This was accomplished in three experiments by comparing 12 minimally-tobacco-deprived control smokers with 12 outpatient smokers, the latter being assessed under double-blind, placebo-controlled (vs. nicotine) conditions. Experiment 1 used a passive, non-task paradigm to examine the mismatch negativity (MMN) ERP component, an index of early auditory deviance detection. Patients exhibited reduced MMNs to frequency and duration deviants compared to controls, and nicotine increased patients' duration MMN to a level comparable to that seen in controls. Experiment 2 used a novel auditory-auditory distraction paradigm that embeds task-irrelevant deviant features within task-related stimuli requiring location discrimination. Deviants caused RTs to be prolonged in patients and controls. Patients' MMN did not differ from controls' but attentional switching, reflected in the P3a ERP, was attenuated in patients. Nicotine increased patients' MMN to small deviants such that it was no longer smaller than the MMN to large deviants. Experiment 3 used an auditory-visual distractor paradigm requiring participants to discriminate visual letters vs. numbers preceded by task-irrelevant auditory stimuli of standard and deviant frequencies. Reaction times were prolonged by deviants in patients and controls and the MMN of patients to small deviants was diminished. Nicotine increased the MMN to small deviants and reduced RT prolongation and the involuntary attentional switching indexed by the P3a ERP associated with large deviants. Overall, these experiments demonstrated that nicotine can reduce distractibility and can normalize aberrant neural processing of distracting events in schizophrenic patients.
Dedication and Acknowledgements

I dedicate this thesis to my brother, Pierre Dulude, whose brilliant legal career was destroyed by schizophrenia when he was in his early thirties. In the thirty years that followed this diagnosis, Pierre has never been able to return to his beloved field of law. In spite of all the catastrophes he has endured, he is one of the kindest and most cheerful people I know. I have sometimes seen him sad, but I have never seen him bitter. He is my close friend and one of my heroes. I wish he could break his addiction to nicotine.

I owe deep thanks to the members of my thesis committee, Drs. Ken Campbell, Hélène Plamondon and Bob Stelmack. All three have been my teachers and mentors over many years and were there for me whenever I asked for their help. In particular, I am profoundly grateful to Dr. Ken Campbell, who put his encyclopedic knowledge at my disposal.

Finally but not least, I thank my thesis advisor, Dr. Verner Knott. He took me on as a student even though my background in the sciences was much weaker than that of many other applicants. He fostered a congenial and egalitarian atmosphere in our lab at the Royal Ottawa Hospital in which there are no stupid questions and everyone helps everyone else. In the many jobs I have held in my life, I have rarely seen such a happy workplace. Most of all, Dr. Knott himself was always available, and very patient with this oldest and slowest of his students.

Special thanks also to all those who participated in my experiments, and of course to my ever-supportive husband, Leonard Shifrin.
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1.0 GENERAL INTRODUCTION

1.1 INTRODUCTION TO SCHIZOPHRENIA

Schizophrenia is a devastating illness. Although great progress has been made in the past 30 years in understanding it and finding ways to diminish its effects, it continues to ravage millions of families, inspiring a massive research effort evidenced by more than 75,000 entries being elicited by the word "schizophrenia" on the PubMed Internet search site. Among these thousands of studies of schizophrenia, several hundred analysed the disease by examining brain waves called event-related potentials (ERPs), which are amplified and recorded from an electroencephalogram (EEG). ERPs have proved particularly effective in analysing attention dysfunctions, which are among the main characteristics of schizophrenia. Until the 1990s, the bulk of ERP research on attention in schizophrenia was focussed on controlled information processing as reflected by a single ERP component, known as the P300 (also P3b).

This focus has been challenged in recent years and some experts have suggested that the schizophrenic attention deficit revealed in ERP research on controlled information processing may actually be secondary to impairments in pre-attentive automatic processes that are reflected in other ERP components. In particular, some pre-attentive ERPs obtained while subjects were performing distraction tasks are believed to reflect the orienting response, which is a rapid involuntary reaction that switches attention toward new or unexpected distracting stimuli. Abnormal distractibility is a hallmark of schizophrenia.

Another, separate line of research was inspired by the facts that nicotine/smoking improves some types of attention in healthy people (especially short-term focussed attention), and that nicotine appears to be used as self-medication by schizophrenic patients, who have abnormally high rates of cigarette smoking. Preliminary findings suggest that nicotine/smoking improved sustained attention, selective attention, visuospatial working memory and verbal working memory in schizophrenic patients who had taken nicotine compared with patients who had not taken nicotine.

The main purpose of this thesis was to combine these separate lines of research by using pre-attentive ERPs and measures of behavioural performance (accuracy, reaction time) to examine the processing of distracting events of schizophrenic patients and to assess the effects of acute nicotine on this processing. Three placebo-controlled, double-blind
Nicotine and schizophrenia experiments were performed, using different auditory distraction tasks/paradigms to elicit behavioural measures (reaction time, accuracy) and the pre-attentive ERP components that reflect the brain's orienting-reorienting response (including mismatch negativity or MMN, P3a and reorienting negativity or RON) in nicotine-deprived schizophrenic smokers who have ingested nicotine.

The rest of the introduction presents a summary of research findings and theories in relevant areas, including the symptoms and neuropathology of schizophrenia and its cognitive deficits, particularly in working memory and attention; the effects of nicotine/smoking on humans, especially on cognitive performance; and ERP research on the neural processes related to attention orienting and reorienting in healthy people and in schizophrenic patients. The introduction ends with a description of the objectives and hypotheses of the three linked experiments that were performed for this thesis. This is followed by detailed reports of each of the three experiments and an overall conclusion.

1.2 SCHIZOPHRENIA: SYMPTOMS, COURSE AND CAUSES

Schizophrenia is a mental illness affecting 1% of the world population (Andreasen, 2000). It is characterized by loss of contact with reality, disruptions in social and occupational functioning, and disintegration of personality evidenced by a disorder of feeling, thought and conduct (Merriam-Webster Medical Dictionary, 2002). Its symptoms have been divided into three main groups: psychotic or "positive" symptoms, deficit or "negative" symptoms, and cognitive impairment symptoms (Wong & Van Tol, 2003). Positive symptoms include hallucinations, which are abnormalities in perception, such as hearing voices; delusions, which are abnormalities in referential thinking, often paranoid or grandiose; disorganized thought, evidenced by disordered speech and abnormalities in language; and disorganized behaviour. Negative symptoms consist of a diminution or absence of mental functions that are normally present, including alogia, a decrease in the fluency of ideas and language; affective blunting, a diminution in the ability to express emotions; avolition, a decrease in the ability to initiate and pursue goal-directed activity; and anhedonia, a decrease in the ability to seek out and experience pleasure. Symptoms differ greatly across individuals and most patients display a mixture of positive and negative symptoms (Andreasen & Black, 1999; Bowie & Harvey, 2005).
Nicotine and schizophrenia

The Diagnostic and Statistical Manual of Mental Disorders [DSM-IV; American Psychiatric Association (APA), 1994] specifies that schizophrenia symptoms must persist for at least six months and must not be due to another psychiatric problem (such as schizoaffective disorder, mood disorder with psychotic features or delusional disorder), to drugs or to a general medical condition. The first overt symptoms typically appear between the late teens and mid-30s and thereafter usually develop slowly over months or years. Symptoms such as sleep disruptions, difficulties of concentration, deterioration in social and occupational functioning and increasing isolation may not be noticed until the disease progresses and psychotic symptoms appear (Health Canada, 2004; Wong et al., 2003).

The DSM-IV states that "because of variability in definition and ascertainment, an accurate summary of the long-term outcome of schizophrenia is not possible" (APA, 1994). Medication improves symptoms in most cases but only about 15% of patients make a complete recovery (Harrison et al., 2001; Robinson, Woerner, McMeniman, Mendelowitz, & Bilder, 2004). Many schizophrenic patients become functionally disabled and experience relapses that require hospitalization or supervision throughout their lives. The life expectancy of people who suffer from schizophrenia is significantly reduced; approximately 10% commit suicide (Andreasen and Black, 1999; Hannerz, Borga, & Borritz, 2001).

The causes of schizophrenia are not fully understood. The long-dominant dopamine hypothesis, which stated that schizophrenia was mainly caused by an excess of that neurotransmitter, has increasingly been challenged (Bennett, 1998; Javitt, 2007; Willner, 1997). More recent research also implicates N-methyl-D-aspartate (NMDA) glutamate receptor dysfunction (Javitt & Coyle, 2004). This receptor participates in regulating dopamine release and plays a critical role in brain development, learning, memory and neural processing in general. Current scientific opinion also favours the neurodevelopmental hypothesis, which holds that "schizophrenia has a neurobiological and genetic basis, with environment being a modulating factor but not the primary cause" (Marenco & Weinberger, 2000; Wong et al., 2003, p. 270). The gist of this hypothesis is that some people are born with a genetic predisposition for schizophrenia, but they may or may not develop the disease depending on the presence of risk factors favouring schizophrenia or of protective factors against schizophrenia (Green, 2001).
Genetic studies suggest that the heritability of schizophrenia is substantial, accounting for about 70 percent of the risk (Tsuang, 2000). The risk of developing schizophrenia is 45%-50% for the monozygotic twin of an affected patient, compared with only 15%-17% for a dizygotic twin, 2% for a third-degree relative and 1% for the general population (Dikeos, 2001). The remaining 30% of the schizophrenia risk is attributed to environmental factors such as brain injury during pregnancy, delivery or childhood, and, less prominently, psychosocial stressors such as separation from the family (Hoek, Brown, & Susser, 1998; Gearon, Kaltman, Brown, & Bellack, 2003). Being female appears to be a protective factor: women have a lower rate of schizophrenia, a later age of onset and a more favourable course, especially in young women (Aleman, Kahn, & Selten, 2003; Leung & Chue, 2000).

The DSM-IV criteria are structured in such a way that two patients with schizophrenia may have no overlapping symptoms. This increases the possibility that "schizophrenia is a clinical syndrome and not a single disease" (Carpenter, Kirkpatrick, & Buchanan, 1999, p. 473; Garver, 1997), in the same way that the "dementia" syndrome eventually evolved into Alzheimer's disease, multi-infarct dementia, Parkinson's dementia, etc. This possibility raises concerns about the power of current schizophrenia studies that group together all types of schizophrenic patients without regard for differences in their symptoms (Wong et al., 2003). It also raises the question of whether there exists a core or fundamental theme that unites the diversity of schizophrenia symptoms.

Some believe that schizophrenia is a "heterogeneous disorder" with "a number of meaningful and stable subtypes" (Seaton, Goldstein, & Allen, 2001, p. 45). This approach produces study designs that distinguish patients on the basis of symptoms (with hallucinations vs. without hallucinations, cognitively impaired vs. non-impaired) or risk factors (genetic risk, early neurological illness) or disease course (early vs. late onset, good vs. poor premorbid functioning) or clinical-DSM subtypes (paranoid vs. non-paranoid). Others agree with the pioneers of schizophrenia, Kraepelin and Bleuler, that schizophrenia is probably a neurocognitive disorder whose heterogeneous symptoms are the downstream effects of a fundamental cognitive process that affects specific circuitry in the brain (Andreasen & Black, 1999; Frith 1992). Bleuler believed that "patients who developed this illness suffered a pervasive disruption of their mental processes..." He chose the name
Inspired by this image, Andreasen (1999) proposed redefining schizophrenia as a unitary "misconnection syndrome" reflecting a disorder in neural circuits caused by the convergence of multiple genetic and environmental factors. If enough "schizophrenogenic" factors accumulate, the neural dysfunction occurs and produces symptoms that may wax and wane and vary from one person to another. Comparing schizophrenia to cancer, which has many forms but is defined as an "abnormal regulation of cell growth and death" (p. 782), Andreasen argued that (1) schizophrenia should not be identified by its symptoms, but by the more fundamental disruption in mental processes occurring as a consequence of a disruption in neural circuitry; and (2) this fundamental neural disruption should be the main focus of research on schizophrenia.

1.3 NEUROPATHOLOGY AND TREATMENT OF SCHIZOPHRENIA

In this section, the neuropathology of schizophrenia is examined from three perspectives: the endophenotypes of schizophrenia, the main neurological abnormalities of schizophrenic patients, and the hypothesized role of neurotransmitters in that disease. Modern mainstream drug treatments for schizophrenia are also described.

1.3.1 Endophenotypes of Schizophrenia

Psychiatric endophenotypes are internal genetic-and-environmental characteristics that are discoverable by objective tests (Gottesman & Shields, 1973). They are associated with an illness, are heritable, exist whether the illness is active or dormant, and are found in the close relatives of affected patients at a higher rate than in the general population. The following characteristics have been suggested as possible endophenotypes of schizophrenia (Gottesman & Gould, 2003).

Eye-tracking dysfunction has long been identified as a characteristic of schizophrenia. Normal eye movements are either saccadic (brief and extremely rapid) or smooth and controlled (smooth pursuit, when following a moving object such as a pendulum). Many studies found that schizophrenic patients and their relatives have deficiencies in smooth pursuit eye movements (Calkins & Iacono, 2000; Lee & Williams, 2000).
**Prepulse inhibition** (PPI) is verified with a test that measures the startle response to a loud tone. In healthy people, a lower-volume warning sound (the prepulse) reduces the startle response, but this effect is weaker in schizophrenic patients and their relatives (Braff, Grillon, & Geyer, 1992; Cadenhead, Swerdlow, Shafer, Diaz, & Braff, 2000).

**Gating of P50 auditory event-related potentials (ERPs).** ERPs are patterns of brain electrical activity that occur while subjects perform specific cognitive tasks. In a common task using successive closely paired stimuli, healthy subjects typically show inhibitory filtering or "gating," manifested in a diminished P50 response to the second stimulus. Schizophrenic patients and their close relatives routinely fail to show a diminished response to the second stimulus (Light & Braff, 1999).

### 1.3.2 Main Neurological Abnormalities

Hundreds of abnormalities have been found in the brains of schizophrenic patients. Reviews by Harrison (1999) and Wong et al. (2003) identified the following as the main ones on which a broad consensus has been reached. A summary of these abnormalities appears in Table 1 along with a selection of their cognitive and symptom correlates.

**Larger lateral and third brain ventricles** were found in schizophrenic patients than in healthy controls by a large number of CT (Computed Tomography) and MRI (Magnetic Resonance Imaging) studies as well as post-mortem investigations. Lawrie and Abukmeil (1998) reported a median 40% increase in ventricular size in schizophrenia.

**Smaller weight and volume of cortical brain tissue** was also found in schizophrenia, averaging 3% less than normal overall, with grey matter being more affected than white matter (Lawrie et al., 1998). The largest discrepancies in brain volume between schizophrenic patients and controls were in the temporal lobe (8%), in medial temporal structures (4-12%; including the hippocampus, parahippocampal gyrus and amygdala) and in the thalamus. Except for the dorsal thalamic nuclei, which are smaller and have fewer neurons in schizophrenic patients than in healthy people, the smaller brain volume of patients is not due to having fewer neurons but instead to having reduced neuropil and neuronal size, with reduced synaptic and dendritic markers, especially in the hippocampus (Harrison, 1999).
Table 1. Main Neurological Abnormalities in Schizophrenia and Their Correlates

<table>
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<tr>
<th>Neurological Abnormality</th>
<th>Cognitive and Symptom Correlates</th>
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<tr>
<td>Larger lateral and third brain ventricles</td>
<td>Negative symptoms and poorer cognition are associated with increased ventricular size (Kareken et al., 1996)</td>
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<tr>
<td>Less cortical brain tissue (weight and volume), especially in temporal lobe overall and in medial temporal structures, including the hippocampus and amygdala</td>
<td>Sustained attention impairment is linked to frontal cortex and tempoparietal regions (Buchsbaum et al., 1990)</td>
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<tr>
<td>Hypo-activity and hyper-activity in dorsolateral prefrontal cortex (DLPFC).</td>
<td>Auditory hallucinations and severity of thought disorder are linked to decreased superior temporal gyrus size (Barta et al., 1990; Shenton et al., 1992)</td>
</tr>
<tr>
<td>Smaller cortical and hippocampal neurons, fewer synaptic and dendritic markers in the hippocampus</td>
<td>Apathy symptoms are linked to reduced bilateral frontal lobe volumes (Roth et al., 2004)</td>
</tr>
<tr>
<td>Smaller thalamus with fewer dorsal thalamus neurons</td>
<td>Impairments in working memory and attentional set-shifting are linked to DLPFC (Barch et al., 2002; Pantelis &amp; Maruff, 2002)</td>
</tr>
<tr>
<td>Altered cerebral asymmetry with decreased lateralization</td>
<td>Negative symptoms, impairment in conscious memory and recognition of facial emotion are linked to hippocampus and amygdala (Gur et al., 2002; Weiss &amp; Heckers, 2001)</td>
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<td></td>
<td>Sustained attention is linked to gray matter decrease in thalamic nucleus (Salgado-Pineda et al., 2003)</td>
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<td></td>
<td>Lateralization due to language is reduced in schizophrenia; decreased language lateralization is associated with more severe hallucinations (Sommer, Ramsey &amp; Kahn, 2001)</td>
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Hypo-activity of the dorsolateral prefrontal cortex (DLPFC) is a common finding in schizophrenia research (Andreasen et al., 1992; Callicott et al., 1998), but studies using functional magnetic resonance imaging (fMRI) during the performance of working memory tasks have produced contradictory results, with some findings of hypofrontality and others of hyperfrontality in schizophrenic subjects compared with controls (Manoach et al., 1999, Sabri et al., 1997). Other experiments suggest that both findings are valid and are associated with different types and levels of difficulty of the tasks and the characteristics of the patients (Manoach, 2003; Sabri et al.).

Cerebral asymmetry is normal in healthy individuals, particularly in language centers which are typically located in the left hemisphere (Sommer et al., 2001).

Lateralization for language and other purposes is reduced or even reversed in schizophrenic
patients and in some of their relatives, and the abnormalities of the disease are more pronounced in the left hemisphere (Crow, 1997; Davies, Russell, Jones, & Murray, 1998).

As Table 1 shows, the main neuropathological abnormalities of schizophrenic patients have been linked to their major cognitive disorders as well as to positive and negative symptoms. These associations are misleading because they give the impression that cognitive deficits and symptoms can be attributed to lesions in specific parts of the brain. In reality, all these abnormalities and their cognitive and symptom correlates are consistent with Andreasen's (1999) hypothesis that schizophrenia is a "misconnection syndrome" between different circuits in the brain. For example, it is now widely believed that the memory impairments of schizophrenia are likely caused by a failure in connectivity between the prefrontal cortex and the hippocampus, thalamus and cerebellum (Weiss and Heckers, 2001).

1.3.3 Role of Neurotransmitters

A large body of evidence suggests that several neurotransmitter systems, including dopamine, glutamate, GABA (γ-aminobutyric acid), serotonin, cholinergic system, and others, are involved in the pathophysiological processes which are responsible for the various schizophrenia symptoms (see review in Abi-Dargham & Guillin, 2007). Over the past 50 years, dopamine has captured most attention. The dopamine hypothesis of schizophrenia was first suggested by Carlsson and Lindqvist (1963). They hypothesized that hyperactivity of dopamine transmission was responsible for the positive symptoms in this disease. This hypothesis was based on two sets of findings. In one set, correlations were found between clinical doses of antipsychotic drugs and their potency to block dopamine D2 receptors (Creese, Burt, & Snyder, 1976; Seeman & Lee, 1975). In addition, it was observed that dopamine-enhancing drugs had psychosis-inducing effects (reviewed by Angrist & van Kammen, 1984; Lieberman, Kane & Alvir, 1987). Dopamine terminals and D2 receptors are mainly localized in subcortical regions such as the striatum and the nucleus accumbens (Guillin, Abi-Dargham, & Laruelle, 2007).

Increasing awareness of negative and cognitive schizophrenia symptoms over the following decades led to a modification of the original dopamine hypothesis. Studies using fMRI suggested that these symptoms were associated with altered prefrontal cortex (PFC) functions (see review by Knable & Weinberger, 1997). Many experiments then documented
the importance of prefrontal dopamine transmission at D1 receptors for optimal PFC performance (reviewed by Goldman-Rakic et al., 2000). A new hypothesis was formulated suggesting that deficits in dopamine transmission at D1 receptors might be responsible for the cognitive and negative symptoms of schizophrenia (Davis, Kahn, Ko, & Davidson, 1991; Weinberger, 1987). The merging of the classic and reformulated dopamine theories of schizophrenia led to the current predominant view that schizophrenia is characterized by an imbalance between hyperactive subcortical D2 receptors linked with positive symptoms, and hypostimulation of D1 receptors in the PFC linked with negative symptoms and cognitive impairments (Guillin et al., 2007).

Alternative neurochemical models of schizophrenia were also proposed. Some of them involved glutamatergic mechanisms in general and N-methyl-D-aspartate (NMDA) receptors in particular. Most prominent among them is the PCP/NMDA model of schizophrenia (Javitt, 2007). This theory was formulated 15 years ago when it was observed that phenyclidine (PCP, known by street users as "angel dust") and similarly-acting ketamine, which block neurotransmission at NMDA-type glutamate receptors, induced psychotic symptoms and neurocognitive disturbances similar to those of schizophrenia (Krystal et al., 1994; Lahti, Weiler, Michaelidis, Parwani, & Tamminga, 2001; Malhotra et al., 1996; Newcomer et al., 1999). Unlike dopamine agonists such as amphetamine, which produced patterns of symptoms markedly different from those of schizophrenia, NMDA antagonists induced positive, negative and cognitive symptoms of schizophrenia. Studies of dopamine-glutamate interactions suggested that the hyperactivity of dopamine D2 receptors observed in schizophrenia might be associated with deficits in glutamatergic functioning (see review by Javitt, 2007). This led to the hypothesis that NMDA dysfunction may be the underlying cause of secondary dopaminergic dysregulation in striatal and prefrontal brain regions.

Another line of research considered evidence indicating that some of the cognitive impairments commonly found in schizophrenia could be caused by disturbances in neurotransmission by a subset of GABA neurons in the dorsolateral prefrontal cortex (DLPFC; see review by Lewis & Hashimoto, 2007). These disturbances in GABA neurons are believed to cause alterations in the inhibitory regulation of pyramidal neurons, leading to a reduced capacity for the synchronization of neuronal activity at gamma frequencies that is essential for normal working memory function (Wilson, O'Scalaidhe & Goldman-Rakic,
Nicotine and schizophrenia (1994; Rao, Williams, & Goldman-Rakic, 2000). As discussed later in this introduction, working memory impairments are a core feature of schizophrenia. Postmortem studies of schizophrenic patients consistently find reduced expression of an enzyme that synthesizes GABA (Torrey et al., 2005). Several possible mechanisms have been suggested as the cause of these abnormalities in GABA neurotransmission (Lewis & Hashimoto). Among the mechanisms with the strongest empirical basis are alterations in NMDA receptor-mediated excitatory neurotransmission.

Serotonin (5-HT) alterations have also long been suspected to play a role in schizophrenia. A recent review of research in that area concluded that no clear picture of specific serotonergic alterations has yet emerged in schizophrenia (Abi-Dargham, 2007). However, current evidence suggests that serotonin agents have a modulatory effect on dopamine transmission that may contribute to the therapeutic effects of atypical antipsychotic medication (see section on drug treatment below). Specifically, administration of the 5-HT precursor tryptophan produced some alleviation of negative symptoms in schizophrenic patients (reviewed by Abi-Dargham).

Yet another hypothesis proposed that dysregulation of central cholinergic signaling contributes to the pathophysiology of schizophrenia (reviewed by Berman, Talmage, & Role, 2007). This hypothesis is particularly relevant to this thesis because of the established role of cholinergic/acetylcholine circuits in the tuning of attention (Sarter, Nelson, & Bruno, 2005). Berman et al. provide the following overview of cholinergic transmission:

Cholinergic innervation of cortical and striatal brain areas is extensive and diffuse (...). Receptors for Ach (AChRs) come in two broad classes – ionotropic (nicotinic) and metabotropic (muscarinic) – each class having multiple subtypes with both opposing and synergistic actions. Activation of these receptors regulates neuronal excitability (...). ACh can act as a tonic, diffuse signal, modulating the release of ACh and other transmitters, including dopamine, glutamate, and GABA. Alternatively, ACh can exert its effects via highly localized and directed interactions with neuronal AChRs to increase or decrease neuronal firing (p. 194).

Because of the complexity and pervasiveness of cholinergic circuits, it is difficult to determine how acetylcholine achieves its effects. However, it has been established that it plays an important role in supporting neurocognitive and motivational functions of the prefrontal cortical, hippocampal, and ventral tegmental projections to the striatum (for
reviews see Cragg, 2006; Gotti & Clementi, 2004; Martin & Freedman, 2007; Mesulam, 2004; Sarter et al, 2005; Smythies, 2005; Wonnacott, Sidhpura, & Balfour, 2005). Several studies have found alterations in both nicotinic and muscarinic receptors in the brains of schizophrenic patients (reviewed by Berman et al., 2007).

Most particularly, a postmortem study of brain tissue (Freedman, Hall, Adler, & Leonard, 1995) noted that schizophrenic patients who had been smokers had fewer α7 nicotinic acetylcholinergic receptors (nAChRs) in the hippocampus than healthy smokers. Another postmortem study (Guan, Zhang, Blennow, & Nordberg, 1999) found decreased levels of the same receptors in the frontal cortex of schizophrenic patients. This reduction may result in a failure of cholinergic activation of inhibitory interneurons. In turn, this would have a negative effect on the filtering of responses to redundant sensory stimulation. This type of impairment is consistent with the P-50-indexed auditory sensory gating deficit of schizophrenic patients that was described above in the endophenotypes of schizophrenia.

1.3.4. Drug Treatment of Schizophrenia

Early treatment of schizophrenia is important because it may improve long-term outcome and may slow or stop deterioration (Herz & Marder, 2002). The standard treatment is antipsychotic medication. As described in Table 2, these drugs mainly target neurotransmitters. The first-generation antipsychotic drugs were dopamine (D2) blockers/antagonists, while the second-generation drugs introduced over the past 15 years have more varied action, targeting dopamine (D1, D2) and/or serotonin (5-HT2A, 5-HT2,3), acetylcholine and norepinephrine.

The disadvantage of the first-generation drugs was their parkinsonian side effects (dystonia, akathisia, bradykinesia, tremor) caused by dopamine blockage in the basal ganglia (Freedman, 2003). These symptoms caused patient noncompliance and were partly countered by antiparkinsonian (anticholinergic) medications. The second-generation drugs have improved therapeutic effects, especially on negative symptoms, without the marked adverse effects on movement of the earlier drugs. Apart from clozapine, which has a serious known side effect (agranulocytosis) requiring frequent monitoring of the leukocyte count, the main side effects of some of the second-generation antipsychotics are sedation, moderate
Table 2. Antipsychotic Drugs and Their Effects (Freedman, 2003)

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Type of drug</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine D2 antagonism</td>
<td>First-generation (haloperidol)</td>
<td>Blockade of dopamine facilitation of pyramidal-neuron response</td>
</tr>
<tr>
<td>D2 and 5-HT$_{2A}$ antagonism</td>
<td>Second-generation (olanzapine, risperidone, quetiapine, ziprasidone)</td>
<td>Blockade of dopamine facilitation of pyramidal-neuron response and serotonin facilitation of glutamate release</td>
</tr>
<tr>
<td>Multiple actions</td>
<td>Clozapine</td>
<td>D1, D2 and 5-HT$_{2,3}$ antagonism, leading to decreased pyramidal-neuron responses; increased acetylcholine release and norepinephrine antagonism, leading to increased interneuron regulation of pyramidal neurons</td>
</tr>
<tr>
<td>Mixed dopaminergic agonism and antagonism</td>
<td>Aripiprazole</td>
<td>Facilitation of low-level stimulation of dopamine receptors, blockade of higher levels of stimulation</td>
</tr>
<tr>
<td>Dopamine D2 and D3 antagonism</td>
<td>Amisulpride</td>
<td>Blockade of cortical dopamine receptors, but not those in basal ganglia</td>
</tr>
</tbody>
</table>

movement disorder, and substantial weight gain that has been linked to an increased risk of diabetes (Freedman). The newer antipsychotic drugs that cause less weight gain than the others, ziprasidone (Geodon), amisulpride (Solian) and aripiprazole (Abilify), are not available in Canada except within clinical trials (Black, 2003; Buckley, 2003; Daniel et al., 1999). Movement disorder is still controlled by means of antiparkinsonian medication.

1.4. COGNITIVE DEFICITS IN SCHIZOPHRENIA

1.4.1 Prevalence of Cognitive Deficits in Schizophrenia

Part of the evidence in favour of a neurodevelopmental cause for schizophrenia consists of many studies showing a significant - though small - link between having a low IQ in childhood and having a greater likelihood of developing schizophrenia later in life (Marenco & Weinberger, 2000). Also in support of the neurodevelopmental hypothesis, many studies found that marked cognitive abnormalities were already present in patients at the onset of schizophrenia and that their neuropsychological profiles remained relatively stable after onset while some actually improved, perhaps because of symptom reduction (Censits, Ragland, Gur, & Gur; 1997; Heaton et al., 2001; Rund, 1998). Cognitive deficits
are slightly improved but not normalized by current antipsychotic medications (Weickert et al., 2003).

Many comparisons of schizophrenic patients and healthy controls revealed extensive deficits in patients' executive function, attention, memory and general intellectual capacities, including lower IQs (Goldberg, Gold, Greenberg, & Griffin, 1993; Heinrichs & Zakzanis, 1998; Nelson et al., 1990). On the other hand, other studies found some relatively high-functioning groups of schizophrenic patients whose cognitive performances were indistinguishable from those of healthy people (Dudek, 1969; Goldstein & Shemansky, 1995; Palmer et al., 1997). Only part of these inconsistencies were due to differences in the samples and in the tests performed.

On the basis of these earlier findings and of their own neuropsychological study of 117 patients admitted to a hospital with chronic schizophrenia, Weickert and Goldberg (2000) hypothesized that the cognitive deficits associated with schizophrenia reflected three developmental patterns: a first pattern, involving about 25% of patients, in which profound and widespread cognitive deficits were manifest from early development prior to onset of psychotic symptoms; a second pattern, for about 50% of patients, of more limited deficits in executive function, attention and episodic memory that roughly coincided with the emergence of psychotic symptoms; and a third pattern, involving about 25% of patients, whose cognitive profiles were normal with the exception of subtle deficits in executive function/working memory and possibly attention. The results for this last group suggested to Weickert and Goldberg that deficits in executive function and attention may be the core features of schizophrenia.

Studies such as Weickert and Golberg's (2000) and most earlier ones have several limitations. Most of their subjects were chronic schizophrenic patients who had usually been medicated for several years. The precise effects of medication on cognitive functioning are still unclear: reviews suggest that the newer atypical antipsychotics improve cognitive performance in schizophrenic patients (Keefe, Silva, Perkins, & Lieberman, 1999; Meltzer & McGurk, 1999), but other studies indicate that common adjunctive medication such as anticholinergic anti-parkinsonian drugs can impair attention and complex memory (Brébion, Bressan, Amador, Malaspina, & Gorman, 2004; Minzenberg, Poole, Benton, & Vinogradov, 2004). Findings of generalized cognitive deficits may reflect non-controlled factors such as
adolescent onset, which disrupts the educational process, or depressed motivation due to a higher prevalence of negative symptoms in chronic patients (Lussier & Stip, 2001; Thaker, 2000). The earlier studies tested patients who were more severely ill because they had to meet the stricter DSM-III-Revised diagnostic criteria for schizophrenia (Gold, Arndt, Nopoulos, O'Leary, & Andreasen, 1999; Saykin et al., 1991). Perhaps most important, many studies used hospitalized patients (Bilder et al., 1992; Censits et al., 1997; Riley et al., 2000), who are not representative of the schizophrenic population: in Canada, the rate of hospitalization of schizophrenic patients is only about 10% for men and 7% for women (Health Canada, 2004).

Two Canadian teams overcame some of these limitations by administering a battery of cognitive tests to first-episode, mostly-medicated community-living patients. The first study, by Townsend, Malla and Norman (2001), included 107 outpatients and no control group and found that patients performed in the average range on most measures, including intelligence scores. However, the results suggested a subtle but significant decline in IQ following onset of psychosis, which seems to contradict earlier findings that neuropsychological profiles remain stable after onset. Deficits were found in executive functions (-1.0 S.D.) and in speed of information processing (almost 2.0 S.D. below the norm on one test), confirming evidence of reduced processing speed among adolescents who later developed schizophrenia (Tauscher-Wisniewski, 1999). When 83 of the outpatients were retested a year later (Townsend, Norman, Malla, Rychlo, & Ahmed, 2002), they showed normal executive functions but their processing speed was still more than 1.5 S.D. below the norm.

The other Canadian team (Addington, Brooks and Addington, 2003) tested 312 first-episode medicated outpatients and 66 control subjects. The outpatients performed above average on IQ estimates but showed deficits (in z-scores and compared to controls) on a wide range of measures including verbal fluency, verbal memory, working memory, attention and early information processing. A subgroup of 30% of patients had significantly lower scores on every test, while the other 70% had normal working memory (and perhaps other) scores. Studies of first-episode patients who had never been medicated (Mohamed, Paulsen, O'Leary, Arndt, & Andreasen, 1999; Lussier & Stip, 2001) found extensive generalized and specific cognitive deficits, but these results were criticized because of possible confounding
by acute psychotic symptoms that may have interfered with performance (Townsend et al., 2001).

This review of research on cognitive deficits in schizophrenia leads one to agree with Green (1998), who concluded that "there is no agreed-upon, single neuropsychological profile for schizophrenia" (p. 30). According to Green, this absence of a consistent profile could be explained (1) by a global generalized deficit alone, or a global deficit against which a faint cognitive profile for schizophrenia is difficult to discern; (2) by several groups of patients who have their own profiles; (3) by the involvement of multiple brain regions or circuits; and (4) by the involvement of a limited number of neural circuits which differ from patient to patient because of different neurodevelopmental events, genetic risk factors or learning history.

1.4.2. Main Cognitive Deficits and Functional Significance

The research described above suggests that the main cognitive deficits associated with schizophrenia are in attention, working memory and executive function. In fact, these three cognitive elements are so closely intertwined as to be almost inseparable. As described in greater detail below, the executive function is now considered to be the main component of working memory (Baddeley, 1986), and one of the executive's functions is to direct attention. As a result, dysfunction in working memory/executive function can have serious repercussions on attention and vice-versa, so that experiments focusing on separate deficits in these cognitive elements must necessarily present a simplified view of the way the mind works.

As well as examining the nature of the schizophrenic deficits in working memory/executive function and attention, researchers analyzed the relationships between these deficits and the symptoms of schizophrenia, and looked at the functional consequences of the deficits and symptoms in everyday life. Functional consequences are ways in which cognitive deficits may affect patients' ability to retain, acquire, or relearn skills that are needed to function in the real world (Green, 1996). Specific deficits have been closely linked to functional impairments in schizophrenia (Addington & Addington, 1999; Dickerson, Boronow, Ringel, & Parente, 1999; Green, 1996, 2000), to the point where it was estimated
that cognitive function predicted over 40% of the variance in scores on an assessment of activities of daily living (Velligan et al., 1997).

The relationship between cognitive deficits and clinical symptoms is more elusive. Cognitive deficits are associated with high levels of negative/deficit symptoms, but the cognitive impairments persist even when the negative symptoms diminish over time, suggesting that they are independent factors (Harvey et al., 1996; Hughes et al., 2003). Links between cognitive deficits and positive/psychotic symptoms are less consistent and when medication reduces hallucinations and delusions, the cognitive impairments remain (Gold et al., 1999; Keefe, 2000; Kuperberg & Heckers, 2000).

As a result, it was suggested that cognitive status is a more durable indicator of underlying schizophrenic disorder than the less stable psychotic symptoms (Elvevag & Goldberg, 2000). This is supported by the facts that remitted schizophrenic patients still have cognitive deficits and that clinically unaffected relatives of schizophrenic patients exhibit some cognitive impairments (Cadenhead & Braff, 2000). On the other hand, a study by Norman et al. (1999) concluded that stabilized post-treatment schizophrenia symptoms, and especially disorganization symptoms such as thought disorder and inappropriate affect (Liddle, 1987), were better predictors of community functioning than cognitive measures.

1.4.2.1. Working Memory and Executive Function in Schizophrenia

Working memory is a hypothetical model proposed by Baddeley (1986). It is the capacity to manipulate information while holding intermediate products, goals, and associated strategies in mind; one example is doing mental arithmetic. It is a limited-capacity system that includes three components: (1) the central executive, an active attention-control system which presides over the other working memory components and which coordinates, schedules and plans mental operations; (2) the articulatory or phonological loop sub-system, which actively maintains verbal information in mind for a very short period (seconds); (3) the visuospatial sketchpad sub-system, which retains and manipulates images in mind for a very short time. Working memory is crucial for reasoning, learning and comprehension; the executive function is necessary to use abstract concepts, to work out the strategies for problem solving, especially in new situations, and to execute these strategies while self-monitoring one's mental or physical processes (Sharma & Antonova, 2003).
Working memory has been linked to the dorsolateral prefrontal cortex and it has been argued that some of the most profound cognitive symptoms of schizophrenia can be attributed to deficits in working memory (Goldman-Rakic, 1991, 1994; Jansma, Ramsey, Van Der Wee, & Kahn, 2004). Working memory impairments are likely to be the underlying cause of many negative symptoms in schizophrenia, making it difficult for patients to maintain social relationships, to keep jobs and to live independently (Green, 1996; Keefe, 2000). Since patients with working memory deficits who finish a complicated sentence are likely to have lost their original intention, it is not surprising that an association was also found between these deficits and positive symptoms like thought disorder, evidenced by speech filled with loose associations and derailments (Kerns & Berenbaum, 2002; Spitzer, Braun, Hermle, & Maier, 1993). Keefe's (2000) review concluded that all three components of working memory were impaired in schizophrenic patients.

1.4.2.2. Attention in Schizophrenia

Attention enables us to identify relevant stimuli in our environment, to focus on a particular stimulus while ignoring irrelevant or distracting stimuli (selective attention), to shift our focus from one stimulus to another (switching attention), to maintain focus on a stimulus for a period of time until we are done with it (sustained attention or vigilance), to monitor or respond to several stimuli at the same time (divided attention), and to allow the transfer of the stimulus to higher-level processes (Sharma & Antonova, 2003).

Attention dysfunction is one of the hallmarks of schizophrenia. Because these patients often seem distracted and complain of being overwhelmed by stimuli, clinicians often say they seem to suffer from "attentional" problems (Green, 1998). As a result, patients may fail to pay attention to relevant stimuli or to the flow of conversation, which would contribute to negative symptoms such as social withdrawal (Keefe, 2000). Since attention is a prerequisite to many other cognitive processes, dysfunctions in attention can cause or aggravate deficits in working memory and executive function (Luck & Gold, 2008). In their review of research on cognition in schizophrenia, Bowie and Harvey (2005) concluded the following about attention:

The presence and severity of attentional impairments, possibly more than some other cognitive deficits, are associated with higher severity of positive symptoms (Green & Walker, 1986; Walker & Harvey, 1986). Greater impairments in attention have been
reported to be predictive of poor treatment response (Goldman et al., 1993), and to identify chronic patients who do poorly when their medication dosage is reduced (Green et al., 1993).

Impairments in vigilance, meaning the ability to sustain effort and attention while discriminating target and nontarget stimuli, are (.....) associated with greater deficits in social problem solving and in the ability to acquire skills in training programs (Green, 1996). Because attention is the foundation for other, higher-order cognitive skills, attentional deficits are likely to limit success in many functional domains and are thus an important feature of cognitive impairment in the illness (p. 616).

A common early hypothesis about the nature of the basic cognitive problem in schizophrenia was that schizophrenic patients had deficits in initiating and maintaining "the selectivity which normal attention ordinarily exercises among the sensory impressions," so that "almost everything is recorded that reaches the senses" (Bleuler, 1911/1950, p. 68). Some early tests of selective attention focused on the abnormal incapacity of schizophrenic patients to ignore distractions. McGhie, Chapman and Lawson (1965) used auditory and visual tests of immediate recall of digits and letters presented with and without distractors to demonstrate that schizophrenic patients were significantly more impaired by distractors than control subjects.

Oltmanns and Neale (1975) criticized these tests for their lack of rigour and introduced the more standardized Digit Span Distraction Test (DSDT), in which digits were recalled in a non-distraction condition (where a female voice read the target information) and a distraction condition (where a male voice read irrelevant digits in the intervals between the target digits). The DSDT demonstrated that schizophrenic patients were more vulnerable to auditory distraction than healthy people. Auditory distractibility was associated with thought disorder symptoms (Harvey, Earle-Boyer, & Levinson, 1986; Moser, Cienfuegos, Barros, & Javitt, 2001).

One of the more popular modern tests of selective attention is the Stroop Color and Word Test (Stroop, 1935), which also measures mental flexibility. Subjects must either read the words "red", "green" and "blue," or identify the ink colour in which they are printed; the words (red, for example) are printed in colours that are congruent (red) or incongruent (blue) with their meaning. This task requires the subject to focus on one dimension of the stimulus while ignoring or inhibiting another, which typically makes healthy subject especially slow in naming the ink colour in which the word is written, because they must inhibit their
overlearned tendency to read the word. Several studies found that schizophrenic patients have even greater difficulty with this task, showing greater slowing, and sometimes failure, when the ink colour and the word are incongruent, because they are unable to focus on one dimension while inhibiting the other (Egeland et al., 2003; Everett, LaPlante, & Thomas, 1989; Grapperton & Delage, 1999).

However, other studies reported different Stroop results, such as no differences in colour-incongruent interference coupled with increased facilitation in the schizophrenia group: they were faster than healthy controls in the colour-congruent condition (Carter, Robertson, & Nordahl, 1992; Henik et al., 2002). Some results varied with the schizophrenia subtype or with symptoms. In Carter, Robertson, Nordahl, O'Shora-Celaya and Chaderjian (1993), patients of the undifferentiated subtype showed increased facilitation and normal interference, while patients of the paranoid subtype showed normal facilitation and increased interference. Other researchers (Green & Walker, 1986; Spring, Lemon, Weinstein, & Haskell, 1989) concluded that Stroop interference effects were limited to positive symptom episodes.

Additional selective attention tasks on which schizophrenic patients have shown impairments include dichotic listening (described below under divided attention), the Trail-Making Test, Part A (Reitan & Wolfson, 1985; Heinrichs & Zakzanis, 1998), in which subjects must connect consecutive numbers randomly arranged on a page, the Span of Apprehension Task (SPAN; Asarnow, Granholm, & Sherman, 1991; Addington & Addington, 1997), in which subjects must find a target item in a briefly-flashed array of 1 to 12 items, and backward masking tasks, in which a briefly-presented visual target is followed by a different stimulus (the mask) which disrupts subsequent target identification (McClure, 2001; Green & Nuechterlein, 1999).

**Sustained attention** (vigilance) is the most important type of attention in everyday life. Paying attention is essential to hold a job and to learn new skills, and relationships are difficult to initiate and maintain without providing at least the appearance of being interested in other people's comments and feelings (Green, 1996; Sharma & Antonova, 2003). Sustained attention is often assessed by means of the Continuous Performance Test (CPT; Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956), in which subjects monitor a random series of single number or letters, presented continually at a rate of about one per second, and
are asked to press a button when they detect a specified target. Schizophrenic patients usually miss more targets on the CPT than healthy controls and are more vulnerable to distraction; they also often perform less well on the CPT than on other neuropsychological tests (Nestor & O'Donnell, 1998). Strauss, Buchanan and Hale (1993) found that the CPT was correlated with thought disorder and the SPAN with negative symptoms, but this was contradicted by Addington and Addington (1997).

**Voluntary attention switching** was assessed by means of a variation of the CPT test which had the additional feature of switching attention between auditory and visual modalities. Sutton, Hakereem, Zubin and Portnoy (1961) found that participants with schizophrenia were slower than controls at detecting targets in cross-modal presentations (an auditory stimulus preceded by a visual stimulus or vice-versa) than for auditory ipsimodal presentations (an auditory stimulus preceded by an auditory stimulus). It was hypothesized that healthy controls had more flexible expectations, or that neural traces of the stimuli persisted longer in schizophrenic patients (Baerwald, Sandford & Tryon, 2001; Hanewinkel & Ferstl, 1996).

**Divided attention** is tested by giving subjects two or more simultaneous tasks, or a combination of task(s) and distractor(s). One dual-task example, which also tests auditory selective attention and attention switching, is a dichotic listening (DL) paradigm in which schizophrenic patients and controls are presented simultaneous sound stimuli (for ex. ba, ga) in both the right and left ear through earphones and are instructed to indicate when a sound they hear matches one of the sounds listed on a sheet in front of them. Participants can be directed to attend only their left or only their right ear (selective attention) or to attend to both (divided attention).

DL test results typically show that healthy subjects favour the right-ear stimulus, but that schizophrenic patients (1) do not show such a right-ear advantage or show a reduced one (Kaufman & Trachenco, 1981; Bruder, 1995, Loberg, Hugdahl & Green, 1999), and (2) demonstrate an impairment in the capacity to shift attention to the right or left ear (Green, Hugdahl, & Mitchell, 1994). Since findings of lack of right-ear advantage in schizophrenia were not consistent, it was hypothesized that they may coincide with the presence of positive symptoms like hallucinations or paranoia (Friedman et al., 2001), or with older age or long illness duration (Oie, Rund, Sundet, & Bryhn, 1998). This last hypothesis was supported by
studies showing that young stabilized schizophrenic patients show a normal right-ear advantage (Loberg, Jorgensen, & Hugdahl, 2002).

According to this survey of attention deficits in schizophrenia, some patients show impairments at some time in all types of attention tasks, but no single pattern of attention deficit characterizes all schizophrenic patients at all stages of the disease. A great deal more research needs to be done to establish what types of attention and working memory deficits are characteristic of what subtypes of patients (young or older, medicated or not, in remission or relapse, early or late onset, with positive or negative symptoms, etc.), and to develop theories and reliable tests to distinguish between the different dimensions of attention and working memory.

1.5 NICOTINE, ATTENTION AND SCHIZOPHRENIA

After decades of research, the effects of nicotine on cognition remain unclear but many researchers believe that nicotine and/or smoking improve some aspects of attention in healthy people and in schizophrenic patients. This section presents an introduction to the general effects of nicotine/smoking on humans; a review of findings about the effects of nicotine/smoking on cognition in healthy people; a similar review on the effects of nicotine/smoking on cognition in schizophrenic patients; and a description of the theories put forward to explain how nicotine/smoking enhances attention.

1.5.1 General Effects of Nicotine/Smoking on Humans

In its pure form, nicotine is a highly toxic poison (McKim, 2000). In humans, it is mainly absorbed by smoking tobacco, whose nicotine content (in cured tobacco leaves) is at most around 6%. Nicotine appears to be safe in small doses, though it is only one of more than 4,000 compounds in tobacco smoke, including several carcinogens (Tobacco Advisory Group, 2001). Nicotine affects humans and other creatures by binding to and activating a subtype of neural cholinergic/acetylcholine (ACh) receptors known as nicotinic receptors (nAChR) because of this effect (Purves et al., 1997; Wonnacott, Sidhpura, & Balfour, 2005). The effect is biphasic: low doses activate cholinergic receptors while higher doses can block them. Nicotinic receptors are found in cholinergic synapses throughout the brain and in the peripheral nervous system, as well as in the synapses and cell bodies of neurons that release dopamine, norepinephrine, GABA (γ-aminobutyric acid), glutamate and acetylcholine
Nicotine and schizophrenia (Jones, Sudweeks, & Yakel, 1999; Wonnacott, 1997). Nicotine also causes the release of many other substances that can affect behaviour, including serotonin, beta-endorphin and several hormones (Pomerleau & Pomerleau, 1984; Qhobosheane, Wu, Gu, & Tan, 2004).

Nicotine has complex effects on the central nervous system (CNS). It is believed to act on the neuroregulatory systems that control arousal, mood and cognition. The cholinergic system modulates NMDA receptor function and plays a central role in attention, memory and control of movement (Domino, Mirzoyan, & Tsukada, 2004; Quarta et al., 2007). Higher levels of norepinephrine are associated with increased CNS arousal; increases in dopamine enhance the activity of the dopamine reward system, thereby reinforcing the effects of nicotine. Higher levels of serotonin have an antidepressant effect (Klimek et al., 2001; Mufson, Ginsberg, Ikonomovic, & DeKosky, 2003; Qhobosheane et al., 2004).

Smoking appears to have a genetic component: the smoking behaviour of identical twins who are reared separately is highly correlated (Hughes, 1986; Pomerleau, 1995). The disposition to smoke is not inherited directly, but through variations in structure and biochemistry of the nervous, endocrine and other bodily systems (Zuckerman, 1992; Gilbert & Gilbert, 1995). These variations produce individual differences in dispositions toward certain types of reactions to the environment. Since sex steroids alter dopamine and serotonin neuro-transmission (Staley et al., 2001), smoking has different effects on the CNS of women and men (Algan, Furedy, Demirgoren, Vincent, & Pogun, 1997). Women smoke lighter and fewer cigarettes, and inhale less, but they have greater difficulty in quitting than men (Pogun, 2001).

1.5.2 Effects of Nicotine/Smoking on Cognition in Healthy People

A large number of studies examined the effect of nicotine on cognition in healthy adults but their results have been inconsistent, with some studies producing positive results and other studies negative results for almost all cognitive components. Review studies (Heishman, Taylor, & Henningfield, 1994; updates by Heishman, 1998, 1999, Heishman & Henningfield, 2000) stressed the importance of distinguishing between nicotine studies conducted with deprived smokers (who abstained from smoking for a period of time, usually overnight) and studies conducted with non-deprived smokers or non-smokers. Studies that used deprived smokers were more likely to find that nicotine had enhanced cognitive
Nicotine and schizophrenia performance, especially in finger tapping speed, which is a measure of central processing, and in tasks of sustained and selective attention.

However, studies conducted with deprived smokers cannot conclusively demonstrate that nicotine improved cognitive functions, since tobacco deprivation itself has a negative impact on cognitive performance in smokers (Bell, Taylor, Singleton, Henningfield, & Heishman, 1999; Lyvers, Maltzman, & Miyata, 1994). As a result it is difficult, in studies using deprived smokers, to distinguish between nicotine effects that simply reversed cognitive decrements caused by deprivation, and nicotine effects that enhanced performance beyond that level (Heishman & Henningfield, 2000). According to Heishman (1998), the best way to obtain clear demonstrations of true enhancement of performance due to nicotine is to use subjects who are non-smokers or non-deprived smokers. If deprived smokers must be used, he recommends reporting pre-deprivation as well as post-deprivation results. He also criticizes many studies for failing to use placebo control conditions and single- or double-blind designs, and for using imprecise methods of nicotine dosing such as at-will cigarette smoking.

Placebo-controlled studies that tested the effects of nicotine or smoking on non-smokers and non-deprived smokers produced inconsistent results. The few studies that produced uncontradicted positive effects suggested that nicotine and smoking reliably enhanced finger tapping speed (West and Jarvis, 1986; Perkins et al., 1990, 1994), short-term focussed attention (mostly in choice reaction time tests where subjects press one button for one stimulus and another button for another stimulus; Hindmarch, Kerr, & Sherwood, 1990; Kerr, Sherwood, & Hindmarch, 1991; Le Houezec et al., 1994; Myers, Taylor, Moolchan, & Heishman, 2007) and recognition memory (Perkins et al., 1994). Generally, enhanced response speed was found to be a reliable effect across many types of cognitive tasks (Heishman et al., 1994).

On the other hand, many placebo-controlled studies produced conflicting results on sustained attention/vigilance (positive effects in Foulds et al., 1996; Levin et al., 1998; Mumenthaler et al., 2003; negative or no effects in Wesnes, Warburton, & Matz, 1983; Wesnes & Warburton, 1984); on selective attention (improved performance in smokers in tasks of rapid visual information processing in Gilbert et al., 2005; no effect or impaired performance in non-smokers or non-deprived smokers in Heishman, Snyder, & Henningfield
Nicotine and schizophrenia (1993), Perkins et al. (1994) and Foulds et al. (1996); on **verbal working memory** (Sternberg paradigm: positive in West & Hack, 1991; Kerr et al., 1991; negative in Foulds et al., 1996); and on **recall memory** (positive in Rusted, Graupner, & Warburton, 1995; negative in Dunne, MacDonald, & Hartley, 1986; Hindmarch et al., 1990; Heishman et al., 1993). Finally, a few placebo-controlled studies found uncontradicted negative effects. Nicotine or smoking had no effect or impaired performance in non-smokers or non-deprived smokers in tests of **conditioned learning** (Thornton et al., 1996) and **reasoning and arithmetic** (Dunne et al., 1986; Heishman et al., 1993).

According to Heishman and Henningfield (2000), inconsistent results may be due to sub-optimal doses of nicotine or to the fact that subjects received only one dose during each experimental session. Infrequent dosing can cause nicotine-induced dysphoria in nonsmokers (Hindmarch et al., 1990; Heishman et al., 1993), which may interfere with their performance. To avoid this, Heishman and Henningfield recommended administering ascending doses of nicotine daily to non-smokers for eight consecutive days.

Overall, the results of the placebo-controlled studies suggest that with the right task conditions and the right dosage, nicotine reliably improves short-term focussed attention, recognition memory and response speed in healthy adults, and may also improve sustained attention (vigilance), visual selective attention and working memory.

### 1.5.3. Effects of Nicotine/Smoking on Cognition in Schizophrenia

It is well known that schizophrenic patients have extremely high rates of cigarette smoking, ranging from 60% to 90% (see review by McEvoy & Allen, 2002), which is higher than the rate for other mentally ill patients (Diwan, Castine, Pomerleau, Meador-Woodruff, & Dalack, 1998; Leonard et al., 2001) and much higher than the rate for the general population. Time makes a difference because smoking rates have been declining steadily for decades: 50% of all Canadians aged 15 and over smoked in 1965, compared with 25% in 2003 (Canadian Council for Tobacco Control, 2004). Studies found that 61% of schizophrenic patients in Calgary smoked (Addington, el-Guebaly, Addington, & Hodgins, 1997) and 65% of schizophrenic and other psychotic patients in Montreal (Margolese, Malchy, Negrete, Tempier, & Gill, 2004), compared with roughly 28% of the general population (Health Canada, Tobacco Control Programme, 2004). According to Leonard et
al. (2000), the rate of smoking of schizophrenic patients has diminished much less than that of the general population. Schizophrenic men smoke more than schizophrenic women: in a 1990 survey of American hospitalized schizophrenic patients, de Leon (1995) found rates of smoking of 93% for the men and 70% for the women.

Canadian and U.S. rates cannot be generalized to other countries. In Greece, researchers (Beratis, Katrivanou, & Gourzis, 2001) reported smoking rates of 58% for schizophrenic patients and 42% for the general population, which is a much smaller gap than the 2-to-1 ratio found in Canada. In Spain (Herran et al., 2000), 64% smoked among schizophrenic patients and 51% among healthy controls. In Israel (Itkin, Nemets, & Einat, 2001), smoking rates were 45% for schizophrenic patients and 28% for the whole population. And in Japan, Mori et al. (2003) reported no difference between the smoking rates of schizophrenic patients (34%) and of the general population (37%). These differences suggest that cultural factors play a role.

When Forchuk et al. (2002) asked 100 hospitalized and non-hospitalized schizophrenic patients from London, Ontario, why they smoked, the main motives patients mentioned, in descending order, were sedative effect, control of negative symptoms, addiction, and control of medication side effects. For their part, experts proposed many possible motives, including (1) to obey a neurobiological compulsion; (2) to self-medicate the effects of their abnormal neurophysiology and their clinical symptoms; (3) to counteract the side effects of their medication; (4) to relieve stress and anxiety; and (5) to enhance their cognitive functioning.

Neurobiological compulsion. As mentioned earlier, smoking seems to have a genetic component. This appears to be confirmed by findings that schizophrenic identical twins and their unaffected co-twins had similar rates of smoking that were substantially higher than the rates for healthy controls (Lyons et al., 2002). Another biological link between smoking and schizophrenia was discovered when Freedman et al., (1995), in a study of postmortem brain tissue, found that schizophrenic patients who smoked had fewer α7 nicotinic receptors in the hippocampus than control smokers, which may cause a failure of cholinergic activation of inhibitory interneurons that results in a decrease of the gating or filtering of response to sensory stimulation.
Neurobiological factors may partly explain why cessation of smoking is extremely difficult to achieve in schizophrenic patients (George et al., 2002). According to Ziedonis and George (1997), nicotine withdrawal can exacerbate the clinical symptoms of schizophrenia. Biological factors were also held responsible for the fact that schizophrenic patients smoke more heavily than control smokers; they use more cigarettes per day and inhale more deeply, producing a greater concentration of nicotine in the blood for the same number of cigarettes (Olincy, Young, & Freedman, 1997; Simosky, Stevens, & Freedman, 2002).

Self-medication. Many studies tried to understand the effects of smoking on the clinical symptoms of schizophrenia by comparing schizophrenic smokers and nonsmokers, but the results were conflicting and difficult to interpret. A review by Newhouse, Singh and Potter (2004) concluded that smoking may be a marker for more severe symptomatic forms of the disease, and that smoking may reduce some symptoms for a brief period of time. The most compelling reason to believe that schizophrenic patients smoke to medicate themselves is that nicotine ameliorated or corrected three main endophenotypes of schizophrenia that are shared by patients and their close relatives (see earlier section on Neuropathology of Schizophrenia): nicotine/smoking improved their deficiencies in smooth pursuit eye movement (Olincy, Ross, Young, Roath, & Freedman, 1998), strengthened their prepulse inhibition (PPI) of the acoustic startle response (Kumari, Soni, & Sharma, 2001) and normalized their P50 auditory sensory gating deficit (Adler, Hoffer, Wiser, & Freedman, 1993; Adler et al., 1998).

The most intriguing hypothesis concerning smoking as self-medication came from Zammit et al. (2003), who performed a longitudinal study of more than 50,000 Swedish conscripts. After adjusting for many possibly-confounding variables, they reported that smoking at ages 18-20 was associated with a lower risk of developing schizophrenia, and concluded that smoking may be a protective factor for schizophrenia. This seemed to be contradicted by an Israeli study of more than 14,000 recruits which found a higher prevalence of smoking in apparently-healthy male adolescents who were later hospitalized for schizophrenia (Weiser et al., 2004), but the Israeli researchers conceded that the Swedish study had a longer follow-up (27 years vs. 4-to-16 years), more participants with a much higher rate of smoking (59% vs. 28%), and much more information about important
confounding factors such as drug and alcohol problems and family psychiatric histories. Among the Swedish conscripts, before adjustment for confounders, the smokers were 1.7 times as likely as non-smokers to be hospitalized later for schizophrenia.

**Counteracting side effects of medication.** Older typical antipsychotic drugs such as haloperidol reduce positive symptoms but cause significant parkinsonian side effects and some cognitive impairment (Meltzer, Park, & Kessler, 1999). Newer atypical antipsychotics diminish positive and negative symptoms, produce much fewer parkinsonian effects and appear to slightly enhance cognition (Meltzer & McGurk, 1999). Schizophrenic patients increase their smoking when they start taking the typical drug haloperidol (McEvoy, Freudenreich, Levin & Rose, 1995) and decrease their smoking when they take or switch to an atypical drug (McEvoy et al., 1995). This is believed to occur because smoking diminishes the movement disorders (Simosky et al., 2002) and the cognitive deficits caused by typical drugs (Levin, Wilson, Rose, & McEvoy, 1996). A study of Ontario drug benefit claimants for 1996-1997 (Dewa, Remington, Herrmann, Fearnley, & Goering, 2002) reported that many patients, especially seniors, were still taking the older typical drugs in spite of the fact that seniors are most susceptible to parkinsonian symptoms.

**Relieving stress and anxiety.** Apart from self-report studies in which schizophrenic patients said they smoked to relax or to settle their nerves (Forchuk et al., 2002; Glynn & Sussman, 1990), little evidence exists to support the view that these patients start smoking or continue to smoke because it relieves their feelings of stress and anxiety. In 1991, Pomerleau and Pomerleau wrote that "The relationship between stress and smoking, and a corresponding link between smoking and anxiety reduction, are so well entrenched in the lore concerning cigarette smoking that they have assumed the status of truisms" (p. 599). This was challenged by Parrott (2003, 2004), who alleged that the perceived benefits of cigarettes for mood change were temporary, and that in the longer term the repetitive experience of irritability and other withdrawal symptoms that occur between cigarettes cause smokers to suffer worse daily moods than non-smokers.

To sort out these conflicting views, Kassel, Stroud and Paronis (2003) reviewed the research on smoking and its relation to anxiety and stress (defined as psychological response to taxing situations) in non-mentally-ill people. They concluded that stress was associated with a greater risk to begin smoking; that higher stress levels were correlated with smoking
and with heavier smoking; but that findings on the nature of a possible causal link between smoking and stress were inconsistent. They found that although anxiety-provoking problems were positively correlated with smoking and with heavier smoking, anxiety had not provoked the onset of smoking, but that addiction to smoking may have increased subsequent anxiety disorders. On the question of whether smoking had been effective in reducing stress and anxiety, Kassel et al. found conflicting results for both stress and anxiety. It therefore appears that all allegations about the links between smoking and stress, and between smoking and anxiety, must be studied further before conclusions can be reached.

Enhancing cognitive functioning. Many experts believe that schizophrenic patients smoke to attenuate their cognitive dysfunction (Newhouse, Potter, & Singh, 2004; Rezvani & Levin, 2001). This view is partly supported by findings that the number of cigarettes schizophrenic patients smoked per day was associated with the severity of their cognitive impairments (Taiminen et al., 1998). Only a few placebo-controlled experiments tested the effects of nicotine on cognition in schizophrenic patients, but all of them reported that nicotine had produced at least one type of cognitive improvement in the patients. The participants were all schizophrenic smokers (Levin et al., 1996; Smith et al., 2006; Smith, Singh, Infante, Khandat, & Kloos, 2002), or schizophrenic patients and control subjects who were all smokers (Dépatie et al., 2002; Jacobsen et al., 2004), or patients and controls who were all nonsmokers (Barr et al., 2008). Participants who were smokers were all deprived of nicotine for some period of time, usually overnight.

Uncontradicted positive results from these placebo-controlled studies indicated that nicotine had enhanced visual sustained attention in performances on the Continuous Performance Test (Barr et al., 2008; Dépatie et al., 2002; Levin et al., 1996; Smith et al., 2006) and improved visuospatial working memory in tests of spatial rotation, spatial organization and delayed visual matching to sample (Levin et al., 1996; Smith et al., 2006; Smith, Singh, Infante, Khandat, & Kloos, 2002). Mixed results were obtained for verbal working memory (positive effects in Jacobsen et al., 2004, and Smith et al., 2002; negative effects with the Sternberg paradigm in Levin et al., 1996, and Smith et al., 2006) and negative results for two simple choice-reaction-time tests of short-term focussed attention (Levin et al., 1996; Smith et al., 2002).
Jacobsen et al. (2004) used an n-back task with two levels of verbal working memory (1: respond yes for a back-to-back repetition; 2: respond yes for a repetition separated by a different word) and two levels of selective attention (binaural or dichotic with changing focus). Significant results were obtained only for the most difficult task condition (dichotic 2-back); nicotine improved the performance of schizophrenic patients and worsened the performance of control subjects. Concurrent fMRI scanning showed that nicotine enhanced functional connectivity to a greater degree in schizophrenic than in control subjects during dichotic 2-back task performance. Barr et al. (2008) found that nicotine improved selective attention in schizophrenia patients on a Card Stroop task.

Two other studies that were not placebo-controlled compared the baseline and post-nicotine-nasal-spray performance of participants who were schizophrenic patients (smokers and non-smokers) and healthy controls (smokers and non-smokers). The first study, by Sherr et al. (2002), which was primarily a test of smooth pursuit eye movement, found no effects of nicotine on complex visual sustained attention as measured by the Continuous Performance Test - Identical Pairs (CPT-IP), in which subjects must respond when two identical numbers are shown consecutively. The second study, by Myers et al. (2004), reported that nicotine had significantly improved the performance of schizophrenic patients who were smokers on a delayed visuospatial recognition memory task, but that it had not enhanced visuospatial working memory in a delayed match-to-sample task.

Finally, Silver et al. (2002) compared the finger-tapping rates of hospitalized schizophrenic patients who were smokers and non-smokers, and found that the smokers had a significantly higher finger-tapping rate for both hands. These results support the hypothesis that smoking is associated with faster central processing and that nicotine can ameliorate the abnormally slow responses that have been associated with schizophrenia (King, 1991). Yang et al. (2003) found a strong negative relationship between finger-tapping speed and the dosage of antipsychotic medication.

To compare the effects of nicotine/smoking on the cognitive functioning of healthy and schizophrenic subjects, summary results of the placebo-controlled studies are presented in Table 3. The table makes clear that nicotine/smoking has very different effects on these two groups. Most striking, nicotine/smoking produced reliable improvements in performance on four tests of short-term focussed attention involving healthy subjects, but had
no significant effect in either of two similar tests using schizophrenic participants. Conversely, nicotine/smoking improved the performance of schizophrenic patients on three tests of visual sustained attention/vigilance, but produced contradictory results in sustained-attention tests with healthy participants. Selective attention tests produced mixed results in both patients and healthy participants.

| Table 3. Results of Placebo-Controlled Tests of the Enhancing Effects of Nicotine/Smoking on Cognitive Functioning in Healthy and Schizophrenic Subjects |
|-----------------|---------------------------------|---------------------------------|
| **Type of Results** | **Healthy Subjects** | **Schizophrenic Subjects** |
| Uncontradicted enhancing effect | - short-term focussed attention (4 tests) | - visual sustained attention/vigilance (3 tests) |
| | - recognition memory (1) | - visuospatial working memory (3) |
| | - finger-tapping speed (3) | | |
| | - response speed (many) | | |
| Mixed results | - sustained attention/vigilance (3 positive; 2 negative or no effect) | - verbal working memory (2 positive; 1 negative) |
| | - verbal working memory (2 positive; 1 negative or no effect) | - selective attention (2 positive; 1 negative) |
| | - recall memory (1 positive; 3 negative or no effect) | | |
| | - selective attention (1 positive; 3 negative or no effect) | | |
| Uncontradicted negative effect or no effect | - conditioned learning (1) | - short-term focussed attention (2 tests) |
| | - reasoning/math (2) | | |

1.5.4 Theories of Attention and Nicotine/Smoking

Although more research is needed to produce solid conclusions about the effects of nicotine on cognition, the results shown in Table 3 give credence to the belief that nicotine enhances cognitive performance. The first theory that was developed to explain this phenomenon hypothesized that nicotine, by means of a mechanism that remains unclear, acts as a stimulus barrier that filters out irrelevant and undesirable stimuli, thereby improving concentration (Friedman, Horvath, & Meares, 1974; Knott, 1978). Kassel (1997) expanded this stimulus-filter hypothesis by suggesting that nicotine enhances attentional processing by
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(a) filtering out irrelevant stimuli, and (b) increasing the processing capacity allocated to relevant stimuli.

These proposals were strongly influenced by the two main early modern psychological theories of attention, which are the "filter model" and the "capacity model." Under the filter model, also referred to as "early selection theory" and developed by Broadbent (1958), all stimuli were said to proceed into the system in a parallel manner until they reached an early sensory buffer, at which point an internal filtering mechanism selected some (relevant) stimuli for further processing by a single-channel, limited-capacity central processor, while preventing other (irrelevant) stimuli from advancing further. Broadbent (1977) revised his filter theory to specify that in addition to an early selection based on physical cues (filtering), he also proposed a later selection mechanism (called "pigeonholing") which is based on semantic cues. Treisman (1960) further modified the filter model by suggesting that irrelevant stimuli were attenuated rather than completely blocked.

Filter theories raised the question of why two or more pieces of information could not be processed at the same time. This led to the capacity (or resource) model of attention, in which Kahneman (1973) proposed the notion that attention is a limited-capacity undifferentiated resource that is distributed among all competing processes in a manner that varies with the momentary intentions and enduring dispositions of each individual. This was challenged by Wickens (1984), who argued that attention is divided among multiple resource pools related to the modality of the input (visual or auditory), the stage of processing (perceptual/central or response) and the perceptual/central processing code (verbal or spatial). Unlike Kahneman, Wickens predicted that performance would deteriorate only if two tasks competed for the same resources within the same pool. The capacity model was further qualified when Posner (1978) and Schiffrin and Schneider (1977) distinguished between automatic and controlled processing. Automatic processes are fast, act in a parallel fashion, use little or no capacity, do not interfere with other processes and occur without conscious awareness of intentionality. Controlled processes are slow, serial and capacity demanding.

How do these general attentional models relate to the specific models of nicotine and attention and to research findings on the effects of nicotine/smoking on attention? According
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to the stimulus-filter hypothesis of smoking, nicotine brings about a further narrowing of Broadbent's attentional filter, so that a smaller proportion of stimuli is allowed into the system for processing. According to Kassel's dual hypothesis, nicotine narrows the attentional filter and, additionally, it increases the processing capacity (from Kahneman's capacity model) that is devoted to relevant stimuli so that they are processed more efficiently. The stimulus-filter hypothesis is a plausible explanation for the fact that nicotine has improved the performance of participants who responded to target (relevant) stimuli in the presence of distracting (irrelevant) stimuli (Pickworth, Herning, & Henningfield, 1986; Provost & Woodward, 1991). The capacity-enhancement hypothesis could explain the findings of Lyvers, Boyd and Maltzman (1988), who used electrodermal responses as an index of attention and found that smoking increased skin conductance responses to relevant tones requiring a response, but had no effect on responses to irrelevant tones. The researchers concluded that smoking had not enhanced attention by filtering out irrelevant stimuli, but by selectively enhancing the processes associated with the attended relevant stimuli.

These theories of attention are also very relevant to schizophrenia. Even before Broadbent formulated his filter model, schizophrenic symptoms were blamed on a "broken filter" which caused deficits in these patients' capacity to initiate or maintain selective attention (Nuechterlein & Dawson, 1984; Spring, Weinstein, Freeman, & Sherman, 1991). Formal thought disorder and hallucinations were attributed to a defective filter mechanism that made schizophrenic patients unable to be focally attentive and to ignore environmental events that are irrelevant to current activities (Chapman and McGhie, 1962; Payne & Caird, 1967).

Schizophrenic symptoms were also attributed to an attentional capacity dysfunction. According to Michie, Fox, Ward, Catts and McConaghy (1990), "A dysfunction in any of the hypothesized components of the current models of information processing, such as a disturbance of automatic processing, or in the allocation of capacity, or in the amount of capacity available, would be predicted to have devastating effects on the intellectual functioning and task performance of the affected individual" (p. 210). Whether the attention problems of schizophrenic patients are due to a defective attentional filter, to dysfunctions in
attentional capacity, or to both, it appears that these patients might benefit from nicotine since it has been proposed to alleviate both types of problems (Kassel, 1997).

Newhouse et al. (2004) formulated a new theory of nicotine and cognitive performance that encompasses both healthy and schizophrenic individuals. Based on the Yerkes-Dodson principle (1908) of optimal levels of arousal (too much or too little arousal produces inferior performances), this theory predicts that nicotine will not improve and may even impair cognitive functioning in healthy non-smokers, but that it will enhance cognition in smokers and in some psychiatric patients, including schizophrenics. This is explained by the fact that most healthy non-smokers are already functioning at, or near, their optimal level and will therefore be pushed beyond their optimal point by nicotine, while smokers and schizophrenic patients are operating under sub-optimal conditions and need the enhancing effects of nicotine on their neurotransmitters to bring them to the optimal level that will elicit their best performance. Paradoxically, nicotine appears to stimulate the central nervous system while it inhibits the perception of non-relevant stimuli.

1.6 EVENT POTENTIALS, ATTENTIONAL ORIENTING AND SCHIZOPHRENIA

Most studies of cognition in schizophrenia consist of observing patients and control subjects while they perform cognitive tasks. Theories concerning the nature of schizophrenic dysfunctions are primarily based on patients' deficits in performing such tasks, such as in accuracy of responses, nature of errors or response latencies. As Michie (1995) pointed out, this approach is clearly limited since overt performance measures are opaque to the mental steps that intervene between the presentation of a stimulus and the production of an overt response. The strength of brain event-related potentials (ERPs) is that they make it possible to monitor those intervening steps in order to provide details of normal and abnormal neural processing of information. Other imaging techniques can also analyze neural information processing, but ERPs have the advantage of a vastly superior time resolution: they are a thousand times faster than the other imaging methods (McCarley, Faux, Shenton, Nestor, & Adams, 1991). Particularly important for the purposes of this thesis, ERPs provide a unique means of carrying out a fine-grained analysis of selective attention processes, specifically those processes involved in the focusing of attention on one source of stimuli when there are multiple sources present and in the maintenance of the focus of attention (Michie, 1995, p. 307).
The rest of this section contains an introduction to ERPs, a description of the links between ERPs and the concepts of controlled and automatic pre-attentive information processing, as well as a review of ERP research related to the processes of orienting and reorienting in healthy people and in schizophrenic patients.

1.6.1 Introduction to Event-Related Potentials

Event-related potentials are patterns of brain electrical activity recorded from an electro-encephalogram (EEG) that occur when subjects experience stimuli that can be exogenous or internal (endogenous) to them. These time-locked, scalp-recorded changes in electrical voltage that accompany the presentation of specific stimuli are called "event-related potentials" or "event potentials" or ERPs. ERPs are obtained by averaging brief (~1 second) EEG epochs recorded over 100 or more stimulus trials (Fabiani, Gratton, & Coles, 2000). Averaging cancels out the random electrical activity emanating from brain sites that are not involved in the repeated stimulus presentation, leaving only the neural activity that occurred in response to the stimulus. As shown in Figure 1, this neural activity appears as several positive (P) and negative (N) voltage peaks (called "components") in the ERP waveforms.

Figure 1. ERP waveforms elicited by frequent (dotted line) and rare (solid line) stimuli from the parietal scalp site of a young adult during a visual count task

The main variables in ERP research are: (1) the amplitude or size of the components, defined as the difference (in voltage) between a prestimulus baseline (the horizontal line in Figure 1) and the largest (positive or negative, depending on the point of interest) peak in a given latency window; (2) the latency of the components, defined as the time elapsed (in
milliseconds, or ms) between stimulus onset (see arrow on the scale at the bottom of Figure 1) and the occurrence of the peak/component of interest; and (3) the scalp distribution, which is the change in component amplitude across recording sites on the subjects' scalps (Picton et al., 2000). Specific ERP components reflect unique stages of information processing. ERP components that occur early (roughly within 200 ms of stimulus onset, such as components P50, N1, P2 and N2) are called "exogenous" or "sensory" because they are primarily affected by the physical properties of stimuli, such as their intensity and frequency. Later components (such as P3 and P4) are "endogenous" or "cognitive" because they are primarily elicited by internal cognitive factors (such as the perceived relevance of the stimulus to the task) and can even occur in the absence of external stimuli. The neural generators of ERP components are not well known. Since only ERP peaks produced by neural generators with the proper orientation and configuration are detected at the scalp, it is likely that ERPs represent only a portion, albeit perhaps a sizable portion, of the brain activity associated with specific stimuli (Fabiani et al., 2000; Johnson, 1995).

1.6.2. ERPs and Controlled Vs. Automatic Processing in Schizophrenia

Hundreds of experiments have used ERPs to study schizophrenia. As mentioned earlier (see endophenotypes of schizophrenia; nicotine as self-medication), some of these studies concerned the automatic exogenous P50 component. Unlike healthy subjects, who typically show a diminished P50 response to the second of a pair of consecutive auditory stimuli, thereby demonstrating normal inhibitory filtering/gating of stimuli, schizophrenic patients and their close relatives often fail to show a diminished P50 to the second stimulus (Light & Braff, 1999). This abnormality is reduced when schizophrenic patients take nicotine (Adler et al., 1998).

Until the 1990s, most of the other ERP studies of schizophrenic patients, like the majority of all ERP studies, were devoted to the endogenous P3 component (see Figure 1), also called P3b (reviews: Ford, 1999; Hansenne, 2000; Jeon & Polich, 2003; Muller, Kalus, & Strik, 2001). The stimulus paradigm that is almost invariably used to elicit the P3b is a simple sustained attention task called the "oddball paradigm," in which two stimuli are presented randomly so that one of them - the oddball - appears less frequently than the other. In the auditory version of the oddball paradigm, for example, two tones are presented through

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earphones, with the target (usually higher-frequency) tone occurring less often than the non-target (lower-frequency) tone. Subjects are asked to respond to target tones (by counting the targets, or pressing a button, etc.) and to abstain from responding to non-target tones (Fabiani et al., 2000). The P3b occurs when subjects detect and process infrequent and meaningful changes (oddball stimuli) in the environment. As a result, P3b amplitude and latency reflect controlled information processing. P3b amplitude is correlated with the amount of attentional resources devoted to a task (reviewed in Kok, 2001) and P3b latency is believed to be a measure of stimulus classification speed (see Polich & Herbst, 2000). Many P3b studies (see Ford, 1999) reported decreased amplitudes and longer latencies in schizophrenia in various experimental paradigms. Michie (1995) wrote that, "One of the most robust findings in ERP research into psychopathology is the observation of a P3b amplitude reduction in patients with a diagnosis of schizophrenia" (p. 302).

Since the early 1990s, an increasing proportion of ERP studies have examined the relationship between schizophrenia and the earlier ERP components that reflect automatic pre-attentive information processing. Shelley et al. (1991) were the first to discover an abnormal pre-attentive mismatch negativity (MMN) component in schizophrenic patients. They suggested that the extensive schizophrenic deficits in controlled processing revealed in P3b studies may in fact be secondary to schizophrenic impairments in pre-attentive processing which had yet to be seriously explored. If we assume, like Duncan (1984) and Treisman (1988), that controlled processes operate on the output from earlier automatic pre-attentive processing, it is to be expected that impairments in early pre-attentive processes could have a profound impact on subsequent controlled processes, either because the controlled processes are operating on deficient sensory information, or because they have to take over some of the processing that would normally be carried out by pre-attentive mechanisms (Michie, 1995).

Näätänen (1992) and Cowan (1995) suggested that the MMN component, which detects deviant or novel stimuli in a series of repetitive auditory stimuli, reflects the activity of our involuntary attention-orienting system. (Sokolov, 1963). According to Friedman, Cycowicz and Gaeta (2001),

The orienting response is an involuntary shift of attention that appears to be a fundamental biological mechanism necessary for survival. Orienting is a rapid response to new (never experienced before), unexpected (out of context)
or unpredictable stimuli, which essentially functions as a 'what-is-it' detector.
. . . the detection of the event precedes orienting and, if it is sufficiently deviant, engenders the involuntary capture of attention, enabling the event to enter our consciousness, thus permitting an evaluation of the significance of the stimulus. This could lead, if the event is deemed significant, to behavioral action (p. 356).

Cowan (1995) pointed out that although researchers tend to consider distraction by deviant or novel stimuli as a nuisance that interferes with attention-driven primary task performance, in real life it is rapid attention shifts provoked by novel or deviant stimuli that are more likely to be important. Escera, Yago and Alho (2001) agree that "Surviving in the natural environment requires the rapid switching of attention among potentially relevant stimuli" (p. 877). Schröger and Wolff (1998a) took the Näätänen-Cowan model further by proposing a multi-component attention-orienting-and-reorienting mechanism in which (1) the MMN starts the orienting process by indexing the involuntary automatic detection of change in incoming stimuli; (2) a subsequent P3a components signals an involuntary switch in the orientation of attention toward the novel distractor stimulus; and (3) a late negative component, the reorienting negativity or RON, reflects the reorientation of attention back toward the main task that was disturbed by the distractor stimulus.

1.6.3 Review of Orienting-Related ERPs in Healthy People and in Schizophrenia

As mentioned above, the main ERP components that have been linked to attentional orienting and reorienting are the mismatch negativity (MMN), the P3a and the late reorienting negativity (RON). ERP research on these components in healthy subjects and in schizophrenic patients is reviewed below, as well as research on the N1 component, which overlaps the MMN component and is therefore important in the broader context within which the orienting and reorienting components/processes operate. Since pre-attentive ERPs are automatic and occur even when a subject's attention is not engaged, one of the most effective paradigms to elicit these ERPs are selective attention tasks such as dichotic listening with forced attention to one ear, which require subjects to pay attention to sound stimuli from one ear (attended ear, controlled processing) while ignoring sound stimuli from the other ear (unattended ear, automatic processing). Brief descriptions of the orienting-relevant ERP components and of the effects of schizophrenia are shown in Table 4.
N1 component. This large early ERP, peaking at approximately 80-100 ms, is usually elicited by sounds after a period of silence (Naätänen & Picton, 1987) and is largest over the fronto-central areas of the scalp (Muller-Gass & Campbell, 2002). It is a primarily exogenous component that is difficult to interpret because many components overlap around those latencies. Most researchers agree with Naätänen (1992) that N1 is primarily a sensory ERP which is mostly affected by the physical characteristics of stimuli; the more intense the stimuli, the greater the N1 amplitude. Others (Woldorff & Hillyard, 1991; Vogel & Luck, 2000) insist that the N1 is more than a little endogenous and that attention has a significant direct effect on it. This appears to be confirmed by the fact that the N1 is greater when it is elicited by a stimulus that is the focus of attention (attended). According to Naätänen (1992), however, this N1 attention effect is the result of an increase in another component that overlaps the N1, the "processing negativity." Auditory N1 has been associated with two different neural sources in the auditory cortex, including the auditory cortices on the supratemporal plane, and the auditory association region of the superior temporal cortex (Muller-Gass & Campbell, 2002). Naätänen and Picton (1987) also suggested widespread neural generators across brain regions, such as the motor and premotor cortices, under the influence of the reticular formation and perhaps the thalamus.

N1 and schizophrenia. In an important early dichotic listening study by Baribeau-Braun, Picton and Gosselin (1983), in which medicated schizophrenic patients and healthy control subjects had to focus on one ear to detect oddball sounds among standard ones while ignoring other standard and odd sounds presented to the other ear, the N1 component was larger for controls than for patients and for the attended than for the ignored stimuli. In addition, patients produced no N1 component when sound stimuli were delivered at a slow rate (randomized 500 to 1500 ms) but showed an N1 as large as that of controls when the stimuli were delivered at a faster rate (randomized 250 to 750 ms). The absence of N1 when a longer interstimulus interval was used was interpreted to reflect a problem in the control mechanisms that create and maintain the strategy of selective information processing.
Table 4. Effects of Schizophrenia on ERP Components Involved in Orienting-Reorienting

<table>
<thead>
<tr>
<th>Component</th>
<th>Description</th>
<th>Effect of Schizophrenia</th>
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<tr>
<td>N1</td>
<td>Primarily exogenous/sensory&lt;br&gt;Peaks around 80-100 ms&lt;br&gt;Elicited by physical characteristics of stimuli.</td>
<td>Smaller and delayed&lt;br&gt;Absent if tones delivered slowly</td>
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<tr>
<td>MMN (mismatch negativity)</td>
<td>Endogenous and automatic&lt;br&gt;From 50 ms, peaks around 100-240 ms&lt;br&gt;Elicited by change in repeating stimulus&lt;br&gt;Calculation: deviant minus standard</td>
<td>Smaller to duration-deviant distracting tones; less consistently, smaller to frequency-deviant tones</td>
</tr>
<tr>
<td>P3a</td>
<td>Endogenous and automatic&lt;br&gt;Not dependent on attention&lt;br&gt;Peaks around 300 ms (before the P3b)&lt;br&gt;Elicited by novel/unexpected/deviant stimuli</td>
<td>Smaller and delayed</td>
</tr>
<tr>
<td>RON (reorienting negativity)</td>
<td>Endogenous&lt;br&gt;Not dependent on attention&lt;br&gt;Latency around 480-550 ms&lt;br&gt;Elicited by deviant distractor stimuli</td>
<td>To be determined</td>
</tr>
</tbody>
</table>

Many other N1 studies of schizophrenia found abnormally small amplitudes (see reviews by McCarley et al., 1991; Iwanami, Isono, Okajima, Noda, & Kamijima, 1998) and prolonged latencies (Adler & Gattaz, 1993; Connelly, Gruzelier, Machanda, & Hirsch, 1983) in these patients. These studies also confirmed that differences between the N1 amplitude of schizophrenic patients and controls consistently emerged when stimuli were presented more slowly (interstimulus interval or ISI longer than 2 s; reviewed by Javitt, 2000). This was attributed to the fact that the N1 amplitude of patients reached a plateau around ISI 2s, while the N1 amplitude of controls continued to rise until the ISI reached 5-10 s. However, Shelley, Silipo and Javitt (1999) and Ahveninen et al. (2006) found significant reductions in N1 amplitude in patients with an ISI of 0.5 s. N1 impairments in schizophrenia were correlated with auditory-cortex neuronal abnormalities in neuro-imaging studies (McCarley...
Ahveninen et al. (2006) found reduced N1 in schizophrenic patients and in their unaffected co-twins, suggesting that underlying neuronal deficits might be associated with a genetic predisposition to schizophrenia.

**Mismatch negativity (MMN, see Table 4).** First described by Näätänen, Gaillard and Mäntysalo (1978), the MMN is a small negative component which peaks around 100-250 ms after stimulus onset. Most often studied in the auditory modality, it is automatically elicited by any type of change (of duration, frequency, intensity, location, pattern, etc.) in a repeating series of auditory stimuli, even in the absence of attention or behavioural response. The MMN reflects auditory pre-attentive sensory processing, which signals that an incoming sound was compared to the sensory memory of the features of the previous repeated sounds and was found to differ from it (Näätänen, 1990, 1992). The amplitude of the MMN increases and its latency shortens with increasing difference between the incoming sound and the previous repeated sounds. The memory representation that is required to produce the MMN is stored for approximately 10 seconds during the stimulus-feature-extraction activity reflected in the N1 and other early ERPs. It is developed over several presentations and can become inactive over a silent period (Cowan, Winkler, Teder, & Näätänen, 1993; Muller-Gass et al., 2002). Analogous responses were observed in the other sensory modalities, including the visual, the somatosensory and the olfactory (reviewed in Näätänen, Paavilainen, Rinne, & Alho, 2007).

The MMN is largest over fronto-central areas of the scalp. Neuronal generators of the MMN were reported for the supratemporal auditory cortices, with frontal lobes also playing a role (Doeller et al., 2003; Kircher et al., 2004; Molholm, Martinez, Ritter, Javitt, & Foxe, 2005; Opitz, Rinne, Mecklinger, von Cramon, & Schröger, 2002; Rinne, Degerman, & Alho, 2005; Sabri, Liebenthal, Waldron, Medler, & Binder, 2006; Shalgi & Deouell, 2007; Thönnessen et al., 2008). The MMN is best seen as a difference wave calculated by subtracting the waveform elicited by non-attended repeated standard stimuli from the waveform elicited by non-attended infrequent deviant stimuli in a passive (no-task) paradigm, as shown in Figure 2. This subtraction process removes ERP components that automatically react to the physical characteristics of both standard and deviant stimuli.
Figure 2. Left: Grand-Averaged ERPs Elicited by Standard and Deviant Stimuli in a Distraction Paradigm; Right: Difference Waveform (Deviant Minus Standard) Showing MMN, P3a and RON Components

especially the N1. The MMN ERP that remains after this subtraction reflects the brain's reaction to the change from the previous repeated sound to the new and different sound.

As mentioned earlier, Näätänen (1992) and Cowan (1995) suggested that the MMN is a manifestation of the activity of our involuntary attention-orienting system. This is supported by the fact that the MMN and the orienting response have many features in common. Both are associated with the frontal areas of the brain (Näätänen, 1992). Novel environmental stimuli automatically trigger the orienting response, which focuses attention on them while it attenuates other stimuli. Similarly, the MMN is an automatic alerting system to changes in the environment. When it surpasses a given threshold amplitude, it triggers a series of brain processes that produce an involuntary switch in attention (Schröger, 1997). As a result, the processing of ongoing cognitive tasks ceases, and attention is diverted to the new auditory stimulus. The benefit of the switching of attention toward the auditory distractor is that it makes the observer aware of potentially relevant information. However, there is a cost: the switching of attention may result in a deterioration in performance on the task at hand. This is what is meant by "distraction." Escera, Alho, Winkler and Näätänen (1998) indicate that the P3a, a later centro-frontal positive component that is discussed below, provides the actual index of the switching of attention.

Most studies of the MMN (reviewed in Näätänen et al., 2007) used simple paradigms in which frequent and infrequent stimuli (e.g. tones of 1000 and 1100 Hz, respectively) were
presented in random order, with the infrequent sound eliciting an MMN. In the so-called "oddball" paradigm, frequent tones are called "standard" and infrequent tones "deviant." Since the MMN is elicited irrespective of the subject's attention, no behavioural task is required. However, such tasks are often used to divert subjects' attention away from the MMN-eliciting stimulus sequence in order to prevent enhancements in attention-dependent ERP components such as the N2b. MMN studies (see Näätänen et al., 2007) demonstrated that it is the product of a process of comparison of a new deviant stimulus with memory traces of the repeated previous train of stimuli, and not the result of fresh afferent neural populations activated by deviant stimuli contributing to other components such as the exogenous N1. Most convincing in that regard are (1) the lack of any MMN-type of response to the first stimulus of a sequence, or to stimuli presented with very long inter-stimulus intervals; (2) the MMN elicited by a decrement in stimulus duration or frequency, which cannot be attributed to new afferent neurons; and (3) the MMN elicited by the omission of an element in a repeated stimulus pattern.

The MMN is influenced by many stimulus factors, the most crucial being the probability of the deviant and the degree of its deviance (reviewed in Näätänen et al., 2007). The greater the deviance, that is the difference in physical or other characteristics between the deviant and standard stimuli, the greater the MMN amplitudes and the shorter the MMN latencies. The minimum degree of deviance required to produce an auditory MMN roughly corresponds to the behavioural discrimination threshold. Deviant stimuli with a smaller probability of presentation produce greater and shorter MMN. This means, for example, that all else being equal, an experiment using stimuli that are 30% deviant and 70% standard would produce smaller and slower MMN components than a similar experiment using stimuli that are 10% deviant and 90% standard. This is due (1) to a weaker memory trace being established by the standard stimuli, which is presented less often; and (2) by the fact that more frequent deviant stimuli develop a memory trace of their own that inhibits MMN generation.

Because the MMN has good replicability over short periods of time (two hours in Escera & Grau, 1996; one month in Pekkonen, Rinne, & Näätänen, 1995; one week in Tervaniemi et al., 1999), it has clinical utility with some populations. In healthy subjects, Lang et al. (1990) used it to assess the accuracy of tone pitch discrimination in high-school
pupils; Bazana and Stelmack (2002) reported shorter MMN latencies in subjects with higher mental ability. In clinical populations, associations were found between MMN amplitudes and speech perception in cochlear-implant patients (Kraus et al, 1993; Groenen, Snik & van der Broek, 1996; Kelly, Purdy & Thorne, 2005; Roman, Canévet, Marquis, Triglia, & Liégeois-Chauvel, 2005). Aaltonen, Tuomainen, Laine, & Niemi (1993) used MMN to assess perceptual deterioration caused by brain lesions; and Kraus et al. (1996) found it useful to identify speech-discrimination difficulties in children with learning problems. Studies with clinical populations were careful to use short inter-stimulus intervals to prevent memory decay from affecting the results. This would happen if the memory trace of the standard stimuli did not last until the delivery of a deviant stimulus. Pekkonen, Hirvonen, Jääskeläinen, Kaakkola and Huttunen (1994) used this logic to examine sensory memory duration in Alzheimer's disease. They found normal MMN in these patients at a short ISI of 1 s, but at 3 s controls exhibited an MMN while the patients did not. Similar studies with schizophrenic patients are reviewed below.

**MMN and schizophrenia.** Shelley et al. (1991) were the first to use the MMN to study schizophrenia. Medicated schizophrenic patients and control subjects performed a simple visual discrimination task presented on a computer screen while they heard (and were instructed to ignore) distractor tones of short (50 ms) and long (100 ms) duration. In half the trials blocks, the long tones were the deviants (probability 10%) and the short tones were the standard (90%); in the other half, the deviant tones were short and the standard tones were long. The duration-deviant MMNs of the patients were smaller than those of controls in the long-deviant condition but not in the short-deviant condition. There were no differences in MMN latencies between the groups. A similar study by Catts et al. (1995) established that patients' medication status made no difference since the same results were replicated with non-medicated patients. It was concluded from these studies that schizophrenic patients had abnormal pre-attentive temporal processing of auditory events.

Javitt and colleagues were the first to report attenuated MMN to auditory frequency deviants (1000 Hz standard; 1024 Hz deviants) in medicated (Javitt, Doneshka, Zylberman, Ritter, & Vaughan, 1993) and non-medicated (Javitt, Doneshka, Grochowski, & Ritter, 1995) schizophrenic patients. There were no differences in latencies between patients and controls.
Since these early studies by Shelley et al. (1991) and Javitt et al., many experiments on the MMN in schizophrenia were performed. The authors, stimulus characteristics and outcome of most of these experiments are described in Table 5 for duration deviants and in Table 6 for frequency deviants. In 2005, Umbricht and Krljes published their report of a meta-analysis of 32 studies comparing the MMN of schizophrenic patients with the MMN of controls. They concluded that diminished MMN amplitudes are a robust feature in chronic schizophrenia which strongly suggests that the auditory sensory memory of these patients is significantly impaired. MMN elicited with tones that deviated in duration were more diminished than MMN elicited with tones that deviated in frequency. The effect size for MMN to duration deviants was 40% larger than the effect size for frequency MMN. Of the studies included in the meta-analysis, 23 used only frequency deviants, 14 used only duration deviants, and only three investigated both frequency and duration deviants in the same patients.

The meta-analysis identified two stimulus characteristics that produced the greatest effect sizes. On the basis of studies by the same team of researchers (Javitt, Grochowski, Shelley, & Ritter, 1998; Shelley et al., 1999) who systematically varied the probability of frequency deviants, it was confirmed that smaller deviant probabilities produced larger effect sizes. Umbricht and Krljes also reported that the effect of the degree of deviance (between deviant and standard stimuli) differed by type of stimulus. In studies investigating frequency MMN, the largest effect sizes were associated with deviances of 10% or less. In studies examining duration MMN, larger duration differences were associated with larger effect sizes.

Javitt, Shelley and colleagues, after extensive examination of the effects of deviant-stimulus probability and degree of deviance on the MMN deficit in schizophrenia, concluded that this deficit is greatest under conditions when MMN is largest in healthy people. This pattern is similar to the one described earlier for the N1 impairment in schizophrenia relative to the lengthening of the ISI. In all these cases, the ERPs of schizophrenic patients and healthy controls start at a similar level and rise in a parallel manner until a point where they diverge because patients' ERPs plateau prematurely, while the ERPs of healthy people continue to rise until they reach their own higher plateau.
Table 5. MMN Duration- Deviant Studies in Schizophrenia (Umbricht & Krijes, 2005)

<table>
<thead>
<tr>
<th>Author</th>
<th>Stimulus characteristics</th>
<th>95% CI</th>
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<tbody>
<tr>
<td></td>
<td>Standard (ms)</td>
<td>Deviant (ms)</td>
</tr>
<tr>
<td>Shelley et al. (1991)</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>Lembreghts &amp; Timsit-Berthier (1993)</td>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td>Catts et al. (1995)</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>Kasai et al. (1999)</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>Javitt, Shelley, Silipo</td>
<td>100</td>
<td>250</td>
</tr>
<tr>
<td>&quot; &quot; et al. (2000)</td>
<td>100</td>
<td>250</td>
</tr>
<tr>
<td>Michie et al. (2000)</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>Todd et al. (2000)</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>Baldeweg et al. (2002)</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>Kasai et al. (2002)</td>
<td>100</td>
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<tr>
<td>Michie et al. (2002)</td>
<td>50</td>
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<tr>
<td>Todd et al. (2001)</td>
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<td>125</td>
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<tr>
<td>Todd et al. (2003)</td>
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<td>125</td>
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<tr>
<td>Umbricht et al. (2003)</td>
<td>100</td>
<td>250</td>
</tr>
<tr>
<td>Bramon et al. (2004)</td>
<td>25</td>
<td>50</td>
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</table>

*P value

Brockhaus-Dumke (2005) 80 40 10 \( p=0.046 \)
Light & Braff (2005a) 50 100 10 \( p=0.001 \)
Light & Braff (2005b) 50 100 15 \( p=0.001 \)
Table 6. MMN Frequency-Deviant Studies in Schizophrenia (Umbricht & Krljes, 2005)

<table>
<thead>
<tr>
<th>Author</th>
<th>Stimulus characteristics</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Standard (ms)</td>
<td>Deviant (ms)</td>
</tr>
<tr>
<td>Javitt et al. (1993)</td>
<td>1000</td>
<td>1024</td>
</tr>
<tr>
<td>Javitt et al. (1995)</td>
<td>1000</td>
<td>1024</td>
</tr>
<tr>
<td>Kathmann et al. (1995)</td>
<td>600</td>
<td>1000</td>
</tr>
<tr>
<td>Alain, Hargrave et al. (1998)</td>
<td>1000</td>
<td>1122</td>
</tr>
<tr>
<td>Hirayasu et al. (1998)</td>
<td>1000</td>
<td>1200</td>
</tr>
<tr>
<td>Javitt, Grochowski et al.</td>
<td>1000</td>
<td>1850</td>
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<tr>
<td>(1998)</td>
<td>1000</td>
<td>1850</td>
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<tr>
<td>Umbricht et al. (1998)</td>
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<tr>
<td>Kirino and Inoue (1999)</td>
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<td>Schall et al. (1999)</td>
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<tr>
<td>Shelley et al. (1999)</td>
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<tr>
<td>Umbricht et al. (1999)</td>
<td>1000</td>
<td>1200</td>
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<tr>
<td>Javitt et al. (2000a)</td>
<td>1000</td>
<td>1050</td>
</tr>
<tr>
<td>Javitt et al. (2000b)</td>
<td>1000</td>
<td>1100</td>
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<tr>
<td></td>
<td>1000</td>
<td>1100</td>
</tr>
<tr>
<td>Michie et al. (2000)</td>
<td>633</td>
<td>700</td>
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<td></td>
<td>633</td>
<td>1000</td>
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<tr>
<td>Jessen et al. (2001)</td>
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<td>1100</td>
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<tr>
<td>Salisbury et al. (2002)</td>
<td>1000</td>
<td>1200</td>
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<td>Shinozaki et al. (2002)</td>
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<td>Sato et al. (2003)</td>
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<td>2000</td>
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<tr>
<td>Umbricht et al. (2003)</td>
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<td>1500</td>
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<td>Brockhaus-Dumke et al. (2005)</td>
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<tr>
<td>Korostenskaja et al. (2005)</td>
<td>1000</td>
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</table>
On the other hand, the Javitt and Shelley team concluded that prolonged ISIs did not cause an MMN deficit in schizophrenia. Shelley, Javitt, & Vaughan (1996) found that ISIs up to 3 s did not differentially affect patients and control. This was confirmed by Javitt et al. (1998), who also found no differential effects within intervals ranging from 50 ms to 3 s. Shelley et al. (1999), using ISIs ranging from 250 ms to 4.5 s, also concluded that MMN amplitudes were similarly reduced in both patients and controls with lengthening ISIs, with the result that longer ISIs did not create significant differences. These ISI findings were important because they made it clear that the MMN deficits of schizophrenic patients were not caused by a faster decay of their sensory memory traces. Instead, Javitt et al. concluded that these deficits were likely due to inaccurate encoding of stimulus features, resulting in flawed memory traces. This theory was further supported by a behavioural study by Javitt, Shelley and Ritter (2000) which found significant correlations between patients' reduced MMN amplitudes and their impaired tone-matching performance.

Finally, Javitt (2000) found that decreased MMN amplitude and tone-matching deficits in schizophrenic patients were correlated with the severity of their negative symptoms. This was consistent with findings by Light and Braff (2005) of a strong correlation between the MMN amplitude of schizophrenic patients and their general-ability-of-functioning (GAF) scores. The review by Umbrich and Krljes (2005) listed several associations between reduced MMN amplitudes and clinical symptoms: three studies reported associations between reduced MMN and increased positive symptoms, especially hallucinations (Youn, Park, Kim, Kim, & Kwon, 2003; Hirayasu et al., 1998; Schall, Catts, Karayanidis, & Ward, 1999); six studies found associations between reduced MMN and increased negative symptoms (Catts et al., 1995; Grzella et al., 2001; Hirayasu et al.; Javitt et al, 2000a; Kasai et al., 2002; Schall et al., 1999). Other studies confirmed that antipsychotic medication did not affect the MMN deficits of schizophrenic patients (Umbricht et al., 1998; Schall et al., 1998).

P3a sub-component (see Table 4). The P300 or P3 ERP consists of a family of positive components which has two main subtypes (Friedman, Cycowicz et al., 2001). The first subtype, P3b, which was referred to earlier, reflects controlled information processing and is typically elicited by correctly-detected oddball target stimuli (Polich & Criado, 2006).
The P3b reaches maximum amplitude in the parietal area. The second subtype, called the P3a, was first elicited by adding highly-deviant, task-irrelevant stimuli to the traditional oddball task (Courchesne, Hillyard, & Galambos, 1975; Squires, Squires, & Hillyard, 1975). These new stimuli elicited significantly different P3 components than the ones elicited by target stimuli. The P3a, as the new sub-component was called, is usually larger than the P3b, has an earlier latency and reaches maximum amplitude in frontal-to-central regions. When the P3a is elicited by perceptually novel "distractor" stimuli (dog bark, telephone ring) that are not repeated, it is called a "novelty P3" (Polich & Criado, 2006).

The P3a is believed to reflect the involuntary redirection of attention away from the ongoing task toward the distractor or novel stimulus (Friedman, Cycowicz et al., 2001). In support of this interpretation, the P3a is larger when it is associated with a skin-conductance response, which is one of the autonomic nervous system reactions that accompany the involuntary orienting of attention (Lyytinen, Blomberg, & Näätänen, 1992; Sokolov, Spinks, Näättänen, & Lyytinen, 2002). Even more convincing, Schröger and Wolff (1998b) found that in contrast to the MMN, the P3a and the RON (reorienting negativity) were only elicited in trials which had shown a reaction time prolongation to task-irrelevant deviant tones, indicating that subjects' attention had switched from the task to the distracting stimuli. According to Schröger's theories (1997), the orienting response reflected in the P3a to irrelevant deviant stimuli is always preceded by an MMN which detects these same stimuli. However, the MMN is not always followed by a P3a, because the P3a occurs only if the distractor stimuli are sufficiently deviant (Friedman, Cycowicz et al., 2001).

Neural generators of the P3a were localized in the frontal and temporal lobes (Escera, Alho, Schröger, & Winkler, 2000) and the P3a is greatly reduced in patients with dorsolateral prefrontal lesions (Daffner et al., 2000; Knight, 1984). There is also evidence for contribution to the P3a from a network of cortical regions, including the auditory cortex (Opitz, Mecklinger, Friederici, & von Cramon, 1999), posterior hippocampus (Knight, 1998), temporoparietal junction (Downar, Crawley, Mijulis, & Davis, 2000; Knight, Scabini, Woods, & Calyworth, 1989), medial frontal gyrus McCarthy, Luby, Gore, & Goldman-Rakic, 1997), and anterior cingulate gyrus (Menon, Ford, Lim, Glover, & Pfefferbaum, 1997). However, the sources of the P3a remain an issue of debate.
In recent years, a great deal of discussion and research has taken place on the subject of the automaticity of the P3a. The question is whether the P3a generation is an automatic process, or whether it is affected by attention or by the cognitive requirements of the tasks used to elicit this component. So far, these efforts have produced contradictory results (see Escera, Alho et al., 2000; Friedman, Cycowicz et al., 2001; Hagen, Gatherwright, Lopez, & Polich, 2006; Lavie, 2005; Polich & Comerchero, 2003; Muller-Gass, Macdonald, Schröger, Sculthorpe, & Campbell, 2007; Muller-Gass & Schröger, 2007; San Miguel, Corral, & Escera, 2008; Zhang, Chen, Yuan, Zhang, & He, 2006). These issues will be examined further in Experiments 2 and 3 below.

P3a and schizophrenia. The P3a has been investigated much less than the P3b in schizophrenia. Many studies of schizophrenia and the P3a were performed as an afterthought in experiments whose main focus was the ubiquitous P3b. The paradigm used was often the classic oddball task, with frequently-occurring "standard" stimuli (usually low tones) and infrequent "oddball" stimuli (usually high tones), with subjects being asked to respond to the oddballs. In recent years, the P3a was more often elicited with "novelty oddball" paradigms, in which the classic oddball task was augmented by including additional unique "novel" stimuli.

Most of these studies reported reduced P3a amplitudes in schizophrenic patients compared with controls (Alain, Bernstein, Cortese, Yu, & Zipursky, 2002; Devrim-Ucok, Keskin-Ergen, & Ucok, 2006; Frodl et al., 2001; Grillon, Courchesne, Ameli, Geyer, & Braff, 1990; Grzella et al., 2001; Laurens, Kiehl, Ngan, & Liddle, 2005; Mathalon, Ford, Pfefferbaum, 2000; Merrin & Floyd, 1994; van der Stelt, Frye, Liberman, & Belger, 2004; Valkonen-Korhonen et al., 2003). Two studies found prolonged P3a latencies (Frodl et al., 2001; Merrin & Floyd) in these patients. One study (Schall et al., 1999) found greater P3a amplitudes in patients than in controls. Two studies (Kogoj, Pirtosek, Tomori, & Vodusek, 2005; Michie et al., 2002) showed no P3a amplitude differences between patients and controls. Michie et al. found that first-degree relatives of patients had greater P3a amplitudes than patients, but that the P3a of both relatives and patients did not differ from the P3a of controls.
Devrim-Ücok et al. (2006) found that novelty P3a was reduced in patients with chronic schizophrenia but not in first-episode patients, which suggested an increase in P3a impairment with disease progression. This was contradicted by Valkonen-Korhonen et al. (2003), who found diminished P3a components in first-episode patients. In experiments by Kogoj et al. (2005), the stimuli that were the standard and the deviants in one sequence were switched in the next sequence so that the standard became the deviant and vice-versa. In control participants, there was a significant enhancement in P3a amplitude when the distractors became the target stimuli, but it made no difference in the patients. This led the researchers to conclude that schizophrenic patients had a diminished capacity to allocate their attentional resources adequately between target and distractor stimuli.

Laurens et al. (2005) used event-related fMRI to elucidate the functional abnormality underlying the attenuated P3a they had observed in schizophrenic patients. They found underactivity in several relevant brain areas during novel stimulus processing. In particular, dysfunction within the right amygdala-hippocampal complex and widespread paralimbic cortex suggested that patients were less engaged by the novel stimuli than controls, and were therefore less able to effectively assess their potential significance for ongoing behaviour. Marked abnormality in patients' right temporo-parietal-occipital junction suggested that patients would have difficulty in extracting the relevance (or rather, the irrelevance) of the novel stimuli for subsequent behaviour. Marked abnormality in patients was also apparent within a dorsal frontoparietal system that is involved in identifying the characteristics of salient events and in specifying cognitive plans/intentions that target these events for behaviour.

Three studies examined the functional significance of diminished P3a components in schizophrenia. In van der Stelt, Frye, Lieberman and Belger (2004), an inverse correlation was found between P3a amplitudes and illness duration. In Mathalon, Ford and Pfefferbaum (2000), reduced auditory P3a were associated with exacerbated depression-anxiety symptoms in the patients. Turetsky, Colbath and Gur (1998) found that P3a amplitudes increased with improvements in auditory hallucinations. Schall et al. (1999) found that large P3a amplitudes predicted a poor response to clozapine treatment.
Late reorienting negativity (RON; see Table 4). The RON, which has a fronto-central distribution and occurs approximately 480 to 550 ms after stimulus onset, was first identified by Schröger and Wolff (1998a). According to them, the RON is not to be confused with the similar slow negative orienting (O) wave identified by Loveless and Sanford (1974) or the slow contingent negative variation (CNV) wave postulated by Rohrbaugh, Syndulko and Lindsley (1978). Although the morphology and distribution of the RON resembles those of these other late negative waves, the RON wave is differentiated by its specificity to the occurrence of task-irrelevant deviant stimuli while subjects were performing a two-choice discrimination task. As a result, Schröger and Wolff concluded that the RON did not reflect a global deviance-related effect. Instead, they hypothesized that it reflected the return of attention from task-irrelevant toward task-relevant stimuli after distraction occurred. Scalp-current density (SCD) analysis suggested frontal generators for the RON (Schröger, Giard, & Wolff, 2000).

Schröger and Wolff's theories about the late reorienting negativity were supported and expanded in several subsequent studies (Berti and Schröger, 2001, 2003, 2006; Berti, Roeber, & Schröger, 2004; Escera et al., 2000; Escera, Yago, & Alho, 2001; Munka & Berti, 2006; Roeber, Berti, Widmann, & Schröger, 2005; Schröger, Giard et al., 2000; Wetzel, Berti, Widmann, & Schröger, 2004; Yago, Corral, & Escera, 2001). It was found that RON has larger amplitude to more task-disrupting events (Berti & Schröger, 2001; Escera et al., 2001; Schröger, Giard et al., 2000) and that it was correlated with events of the primary task, such as reaction time (Escera et al., 2000). Munka et al. (2006) suggested that the RON component reflects two functionally distinct processes of attentional allocation after distraction: (1) refocusing on task-relevant information on the working memory level; and (2) general reorientation of attention, e.g. preparation for the upcoming task. Recent experiments by Berti (2008) appear to support these proposals.

RON and schizophrenia. A search of the PubMed Internet search site did not produce any studies that examined the RON component in schizophrenic patients. However, the fMRI study by Laurens et al. (2005) found dorsal frontoparietal hypoactivity which suggested that these patients experienced particular difficulty in reorienting processing resources when a salient deviant stimulus had interrupted a current task. In a different but
related line of research, Kähkönen et al. (2002) used healthy participants and a distraction paradigm to assess the effects of the dopamine D2-receptor antagonist haloperidol on involuntary attention shifting. They found that deviant distractors had caused marked increases in reaction time and had elicited MMN, P3a and RON responses, and that RON was significantly reduced and delayed in the group that ingested haloperidol. These findings suggested that the modulation of dopamine transmission by haloperidol may impair the switching of attention back to the relevant task after distraction in schizophrenic patients.

1.6.4. Research on the Effects of Nicotine/Smoking on Orienting-Related ERPs

According to Knott, Kerr, Hooper, & Lusk-Mikkelsen (1995), creative and diligent research on the endogenous ERPs may serve as a powerful unintrusive technique for studying the cognitive-behavioural processes that may be altered by nicotine/smoking. Review studies by Knott (1989), Pritchard, Sokhadze and Houlihan (2003) and Polich et al. (2006) contributed to the summary of research on the effects of nicotine-smoking on ERPs that is presented below. This summary does not cover all ERP research on the effects of nicotine, most of which is devoted to the P3b component. In general, P3b amplitude increases and P3b latency decreases immediately after smoking (reviewed by Polich et al., 2006). The only published study that examined the effect of nicotine on the P3b in schizophrenia, by Kodama et al. (1998), used an oddball task and found that smoking resumption after abstinence decreased P3b amplitude in patients while it increased it in healthy subjects. Kodama et al. concluded that nicotine differentially affects arousal in healthy subjects and in schizophrenic patients.

The following summary focuses on the ERPs that are more closely involved with the attentional orienting/reorienting mechanism, including N1, MMN, P3a and RON. Unless specified otherwise, the subjects of these studies were healthy individuals who were either abstaining (usually overnight), minimally abstaining (1-3 hours) or non-abstaining smokers as well as non-smokers. Experimental subjects either smoked cigarettes or absorbed nicotine through other means, such as gum, patch or injection.

N1 amplitude. Almost all experiments that elicited ERPs with visual task paradigms reported that nicotine/smoking had no effect on N1 amplitudes (Ilan & Polich, 1999: memory scanning task; Ilan & Polich, 2001: Stroop task; Knott, 1985, 1986: visual
reaction time tasks; Knott, Bosman, Mahoney, Ilivitsky, & Quirt, 1999: choice reaction time
task; Knott, Mohr, Mahoney, Engeland, & Ilivitsky, 2002: Alzheimer patient subjects; Le
Houezec et al., 1994: choice reaction time task; Michel, Hasenfratz, Nil, & Bättig, 1988:
rapid visual information processing task - RVIP). Exceptionally, Houlihan, Pritchard and
Robinson (2001) found that nicotine/smoking had decreased N1 amplitude in response to
negative probes in a Sternberg-type memory-scanning task.

Knott (1986) examined the effects of smoking on ERPs with a distraction paradigm
that involved an **auditory warning/distracting stimulus** followed by visual task-related
stimuli (simple choice and four-choice tasks). The results indicated that tobacco had
interacted with intensity and task condition to produce an increase in N1 amplitude in ERPs
elicited by the distractor stimuli. But in a similar experiment using only a simple-choice
task, Knott (1985) found that smoking had no effect on N1 amplitudes elicited by distractor
stimuli. Ascioglu, Dolu, Golgeli, Suer and Ozesmi (2004) found no differences in N1
amplitudes between chronic smokers and non-smokers in an **auditory oddball** experiment.

**N1 latency.** In passive (no-task) **visual** experiments using light flashes as stimuli,
Golding (1988) and Woodson et al. (1982) reported no effect of smoking on N1 latencies.
These studies were criticized by Pritchard et al. (2004) for failing to record ERPs from a
scalp location situated directly over the brain's occipital (visual) cortex. In addition,
Pritchard et al. agreed with Knott (1989) that passive experiments are not completely without
merit but are not very useful in assessing cognitive or performance efficiency.

Most experiments using **visual tasks** found no effect of nicotine/smoking on N1
latency (Ilan & Polich, 1999, 2001; Knott, Bosman, Mahoney, Ilivitsky, & Quirt, 1999;
Knott, Mohr et al., 2002; Le Houezec et al., 1994; Michel et al., 1988). The only exception
was the study by Houlihan et al. (2001) which reported that nicotine/smoking had shortened
N100 latency to both memory-set and probe stimuli in a Sternberg-like task. The **auditory
oddball** study by Ascioglu et al. (2004) found no differences in N1 latencies between chronic
smokers and non-smokers.

**Mismatch negativity (MMN).** The only published study of nicotine and the MMN
in schizophrenia is a recent experiment by Inami, Kirino, Inoue, Suzuki and Arai (2007).
They used a passive paradigm in which nonsmoking hospitalized schizophrenic patients and
healthy control subjects were administered placebo and nicotine transdermally (in separate sessions) and watched a silent movie while they heard tones through earphones. Most of the tones (95%) had a frequency of 1000 Hz while the rest (5%) had a frequency of 1050 Hz. Nicotine had no effect on the MMN amplitudes or latencies of the patients but it shortened the MMN latencies of control participants. Inami et al. concluded that the lack of a similar latency effect in patients may be due to an abnormally low α7 nicotinic receptor function.

Significant nicotine effects were found in the MMN of other populations. Engeland, Mahoney, Mohr, Ilivitsky and Knott (2002) examined the effects of nicotine on the MMN of Alzheimer patients who had and who had not been treated with the cholinesterase inhibitor tacrine. In the non-tacrine-treated patients, nicotine increased MMN amplitude and decreased MMN latency. In the tacrine-treated group, nicotine decreased MMN latency but did not affect MMN amplitude, suggesting that nicotine improved sensory memory. On the other hand, Knott et al. (2006) found no significant nicotine effects on the MMN components of healthy smokers who performed an auditory duration-discrimination task with tones that featured rare frequency deviations. Inami, Kirino, Inoue and Arai (2005) observed shortened MMN latencies in healthy non-smoking volunteers who were administered nicotine. Harkrider and Hedrick (2005) found enlarged MMN amplitudes in healthy non-smokers and smokers who were administered nicotine.

Finally, Baldeweg, Wong and Stephan (2006) used a novel stimulus paradigm with continuously changing (roving) standard stimuli in order to examine the effects of nicotine on auditory sensory memory in healthy minimally-abstaining smokers (4 hours) as measured with the MMN. The purpose of this paradigm was to measure the effects of different numbers of stimulus repetitions on encoding of new stimuli. They found that nicotine increased MMN amplitudes by enhancing a frontal positive ERP to standard stimuli, while the negativity to deviant stimuli remained unaffected. As a result, they concluded that nicotinic agonists might ameliorate the MMN deficits of schizophrenic patients by improving stimulus encoding and sensory memory trace formation.

P3a. The P3a components generated by rare target stimuli and by rare non-target distracting stimuli in Experiments 2 and 3 of the Knott, Kerr et al. studies (1995) did not show a nicotine/smoking effect. Knott et al. (2006) also failed to find a significant nicotine
effect on the P3a of healthy smokers who performed a duration-discrimination task with tones that featured rare (5%) task-irrelevant frequency increments and decrements. On the other hand, Haarer and Polich (2000) reported that smoking/nicotine had decreased P3a amplitudes to distractors in a visual oddball task. This decrease was greater in occasional smokers than in regular smokers. The decreased P3a was accompanied by a lengthening of reaction time in the occasional smokers and a shortening of reaction time in the regular smokers.

**Late reorienting negativity (RON).** Knott et al. (2006) found no significant nicotine effect on the RON in healthy smokers who performed a duration-discrimination task with tones that contained task-irrelevant frequency deviations.

Table 7 summarizes the studies on the effects of nicotine/smoking on the ERP components that were directly or indirectly related to the orienting/reorienting mechanism. As the right-hand columns of this table demonstrate, most N1 studies did not find significant nicotine effects. P3a and RON studies have been too few to be able to detect a pattern. On the other hand, the studies of the effects of nicotine on the MMN show very promising results: five out of six of these experiments found significant nicotine effects. Half of them (Baldeweg et al., 2006; Engeland et al., 2002; Harkrider et al., 2005) found increased MMN amplitudes, and two out of five (Inami et al., 2005; Inami et al., 2007) found shortened MMN latencies. These results suggest that nicotine is effective in improving the pre-attentive detection of changes in the environment that is indexed by the MMN component.

### 1.7 SUMMARY OF INTRODUCTION AND THESIS DIRECTION

Schizophrenia is characterized by profound deficits in cognition, particularly in attention (Bowie et al., 2005). Behavioural studies that examined voluntary/controlled cognitive operations in schizophrenia patients have found disturbances in attention and increased distractibility. Inappropriate switches of attention in these patients suggest that they may be experiencing deficits in filtering out task-irrelevant distracting information (Ravizza, Robertson, Carter, Nordahl, & Salo, 2007). Performance studies do not provide information on the mental steps that intervene between the presentation of a stimulus and the production of an overt response. EEG-derived event-related potentials allow us to monitor these mental
### Table 7. Effects of Nicotine/Smoking on Orienting-Reorienting-Related ERPs
(* indicates that study subjects were non-or-minimally-abstaining smokers or non-smokers)

<table>
<thead>
<tr>
<th>ERP</th>
<th>Researchers</th>
<th>Date</th>
<th>Type</th>
<th>Amplitude</th>
<th>Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>* Woodson et al. (no-task)</td>
<td>1982</td>
<td>visual</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>Knott</td>
<td>1985</td>
<td>visual</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>Knott (distractor stimuli)</td>
<td>1985</td>
<td>auditory</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>Knott</td>
<td>1986</td>
<td>visual</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>Knott (distractor stimuli)</td>
<td>1986</td>
<td>auditory</td>
<td>increased</td>
<td>none</td>
</tr>
<tr>
<td>* Golding (no-task)</td>
<td>1988</td>
<td>visual</td>
<td>-</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>* Michel, Hasenfratz et al.</td>
<td>1988</td>
<td>visual</td>
<td>none</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>* Le Houezec et al.</td>
<td>1994</td>
<td>visual</td>
<td>none</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>Ilan &amp; Polich</td>
<td>1999</td>
<td>visual</td>
<td>none</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>Knott, Bosman et al.</td>
<td>1999</td>
<td>visual</td>
<td>none</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>* Houlihan, Pritchard et al.</td>
<td>2001</td>
<td>visual</td>
<td>decreased</td>
<td>decreased</td>
<td></td>
</tr>
<tr>
<td>Ilan &amp; Polich</td>
<td>2001</td>
<td>visual</td>
<td>none</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>* Knott, Mohr et al. (Alzheimer subjects)</td>
<td>2002</td>
<td>visual</td>
<td>none</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>* Ascioglu et al.</td>
<td>2004</td>
<td>auditory</td>
<td>none</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>MMN</td>
<td>* Engeland, Mahoney et al. (Alzheimer patients)</td>
<td>2002</td>
<td>auditory</td>
<td>increased in non-treated</td>
<td>decreased</td>
</tr>
<tr>
<td></td>
<td>* Inami et al.</td>
<td>2005</td>
<td>auditory</td>
<td>none</td>
<td>decreased</td>
</tr>
<tr>
<td></td>
<td>* Harkrider</td>
<td>2005</td>
<td>auditory</td>
<td>increased</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>Knott, Scherling et al.</td>
<td>2006</td>
<td>auditory</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>* Baldeweg et al.</td>
<td>2006</td>
<td>auditory</td>
<td>&quot;roving&quot;</td>
<td>increased</td>
<td>none</td>
</tr>
<tr>
<td>* Inami et al. (schizophrenic patients)</td>
<td>2007</td>
<td>auditory</td>
<td>none</td>
<td>decreased controls</td>
<td></td>
</tr>
<tr>
<td>P3a</td>
<td>Knott, Kerr et al. (Exp. 2)</td>
<td>1995</td>
<td>2 audit.</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>Knott, Kerr et al. (Exp. 3)</td>
<td>1995</td>
<td>3 audit.</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>Haarer &amp; Polich</td>
<td>2000</td>
<td>visual</td>
<td>decreased</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>Knott, Scherling et al.</td>
<td>2006</td>
<td>auditory</td>
<td>decreased &amp; increased</td>
<td>none</td>
</tr>
<tr>
<td>RON</td>
<td>Knott, Scherling et al.</td>
<td>2006</td>
<td>auditory</td>
<td>none</td>
<td>none</td>
</tr>
</tbody>
</table>
steps in order to gain a better understanding of disturbances in pre-attentive sensory processing (Heinrichs, 2005; van der Stelt & Belger, 2007). The MMN is the first measurable brain reaction to auditory changes in our environment. It alerts us to unexpected and potentially important and dangerous events. The MMN is generated in the auditory cortices with possible prefrontal contribution (Turetsky et al., 2007). Diminished MMN amplitudes are a robust feature in schizophrenia research (reviewed by Umbricht & Krljes, 2005).

Schizophrenic patients have a very high rate of smoking and some experts believe it is partly because nicotine alleviates their cognitive deficits (Newhouse et al., 2004). This is supported by findings in placebo-controlled behavioural studies that nicotine has improved visual sustained attention (Barr et al., 2008; Dépatie et al., 2002; Levin et al., 1996), visuospatial working memory (Levin et al., 1996; Smith et al., 2002; Smith et al., 2006) and selective attention (Barr et al., 2008; Jacobsen et al., 2004) in schizophrenic patients. It is believed that nicotine can correct cognitive deficits in schizophrenia because it binds to and activates α7 nicotinic acetylcholine (ACh) receptors (Martin & Freedman, 2007). Acetylcholinergic pharmacotherapies are currently being tested to determine whether they can reduce cognitive deficits in schizophrenia patients (Olincy et al., 2006; Freedman et al., 2008). Nicotine has also increased auditory MMNs in three non-schizophrenic populations (Baldeweg et al., 2006; Engeland et al., 2002; Harkrider et al., 2005). Baldeweg et al. suggested that nicotinic agonists might enhance the MMN by improving stimulus encoding and sensory memory trace formation.

The two objectives of Experiment 1 of this thesis were to replicate previous findings of MMN-indexed early acoustic processing disturbances in schizophrenic smokers, and to examine the effects of acute nicotine treatment on their MMN response. Given past findings, it was predicted that (1) schizophrenic patients in the placebo condition would exhibit attenuated MMN components compared with controls; and (2) nicotine would increase the MMN amplitude of schizophrenic patients.

According to current theories of attention orienting (Näätänen et al., 2007; Schröger & Wolff, 1998a), the MMN-indexed process of change detection in the environment may signify a call for, or the initiation of, the involuntary orientation of focused attention away from the task at hand and toward the new/different acoustic stimulus detected by the MMN mechanism. This redirection of attention is signaled on the scalp by the P3a, an ERP which is
associated with frontal generators (Friedman, Cycowicz et al., 2001). A switch in attention only occurs when the change that is indexed by the MMN is strong enough. Studies that simultaneously monitored ERPs and behavioural performance found that the switch in attention reflected in the P3a was often accompanied by a deterioration in performance (accuracy and reaction time) on the original task (Escera, Alho, Schröger, & Winkler, 2000), presumably caused by attentional distraction. This deterioration in performance offers independent evidence that task-related processes were interrupted by irrelevant distracting stimuli. These studies also suggested the existence of a third and late component, the reorienting negativity or RON, which appeared to reflect the reorienting of attention back toward the main task that was disrupted by the distractor stimuli. Larger auditory changes in the environment produce larger MMN and P3a ERPs and greater behavioural distraction (Berti, Roeber, & Schröger, 2004). This so-called "bottom-up" effect of stimuli is less marked in schizophrenia patients than in controls (Javitt et al., 1998; Shelley et al., 1999).

The P3a amplitudes of schizophrenic patients are often diminished compared with the P3a amplitudes of controls (see Table 4 and related text). This is paradoxical because it suggests that patients are less distractible than controls, since smaller P3a components are less likely than larger P3a components to be associated with a switch of attention toward irrelevant deviant stimuli. Another interpretation is possible, however, because Näätänen's (1990, 1992) model specifies that the threshold for the switching of attention may vary across individuals and groups. It is therefore possible that the threshold for the switching of attention is unusually low for schizophrenic patients, so that even a distracting stimulus resulting in a small P3a might be sufficient to cause an attentional switch.

Findings on the effects of nicotine on cognitive and attentional performance in schizophrenic patients are also paradoxical. On the one hand, behavioural studies have demonstrated that nicotine can improve performance in schizophrenic patients by enhancing their vigilance and working memory and selective attention (see Table 3 and related text). On the other hand, ERP studies have found that nicotine increased pre-attentive processing as indexed by enhanced MMN amplitudes (see Table 7 and related text). Larger MMN components are generally associated with larger P3a components reflecting switches in attention, which are usually accompanied by greater distraction effects. The only two studies that examined the effect of nicotine on the P3a produced contradictory results. According to
Knott et al. (1995), smoking/nicotine had no effect on the P3a elicited by auditory distractors. For their part, Haarer and Polich (2000) reported that smoking/nicotine had decreased P3a amplitudes to distractors in a visual oddball task. This decrease was greater in occasional smokers than in regular smokers. The decreased P3a was accompanied by a lengthening of reaction time in the occasional smokers and a shortening of reaction time in the regular smokers. On the basis of these results, Pritchard et al. (2004) proposed the following hypothesis (p. 974):

Given such a scant database, any summary of P3a results must de facto be more of a working hypothesis. It may be that smoking/nicotine affects P3a in the visual but not the auditory modality. It also may be that an optimal P3a amplitude exists, with too much or too little attention being captured by the distracters negatively affecting rapid processing of the targets. In occasional smokers, smoking/nicotine may decrease P3a amplitude too much, missing the optimal amplitude. In contrast, in regular smokers, smoking/nicotine may decrease P3a amplitude at or near the optimal amplitude.

The other objective of this thesis was to try to resolve the contradictions described above by examining the simultaneously-recorded behavioural performance results and MMN, P3a and RON components of schizophrenic smokers following the occurrence of potentially distracting events. These behavioural results and components were obtained by means of novel auditory-auditory (in Experiment 2) and auditory-visual (in Experiment 3) distraction paradigms that provide objective measures of behavioural distraction and of the cerebral processes involved in deviance and distraction, including the ways in which these processes may be impaired in schizophrenia and altered by nicotine.
EXPERIMENT 1
MMNs to Duration and Frequency Deviants
in Schizophrenic Patients and Controls

2.0. Introduction

2.0.1. Schizophrenia and attention

Attention dysfunction is a hallmark of schizophrenia (Green, 1998). In particular, schizophrenic patients have profound problems with selective attention, which is the capacity to focus attention on salient cues while ignoring irrelevant distracting stimuli (Braff, 1993). According to Braff, this impairment in the capacity of patients with schizophrenia to process competing stimuli in a normal manner may be due to excess stimulation resulting from sensory overload, or to patients' incapacity to mobilise and allocate resources, or to an excess of resources being allocated to task-irrelevant stimuli, or to a disruption of automatic processes when resource-demanding controlled processing is used to perform what should normally be resource-free automatic early-sensory-processing operations.

2.0.2. Mismatch negativity (MMN)

Since Shelley et al. (1991) first reported reduced MMN brain event-related potentials (ERPs) in schizophrenic patients, it has become increasingly clear that the main causes of enhanced distractibility in these patients may not be found in conscious controlled information processes, but in pre-attentive automatic cognitive processes indexed by the MMN and related components. First described by Näätänen et al. (1978), the MMN is a small negative component which peaks around 100-250 ms after stimulus onset. Most frequently studied in the auditory modality, it is automatically elicited by any type of change (of duration, frequency/pitch, intensity, location, pattern, etc.) in a repeating series of auditory stimuli, even in the absence of attention or behavioural response. The MMN is an index of our automatic alerting system to changes in the environment. When it surpasses a given threshold amplitude, it triggers a series of brain processes that produce an involuntary switch in attention toward the new – distracting – stimulus (Berti & Schröger, 2001).

The MMN reflects auditory pre-attentive sensory processing, which signals that an incoming sound was compared to the sensory memory of the features (such as frequency, duration, intensity, location, pattern, etc.) of the previous repeated sounds and was found to
differ from them (Näätänen, 1990, 1992). The amplitude of the MMN increases and its latency shortens with increasing differences between the incoming sound and the previous repeated sounds. MMN generation therefore depends on the context in which a specific stimulus is presented. As a result, Umbricht and Krljes (2005, p. 2) defined the MMN as "an index of the auditory sensory or 'echoic' memory and of context-dependent information processing."

The MMN is largest over fronto-central areas of the scalp. Neuronal generators of the MMN were reported for the supratemporal auditory cortices, with frontal lobes also playing a role (Doeller et al., 2003; Kircher et al., 2004; Molholm et al., 2005; Opitz et al., 2002; Rinne et al., 2005; Sabri et al., 2006; Shalgi & Deouell, 2007; Thönnessen et al., 2008). The MMN is best seen as a difference wave calculated by subtracting the waveform elicited by non-attended repeated standard stimuli from the waveform elicited by non-attended infrequent deviant stimuli in a passive (no-task) paradigm. This subtraction process removes ERP components that automatically react to the physical characteristics of both standard and deviant stimuli, especially the N1. The MMN ERP that remains after this subtraction reflects the brain's reaction to the change from the previous repeated sound to the new and different sound.

2.0.3. Schizophrenia and MMN

A meta-analysis of 32 studies of the MMN in schizophrenia (Umbricht & Krljes, 2005) sheds more light on early sensory processing deficits in this disorder. It concluded that diminished MMN amplitudes are a robust feature in chronic schizophrenia which strongly suggests that the auditory sensory memory and auditory information processing of these patients are significantly impaired. MMN elicited with sounds that deviated in duration were more reduced than MMN elicited with sounds that deviated in frequency. MMN reductions were particularly pronounced in patients with severe cognitive deficits, especially in episodic memory (Umbricht, Koller, & Bieber, 2004). Since MMN deficits were not observed in other major psychiatric disorders such as major depression and bipolar disorder (Umbricht et al., 2003), the MMN may be a useful non-intrusive, objective tool to help diagnose the disease.
The causes of MMN impairment in schizophrenia are still unclear. Javitt et al. (1998) speculated that it may reflect inaccurate encoding of stimulus features, resulting in flawed sensory-memory traces. This theory was suggested by their finding that the MMN amplitude of patients was less sensitive to changes in stimulus features than the MMN amplitude of controls. It was further supported by a behavioural study (Javitt et al., 2000a) which found significant correlations between patients' reduced MMN amplitude and their impaired tone-matching performance. In addition, Javitt (2000) found that the decreased MMN amplitude and tone-matching deficit of the patients were correlated with the severity of their negative symptoms, such as social withdrawal.

MMN also relies on the next phase of auditory sensory memory, in which sensory-memory traces are maintained over time and are incorporated into the current context (Cowan, 1995). Javitt et al. (1998) used different inter-stimulus intervals (ISIs) to test the possibility that the reduced MMN amplitude of schizophrenic patients could also be due to an accelerated decay in their sensory memory for tone properties over time. They obtained similar MMN amplitude responses in patients and controls to changes in ISIs, which supported the view that the MMN reduction in schizophrenia is not caused by a faster decay of sensory information.

Another possible cause of MMN amplitude reduction in schizophrenia is a deficiency in the comparison process itself (Javitt et al., 1998). According to the model adjustment theory (Winkler, Karmos, & Näätänen, 1996), an MMN response indicates that the auditory system has updated its model of the acoustic environment to incorporate the features of a deviant sound stimulus. Larger deviations require larger adjustments, that are reflected by larger MMN amplitudes. Less frequent deviations (i.e. lower deviant probability) also produce a larger MMN to deviant stimuli. Failure to update the model would result in reduced MMN amplitudes.

Other studies suggested different explanations. One is that poor encoding of stimulus features may occur only in patients with more severe cognitive deficits (Todd et al., 2003), and that the main impairment may be a failure of coordination between different brain regions responsible for detecting and switching to a stimulus change (Ford, Krystal, & Mathalon, 2007; Jacobsen et al., 2003). Other researchers suggest there may be a flaw in the
activation of a frontal-lobe attention-switching mechanism (Baldeweg, Klugman, Gruzelier, & Hirsch, 2002; Sato et al., 2003).

Human and animal studies on the neurochemical basis of the MMN impairment in schizophrenia implicated N-methyl-D-aspartate (NMDA) receptor hypofunction (Javitt, Steinschneider, Schröder, & Arezzo, 1996; Kreitschmann-Andermahr et al., 1999; Umbricht et al., 2000; Umbricht et al., 2004). Acetylcholine, acting upon the nicotinergic α7 sub-receptor, is an important modulator of NMDA receptor function (Quarta et al., 2007).

2.0.4. Schizophrenia and nicotine

A postmortem study of brain tissue (Freedman et al., 1995) noted that schizophrenic patients who had been smokers had fewer α7 nicotinic acetylcholinergic receptors (nAChRs) in the hippocampus than healthy smokers. Another postmortem study (Guan et al., 1999) found decreased levels of the same receptors in the frontal cortex of schizophrenic patients. This reduction may result in a failure of cholinergic activation of inhibitory interneurons. In turn, this would have a negative effect on the filtering of responses to redundant sensory stimulation.

These filtering impairments in schizophrenia have been consistently indexed by a midlatency (~ 50 ms) positive ERP component (P50) in a paired-auditory-stimulus paradigm. These responses are indexed by the P50 ERP, which is elicited in a passive paradigm presenting successive paired auditory stimuli. Healthy subjects typically show inhibitory filtering or "gating," manifested in a diminished P50 response to the second stimulus of closely (<500 ms) paired stimuli. Schizophrenic patients routinely fail to show a diminished response to the second stimulus (Light & Braff, 1999). This P50-indexed auditory sensory gating deficit was normalized in patients and relatives of patients with acute smoking and nicotine gum administration (Adler, Hoffer et al., 1993; Adler et al., 1998). More recently, increased inhibition of P50 auditory evoked responses in schizophrenia was evidenced with DMXB-A, a novel partial α7 nAChR agonist (Olincy et al., 2006). Nicotine can correct this deficit in schizophrenic patients because it binds to and activates nicotinic receptors. These receptors activate many functions of the brain by modulating the release of multiple neurotransmitters, including acetylcholine, dopamine, norepinephrine, serotonin, glutamate and GABA, which have been associated with neuronal inhibition (Berman et al., 2007).
These postmortem and P50 gating results, along with genetic findings of abnormalities in the encoding of the α7 nAChR in schizophrenia (Martin, Kem, & Freedman, 2004; Harrison & Weinberger, 2005), may help to explain why schizophrenic patients have very high smoking rates (61%-65% in Canada; Addington, et al., 1997; Margolese et al., 2004). They smoke more than other mentally ill patients (Diwan et al., 1998) and much more than the general population (25% for all Canadians; Health Canada, Tobacco Control Programme, 2004). These physiological findings also support the theory that schizophrenic patients smoke as self-medication aimed at activating the α7 receptor, perhaps to compensate for its lower-than-normal expression, and to relieve associated cognitive and clinical symptoms (Lasser et al., 2000).

2.0.5. Nicotine and cognition

Kassel (1997) suggested that nicotine improves cognition in two ways: by narrowing the brain's internal stimulus filter that blocks irrelevant (non-attended) stimuli (see Broadbent, 1958), thereby preventing stimulus overload; and by increasing the neural cognitive resources (see Kahneman, 1973) allocated to the processing of relevant (attended) stimuli. It remains unclear whether nicotine's effects on cognition are direct, or whether they are mediated through effects on mood and arousal (Waters & Sutton, 2000). Inspired by the Yerkes-Dodson principle of optimal levels of arousal (too much or too little arousal produces inferior performances), Newhouse, Potter et al. (2004) hypothesized that nicotine would not improve and may even impair cognitive functioning in healthy non-smokers who are already at or near their optimal level, but would enhance cognition in smokers and in some psychiatric patients who need the arousing effect of nicotine to produce their best performance.

This Newhouse, Potter et al. (2004) theory is supported by a study in which nicotine impaired the spatial working memory of healthy smokers (Park, Knopick, McGurk, & Meltzer, 2000). On the other hand, acute administration of nicotine to non-patients has improved their response speed (Heishman et al., 1994), their focussed, sustained and divided attention (Foulds et al., 1996; Hindmarch et al., 1990; Kerr et al., 1991; Le Houezec et al., 1994; Levin et al., 1998; Mumenthaler et al., 2003) and their short-term memory (Kerr et al., 1991; Perkins et al., 1994; Rusted et al., 1995; West & Hack, 1991). Nicotine administered
to schizophrenic patients has improved their visual sustained attention (Dépatie et al., 2002; Levin, Wilson et al., 1996), working memory (Jacobsen et al., 2004; Levin et al., 1996; Smith, Singh et al., 2002) and selective attention (Barr et al., 2008; Jacobsen et al., 2004). Finally, a transdermal nicotine patch reversed working memory and attentional deficits in schizophrenic patients who exhibited medication-induced (haloperidol) cognitive deficits (Levin, Wilson et al., 1996).

2.0.6. Nicotine and the MMN

Studies of the effects of nicotine in non-patients found that it increased N1 amplitude (Knott, 1986, 1989) and reduced N1 latency (Houlihan et al., 2001). Only one, very recent, published study by Inami et al. (2007) examined nicotine and the MMN in schizophrenia. Inami et al. used a passive paradigm in which nonsmoking hospitalized schizophrenic patients and healthy control subjects were administered placebo and nicotine transdermally (in separate sessions) and watched a silent movie while they heard tones through earphones. Most of the tones (95%) had a frequency of 1000 Hz while the rest (5%) had a frequency of 1050 Hz. Nicotine had no effect on the MMN amplitudes or latencies of the patients but it shortened the MMN latencies of control participants. Inami et al. concluded that the lack of a similar latency effect in patients may be due to an abnormally low α7 nicotinic receptor function.

Significant nicotine effects were found in the MMN of other populations. Engeland et al. (2002) examined the effects of nicotine on the MMN of Alzheimer patients who had and who had not been treated with the cholinesterase inhibitor tacrine. In the non-tacrine-treated patients, nicotine increased MMN amplitude and decreased MMN latency. In the tacrine-treated group, nicotine decreased MMN latency but did not affect MMN amplitude, suggesting that nicotine improved sensory memory. Inami et al. (2005) observed shortened MMN latencies in healthy non-smokers who were administered nicotine. Harkrider et al. (2005) found enlarged MMN amplitudes in healthy non-smokers and smokers who were administered nicotine.

Finally, Baldeweg et al. (2006) used a novel stimulus paradigm with continuously changing (roving) standard stimuli in order to examine the effects of nicotine on auditory sensory memory in healthy minimally-abstaining smokers (4 hours) as measured with the
MMN. The purpose of this paradigm was to measure the effects of different numbers of stimulus repetitions on encoding of new stimuli. They found that nicotine increased MMN amplitudes by enhancing a frontal positive ERP to standard stimuli, while the negativity to deviant stimuli remained unaffected. As a result, they concluded, nicotinic agonists might ameliorate the MMN deficits of schizophrenic patients by improving stimulus encoding and sensory memory trace formation.

2.0.7. Objectives and hypotheses

The primary objectives of this experiment are twofold and include: a) a comparison of schizophrenic smokers and control smokers with respect to the pre-attentive detection of stimulus deviance, as indexed by the MMN; and b) an examination of the effects of nicotine on MMN in schizophrenic smokers. Within these objectives MMN was elicited by both frequency and duration deviants. The N1 ERP component to standard stimuli was also evaluated to determine whether any group differences or nicotine effects are related to early encoding of sensory features. Given previous research findings, it was predicted that frequency and duration MMNs would be attenuated in patients (vs. controls) and that nicotine (vs. placebo) would increase the frequency and duration MMN amplitudes of patients. As a secondary objective, the experiment examined the relationship between patients' clinical symptoms, including smoking withdrawal symptoms, and MMN indices, and between patients' medication and the MMN.

2.1. Method

2.1.1. Participants

Thirty-one ambulatory, antipsychotic-medicated, community-dwelling outpatients from the Schizophrenia Clinic of the Royal Ottawa Mental Health Centre, and 19 healthy individuals recruited through advertisements in local newspapers, were screened for this experiment. However, eleven of the patients, including all three female patients, failed to keep their test appointments, mostly because they were unable to abstain from smoking for three hours, and data from eight other outpatients and seven of the healthy individuals were eventually excluded from the study analysis due to incomplete test sessions, failure to comply with smoking abstinence instructions, excessive recording artefacts or gender matching problems. The total remaining participants therefore included 12 outpatients
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(males = 12; age range 30-57, mean 41) and 12 healthy control participants (males = 12; age range 30-54, mean 42). Only patients who met DSM-IV diagnostic criteria for chronic schizophrenia, and who were judged to be in a non-acute stable phase of their illness for at least four weeks prior to study enrolment, were included in the study. Patients’ symptoms were rated (by their psychiatrist) using a 30-item scale with 16 general-psychopathology-symptom items, seven positive-symptom items and seven negative-symptom items (Positive and Negative Syndrome Scale: PANSS; Kay, Opler, & Lindenmayer, 1988, 1989). Patients were receiving antipsychotic medication, with the majority receiving second-generation antipsychotics. All subjects received an honorarium for their participation.

Participants were all right-handed, with a body-mass index (BMI) below 35, a smoking history of more than five years and currently smoking (with inhalation) a minimum of 12-15 cigarettes per day, and normal or corrected-to-normal hearing (hearing loss no greater than 20 dB at the tone frequencies used in the experimental conditions). Potential participants were excluded if they were diagnosed with any DSM-IV disorder other than schizophrenia, or if they had suffered a head trauma in the past year, had abused any substance other than tobacco within six months of study participation, or suffered from unstabilized severe physical illnesses or diseases compromising the central nervous system. Potential control participants were excluded if they had a current or past personal history of psychiatric illness (including substance abuse) or a close relative who had been diagnosed with schizophrenia. Patients were also excluded if they reported any health condition contraindicating the use of nicotine gum.

To ensure that controls and patients were matched on intelligence and smoking-related factors, they completed the North American Reading Test (NART; Blair & Spreen, 1989; see Appendix A), which is an approximate measure of intelligence, the 8-item 15-point Modified Fagerstrom Test for Nicotine Dependence (FTND: Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991; see Appendix B), and the Modified Reasons for Smoking Scale (MRSS; Berlin et al., 2003; see Appendix C). The seven factors assessed by the 21-item MRSS are addiction, pleasure, tension reduction or relaxation, social, stimulation, habit and sensorimotor/ handling. Participants gave their written informed consent for the experiment, which was approved by the research ethics boards of the Royal Ottawa Health Care Centre and the University of Ottawa. All subjects were paid for their participation.
2.1.2. General procedure

Testing took place between 12:00 and 17:00 at the Clinical Neuroelectrophysiology and Cognitive Research Laboratory of the Royal Ottawa Mental Health Centre. All participants were instructed to abstain overnight from alcohol, caffeine and any drug other than the patients' medication, and were requested to refrain from smoking for three hours before the tests. Control participants were required to attend one test session lasting approximately 2.5 hours while patients were required to perform the same tests twice, in two separate sessions lasting approximately 3-3.5 hours each. Patients' sessions were longer because they involved a nicotine-or-placebo administration procedure. Upon their first arrival at the lab, adequacy of all participants' hearing was tested with 750 Hz and 1000 Hz tones, using a descending method-of-limits procedure, before EEG recording commenced. All thresholds were at or below 20 dB (SPL). Participants were then questioned about their abstinence from smoking, alcohol and drugs. Carbon monoxide (CO) levels were also assessed by means of an instrument measuring their expired-breath CO level (Vitalograph Breath CO instrument, Vitalograph Inc., Lenexa, Kansas). Participants were then taken into a sound-attenuated, electrically-shielded recording chamber and sat in a comfortable chair while electrodes were applied. During this application, patients were administered nicotine or a placebo (see nicotine procedure below). The drug conditions were not administered to the controls. Following electrode placement and nicotine or placebo absorption (in patients), electrophysiological data were acquired over a 30-40 minute interval which allowed for several 2-3 minute breaks. Frequent rest periods were required to maintain patient cooperation. At the end of the recordings, participants completed the Tobacco Withdrawal Symptom Checklist (TWSC; Hughes & Hatsukami, 1986; see Appendix D and description below).

2.1.3. Nicotine and placebo administration

Nicotine was administered within a randomized, double-blind, placebo-controlled, cross-over design with half of the patients receiving nicotine in the first session and placebo in the second session, and the remaining half receiving nicotine and placebo in the reverse order. Nicotine was administered orally as two 4-mg pieces of Nicorette Plus polacrilex gum (Hoechst Roussel). The placebo gum (containing no nicotine) was a commercial gum similar
in size, shape and texture. To reduce any perceptual and sensory differences between the two, patients wore a blindfold while putting the gum pieces in their mouths. Also, a drop of mint oil was placed on each gum and participants wore nose plugs throughout the chewing period. During that period, which lasted 25 minutes as specified by the Nicorette Plus guidelines, patients heard a taped voice every minute asking them to chew ("bite twice"). After each bite, they "parked" the gum between their teeth and gums. After the chewing period, the gum was discarded and patients were given a strong commercial mint gum to chew for five minutes to help disguise any placebo-nicotine difference.

Cigarette smoking yields a rapid delivery of nicotine to the bloodstream, resulting in sharp peaks in blood nicotine concentration. The peak of plasma nicotine concentration achieved within ten minutes of smoking an average-nicotine-yield cigarette is approximately 35 nanograms per milliliter, followed by a trough at 15 nanograms per millilitre within 30 minutes (Russell, 1988). After chewing one piece of 4-mg nicotine gum for 30 minutes, blood concentration reaches a peak of about 18 nanograms per millilitre of nicotine (Russell, Raw & Jarvis, 1980). Chewing two pieces of 4-mg nicotine gum results in peak blood levels of about 36 nanograms per milliliter within 30 minutes after the initiation of chewing, which approximates the effect achieved ten minutes after smoking a cigarette. The elimination half-life of nicotine is approximately 120 minutes (Benowitz, Jacob, Jones, & Rosenberg, 1982; Feyerabend, Ing, & Russel, 1985).

2.1.4. Stimuli

Auditory stimuli of 80 dB (SPL) were presented binaurally through headphones while participants watched a silent nature documentary. In the frequency-deviant paradigm, the tones (10 ms rise/fall) lasted 50 ms and varied in frequency, with 95% of the tones (standards) being 1000 Hz and 5% of the tones (deviants) being 1100 Hz. In the duration-deviant paradigm, the tones (10 ms rise/fall) had a frequency of 1000 Hz and varied in duration, with 95% (standards) lasting 100 ms and 5% (deviants) lasting 50 ms. A stimulus was presented every 300 ms. In each of the two paradigms, tones were presented in three blocks, with 2-3 minute breaks between the blocks. Within each block, a total of 532 standards and 28 deviants were presented, i.e. a total of 1596 standards and 84 deviants per paradigm. The frequency-deviant paradigm was always presented first, followed by the
duration-deviant paradigm. Within each block in both paradigms, stimuli were presented in a pseudo-random order with the exception that no two deviant tones could occur in sequence. Participants were instructed to concentrate their attention on the silent video and to ignore the headphone sounds.

2.1.5. EEG recording

The EEG was recorded with tin electrodes placed on midline frontal (Fz), central (Cz) and parietal (Pz) scalp positions according to the international 10-20 system (Jasper, 1958; Cooper, Osselton, & Shaw, 1969). Scalp electrical activity was recorded in a monopolar manner, the reference being to linked earlobes. Two additional electrodes, one on the left supra-orbital ridge and one on the external canthus of the left eye, recorded electrooculographic (EOG) activity in one channel, with a mid-forehead electrode serving as ground. Electrode impedances were kept below 5 kOhms. The EEG and EOG signals were recorded continuously with an analog-to-digital sampling rate of 256 Hz, using amplifier bandpass filters set at 0.1-30.0 Hz. Digital data were stored on hard disk for later off-line ERP processing and analysis. Off-line, the continuous EEG signals were reconstructed into 500 ms epochs (or "trials"), beginning 50 ms prior to stimulus onset. Eye movement and blink artifact were removed from the EEG signals using an algorithm operating in the time and frequency domains (Woestenburg, Verhaten & Slangent, 1983). Ocular-corrected trials with amplitudes exceeding +/-100 μV were excluded from further analyses. For each participant and drug condition, trials were averaged separately for correctly-detected standard and deviant stimuli and then sorted according to scalp recording site. A minimum of 55 artifact-free correctly-detected deviant stimulus trials was required to retain a participant's ERP averages in the final analysis.

Amplitudes and latencies of the ERP components were based on latency windows taken from grand-average waveforms. All ERP components were measured relative to the average of all data points in the pre-stimulus baseline. N1 latency for the frequency paradigm was defined at Fz (where it was largest) as the latency corresponding to the peak negativity occurring during the 50-150 ms latency range. N1 amplitude for the frequency paradigm was defined as the average of the amplitude points (relative to the average pre-stimulus voltage) within a 50 ms window around each individual's peak negativity, i.e. 25 ms pre-peak and 25
ms post-peak. N1 latency and amplitude for the duration paradigm were defined in the same manner except that the 50-200 ms latency range was used in identifying the peak negativity. The MMN was measured in the difference wave, calculated by subtracting point-by-point the ERP to the standard from that of the deviant. The difference wave removes processing that is common to both the standard and the deviant, leaving only the difference in processing (for example, the MMN). MMN latency for frequency deviants was defined at Fz as the latency corresponding to the peak negativity occurring during the 70-225 ms latency range, which is the site exhibiting maximal MMN amplitude, and MMN amplitudes were defined as averages of the amplitude points within a 50 ms window around each individual's peak negativity. MMN latency and amplitude for duration deviants were defined in the same manner as MMN latency and amplitude for frequency deviants except that the 70-300 ms latency range was used.

2.1.6. Smoking withdrawal ratings

Smoking withdrawal symptoms were assessed at the end of each test session with the TWSC to determine whether alterations in behaviour and in ERPs by nicotine were related to withdrawal relief. The seven items of the self-report TWSC questionnaire, which are derived from the DSM-IV list of withdrawal symptoms (American Psychiatric Association, 1994), are irritability, frustration or anger, difficulty concentrating, restlessness, anxiety or nervousness, hunger, depressed mood, and desire to smoke. For each item, participants were asked to choose on a four-point scale (0=not present, 1=mild, 2=moderate, 3=severe) the answer that best described how they felt. Scores for each symptom rating were summed to form a single TWSC index.

2.1.7. Analysis

Statistical analyses were performed using SPSS (Statistical Package for Social Sciences, 15th Edition). Three analyses of variance (ANOVAs) were run on ERP amplitudes and latencies (N1 and MMN). Separate mixed-design ANOVAs compared the ERPs of controls with those of patients in the placebo condition, and the ERPs of controls with those of patients in the nicotine condition, using one between-subjects factor with two levels (group: controls vs. patients) and one within-subjects factor with two levels (paradigm: frequency vs. duration). Repeated-measures ANOVAs compared the ERPs of patients in the
placebo condition with the ERPs of patients in the nicotine condition, using two within-subjects factors (condition: placebo vs. nicotine; paradigm: frequency vs. duration). Greenhouse-Geisser corrections were applied when appropriate to compensate for sphericity (equal covariance) violations. Since all the effects were the subject of specific a priori hypotheses based on previous research findings, a .05 level of significance was used in all analyses.

T-tests were used to determine whether control and patient participants differed on personal characteristics including age, education, BMI, number of cigarettes smoked per day, breath CO level, scores on the NART, FTND, and MRSS; whether the TWSC scores of patients with placebo differed from those of controls and patients with nicotine; and to compare the numbers of EEG trials per average analysed for each group, condition and paradigm. Pearson Product Moment Correlation or non-parametric equivalents were used to assess the relationships between frequency MMN and duration MMN, between MMNs and PANSS scores, between MMNs and TWSC ratings, and between MMN and patients' medication.

2.2. Results

2.2.1. Participant Characteristics

Demographic and clinical characteristics of participants are in Table 8, as well as results of independent-samples t-tests comparing patients and controls. No significant differences were found between control and patient participants for any personal characteristic, including age, schooling, body-mass index, number of cigarettes per day, CO levels, intelligence (excluding four patients whose English was poor), degree of nicotine dependence or reasons for smoking. Scores on the FTND (12 for patients and 11 for controls) indicated that both groups were heavily dependent on nicotine (7 points or more = heavy dependence). Controls and patients did not differ with respect to tobacco withdrawal symptoms, nor was there any differences in withdrawal symptoms when patients were in the placebo condition ($M=8.58; SE=1.5$) and when they were in the nicotine condition ($M=10.75; SE=1.4$) [$t(11) = 1.29, p<.22$].
Table 8. Mean (SE) Characteristics of Schizophrenic Patients and Control Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n = 12)</th>
<th>Controls (n = 12)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>41 (2.4)</td>
<td>42 (2.5)</td>
<td>-0.48</td>
<td>.64</td>
</tr>
<tr>
<td>Years of schooling</td>
<td>12 (0.2)</td>
<td>13 (0.2)</td>
<td>-0.55</td>
<td>.59</td>
</tr>
<tr>
<td>BMI</td>
<td>25 (1.5)</td>
<td>24 (0.9)</td>
<td>0.24</td>
<td>.42</td>
</tr>
<tr>
<td>Cigarettes per day</td>
<td>26 (2.8)</td>
<td>23 (1.3)</td>
<td>1.12</td>
<td>.26</td>
</tr>
<tr>
<td>CO level</td>
<td>16 (1.5)</td>
<td>18 (1.9)</td>
<td>-0.68</td>
<td>.50</td>
</tr>
<tr>
<td>NART *</td>
<td>107 (1.7)</td>
<td>112 (2.2)</td>
<td>-1.93</td>
<td>.07</td>
</tr>
<tr>
<td>TWSC**</td>
<td>9 (1.5)</td>
<td>8 (0.9)</td>
<td>0.43</td>
<td>.67</td>
</tr>
<tr>
<td>FTND</td>
<td>12 (0.7)</td>
<td>11 (0.7)</td>
<td>1.07</td>
<td>.30</td>
</tr>
<tr>
<td>MRSS-addiction</td>
<td>6 (0.6)</td>
<td>5 (0.6)</td>
<td>0.39</td>
<td>.70</td>
</tr>
<tr>
<td>MRSS-pleasure</td>
<td>9 (0.6)</td>
<td>8 (0.5)</td>
<td>1.92</td>
<td>.07</td>
</tr>
<tr>
<td>MRSS-relaxation</td>
<td>7 (0.9)</td>
<td>7 (0.8)</td>
<td>0.20</td>
<td>.84</td>
</tr>
<tr>
<td>MRSS-social</td>
<td>4 (0.5)</td>
<td>3 (0.4)</td>
<td>1.43</td>
<td>.17</td>
</tr>
<tr>
<td>MRSS-stimulation</td>
<td>5 (0.9)</td>
<td>5 (0.5)</td>
<td>0.00</td>
<td>1.00</td>
</tr>
<tr>
<td>MRSS-habit</td>
<td>6 (0.9)</td>
<td>4 (0.7)</td>
<td>0.15</td>
<td>.89</td>
</tr>
<tr>
<td>MRSS-sensorimotor</td>
<td>5 (0.8)</td>
<td>6 (0.8)</td>
<td>0.90</td>
<td>.38</td>
</tr>
<tr>
<td>PANSS (positive)</td>
<td>14 (1.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS (negative)</td>
<td>14 (1.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS (general pathology)</td>
<td>25 (1.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td></td>
<td>97 (43.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Four patients were excluded because of their poor knowledge of English.
** Average for both patient sessions.

PANSS scores for the patients averaged 53 (14 + 14 + 25) and ranged from 34 to 77.

According to a study (Leucht et al., 2005) that translated PANSS scores into ratings on the Clinical Global Impressions Scale (CGI; Guy, 1976), which is used by psychiatrists to obtain a global picture of patients' overall clinical state, the CGI ratings of this experiment's patient participants were roughly as follows: none at score 1 = normal, not at all ill; 2 at score 2 = borderline mentally ill; 5 at score 3 = mildly ill; 4 at score 4 = moderately ill; 1 at score 5 = markedly ill; none at score 6 = severely ill; and none at score 7 = extremely ill.
2.2.2. EEG Measures - General

Table 9 displays the number of EEG trials to standard and deviant stimuli included in the analyses for each group, condition and paradigm.

Table 9. Mean (SE) Trials per Average ERP to Standard and Deviant Stimuli

<table>
<thead>
<tr>
<th></th>
<th>Frequency paradigm</th>
<th></th>
<th>Duration paradigm</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standards</td>
<td>Deviants</td>
<td>Standards</td>
<td>Deviants</td>
</tr>
<tr>
<td>Controls</td>
<td>1620.3(90.2)</td>
<td>86.7(4.9)</td>
<td>1652.8(75.3)</td>
<td>87.8(4.3)</td>
</tr>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>placebo</td>
<td>1497.3(57.6)</td>
<td>79.3(2.8)</td>
<td>1429.9(30.0)</td>
<td>74.3(1.4)</td>
</tr>
<tr>
<td>nicotine</td>
<td>1490.7(74.6)</td>
<td>77.6(4.2)</td>
<td>1461.3(50.2)</td>
<td>77.6(2.9)</td>
</tr>
</tbody>
</table>

Controls had more trials per average ERP than patients in all categories, but the only statistically significant differences were between controls and patients in the duration paradigm: controls had significantly more trials per average ERP than patients in the placebo condition for both types of stimuli [standard: \( t(22) = -2.75, \ p < .02 \); deviant: \( t(22) = -2.96, \ p < .01 \)], and controls had more trials per average ERP than patients in the nicotine condition for standard stimuli [\( t(22) = -2.12, \ p < .048 \)].

Grand-averaged raw waveforms for the frequency and duration paradigms are presented in Figure 3. For each paradigm, the figure shows the waveforms elicited in Fz, Cz and Pz by standard and deviant stimuli in control participants, patients in the placebo condition and patients in the nicotine condition.
Figure 3. Grand-Averaged Waveforms to Standard and Deviant Stimuli in Passive Frequency and Duration Paradigms

FREQUENCY PARADIGM

- Patients-placebo
- Patients-nicotine

DURATION PARADIGM

- Cz

Controls

Standard

Deviant
Grand-averaged difference waveforms for the frequency and duration paradigms for the same participants are shown in Figure 4. The MMN, a large fronto-central negativity, is apparent 150-250 ms after onset of the deviant stimulus.

**Figure 4. Grand-Averaged Difference Waveforms in Frequency and Duration Paradigms for Controls and for Patients in the Placebo and Nicotine Conditions**

2.2.3. N1 and MMN in Frequency Paradigm

Means and standard error values for N1 ERPs at Fz to standard stimuli for the frequency paradigm are shown in Table 10. Analyses of these N1 amplitudes and latencies to standard stimuli failed to find any significant differences between control participants, patients with placebo and patients with nicotine.
Means and standard error values for MMN amplitudes and latencies elicited with frequency deviants are shown in Table 11. For frequency deviants, the MMN amplitude of controls was significantly greater than the MMN amplitude of patients in the placebo condition \([F(1,22)=15.53, p<.001, \eta^2=.41]\). MMN amplitudes of controls and patients with nicotine also differed for frequency deviants \([F(1,22)=9.38, p<.01, \eta^2=.30]\), indicating that patients who took nicotine still had a significantly reduced MMN. In other words, the MMN of patients was significantly smaller than that of controls, whether the patients took nicotine or not. Analyses of MMN latencies to frequency deviants failed to reveal any significant differences between controls, patients with placebo and patients with nicotine.

### Table 10. Mean (SE) N100 Amplitudes and Latencies at Fz to Standard Stimuli in Frequency and Duration Paradigms

<table>
<thead>
<tr>
<th></th>
<th>Amplitude (µV)</th>
<th>Latency (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency</td>
<td>Duration</td>
</tr>
<tr>
<td>Controls</td>
<td>-0.20(0.1)</td>
<td>-0.56(0.2)</td>
</tr>
<tr>
<td>Patients with Placebo</td>
<td>-0.06(0.1)</td>
<td>-0.43(0.1)</td>
</tr>
<tr>
<td>Patients with Nicotine</td>
<td>-0.16(0.1)</td>
<td>-0.44(0.1)</td>
</tr>
</tbody>
</table>

### Table 11. Mean (SE) MMN Amplitudes and Latencies to Frequency and Duration Deviants

<table>
<thead>
<tr>
<th></th>
<th>Amplitude (µV) at Fz</th>
<th>Latency (ms) at Fz</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency</td>
<td>Duration</td>
</tr>
<tr>
<td>Controls</td>
<td>-1.69(0.2)</td>
<td>-1.3(0.3)</td>
</tr>
<tr>
<td>Patients with Placebo</td>
<td>-0.58(0.2)</td>
<td>-0.58(0.2)</td>
</tr>
<tr>
<td>Patients with Nicotine</td>
<td>-0.76(0.2)</td>
<td>-1.18(0.2)</td>
</tr>
</tbody>
</table>
2.2.4. N1 and MMN in Duration Paradigm

Means and standard error values for N1 ERPs for the duration paradigm are shown in Table 10. There were no significant differences in N1 amplitude or latency to standard stimuli between controls, patients with placebo and patients with nicotine.

Means and standard errors for MMN amplitudes and latencies elicited with duration deviants are shown in Table 11. With duration deviants, the MMN amplitude of controls was significantly greater than the MMN amplitude of patients in the placebo condition \( F(1, 22) = 5.02, p < .04, \eta^2 = .19 \). However, the MMN amplitude of controls and that of patients in the nicotine condition did not significantly differ from each other, which suggests that nicotine altered the MMN deficit of the patients. The MMN amplitude of patients in the nicotine condition was significantly greater than the MMN amplitude of patients in the placebo condition \( F(1, 11) = 8.53, p < .01, \eta^2 = .44 \). Analyses of MMN latencies to duration deviants failed to find any significant differences between controls and patients in the placebo condition, but patients in the nicotine condition had significantly longer latencies to duration deviants than control participants \( F(1, 22) = 7.36, p < .01, \eta^2 = .25 \). There were no significant differences in latencies between patients in the two conditions.

2.2.5. Comparison of Duration and Frequency MMNs

The difference waveforms shown in Figure 4 suggest that there were substantial differences between the MMN amplitudes and latencies generated in response to frequency and duration deviants. This is partly confirmed by analyses that reveal differences in amplitudes and latencies by type of deviant. MMN amplitudes of control participants were larger for frequency deviants than for duration deviants \( F(1, 22) = 4.99, p < .04, \eta^2 = .19 \). This was not the case for patients in the placebo or nicotine conditions, whose amplitudes did not differ for the two types of deviant. There was more unanimity in latencies: controls \( F(1, 22) = 19.66, p < .00, \eta^2 = .47 \), patients in the placebo condition \( F(1, 22) = 32.40, p < .00, \eta^2 = .60 \), and patients in the nicotine condition \( F(1, 22) = 70.96, p < .00, \eta^2 = .76 \) all had significantly longer MMN latencies to duration deviants than to frequency deviants. The only significant difference between the groups was in the duration paradigm, where patients who were administered nicotine had longer MMN latencies than control participants \( F(1, 22) = 7.36, p < .01, \eta^2 = .25 \).
2.2.6. Correlations MMN, PANSS Scores, TWSC ratings and Medication  
Reduced duration MMN amplitudes of patients in the placebo condition were significantly associated with higher scores on the general pathology subscale of the PANSS [Kendall's tau(12) = -.47, p < .04]. Also in patients in the placebo condition, MMN amplitudes were correlated with specific symptoms from the positive subscale of the PANSS: attenuated duration and frequency MMN amplitudes were associated with higher degrees of grandiosity [duration: Kendall’s tau(12) = -.51, p < .04; frequency: Kendall's tau(12) = -.55, p < .03]. Shorter duration MMN latencies of patients with placebo were significantly associated with a greater likelihood of hallucinations [duration: Kendall's tau(12) = -.62, p < .01; frequency: Kendall's tau(12) = -.60, p < .02]. Patients' doses of antipsychotic medication (measured in chlorpromazine equivalents; Bezchlibnyk-Butler & Jeffries, 2006) were not correlated with MMN amplitudes or latencies or with PANSS scores. There were no significant correlations between "change" scores for MMN amplitudes (i.e. nicotine amplitudes minus placebo amplitudes) and "change" ratings for the TWSC (i.e. ratings for nicotine condition minus ratings for placebo condition).

Frequency MMN amplitudes of patients in the placebo condition were positively correlated with their duration MMN amplitudes [Pearson’s r(12) = .77, p < .004]. Similar but less strong positive correlations were found between the frequency and duration MMN amplitudes of patients in the nicotine condition [Pearson’s r(12) = .65, p < .02] and between the frequency and duration MMN amplitudes of control participants [Pearson’s r(12) = .62, p < .032].

2.3. Discussion  
The experiment evaluated the hypotheses that the well-established MMN deficits of schizophrenic patients would also be observed in minimally-abstaining (3 hours) schizophrenic smokers, and that such deficits might be altered with acute nicotine intake. The findings replicated previous studies showing that patients had significantly diminished MMN amplitudes following presentation of both frequency and duration deviants. Nicotine partially corrected this attenuation, increasing MMN amplitude in the duration paradigm but not in the frequency paradigm. Nicotine also lengthened MMN latencies associated with duration deviants. These effects were independent of early sensory encoding, as N1...
amplitudes and latencies were similar in patients and controls and were not affected by nicotine administration. Further, diminished MMNs and their restoration by nicotine in patients appeared to reflect an absolute effect of nicotine and were not related to smoking withdrawal intensity or to nicotine-induced withdrawal relief.

2.3.1. Schizophrenia and the N1

N1 is a so-called "mesogenous" component that is primarily affected by the physical characteristics of stimuli but is also affected by the attentional demands of task paradigms (Muller-Gass & Campbell, 2002). The present experiment did not find any statistically significant N1 differences in amplitude or latency between controls, patients in the placebo condition and patients in the nicotine condition in either the frequency or the duration paradigms. Nevertheless, N1 amplitudes to standard stimuli were largest in controls, smaller in patients with nicotine and smallest in patients with placebo. The failure to find patient-control differences could be due to the small number of subjects. Another possible cause is the fact that N1 was very small in all groups due to the very rapid rate of stimulus presentation (ISI of 0.3 s). A repeating sound presented at a high rate (ISI below approximately 1 s) elicits a very small N1 in healthy subjects (Naatanen & Picton, 1987; Naätänen, 1992).

Javitt (2000) reviewed the effects of the rate of stimulus presentation in the few studies that examined differences in N1 amplitude between controls and schizophrenic patients (Bruder & al., 1999; Ford et al., 1994; Roth, Horvath, Pfefferbaum, & Kopell, 1980; Shagass, Straumanis, Roemer, & Amadeo, 1977; Shelley et al., 1999). In healthy controls, N1 amplitude normally increased with increasing ISI, reaching a plateau once the ISI was in the range of 5-10 s. Differences in N1 amplitude between controls and schizophrenic patients emerged when relatively fast presentation rates (0.8-1.5 s) were employed, but these differences were not usually significant. Significant differences consistently emerged when stimuli were presented more slowly (ISI longer than 2 s). This was attributed to the fact that the N1 amplitude of patients reached a plateau around ISI 2 s, while the N1 amplitude of controls continued to rise until the ISI reached 5-10 s. On the other hand, Shelley et al.

1 There is some controversy about whether N1 itself is directly affected by attention or whether an independent negative component, the Processing Negativity (PN) is modulated by attention. However, N1 and PN overlap and summate at the scalp, thus creating a composite N1 + PN negativity.
(1999), as well as Ahveninen et al. (2006), found significant reductions in N1 amplitude in schizophrenic patients with an ISI of 0.5 s. N1 impairments in schizophrenia were correlated with auditory-cortex neuronal abnormalities in neuroimaging studies (McCarley & al., 1999) and in postmortem studies of cortical pyramidal cells (Sweet et al., 2004). Ahveninen et al. (2006) found reduced N1 in schizophrenic patients and their unaffected co-twins, suggesting that underlying neuronal deficits might be associated with a genetic predisposition to schizophrenia.

2.3.2. Schizophrenia and MMN amplitudes

The present experiment established that schizophrenic patients who smoke but who are deprived of nicotine for three hours have the same reduced duration and frequency MMN that has been found in previous schizophrenia studies in which the smoker or non-smoker status of the patients was not disclosed. Unlike most other studies, which used only frequency deviants (most commonly) or only duration deviants (Umbricht & Krljes, 2005), this experiment compared MMN components elicited by both deviants in the same sample of patients and control participants. Contrary to the conclusion of the meta-analysis by Umbricht and Krljes, which found an overall effect size for duration MMN that was about 40% larger than the effect size for frequency MMN, this experiment found a larger effect size for patients' MMN deficits elicited by frequency deviants (.41) than for MMN deficits elicited by duration deviants (.19).

A likely reason for the discrepancy between the present study and the other studies is that the duration paradigm used in this study was somewhat different. In this study's frequency paradigm, the standard stimulus was a 1000-Hz tone lasting 50 ms with a probability of 95% while the deviant stimulus was a 1100-Hz tone lasting 50 ms with a probability of 5%. This combination of a small difference between the standard and deviant frequencies (10%:1000 vs. 1100 Hz) with a small deviant probability (5%) was found in past studies (Umbricht & Krljes, 2005) to be ideal to elicit the greatest impairments in the MMN of schizophrenic patients in a frequency paradigm. In this study's duration paradigm, the standard was a 1000-Hz tone lasting 100 ms with a probability of 95% while the deviant was a 1000-Hz tone lasting 50 ms with a probability of 5%. Although the combination of a large difference between the standard and deviant durations (50%: 100 vs. 50 ms) with a small
deviant probability (5%) was also found to be optimal to produce MMN impairments in schizophrenia patients in a duration paradigm (Umbricht & Krlejs), previous studies have found greater MMN deficits in schizophrenic patients when the duration deviant stimulus is longer than the standard stimulus, instead of shorter as was the case in the present study (Shelley et al., 1991; Catts et al., 1995).

There are serious methodological problems with the use of longer duration deviants. A long duration stimulus will elicit an N1 at its onset ("N1on") and at its offset ("N1off") (Naatanen & Picton, 1987). When the deviant has a longer duration than the standard, the deviant will elicit the MMN because it elicits a change in a specific feature (duration). Unfortunately, the offset of the longer duration deviant will also elicit N1-off afferent processes occurring at about the same time as the MMN. Thus, whatever difference is found between controls and patients might be a result of an abnormal N1 or an abnormal MMN. When the standard has a longer duration than the deviant, the N1-off to the standard occurs at about the same time as the MMN to the deviant. This may attenuate the MMN during the subtraction process, but the negativity that is apparent in the difference wave can be attributed only to the MMN. Control-patient differences would thus be expected to be smaller when the duration of the deviant is shorter than that of the standard. This is precisely what was found in the present study. This difference can however be attributed only to reduced MMN activity. The MMN effect was thus similar when both frequency and duration deviants were employed.

Another factor that might have influenced the present findings is a recently-discovered age effect on the MMN. In a study designed to compare the effects of many stimulus manipulations, Todd et al. (2007) used either duration, frequency or intensity deviants to examine the MMN in younger (mean age 25) and older (mean age 42) schizophrenic patients and age-matched healthy controls. In younger patients, duration and intensity MMNs were significantly reduced but frequency MMN was normal, while in older patients with a longer length of illness, the frequency MMN was most reduced, the duration MMN was less reduced and the intensity MMN was the same as that of controls. Close examination of their data revealed that age did not have an equal impact on the MMN elicited by different features. In particular, the age-related decline in the duration MMN of control subjects was much sharper than their decline for frequency MMN, while the patients' age-
related decline was much greater for frequency MMN. Duration MMN had changed little with age in the patients, perhaps because it had already been much reduced when they were young. Since the participants in the present experiment had mean ages of 41 for patients and 42 for controls, the age factor may also have diminished the MMN difference in the duration paradigm.

Michie et al. (2002) maintain that the duration MMN is a more sensitive index of change detection than the frequency MMN:

With respect to frequency, it is well known that within auditory cortex, there exists a tonotopic frequency map such that sounds that activate different frequency-specific regions of the basilar membrane are represented in different areas within auditory cortex (Phillips & Irvine, 1981). Indeed, when an MMN is produced in response to a frequency deviant, the MMN has been shown to derive from activity within the region of the tonotopic map corresponding to the deviant stimulus frequency (Tiitinen et al., 1993).

The processing of a sound's duration by auditory cortex is less well understood; however, investigations of cat auditory cortex have led to the proposal that acoustic stimuli are processed within the auditory system as a contiguous sequence of short time epochs that are partially processed at lower levels but are recompiled at the level of the auditory cortex (He, 1998). The encoding of stimulus duration may therefore require more complex computations at the level of auditory cortex than frequency encoding, making the process more vulnerable to error due to auditory cortex defects, either in anatomy (Shenton, Dickey, Frumin, & McCarley, 2001) or connectivity (Friston & Frith, 1995).

Strong correlations were found in this experiment between the frequency and duration MMN amplitudes of schizophrenic patients who took placebo (.77), as well as between the frequency and duration MMN amplitudes of patients who took nicotine (.65) and of control participants (.62). These associations strongly suggest that even though the mental processes underlying the elicitation of frequency MMNs and duration MMNs are different, they are closely connected in the patients, whose MMN deficits have been linked to severe cognitive impairments (Baldeweg et al., 2004; Umbricht et al., 2004).

Recent findings raised the possibility that the MMN could offer a biological marker of post-onset progressive cognitive deterioration in schizophrenia (Umbricht & Krljes, 2005). If this were empirically validated, it could have profound theoretical and clinical implications for understanding and treating schizophrenia (van der Stelt & Belger, 2007). Considerable evidence from animal and human studies implicate deficient NMDA receptor functioning in
MMN deficits, since this receptor system is critical in the early phase of stimulus encoding (Krystal et al., 2003). NMDA dysfunction would also explain many cognitive problems that are common in schizophrenia, particularly in episodic memory (Umbricht & Krijes, 2005). NMDA receptors are indirectly activated by nicotine (Purves et al., 1997).

2.3.3. Schizophrenia and MMN latencies

The MMN latency differences that were found in this experiment included a nicotine effect that will be discussed later and a paradigm effect in which all groups and conditions had shorter MMN latencies for frequency deviants than for duration deviants. This paradigm effect was due to characteristics of the stimuli used in the two paradigms. In the frequency paradigm, the difference or mismatch between the standard and deviant stimuli (between the 1000 Hz standards and the 1100 Hz deviants) was immediately perceivable upon stimulus onset, while in the duration paradigm, the mismatch between the longer standard tone (100 ms) and the shorter deviant tones (50 ms) was only perceivable upon offset of the shorter tone. As a result, the latencies are roughly 50 ms longer for the duration paradigm than for the frequency paradigm.

2.3.4. Nicotine and duration MMN

In this experiment, nicotine appears to have had a normalizing effect on the duration MMN deficit of schizophrenic patients while it had little effect on their frequency MMN deficit. According to Baldeweg et al. (2006), nicotine modulation of the MMN can occur in one of two main ways:

It could either affect pre-attentive deviance detection, i.e. the attentional switch associated with the frontal MMN (Naatanen & Michie, 1979), or improve stimulus encoding and memory trace formation . . . If the former prediction is correct, one would expect an enhancement by nicotine of the deviant-associated negativity. In contrast, if the latter hypothesis is correct and acetylcholine affects the early stages of stimulus acquisition, as pharmacological studies suggest (Miranda and Bermudez-Rattoni, 1999), then we predicted nicotine effects on the standard ERP.

As shown in Figure 3, which presents the grand-averaged raw waveforms to standard and deviant stimuli in the frequency and duration paradigms for this experiment, there is no doubt that the main effect of nicotine in the duration paradigm (at the bottom) was to enhance the deviant-associated negativity. According to Baldeweg et al. (2006), therefore, this should
indicate that nicotine facilitated acoustic change detection processes in the auditory cortex and/or frontal cortices. Also, as N1 was not affected, it can be assumed that nicotine effects were specific to the change detector mechanism and did not involve alterations in the transient detector. This is consistent with Näätänen's (2003) view that:

One of the central lines of current MMN research on schizophrenia consists of studies aiming at determining the effects of this pathology on the two main intracranial processes generating the scalp-recorded MMN, viz., those occurring in the auditory and frontal cortices. In the light of the results obtained so far, it appears that the frontal generators are, in general, much more affected than the auditory-cortex ones.

On the other hand, the view that frontal generators are mainly responsible for the MMN impairment of schizophrenic patients has become less convincing in recent years. For one thing, many studies using EEG (Alain, Woods, & Knight, 1998), MEG (magnetoencephalography; Rosburg, Haueisen, & Kreitschmann-Andermahr, 2004; Thönnessen et al., 2008), fMRI (functional magnetic resonance; Jääskeläinen et al., 2004; Kircher et al., 2004) and PET (positron emission tomography; Müller, Jüpter, Jentzen, & Müllert, 2002) paradigms confirmed that the main generators of the MMN are located in the supratemporal cortex. Secondly, Javitt et al. (1998) suggested, on the basis of their findings of diminished MMN sensitivity to stimulus features in schizophrenia, that the most likely cause of this impairment was inaccurate stimulus encoding, which is associated with temporal cortices (Oknina et al., 2005). Thirdly, the role of the frontal generators of the MMN is still unclear, as explained by Rinne et al. (2005):

The role of IFC (inferior frontal cortex) in auditory change detection and analysis still remains to be clarified. Originally, it was suggested that the frontal lobe contribution to MMN mechanism signifies the initiation of switching of attention (Näätänen, 1990) (...) Alternatively, it has been suggested that, instead of attention switching, the IFC activation is related to a contrast enhancement mechanism which would be activated when the STC (supra-temporal cortex) system gets in difficulty in discriminating stimuli (Doeller et al., 2003; Opitz, Rinne, Mecklinger, von Cramon, & Schröger, 2002). In addition to these hypotheses, it is also possible that the IFC activation detected by fMRI might be related to an inhibitory system that allows the subjects to ignore the sound changes when no change-related response is required.

On the basis of these arguments, it can be concluded that the respective roles of the temporal and frontal generators of the MMN are not sufficiently understood at this point to
determine which mechanism was responsible for the nicotine-induced normalization of the MMN amplitudes to duration deviants of schizophrenic patients in this experiment.

In contrast to earlier studies that observed a shortening of MMN latencies with nicotine in both non-patients and demented patients (Engeland et al. 2002; Inami et al., 2005), the enhancement in the duration MMN amplitudes of schizophrenic patients by nicotine in this experiment was accompanied by an increase in latency resulting in significantly longer MMN latencies in patients than in controls. If the nicotine-induced enhancement in MMN amplitudes in patients indicates that nicotine facilitated a more effective neural processing of new environmental stimuli, it could perhaps be concluded that their lengthened MMN latencies reflect a deeper processing that takes more time than the shallower, less accurate processing that occurred when patients took placebo. On the other hand, one could also argue that the improved acoustic change detection brought about by nicotine was done at a cost of slower processing. The nicotine-induced changes in the MMN amplitudes and latencies of schizophrenic patients are consistent with Kassel’s (1997) hypothesis that nicotine would improve the neural systems that deal with irrelevant stimuli and would increase the neural resources allocated to the processing of potentially relevant stimuli, as evidenced by greater and slower duration MMNs.

Another interesting aspect of the effects of nicotine on the MMN of schizophrenic patients is that these effects may be specific to these patients. When Baldeweg et al. (2006) examined the MMN of healthy smokers administered nicotine or a placebo after a 4-hour smoking abstention, they found that nicotine-enhanced MMNs were related to a significantly enhanced positive (80-200 ms) component for the standard stimuli and that its effects on the deviant-related negativity (MMN) was not significant. This possible difference in the effects of nicotine on schizophrenic patients and healthy smokers provides partial support to the hypothesis of Newhouse, Potter et al. (2004), who believed that nicotine may improve aberrant cognition in smokers and psychiatric patients, but that it would have no effect or may even worsen cognitive functioning in healthy non-smokers who are already at their optimal level. On the other hand, the difference between Baldeweg et al.’s nicotine effects and the nicotine effects found in this study may be due to Baldeweg’s use of an unusual paradigm with continuously changing ("roving") standard stimuli.
Nicotine-altered duration MMNs were observed to be independent of smoking withdrawal symptoms, which suggests that nicotine's effect on pre-attentive change detection is not mediated via withdrawal relief mechanisms. This conclusion is further supported by previous findings of nicotine-induced MMN latency shortening and MMN amplitude augmentation in both smokers and non-smokers (Baldeweg et al., 2006; Harkrider et al., 2005; Inami et al., 2005). Although MMN amplitudes of non-patient smokers have been reported to be larger than those of non-smokers (Harkrider et al.), it is not clear from this study whether chronic smoking in schizophrenia, which acts to upregulate low-affinity α7 nicotinic acetylcholine receptors (Benwell, Balfour, & Anderson, 1988; Leonard et al., 2000), alters MMN-indexed pre-attentive mechanisms.

Given evidence of NMDA receptor hypofunction in schizophrenia and findings which demonstrate that NMDA antagonists selectively abolish MMN-like activities without affecting such sensory ERPs as N1 (Javitt et al., 1996; Umbricht et al., 2000; Umbricht et al., 2004), nicotine may have restored duration MMNs in patients by glutamatergic release following activation of α7 nicotinic receptors co-localized on NMDA terminals. However, this theory fails to explain why nicotine affected frequency and duration change detection differently. It is also possible that nicotine-induced correction of MMN may be mediated via the muscarinic acetylcholine system as antagonists of this receptor system have been shown to attenuate MMN in healthy controls, but this effect was specific for frequency MMNs and not for duration MMNs, and the attenuation was accompanied by a delayed N1 latency (Pekkonen et al., 2001).

2.3.5. Clinical ratings, medication, withdrawal symptoms and the MMN

Out of the 22 studies reviewed by Umbricht and Krljes (2005) that examined associations between MMN amplitudes and clinical symptoms, three studies reported associations between reduced MMN amplitudes and increased positive symptoms, especially hallucinations (Youn et al., 2003; Hirayasu et al., 1998; Schall et al., 1999), six studies found associations between reduced MMNs and increased negative symptoms (Catts et al., 1995; Grzella et al., 2001, Hirayasu et al., Javitt et al., 2000; Kasai et al., 2002; Schall et al., 1999), while the rest of the studies did not find any associations. These differences in association cannot be attributed to differences in stimuli since all the studies that found significant
associations used frequency paradigms, with the sole exception of the study by Schall et al. (1999) that used a duration paradigm.

This experiment supports previous findings of an association between diminished MMN ERPs and positive schizophrenia symptoms, though in this experiment the strongest link was not between MMN amplitudes and hallucinations, but between reduced frequency and duration MMN amplitudes and increased grandiosity (delusions of grandeur) in placebo patients and, to a lesser degree, between reduced frequency MMN amplitudes and increased delusions and excitement in placebo patients. However, increased hallucinations were significantly associated with shorter duration MMN latencies in placebo patients, and with longer frequency MMN latencies in patients with nicotine.

No associations were found between patients' MMN amplitudes or latencies and their dose of antipsychotic medication. There were also no significant correlations between patients' MMN and their scores on the TWSC, meaning that their MMN did not seem to have been affected by nicotine withdrawal symptoms. Finally, there was no relation between nicotine-induced change scores for MMN amplitudes and change ratings for the TWSC.

2.4. Limitations and Conclusion

The methodology of this experiment had many strengths, the main one being its double-blind, placebo-controlled, crossover design, which eliminated researcher and subject bias and diminished individual differences. The use of gum instead of cigarettes made it possible to control the amount of nicotine that was absorbed. On the other hand, nicotine nasal spray produces more rapid peak increases in blood nicotine that are similar to those of nicotine, and it also allows for improved control over the amount of nicotine absorbed (Henningfield & Keenan, 1993). This experiment also failed to adjust the dose of nicotine for individual weight differences and did not measure blood nicotine levels, which would have made it possible to pursue dose-response effects.

Studies conducted with deprived smokers have also been criticized because they cannot demonstrate that nicotine absolutely improved cognitive measures, since tobacco deprivation itself has a negative impact on cognition in smokers (Bell et al., 1999). To minimize this factor, this study used smokers who were minimally deprived (three hours) and monitored their tobacco withdrawal symptoms during their participation in a placebo gum
session and a nicotine gum session. The result was that there was no significant difference in withdrawal symptoms between patients' placebo and nicotine sessions, which suggests that withdrawal symptoms did not play a significant role in this experiment. This was further confirmed by the lack of association between MMNs and tobacco withdrawal symptoms, as well as between MMN change scores and TWSC change ratings.

Another weakness of this study is its small number of participants. In addition to the problem of failing to find significant effects for lack of power, the heterogeneous nature of schizophrenia makes it important to use large subject sample sizes of both patients and their unaffected biological relatives (van der Stelt & Belger, 2007). This study would also have been enriched by having both patients and controls take acute nicotine, instead of only patients, and by having non-smoking as well as smoking participants. There is of course an ethical concern when nicotine is administered to non-smoking participants.

This study would also have been improved by having a larger number of electrodes, instead of only electrodes at Fz, Cz, and Pz. Kujala, Tervaniemi and Schröger (2007) recently recommended that "when possible, it is advisable to have a larger set of electrodes in MMN recording. Having Fz, Cz, and Pz as well as the left and right mastoids as a minimum is helpful in separating the MMN from some other ERP components like the N1 and N2b."

Other limitations of this study relate to the medication status of patients and the generalizability of study findings. Since patients who were invited to participate in this experiment were chosen because they were exceptionally "high-functioning" (the psychiatrists' term) and able to perform relatively complex tasks for other experiments, the results may not be generalizable to all schizophrenic patients. Most relevant to this experiment, only one of the 12 patients who participated was rated by his psychiatrist (in the PANSS) as having "poor attention," and that patient was judged to have only a "mild" attention problem. The fact that all the patients were taking antipsychotic medication was not considered a problem since studies found no effect of typical or atypical antipsychotics on MMN despite symptomatic improvement of patients (Schall et al., 1998; Umbricht et al., 1998, 1999). A recent study by Rezvani, Kholdebarin, Dawson and Levin (2007) found that clozapine had impaired attentional function in rats, but only one patient who participated in this study was taking that medication.
Additional studies are needed to clarify the implications of these nicotine-enhanced MMNs with regards to higher-order attentional processes that are frequently attenuated in schizophrenia. Of particular interest is the relationship of nicotine-altered pre-attentive processes and involuntary attentional switching. The P3a, which indexes attention switching, is frequently diminished in schizophrenia. Some of these issues are addressed in the second and third experiments.

**EXPERIMENT 2**

**Auditory-Auditory Distraction Paradigm**

3.0. Introduction

3.0.1 **Attention dysfunctions in schizophrenia**

Schizophrenia has always been characterized by profound deficits in attention (Kraepelin, 1919) but the precise nature of these problems remains unclear. One major outstanding question concerns the relationship between these attention deficits and the demonstrated impairment in schizophrenic patients of functions attributed to the central executive (Bustini et al., 1999; Hutton et al., 2998, Pantelis et al., 1997; Rushe et al., 1999; Zalla et al., 2004). Several research teams are attempting to answer this question by formulating and testing different theories focussing on executive processes associated with the prefrontal cortex.

Birkett, Brindley, Norman, Harrison and Baddeley (2006) suggested that attention deficits in schizophrenia may be caused by a dysfunction of the inhibitory component of executive control. This is consistent with Baddeley's (1986) working memory model, in which two modality-specific subsystems (the phonological loop and the visuospatial sketchpad) are controlled by the central executive. The central executive coordinates the activity of these subsystems and controls attention. Birkett et al.'s schizophrenia theory was not supported when they tested schizophrenic patients with attentional tasks containing different levels of difficulty. Patients performed more poorly than controls in the baseline condition, but they showed no disproportionate decline in performance in the condition that made greater demands on attention.

Another line of research was inspired by a model developed by Posner and Petersen (1990), who suggested that attention consists of three distinct brain networks: the alerting
network, the orienting network, and the executive control (of attention) network. Alerting was defined as the ability to maintain the alert state and to respond to a warning signal. Orienting involves the selection of information among numerous sensory inputs. Executive control of attention involves self-regulation of cognition and emotions, most often measured by requiring a response to one aspect of a stimulus while ignoring a more dominant aspect (for example the Stroop task; Stroop, 1935). Separate studies (Gooding, Braun, & Studer, 2006; Wang et al., 2005) recently examined these networks in schizophrenic patients by means of the attention network test (ANT; Fan, McCandliss, Sommer, Raz, & Posner, 2002). The ANT was designed to measure the efficiency of subjects' alerting, orienting and executive attention networks in a single experiment. Both studies concluded that schizophrenic patients had normal alerting networks, but that they showed a clear deficit in executive network and a smaller deficit in the orienting of attention.

A third theory inspired by the work of Shakow (1962) proposes that a substantial part of the cognitive deficits of schizophrenic patients is caused by a disturbance in an underlying mechanism that is responsible for the representation and maintenance of context information needed to select and execute task-appropriate action (Cohen, Barch, Carter & Servan-Schreiber, 1999; Cohen & Servan-Schreiber, 1992). Instead of postulating separate mechanisms for attention, active memory and inhibition, the context-processing theory proposes a single top-down mechanism of context representations that support task-relevant processes, thereby allowing them to compete effectively against irrelevant stimuli. This theory is consistent with findings of impaired context processing by schizophrenic patients in tasks such as the AX-CPT (Continuous Performance Test; Nuechterlein, 1991), in which there is a delay between context and response, thereby requiring maintenance of context over time (Barch et al., 2001; Holmes et al., 2005; MacDonald III et al, 2005). A context-processing deficit was also suggested to explain the results of a study by Meiran, Levine, Meiran and Henik (2000), in which the set-switching impairment of schizophrenic patients disappeared once the task was modified to eliminate the advantage of remembering contextual information.

Finally, Näätänen's (1990) psychophysiological model of central auditory processing was applied to schizophrenia. Starting with an experiment by Shelley et al. in 1991, many studies suggested that the attention deficits of these patients may be secondary to
impairments in pre-attentive automatic processing reflected in ERP-indexed MMNs. The main focus of these studies has been the Mismatch Negativity (MMN) ERP. A review by Umbricht and Krljes (2005) concluded that MMN deficits are very common in chronic schizophrenia. According to Näätänen (2003), these MMN findings suggest that pathologies appear to be present in the auditory and frontal cortices of schizophrenic patients, but that the frontal generators appear to be much more affected.

3.0.2. Mismatch negativity and the Näätänen model

As discussed in Experiment 1, the MMN ERP is an excellent tool to examine pre-attentive information processing in schizophrenia. It is automatically generated relatively independently of attention (see Näätänen et al., 2007 for recent review) when an incoming auditory stimulus deviates in any way from the memory trace of a repeating series of auditory stimuli (or "standards") that immediately preceded the new stimulus. According to Näätänen (1992) and Cowan (1995), this pre-attentive neural process reflects the activity of our involuntary attention-orienting system, first described by Sokolov (1963), which detects potentially-dangerous deviant or novel stimuli. The MMN is an automatic biological-survival alerting mechanism designed to stimulate humans and animals to explore unexpected events in their environments (Javitt et al., 1995).

Figure 5 shows the model Näätänen (1990; modified for Näätänen et al., 2007) proposed to explain the processing of auditory stimuli. All auditory sensory information (S on the left) is analyzed by the fully-automatic Permanent Feature-Detector and Transient-Detector systems. Information about specific physical stimulus features is stored for a brief period as a sensory-memory trace. (In 1999, Näätänen and Winkler expanded this sensory-memory trace to add a memory trace of the preceding stimulus events or regularities.) In non-task-related sensory analysis, the Transient-Detector System bombards the central executive mechanisms with interrupt signals by activating N1-generator processes (1 on Figure 5). If the interrupt signals exceed a threshold, there is an attentional switch to conscious perception (2) and to the results of previous analysis stored in sensory memory (3). The Permanent Feature-Detector System passes information about the features of incoming stimuli to Sensory Memory (4). When a stimulus corresponding to the existing memory trace occurs, the trace is reinforced and strengthened. Once a solid memory trace has developed, any new
stimulus that differs from it will generate an MMN. The greater the difference between the incoming stimulus and the previous repeated stimuli, the greater the MMN. Production of an MMN sends another attention-switch signal to the central executive (5). Attention is switched (2, 3) when the strength of the attention-switch signal exceeds a variable threshold. This central auditory processing system is automatic, preconscious, extremely rapid, and (mostly) independent of attention.

3.0.3. Schröger and Wolff's theories of attention orienting and reorienting

Schröger and Wolff (1998a) took Näätänen's model further by proposing a multi-component attention-orienting-and-reorienting process in which (1) the MMN starts the orienting process by indexing the involuntary automatic detection of change from the acoustic past; (2) if the extent of change is large enough, a subsequent P3a component signals an involuntary switch in the orientation of attention away from the task at hand and toward the novel distractor stimulus; and (3) a late negative component, the reorienting negativity or RON, reflects the reorienting of attention back toward the main task that was disrupted by the distractor stimulus.

The P3a ERP is a centro-frontal positive ERP component associated with the orienting response (Friedman et al., 2001). It is often elicited in an active three-tone auditory...
oddball paradigm (with standard, target and novel stimuli) where task-related rare target stimuli elicit a later and more parietal maximum P3b ERP. The P3a is elicited automatically when a highly relevant, "attention-grabbing" stimulus, such as a novel or salient sound (e.g. dog bark, telephone ring, etc.), commands frontal lobe involvement (Polich et al., 2006). When the P3a is elicited by perceptually novel stimuli, it is called a "novelty P3". The P3a increases with the distinctiveness of the stimulus and peaks earlier (around 250-300 ms after stimulus onset) and has a more centro-frontal scalp distribution than the P3b.

In support of the theory that the P3a is associated with the orienting response, the P3a is larger in the presence of a skin-conductance response, which is one of the autonomic nervous system reactions that accompany the involuntary orienting of attention (Lyytinen et al., 1992; Sokolov et al., 2002). Even more convincing, Schröger and Wolff (1998b) found that in contrast to the MMN, the P3a and the RON (reorienting negativity) were only elicited in trials which had shown a reaction time prolongation to task-irrelevant deviant tones, indicating that subjects' attention had switched from the task to the distracting stimuli. The cerebral generators of the P3a are thought to include the supratemporal auditory cortex, the anterior and posterior association cortices and the posterior hippocampus (Friedman et al., 2001). However, the sources of the P3a remain an issue of debate. In the process Schröger and Wolff proposed, the P3a is always preceded by an MMN that detects novelty or stimulus deviance (Kujala et al., 2007). The MMN is not always followed by a P3a, because the P3a occurs only when the MMN-related processes are of sufficient strength to trigger a switch in attention (i.e. when the extent of deviance is large).

The reorienting negativity (RON) has a fronto-central distribution and occurs approximately 480 to 550 ms after stimulus onset (Schröger & Wolff, 1998a). It is believed to have multiple frontal generators (Escera et al., 2001; Schröger, Giard et al., 2000), although again little is known about its actual sources. Since it occurs only to task-irrelevant deviant stimuli that elicit a P3a (while subjects were performing a two-choice discrimination task – see description of that task below), Schröger and Wolff concluded that it did not reflect a global deviance-related effect. They hypothesized that it reflected the return of attention from the processing of task-irrelevant deviant stimuli and back toward the processing of the task-relevant stimuli. This was supported by findings that RON has larger amplitude to more task-disrupting events (Berti et al., 2001; Escera et al., 2001; Schröger,
Giard et al., 2000) and is correlated with the extent of deterioration of performance on the primary task, such as a decrease in the accuracy of detection and longer reaction times. Munka et al., (2006) suggested that the RON component reflects two functionally distinct processes of attentional allocation after distraction: (1) refocusing back to the ongoing primary task; and (2) general reorientation of attention, e.g. preparation for the upcoming task.

3.0.4. Schröger's auditory distraction paradigm

Traditional ERP distraction paradigms include task-related and non-task-related (distractor) stimuli that are embedded in different objects or modalities. For example, the pioneer study by Shelley et al. (1991) that first examined the MMN in schizophrenic patients presented target and distractor stimuli in different modalities. Subjects performed a visual task while they heard (and were instructed to ignore) standard and deviant auditory distractor stimuli of short and long duration. In another example by Gaeta et al. (2001), task targets and distractors were presented to subjects in the same modality, with task-relevant tones presented to the attended right ear and task-irrelevant distractor tones presented to the unattended left ear.

By contrast, Schröger's (1997) novel auditory distraction paradigm presents task targets and distractors that are imbedded in the same channel. This is illustrated in Figure 6, which shows a sample of ten auditory stimuli from a Schröger-style paradigm. Two tones that were either short or long in duration are presented. The subject's task is to discriminate the duration of equiprobable tones by pressing an appropriate button. On 20% of the trials, the frequency of the stimuli changes. This infrequent deviant stimulus was irrelevant to the task.

What is unique about the Schröger paradigm is that it provides both behavioural (performance) and physiological measures of the switching of attention. If the processing of the irrelevant stimulus interrupts the central executive controlling attentional allocation, performance on the duration discrimination task should deteriorate. This is because attention will be switched from the ongoing duration-discrimination task and toward the processing of the deviant stimulus. If this is the case, the deviant stimulus will elicit a large MMN (reflecting detection of stimulus change), followed by a P3a (reflecting the interruption of the
central executive and a switch of attention) and subsequently, a RON (reflecting a re-orientation back to the duration-discrimination task). In the Schröger paradigm, the extent of distraction varies directly with many different factors, most importantly the extent of deviance. Small deviants are preferred in MMN research because large deviants also elicit other ERP components such as the N1. As a result, it is difficult to disentangle the attention-orienting effects of the MMN per se from other ERP effects.

In one of the first published studies Schröger and Wolff (1998b) performed using this type of paradigm, their small frequency-deviant stimuli (standards and deviants with frequencies of 700 and 750 Hz, for a deviance of 7%) elicited MMN and P3a components. Importantly, the small-deviant stimuli distracted attentional resources away from the target detection task: hit rates to target stimuli of small-deviant frequency were significantly reduced by 4% relative to targets of standard frequency, and reaction time (RT) to target stimuli of small-deviant frequency was prolonged by about 50 ms relative to targets of standard frequency. These results demonstrated the efficiency of the new paradigm in producing orienting-related behavioural changes and ERPs. The effects of auditory distraction on an intra-modal auditory task are much larger than the effects of auditory distraction on an inter-modal visual task. Escera et al. (1998) observed a significant hit rate
decrease of 2.3% when the visual target stimulus was preceded by an auditory deviant (standards and deviants of 600 and 700 Hz, for a deviance of 17%), and the deviant tones did not significantly affect the RT.

In addition to its ability to induce behavioural measures of distraction, the Schröger paradigm elicits ERPs associated with both target and distractor processing. As a result, the Schröger paradigm meets the two essential criteria for a satisfactory distraction paradigm set out by Tecce, Savignano-Bowman and Meinbresse (1976). These criteria require that the task (1) provide evidence that the distracting stimuli were cognitively processed, such as an MMN and a P3a; and (2) offer independent behavioural evidence that task-related processes were selectively impaired by the distractor stimuli, such as disruption of reaction times or in hit rates for targets associated with irrelevant distractor stimuli. Unlike passive paradigms such as the one used in Experiment 1, which involved no task or behavioural measures, Schröger's paradigm can link stimulus deviance, pre-attentive ERPs and behaviour together to draw conclusions about the relationships and interactions between pre-attentive processing and the subsequent cost of deviance processing, which is performance impairments.

3.0.5. Distraction-related ERPs and schizophrenia

**MMN ERPs.** As discussed in Experiment 1, diminished MMN amplitudes are a robust feature in schizophrenia (reviewed by Umbricht & Krljes, 2005). The MMN amplitude following presentation of both frequency and duration deviants was attenuated in the patients. The MMN components associated with duration deviants were more diminished than the MMN components associated with frequency deviants. The causes of these MMN impairments remain unclear. One theory claims that these deficits may reflect inaccurate encoding of stimulus features. As a result, the stored memory trace of the standard is imprecise. The detection of stimulus change upon presentation of the deviant would thus be more difficult to make (Javitt et al., 2000a). A second theory claims that the problem occurs later, at the time of the subsequent activation of the frontal-lobe attention-switching mechanism (Baldeweg et al., 2002; Sato et al., 2003). A third theory proposes that the main impairment may be a failure of coordination between different brain regions, for example between the temporal and frontal lobes (Ford et al., 2007; Jacobsen et al., 2004). MMN impairment has been associated with N-methyl-D-aspartate (NMDA) receptor hypofunction.
Nicotine and schizophrenia

(Reviewed by Umbricht & Krljes). Acetylcholine, acting upon the nicotinergic α7 sub-receptor, is an important modulator of NMDA receptor function (Quarta et al., 2007).

P3A ERPs. Although the implications of altered MMNs for attention deficits in schizophrenia has yet to be systematically investigated, the P3a index of attentional switching has received extensive study in this disorder. Many of these studies reported reduced P3a amplitudes in schizophrenic patients (Alain et al., 2002; Devrim-Ucok et al., 2006; Grillon et al., 1990; Grzella et al., 2001; Mathalon et al., 2000; Merrin et al., 1994; van der Stelt et al., 2004). One study found prolonged P3a latencies (Merrin et al.) in these patients. One study (Schall et al., 1999) found greater P3a amplitudes in patients than in controls. Two studies (Kogoj et al., 2005; Michie et al., 2002) showed no P3a amplitude differences between patients and controls. Michie et al. (2002) found that first-degree relatives of patients had greater P3a amplitudes than patients, but that the P3a of both relatives and patients did not differ from the P3a of controls. Reductions of the P3a in schizophrenia were associated with dysfunction of the anterior cingulate (Mathalon et al., 2000; Turetsky et al., 1998), and with prefrontal and medial temporal lobe lesions (Knight et al., 1998).

These numerous findings of reduced P3a amplitudes in schizophrenic patients appear to contradict well-known facts about their abnormal distractibility (Braff, 1993). According to the Schröger-Wolff theories described above, decreased P3a levels in patients should lead to the conclusion that the patients are less distractible than controls since they would be less likely to switch attention toward irrelevant deviant stimuli. This is not the only possible conclusion, however, because the Näätänen model (1990, 1992) specifies that the threshold for the switching of attention may vary across individuals and groups. It is therefore possible that the threshold for the switching of attention is unusually low for schizophrenic patients. Thus, even though they may have attenuated MMN and P3a components, they might be sufficient to cause an attentional switch.

Laurens et al., (2005) used event-related fMRI to elucidate the functional abnormality underlying the reduced P3a they had observed in schizophrenic patients. They found underactivity in several relevant brain areas during novel stimulus processing. In particular, dysfunction within the right amygdala-hippocampal complex and widespread paralimbic
cortex suggested that patients were less engaged by the deviant novel stimuli than controls, and were therefore less able to effectively assess their potential significance for ongoing behaviour. Other neural abnormalities also suggested that patients would have difficulty in extracting the relevance (or rather, the irrelevance) of the deviant stimuli for subsequent behaviour.

**RON ERPs.** A search of the PubMed Internet site did not produce any studies that examined the RON component in schizophrenic patients. However, the fMRI study by Laurens et al. (2005) found dorsal frontoparietal hypoactivity which suggested that these patients experienced particular difficulty in reorienting processing resources when a salient deviant stimulus had interrupted a current task.

### 3.0.6. Distraction-related ERPs, schizophrenia and nicotine

Postmortem studies found decreased levels of α7 nicotinic cholinergic receptors in the brains of schizophrenic patients who had been smokers (Freedman et al., 1995; Guan et al., 1999). This reduction may cause a failure of cholinergic activation of inhibitory interneurons that may affect the filtering of responses to redundant or irrelevant distracting sensory stimulation. Filtering impairments in schizophrenia have been consistently indexed by a midlatency positive ERP component, the P50. The P50 is elicited with a task using successive paired auditory stimuli with very short inter-stimulus intervals (<500 ms). Healthy subjects typically show inhibitory filtering or "gating," manifested in a diminished P50 response to the second stimulus, but schizophrenic patients routinely fail to show a diminished response to the second stimulus (Light & Braff, 1999).

It is well established that nicotine normalizes the P50 gating deficit in schizophrenic patients and relatives of patients (Adler et al., 1993; Adler et al., 1998). More recently, increased inhibition of P50 auditory evoked responses in schizophrenia was evidenced with DMXB-A, a novel partial α7 nAChR agonist (Olincy et al., 2006). In the same series of trials, DMXB-A improved patients' scores on attention/vigilance and working memory and reduced their negative symptoms (Freedman et al., 2008). These findings and other studies described in Experiment 1 provide support to the theory that schizophrenic patients smoke as self-medication to relieve early sensory processing deficits that may mediate the cognitive and clinical symptoms of this disorder (Lasser et al., 2000).
Nicotine and schizophrenia

Recently, Inami et al. (2007) examined nicotine and the MMN in schizophrenia. They used a passive paradigm in which nonsmoking hospitalized schizophrenic patients and healthy control subjects were administered placebo and nicotine transdermally (in separate sessions) and watched a silent movie while they heard tones through earphones. Most of the tones (95%) had a frequency of 1000 Hz while the rest (5%) had a frequency of 1050 Hz. Nicotine had no effect on the MMN amplitudes or latencies of the patients but it shortened the MMN latencies of control participants. Inami et al. concluded that the lack of a similar latency effect in patients may be due to an abnormally low α7 nicotinic receptor function.

Nicotine increased MMN amplitude and decreased MMN latency in Alzheimer patients (Engeland et al., 2002). It has been shown to decrease MMN latencies in healthy volunteers (Inami et al., 2005) and to increase MMN amplitudes in healthy smokers and non-smokers (Harkrider et al., 2005). Nicotine also increased MMN amplitudes in healthy smokers by enhancing a frontal positive ERP to standard stimuli (Baldeweg et al., 2006). Baldeweg et al. concluded that nicotinic agonists might ameliorate the MMN deficits of schizophrenic patients by improving stimulus encoding and sensory memory trace formation.

Few studies have examined the effect of nicotine on the P3a in either healthy people or schizophrenic patients. According to Polich et al.’s (2006) recent review of the neuropsychology and neuropharmacology of the P3a, the neurotransmitter most closely associated with the P3a is dopamine. Many studies confirm that nicotine, like many other addictive substances, stimulates the release of dopamine, thereby causing a hedonic response (Barrett, Boileau, Okker, Pihl, & Daghet, 2004; Brody et al., 2004; Montgomery, Lingford-Hughes, Egerton, Nutt, & Grasby, 2007). Polich et al. found that heavy users of tobacco had larger P3a amplitudes than light users. Moreover, nicotine increased P3a amplitude in healthy subjects. The P3a response of schizophrenic patients to nicotine may differ from that of healthy subjects since schizophrenia is characterized by multiple dysfunctions of the dopamine system (Guillin et al., 2007).

3.0.7. Objectives and hypotheses

The main goal of Experiment 2 is to use a paradigm similar to that of Schröger and Wolff (1998a; 1998b) to examine the effects of nicotine on the behavioural task performance and the pre-attentive MMN, P3a and RON ERP components of schizophrenic smokers.
following the occurrence of potentially distracting events. Because this experiment had not previously been carried out in schizophrenic patients, an initial pilot study was run. In this pilot study, minimally-abstaining (3 hours) healthy and schizophrenic smokers were asked to discriminate between short and long tones while task-irrelevant small and large frequency increments embedded in the same tones acted as distractors. Unfortunately, five of the eight patients that were tested were unable to adequately perform the duration-discrimination task. Following consultation with Dr. Schröger (personal communication, 2005), the task was modified. Rather than asking subjects to discriminate the duration of a tone, they were asked to discriminate its location. The tones were randomly presented to either the left or right ear. At rare and random times, the frequency of the tone was changed; this change was irrelevant to the location-discrimination task.

Experiment 2 had two specific objectives. The first was to compare schizophrenic and control smokers with respect to the pre-attentive detection of task-embedded potentially distracting auditory frequency-deviant stimuli and the possible consequent involuntary switching of attention. This was examined by both performance (behavioural) and electrophysiological measures. Performance was assessed by two measures: RT and correct responses ("hit" rates). Distraction occurred if RTs were prolonged or hit rates were decreased following presentation of the deviant relative to the standard. Distraction was also measured electrophysiologically by examining the deviant-elicited MMN and possible P3a and RON components. The second objective was to examine the effects of nicotine on the behavioural performance and the MMN, P3a and RON components of schizophrenic smokers. The N1 ERP to standard stimuli was also evaluated to determine whether any group differences or nicotine effects were related to early encoding of sensory features. The extent of deviance was also manipulated by presenting small and large frequency deviants. Given previous research findings, it was predicted that rare deviant sounds would impair behavioural performance, as evidenced by slower reaction times and reduced hit rates, with greater impairment to larger (vs. smaller) deviants. Greater performance impairments were predicted in patients than in controls. It was also predicted that rare deviant sounds would elicit attenuated MMN, P3a and RON components in patients (vs. controls). Finally, it was predicted that nicotine (vs. placebo) would increase the MMN of patients and improve their behavioural performance, but that nicotine would not increase and may decrease distraction
as indexed by the P3a and consequent RON. As an additional objective, the experiment examined the relationships between patients' clinical symptoms, including smoking withdrawal symptoms, and ERP and behavioural indices, and between patients' medication and ERP and behavioural indices.

3.1. Method

3.1.1 Participants

Twelve male controls and 11 male outpatients from the Experiment 1 participant pool took part in Experiment 2. The inclusion/exclusion criteria, symptoms ratings by treating psychiatrists and the auditory screening were the same as in Experiment 1. To ensure that controls and patients were matched on intelligence and smoking-related factors, they completed the North American Reading Test (NART; Blair et al., 1989; see Appendix A), which is an approximate measure of intelligence, the 8-item 15-point Modified Fagerstrom Test for Nicotine Dependence (FTND: Heatherton et al., 1991; see Appendix B), and the Modified Reasons for Smoking Scale (MRSS; Berlin et al., 2003; see Appendix C). All subjects received an honorarium for their participation.

3.1.2 General procedure

Testing took place between 12:00 and 17:00 at the Clinical Neuroelectrophysiology and Cognitive Research Laboratory of the Royal Ottawa Mental Health Centre. All participants were instructed to abstain overnight from alcohol, caffeine and any drug other than the patients' medication, and were requested to refrain from smoking for three hours before the tests. Control participants were required to attend one test session lasting approximately 2.5 hours while patients were required to perform the same tests twice, in two separate sessions lasting approximately 3-3.5 hours each. Patients' sessions were longer because they involved a nicotine-or-placebo administration procedure. Upon their first arrival at the lab, adequacy of all participants' hearing levels was tested at 750 Hz, 1000 Hz and 1500 Hz, using a descending method-of-limits procedure, before EEG recording commenced. All thresholds were at or below 20 dB (SPL). Participants were then questioned about their abstinence from smoking, alcohol and drugs. Carbon monoxide (CO) levels were also assessed by means of an instrument measuring their expired-breath CO level.
Nicotine and schizophrenia (Vitalograph Breath CO instrument, Vitalograph Inc., Lenexa, Kansas). Participants were then taken in a sound-attenuated, electrically-shielded recording chamber and sat in a comfortable chair while electrodes were applied. During this application, patients were administered nicotine or a placebo (see nicotine procedure below). The drug conditions were not administered to the controls. Following electrode placement and nicotine or placebo absorption (in patients), electrophysiological data were acquired over a 30-40 minute interval which allowed for several 2-3 minute breaks. Frequent rest periods were required to maintain patient co-operation. At the end of the recordings, participants completed the Tobacco Withdrawal Symptom Checklist (TWSC; Hughes et al., 1986; see Appendix D and description below).

3.1.3 Nicotine and placebo administration

Nicotine was administered within a randomized, double-blind, placebo-controlled, cross-over design with half of the patients receiving nicotine in the first session and placebo in the second session, and the remaining half receiving nicotine and placebo in the reverse order. Nicotine was administered orally as two 4-mg pieces of Nicorette Plus polacrilex gum (Hoechst Roussel). The placebo gum (containing no nicotine) was a commercial gum similar in size, shape and texture. To reduce any perceptual and sensory differences between the placebo and nicotine gums, patients wore a blindfold while putting the gum pieces in their mouths. Also, a drop of mint oil was placed on each gum and participants wore nose plugs throughout the chewing period. During that period, which lasted 25 minutes as specified by the Nicorette Plus guidelines, patients heard a taped voice every minute asking them to chew ("bite twice"). After each bite, they "parked" the gum between their teeth and gums. After the chewing period, the gum was discarded and patients were given a strong commercial mint gum to chew for five minutes to help disguise any placebo-nicotine difference.

Cigarette smoking yields a rapid delivery of nicotine to the bloodstream, resulting in sharp peaks in blood nicotine concentration. The peak of plasma nicotine concentration achieved within ten minutes of smoking an average-nicotine-yield cigarette is approximately 35 nanograms per milliliter, followed by a trough at 15 nanograms per milliliter within 30 minutes (Russell, 1988). After chewing one piece of 4-mg nicotine gum for 30 minutes, blood concentration reaches a peak of about 18 nanograms per milliliter of nicotine (Russell...
et al., 1980). Chewing two pieces of 4-mg nicotine gum results in peak blood levels of about 36 nanograms per milliliter within 30 minutes after the initiation of chewing, which approximates the effect achieved ten minutes after smoking a cigarette. The elimination half-life of nicotine is approximately 120 minutes (Benowitz et al., 1982; Feyerabend et al., 1985).

3.1.4 Stimulus paradigm

Participants were asked to discriminate between tones of 80 dB (SPL) presented through headphones to their left or right ear with equal probability for each type of tone. They were instructed to respond as quickly and as accurately as possible with a right mouse button press when the sound was in their right ear and a left button press when the sound was in their left ear. The tones (5 ms rise/fall) lasted 100 ms and varied in frequency: 80% had a frequency of 700 Hz (standards), 10% a frequency of 750 Hz (small deviant), and 10% a frequency of 1200 Hz (large deviant). A stimulus was presented every 1300 ms. The tones were presented in one practice block and four testing blocks, with 2-3 minute breaks between the blocks. The practice block had 96 standards, 12 small deviants and 12 large deviants. It was repeated until a participant obtained 60% correct responses. If a participant was unable to reach that level of proficiency after three practice runs, the test was terminated. Each of the four testing blocks had 200 standards, 26 small deviants and 26 large deviants, for a total of 800 standards, 104 small deviants and 104 large deviants. Within each block, standard and deviant stimuli were presented in a random order with the exception that no two deviant tones could occur in sequence. At random, half of the stimuli were presented to the left ear and half to the right ear. Participants were instructed to keep their eyes open and focused on a fixation point located approximately five feet in front of them.

3.1.5 EEG recording and measures

ERPs were recorded with tin electrodes placed on midline frontal (Fz), central (Cz) and parietal (Pz) scalp positions according to the international 10-20 system (Jasper et al., 1958; Cooper et al., 1969). Scalp electrical activity was recorded in a monopolar manner, the reference being to linked earlobes. Two additional electrodes, one on the left supra-orbital ridge and one on the external canthus of the left eye, recorded electro-oculographic (EOG)
activity in one channel, with a mid-forehead electrode serving as ground. Electrode impedances were kept below 5 kOhms. The EEG and EOG signals were recorded continuously with an analog-to-digital sampling rate of 256 Hz, using amplifier bandpass filters set at 0.1-30.0 Hz. Digital data were stored on hard disk for off-line ERP processing and analysis. Off-line, the continuous EEG signals were reconstructed into 950 ms epochs (or "trials"), beginning 50 ms prior to stimulus onset. Eye movements and blink artifact were removed from the EEG signals using an algorithm operating in the time and frequency domains (Woestenburg et al., 1983). Ocular-corrected trials with amplitudes exceeding +/-100 μV were excluded from further analyses. For each participant and drug condition, trials were averaged separately for correctly-detected standard, small-deviant and large-deviant stimuli and sorted according to scalp recording site. A minimum of 65 artifact-free correctly-detected deviant stimulus trials was required to retain a participant's ERP averages in the final analysis.

Amplitudes and latencies of the ERP components were based on latency windows taken from grand-average waveforms. All ERP amplitudes were measured relative to the average of all data points in the pre-stimulus baseline. N1 latency to standard stimuli was defined at Fz (where it was largest) as the latency corresponding to the maximum peak negativity occurring within the 50-150 ms latency range. N1 amplitude was defined as the average of the amplitude points (relative to the average pre-stimulus voltage) within a 50 ms window around each individual's peak negativity, i.e. 25 ms pre-peak and 25 ms post-peak. The MMN was measured in the difference wave, calculated by subtracting point-by-point the ERP to the standard from that of the deviant. The difference wave removes processing that is common to both the standard and the deviant, leaving only the difference in processing (for example, the MMN). MMN latency was defined at Fz as the latency corresponding to the peak negativity occurring during the 80-220 ms latency range, and MMN amplitude was defined as the average of the amplitude points within a 50 ms window around each individual's peak negativity. P3a and RON amplitudes and latencies were derived from difference waveforms in the same manner as MMN amplitudes and latencies, but for the P3a, latency was defined as the latency corresponding to the peak positivity occurring within the 200-400 ms latency range at Cz, and for the RON, latency was defined as the latency corresponding to the peak negativity occurring within the 450-600 latency range at Fz.
3.1.6 Behavioural measures

Trials with a correct button press to stimuli 100 to 900 ms relative after stimulus onset were considered to be hits. Reaction times (ms) and hit rates (%) were determined separately for standard tones, small-deviant tones and large-deviant tones for control participants and for patients in the placebo and nicotine conditions. Missed responses were not analyzed as they were minimal in number and were not different between groups or between stimuli or drug conditions.

3.1.7 Smoking withdrawal ratings

Smoking withdrawal symptoms were assessed at the end of each session with the TWSC to determine whether alterations in behaviour and in ERPs by nicotine were related to withdrawal relief. The items of the self-report TWSC questionnaire, which are derived from the DSM-IV list of withdrawal symptoms (American Psychiatric Association, 1994), are irritability, frustration or anger, difficulty concentrating, restlessness, anxiety or nervousness, hunger, depressed mood, and desire to smoke. For each item, participants were asked to choose on a four-point scale (0=not present, 1=mild, 2=moderate, 3=severe) the answer that best described how they felt. Scores for each symptom rating were summed to form a single TWSC index.

3.1.8 Analysis

Statistical analyses were performed using SPSS (Statistical Package for Social Sciences, 15th Edition). Analyses of variance (ANOVAs) were run on behavioural measures (reaction times and hit rates) and on ERP amplitudes and latencies (N1, MMN, P3a and RON). Separate mixed-design ANOVAs compared the behavioural measures and ERPs of controls with those of patients in the placebo condition, and the behavioural measures and ERPs of controls with those of patients in the nicotine condition, using one between-subjects factor with two levels (group: controls vs. patients) and one within-subjects factor with three levels for the behavioural measures (type of deviant: standard vs. small-deviant vs. large-deviant) and with two levels for the MMN, P3a and RON (type of deviant: small-deviant vs. large-deviant). Repeated-measures ANOVAs compared the behavioural measures and ERPs of patients in the placebo condition with those of patients in the nicotine condition, using two within-subjects factors (condition: placebo vs. nicotine; type of deviant: small-deviant vs. large-deviant).
Greenhouse-Geisser corrections were applied when appropriate to compensate for sphericity (equal covariance) violations. Since all the effects were the subject of specific a priori hypotheses based on previous research findings, a .05 level of significance was used in all analyses.

Confidence intervals of the means were examined to determine whether MMN, P3a and RON mean amplitudes were significantly different from the zero baseline. T-tests were used to determine whether control and patient participants differed on personal characteristics including age, education, BMI, number of cigarettes smoked per day, breath CO level, scores on the NART, FTND, and MRSS; whether the TWSC scores of patients with placebo differed from those of controls and patients with nicotine; and to compare the numbers of EEG trials analysed for each group, condition and paradigm. Pearson Product Moment Correlation or non-parametric equivalents were used to assess the relationships between behavioural and ERP measures and PANSS scores, TWSC ratings and patients' medication.

3.2 Results
3.2.1 Participant Characteristics

Demographic and clinical characteristics of participants are in Table 12, as well as results of independent-samples t-tests comparing patients and controls. No significant differences were found between control and patient participants for any personal characteristic, including age, schooling, body-mass index, number of cigarettes per day, CO levels, intelligence (excluding three patients whose English was poor), degree of nicotine dependence or reasons for smoking. Scores on the FTND (12 for patients and 11 for controls) indicated that both groups were heavily dependent on nicotine (7 points or more = heavy dependence). Controls and patients did not differ with respect to tobacco withdrawal symptoms, nor was there any difference in withdrawal symptoms between patients in the placebo condition (\(M=7.45; \text{SE}=1.4\)) and patients in the nicotine condition (\(M=9.55; \text{SE}=1.5\)) \([t(10)=1.12, \ p<.29]\).
Table 12. Means (SE) of Characteristics of Patients and Control Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n=11)</th>
<th>Controls (n=12)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>42 (2.6)</td>
<td>42 (2.5)</td>
<td>-0.12</td>
<td>.91</td>
</tr>
<tr>
<td>Years of schooling</td>
<td>12 (0.3)</td>
<td>13 (0.2)</td>
<td>-0.47</td>
<td>.64</td>
</tr>
<tr>
<td>BMI</td>
<td>26 (1.5)</td>
<td>24 (0.9)</td>
<td>0.82</td>
<td>.42</td>
</tr>
<tr>
<td>Cigarettes per day</td>
<td>26 (3.1)</td>
<td>23 (1.3)</td>
<td>1.12</td>
<td>.28</td>
</tr>
<tr>
<td>CO level</td>
<td>17 (1.4)</td>
<td>18 (1.9)</td>
<td>-0.28</td>
<td>.79</td>
</tr>
<tr>
<td>NART *</td>
<td>106 (1.8)</td>
<td>112 (2.2)</td>
<td>-1.89</td>
<td>.08</td>
</tr>
<tr>
<td>TWSC</td>
<td>8 (1.1)**</td>
<td>8 (0.9)</td>
<td>0.32</td>
<td>.75</td>
</tr>
<tr>
<td>FTND</td>
<td>12 (0.7)</td>
<td>11 (0.7)</td>
<td>0.81</td>
<td>.43</td>
</tr>
<tr>
<td>MRSS-addiction</td>
<td>6 (0.7)</td>
<td>5 (0.6)</td>
<td>0.15</td>
<td>.89</td>
</tr>
<tr>
<td>MRSS-pleasure</td>
<td>9 (0.7)</td>
<td>8 (0.5)</td>
<td>1.40</td>
<td>.18</td>
</tr>
<tr>
<td>MRSS-relaxation</td>
<td>7 (1.0)</td>
<td>7 (0.8)</td>
<td>-0.07</td>
<td>.94</td>
</tr>
<tr>
<td>MRSS-social</td>
<td>4 (0.5)</td>
<td>3 (0.4)</td>
<td>1.12</td>
<td>.27</td>
</tr>
<tr>
<td>MRSS-stimulation</td>
<td>5 (1.0)</td>
<td>5 (0.5)</td>
<td>-0.24</td>
<td>.82</td>
</tr>
<tr>
<td>MRSS-habit</td>
<td>3 (0.7)</td>
<td>4 (0.7)</td>
<td>-0.88</td>
<td>.39</td>
</tr>
<tr>
<td>MRSS-sensorimotor</td>
<td>4 (0.8)</td>
<td>6 (0.8)</td>
<td>-1.59</td>
<td>.13</td>
</tr>
<tr>
<td>PANSS (positive)</td>
<td>15 (1.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS (negative)</td>
<td>14 (1.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS (general pathology)</td>
<td>25 (2.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine daily</td>
<td></td>
<td>114 (47.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Three patients were excluded because of their poor knowledge of English.
** The TWSC score for patients is an average of the scores for their two sessions.

PANSS scores for the patients averaged 54 (15 + 14 + 25) and ranged from 34 to 77. According to a recent study (Leuchet et al., 2005) that translated PANSS scores into ratings on the Clinical Global Impressions Scale (CGI; Guy, 1976), which is used by psychiatrists to obtain a global picture of patients' overall clinical state, the CGI ratings of this study's patient participants were roughly as follows: none at score 1 = normal, not at all ill; 1 at score 2 = borderline mentally ill; 5 at score 3 = mildly ill; 4 at score 4 = moderately ill; 1 at score 5 = markedly ill; none at score 6 = severely ill; and none at score 7 = extremely ill.
3.2.2 Behavioural performance

Means and standard errors for behavioural performance measures are shown in Table 13. There were no significant differences in RTs between controls, patients with placebo and patients with nicotine. However, significant main effects of type of deviant were found in the analyses of controls and patients with placebo \([F(1,21)=9.53, p<.001, \eta^2=.31]\), controls and patients with nicotine \([F(1,21)=8.07, p<.001, \eta^2=.28]\), and patients in the placebo and nicotine conditions \([F(1,21)=4.77, p<.03, \eta^2=.32]\). Planned follow-up analyses revealed that all groups and conditions had significantly prolonged RTs to large-deviant stimuli than to standard stimuli (controls: \(p<.003\); placebo: \(p<.007\); nicotine: \(p<.049\)). There was no significant difference between reaction times to small-deviant and standard stimuli.

Controls had significantly higher hit rates than patients with placebo \([F(1,21)=6.29, p<.02, \eta^2=.23]\) and patients with nicotine \([F(1,21)=4.57, p<.04, \eta^2=.18]\). The proportion of misses did not increase following presentation of either the small or large deviant stimuli \([F(1,21)=0.98, p<.37\) for controls vs. patients-placebo]. There were no differences in hit rates between patients in the placebo and nicotine conditions.

Table 13. Mean RTs and Hit Rates to Standard Stimulus and to Small-Deviant and Large-Deviant Stimuli

<table>
<thead>
<tr>
<th></th>
<th>RT (SE) ms</th>
<th>Hits (SE) %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Controls (n=12)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>standard stimulus</td>
<td>382(15.1)</td>
<td>94(1.0)</td>
</tr>
<tr>
<td>small-deviant stimulus</td>
<td>388(15.2)</td>
<td>95(1.0)</td>
</tr>
<tr>
<td>large-deviant stimulus</td>
<td>402(16.5)</td>
<td>95(1.2)</td>
</tr>
<tr>
<td><strong>Patients with Placebo (n=11)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>standard stimulus</td>
<td>398(26.7)</td>
<td>86(3.1)</td>
</tr>
<tr>
<td>small-deviant stimulus</td>
<td>402(26.7)</td>
<td>87(2.8)</td>
</tr>
<tr>
<td>large-deviant stimulus</td>
<td>410(25.0)</td>
<td>88(3.1)</td>
</tr>
<tr>
<td><strong>Patients with Nicotine (n=11)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>standard stimulus</td>
<td>390(21.5)</td>
<td>84(5.3)</td>
</tr>
<tr>
<td>small-deviant stimulus</td>
<td>393(22.5)</td>
<td>85(4.7)</td>
</tr>
<tr>
<td>large-deviant stimulus</td>
<td>407(21.1)</td>
<td>82(6.3)</td>
</tr>
</tbody>
</table>
3.2.3 EEG Results – General

Table 14 displays the number of EEG trials averaged for standard and deviant stimuli included in the analyses for each group and condition. Control participants had more trials than patients for all three stimuli, but the only difference that reached statistical significance was between controls and patients in the nicotine condition for small-deviant stimuli \([t(21) = -2.22, p < .048]\).

### Table 14. Mean (SE) Trials per Average ERP to Standard and Deviant Stimuli

<table>
<thead>
<tr>
<th></th>
<th>Standard stimuli</th>
<th>Small-deviant stimuli</th>
<th>Large-deviant stimuli</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (n=12)</td>
<td>750(11.4)</td>
<td>99(1.4)</td>
<td>97(2.0)</td>
</tr>
<tr>
<td>Patients placebo (n=11)</td>
<td>712(41.7)</td>
<td>93(6.0)</td>
<td>94(5.8)</td>
</tr>
<tr>
<td>Patients nicotine (n=11)</td>
<td>676(49.2)</td>
<td>84(6.3)</td>
<td>87(6.6)</td>
</tr>
</tbody>
</table>

Grand-averaged raw waveforms are shown in Figure 7. It illustrates the waveforms elicited by standard, small-deviant and large-deviant stimuli in control participants, patients in the placebo condition and patients in the nicotine condition. Grand-averaged difference waveforms for small-deviant and large-deviant stimuli are presented in Figure 8. Raw ERPs are usually larger than those observed in the difference wave. As a result, the vertical amplitude scale is 2.5 μV for the raw ERPs (Figure 7) while for the difference waves (Figure 8), the same scale reflects a deflection of only 0.66 μV.

3.2.4 N1 event-related potentials to standard stimuli

Means and standard error values for N1 ERPs to standard stimuli at Fz are provided in Table 15. There were no significant differences in N1 amplitudes or N1 latencies to standard stimuli between control participants, patients in the placebo condition and patients in the nicotine condition.
Figure 7. Grand-Averaged Raw Waveforms to Standard and Deviant Stimuli

- Standard
- Small Deviant
- Large deviant

Controls
Patients-Placebo
Patients-Nicotine

Figure 8. Difference (Deviant Minus Standard) Waveforms for Small-Deviant and Large-Deviant Stimuli

-0.66 pV
-100ms
900ms

-3.86 pV
-100ms
900ms

Nicotine and schizophrenia
Table 15. Mean (SE) N1 Amplitudes and Latencies at Fz to Standard Stimuli

<table>
<thead>
<tr>
<th></th>
<th>Amplitude (μV)</th>
<th>Latency (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (n=12)</td>
<td>-2.47(0.3)</td>
<td>94.66(2.5)</td>
</tr>
<tr>
<td>Patients with Placebo (n=11)</td>
<td>-2.07(0.2)</td>
<td>96.02(2.7)</td>
</tr>
<tr>
<td>Patients with Nicotine (n=11)</td>
<td>-1.90(0.2)</td>
<td>95.67(2.5)</td>
</tr>
</tbody>
</table>

3.2.5 MMN event-related potentials

Table 16 shows means and standard errors of MMN amplitudes and latencies at Fz from difference waveforms to small-deviant and large-deviant stimuli. The asterisks in the table indicate whether the MMN amplitudes were significantly different from the zero baseline. All MMN amplitudes were significantly different from zero except those of patients with placebo to small-deviant stimuli.

Table 16. Mean (SE) MMN Amplitudes and Latencies at Fz to Small- and Large-Deviant Stimuli, with Significance of MMN Amplitudes Compared with Zero Baseline

<table>
<thead>
<tr>
<th></th>
<th>MMN Amplitude</th>
<th>MMN Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Small Deviants</td>
<td>Large Deviants</td>
</tr>
<tr>
<td></td>
<td>μV</td>
<td>μV</td>
</tr>
<tr>
<td></td>
<td>ms</td>
<td>ms</td>
</tr>
<tr>
<td>Controls (n=12)</td>
<td>-0.62(0.2)**</td>
<td>-0.71(0.2)**</td>
</tr>
<tr>
<td>Patients with Placebo (n=11)</td>
<td>-0.28(0.2)</td>
<td>-0.64(0.2)**</td>
</tr>
<tr>
<td>Patients with Nicotine (n=11)</td>
<td>-0.32(0.1)*</td>
<td>-0.67(0.3)*</td>
</tr>
</tbody>
</table>

* p < .05; ** p < .01
ANOVAs failed to find differences between the MMN amplitudes of controls, patients with placebo and patients with nicotine. Only one significant type-of-deviant main effect was found, in the analysis of patients in the placebo and the nicotine conditions \( F(1,10)=5.35, p<.04, \eta^2=.35 \). Planned follow-up analyses of this type-of-deviant effect indicated that the MMN of patients with placebo \( F(1,10)=5.88, p<.036, \eta^2=.37 \) was larger following presentation of the large deviant than following presentation of the small deviant.

MMN latencies did not differ significantly between controls, patients with placebo and patients with nicotine. Only one significant type-of-deviant main effect was found, in the analysis of controls and patients with placebo \( F(1,21)=10.94, p<.003, \eta^2=.34 \). Planned follow-up analyses of this type-of-deviant effect indicated that the MMN latencies of control participants \( F(1,21)=11.85, p<.002 = \eta^2=.34 \) were shorter following presentation of the large deviant than following presentation of the small deviant.

### 3.2.6 P3a event-related potentials

Means and standard error values for P3a amplitudes and latencies are presented in Table 17. The asterisks in the table indicate whether the P3a amplitudes were significantly different from the zero baseline. In spite of the large differences in P3a amplitudes visible in Figure 8, none of these amplitudes were significantly greater than zero, and none of the ANOVA results were significant.

This discrepancy led to a closer examination of the data that revealed important outliers in the P3a amplitudes of one control participant (z score > 2.5). New analyses were performed after replacing these outlying P3a values with the mean P3a values for the other control participants (see corrected data in Table 17). New examinations of the confidence intervals of the means revealed a significant P3a component in controls to large-deviant stimuli. New ANOVAs found that controls had significantly larger P3a amplitudes to large deviants than patients with placebo \( F(1,21)=6.5, p<.02, \eta^2=.24 \) and patients with nicotine \( F(1,21)=6.71, p<.02, \eta^2=.24 \).
Table 17. Mean (SE) P3a Amplitudes and Latencies at Cz to Small-Deviant and Large-Deviant Stimuli, with Significance of P3a Amplitudes Compared with Zero Baseline

<table>
<thead>
<tr>
<th></th>
<th>P3a Amplitude</th>
<th>P3a Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Small Deviants</td>
<td>Large Deviants</td>
</tr>
<tr>
<td></td>
<td>μV</td>
<td>μV</td>
</tr>
<tr>
<td>Controls (n=12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>. original data</td>
<td>0.07(0.2)</td>
<td>0.69(0.4)</td>
</tr>
<tr>
<td>. outlier-corrected</td>
<td>0.23(0.1)</td>
<td>0.93(0.3)**</td>
</tr>
<tr>
<td>Patients with Placebo (n=11)</td>
<td>0.06(0.2)</td>
<td>0.16(0.2)</td>
</tr>
<tr>
<td>Patients with Nicotine (n=11)</td>
<td>0.10(0.2)</td>
<td>0.15(0.2)</td>
</tr>
</tbody>
</table>

**p < .01

Planned follow-up analyses of these P3a amplitude group effects specified that controls had significantly larger P3a amplitudes to large-deviant stimuli than patients with placebo [F(1,21)=6.36, p<.02, r^2=.23] and patients with nicotine [F(1,21)=7.0, p<.02, r^2=.25], but that their P3a amplitudes to small-deviant stimuli were not different. Main effects for type of deviant were found in analyses of controls and patients with placebo [F(1,21)=4.75, p<.04, r^2=.19] and controls and patients with nicotine [F(1,21)=4.15, p<.055, r^2=.17]. Planned follow-up analyses of these type-of-deviant effects revealed that controls had larger P3a amplitudes following presentation of the large deviant than following presentation of the small deviant [F(1,21)=7.66, p<.01, r^2=.27].

Analyses of P3a latencies found significant main effects for type of deviant in the analyses of controls and patients with nicotine [F(1,21)=4.43, p<.04, r^2=.17], and patients in both conditions [F(1,10)=6.23, p<.03, r^2=.38]. Planned follow-up analyses of these type-of-deviant effects revealed that patients in the nicotine condition had shorter P3a latencies following presentation of the large deviant than following presentation of the small deviant [F(1,10)= 8.69, p<.015, r^2=.47].
3.2.7 RON event-related potentials

Table 18 shows means and standard errors of RON amplitudes and latencies at Fz from difference waveforms to small and large deviant stimuli. The asterisks indicate whether the RON amplitudes were significantly different from the zero baseline. Only RON components to large deviants in patients with nicotine were significant. ANOVAs of RON amplitudes found no significant effects.

ANOVAs of RON latencies found main effects for type of deviant in the analyses of controls and patients with placebo \([F(1,21)=7.66, p<.00, n^2=.50]\), of controls and patients with nicotine \([F(1,21)=17.59, p<.00, n^2=.46]\), and of the two patient conditions \([F(1,10)=5.89, p<.04, n^2=.37]\). Planned follow-up analyses of these type-of-deviant effects revealed that RON latencies were shorter following presentation of the large deviant than following presentation of the small deviant in controls \([F(1,21)=15.17, p<.00, n^2=.42]\), in patients with placebo \([F(1,21)=5.88, p<.04, n^2=.37]\), and in patients with nicotine \([F(1,21)=4.31, p<.05, n^2=.17]\).

Table 18. Mean (SE) RON Amplitudes and Latencies at Fz to Small- and Large-Deviant Stimuli, with Significance of RON Amplitudes Compared with Zero Baseline

<table>
<thead>
<tr>
<th></th>
<th>RON Amplitude</th>
<th>RON Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Small Deviants</td>
<td>Large Deviants</td>
</tr>
<tr>
<td></td>
<td>µV</td>
<td>µV</td>
</tr>
<tr>
<td>Controls (n=12)</td>
<td>-0.11(0.2)</td>
<td>-0.07(0.1)</td>
</tr>
<tr>
<td>Patients with Placebo (n=12)</td>
<td>-0.08(0.2)</td>
<td>-0.05(0.3)</td>
</tr>
<tr>
<td>Patients with Nicotine (n=12)</td>
<td>-0.20(0.3)</td>
<td>-0.51(0.2)*</td>
</tr>
</tbody>
</table>

* \(p < .05\)
3.2.8 Correlations

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

3.2.8.1. MMN, P3a, PANSS and TWSC ratings of patients

Smaller MMN amplitudes to large-deviant stimuli in patients with nicotine were associated with having more hallucinations \( r = -0.53, p < 0.04 \). Larger P3a amplitudes of patients with placebo to large-deviant stimuli were associated with higher scores on the negative-symptoms subscale of the PANSS \( r = 0.78, p < 0.005 \). There were no significant correlations between nicotine-induced "change" scores for MMN amplitudes (i.e. nicotine MMN value minus placebo MMN value) and nicotine-induced "change" ratings for the TWSC (i.e. ratings for nicotine minus ratings for placebo).

3.2.8.2. Reaction time, accuracy results and ERPs

Smaller MMN amplitudes to large-deviant stimuli of patients with placebo were associated with longer reaction times to standard \( r = -0.62, p < 0.04 \), small-deviant \( r = -0.63, p < 0.04 \) and large-deviant stimuli \( r = -0.62, p < 0.04 \). Smaller RON amplitudes of controls to small deviants were associated with longer reaction times to standard stimuli \( r = -0.60, p < 0.04 \) and to small-deviant stimuli \( r = -0.58, p < 0.05 \). Larger RON amplitudes of controls to small-deviant stimuli were associated with higher hit rates to standard \( r = 0.84, p < 0.001 \), small-deviant \( r = 0.82, p < 0.001 \) and large-deviant stimuli \( r = 0.68, p < 0.02 \). Larger RON amplitudes of patients with placebo to small deviants were associated with higher rates hit rates to standard stimuli \( r = 0.61, p < 0.046 \). Larger RON amplitudes in patients with placebo to large deviants were associated with higher hit rates to standard \( r = 0.75, p < 0.01 \), small-deviant \( r = 0.64, p < 0.03 \) and large-deviant stimuli \( r = 0.69, p < 0.02 \).

3.2.8.3. Correlations between ERPs, patients' medication and behavioural results

In patients in the placebo condition, larger MMN amplitudes to small deviants were associated with larger P3a amplitudes to small deviants \( r = 0.77, p < 0.006 \). In patients who took placebo, P3a amplitudes to small deviants were negatively correlated with P3a latencies to small deviants \( r = -0.68, p < 0.02 \), and P3a amplitudes to large deviants were positively correlated with P3a latencies to large deviants \( r = 0.65, p < 0.03 \). Patients' doses of antipsychotic
medication (measured in chlorpromazine equivalents; Bezchlibnyk-Butler & Jeffries, 2006) were not correlated with their ERPs (MMN, P3a and RON amplitudes and latencies), behavioural results (hits, reaction times) or PANSS scores.

3.3.0 Discussion

This experiment evaluated the hypothesis that task-irrelevant frequency deviants would produce behavioural and electrophysiological evidence of abnormal detection of stimulus change and subsequent inappropriate switching of attention, resulting in distraction. It was further hypothesized that these behavioural and electrophysiological indicators of distraction would be different in schizophrenic patients and controls and that acute nicotine administration might alter this processing. The conventional Schröger and Wolff (1998b) tone-duration discrimination paradigm was found to be too difficult for the schizophrenic sample. Most patients were making errors on as many as 40% of trials, compared with less than 5% for healthy participants. For this reason, the Schröger and Wolff paradigm was altered. Subjects were asked to detect the ear of delivery of the tones, rather than their duration.

Both patients and controls were able to perform this location-discrimination task but controls had a higher rate of correct detection (around 95%) than the patients (around 87%). This is consistent with previous findings that schizophrenic patients exhibit deficits in identifying sound location. A comparison of the behavioural and ERP results obtained with this location-discrimination paradigm and with the usual Schröger and Wolff duration-discrimination paradigm showed that the location-discrimination paradigm produced much weaker effects than the Schröger and Wolff paradigm. Two possible reasons are suggested to explain this. One is that the presentation of half of the standard stimuli in each ear, instead of all of them in the same ear or in both ears simultaneously, interfered with the formation of a strong memory trace for the standard stimulus. Second is that spatial selection is a very powerful form of selective attention that may be highly resistant to distraction effects.

Nevertheless, reaction times in this experiment following the presentation of unattended large-deviant frequency changes were significantly prolonged in both patients (12 ms) and controls (20 ms), indicating that these deviants had caused some performance deterioration in both groups. Detection rates were not affected by frequency deviance. MMN
amplitudes and latencies of patients and controls did not differ significantly, suggesting that the patients' MMN were not attenuated. This is not an unusual finding since the MMN to frequency deviants of schizophrenic patients was not always diminished in previous studies. The lack of MMN difference could also be due to low statistical power. Patients' MMN to the small deviant was smaller than their MMN to the large deviant. Controls did not exhibit a larger MMN to the large deviant than to the small deviant, but they had shorter MMN latencies to the large deviant than to the small one. The finding of a deviance effect on the MMN in patients but not in controls is surprising because the MMN of patients is usually less sensitive to stimulus change than the MMN of controls. The main reason for the MMN deviance effect in patients is that their MMN amplitude to the small deviant is diminished to the point of being non-significant. A possible cause of this attenuation is the diminished attentional resources of the patients. This is discussed in greater detail below.

Patients had diminished P3a amplitudes to large deviants compared with controls, and neither patients nor controls had significant RONs. The fact that patients had a significant prolongation in reaction time to the large deviant without having a corresponding significant P3a to reflect a switch in attention suggests that Näätänen's model of auditory processing may not apply to schizophrenic patients. However, Näätänen suggested that the threshold for switching attention may vary across individuals and groups. Perhaps this threshold is very low for schizophrenic patients, so that very small changes are sufficient to switch their attention.

Nicotine increased the MMN of patients to small deviants. As a result, patients' MMN to small deviants were no longer different from their MMN to large deviants. Nicotine may have achieved this effect by enhancing the attentional resources allocated to the detection of small stimulus changes. Nicotine had no effect on patients' P3a components but it produced the only significant RON component in this experiment. The fact that only patients in the nicotine condition had a significant RON component (to the large deviant) suggests that patients' reduced attentional capacities require them to exert more top-down effort than controls to return to the task. Nicotine appears to enable this process. All the effects described above were independent of early sensory encoding, as N1 amplitudes and latencies to standard stimuli were similar in patients and controls and were not affected by nicotine.
administration. The nicotine effect appears to reflect an effect of nicotine itself since it was not related to smoking withdrawal intensity or to nicotine-induced withdrawal relief.

3.3.1 Results for healthy subjects in this study vs. results in study by Schröger & Wolff

Part of the objectives of this experiment was to use a paradigm similar to that of Schröger and Wolff's (1998b) because that paradigm had proved successful in obtaining evidence of behavioural distraction and deviance-related ERPs with relatively small deviant stimuli. Since it was not possible to use the same paradigm because of schizophrenic patients' difficulties with the Schröger-Wolff (henceforth referred to as "S-W" in this section) duration-discrimination task, an easier location-discrimination task was substituted following consultation with Dr. Schröger (personal communication, 2005). In spite of this change in paradigm, it was expected that the location-discrimination paradigm would produce similar results to those of the S-W paradigm in healthy participants since they used almost identical task-irrelevant frequency deviants that were embedded in task-relevant tones (small deviant: 7% difference between standards and deviants of 700 and 750 Hz; large deviant: 71% difference between standards and deviants of 700 and 1200 Hz). On the other hand, there were some differences between the deviants in the two paradigms. In this study, standard tones always had a frequency of 700 Hz and a presentation probability of .80, and deviant tones had a probability of .10 each. In the S-W paradigm, probability was .90 for standards and .10 for each deviant (only one deviant was presented in each trial). Also, only the S-W paradigm reversed the role of the standard and deviant frequencies half-way through the trials, so that each frequency was the standard and each was the deviant in half of the trials.

To compare the efficiency of the two paradigms in producing behavioural distraction and deviance-related ERPs, their respective results for healthy participants are presented in Table 19. These results suggest that the S-W duration-discrimination paradigm was much more successful at obtaining both behavioural and ERP effects than this study's location-discrimination paradigm. The S-W results show significantly reduced hit rates (4% for small deviants and 6% for large) following the presentation of both small and large frequency deviants; this study found no change at all in hit rates following either deviant. Both studies found prolongations in RTs following the presentation of deviants, but the prolongations were much longer in the S-W experiment.
Table 19. Results for Healthy Participants, this Study and Schröger and Wolff's (1998b)

<table>
<thead>
<tr>
<th>Behavioural Results</th>
<th>ERP Amplitudes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Decreases in Hits (standard – deviant)</td>
</tr>
<tr>
<td>Schröger-Wolff Study</td>
<td></td>
</tr>
<tr>
<td>.small deviant (7%)</td>
<td>4%**</td>
</tr>
<tr>
<td>.large deviant (71%)</td>
<td>6%**</td>
</tr>
<tr>
<td>Controls in this study</td>
<td></td>
</tr>
<tr>
<td>.small deviant (7%)</td>
<td>0</td>
</tr>
<tr>
<td>.large deviant (71%)</td>
<td>0</td>
</tr>
</tbody>
</table>

* p < .05; ** p < .01; *** p < .001

The difference is particularly striking in RT prolongations to small deviants: they are eight times greater (50 ms vs. 6 ms) in the S-W study than in this study. In this study, the RT prolongation to the small deviant is too small to be significant. Both paradigms elicited significant MMN components to the small and the large deviant. However, the MMNs in the S-W study were more than twice as large as the ones in this study. Study differences are even greater with the P3a components: the P3a to the large deviant of the S-W study is three times larger than the P3a to the large deviant in this study. The P3a to the small deviant of the S-W study is six times larger than the P3a in this study, where the P3a to the small deviant is too small to be significant.

Why did the location-discrimination paradigm produce much weaker distraction and deviance effects than the S-W paradigm? One possibility is that presenting half of the standard stimuli in each ear, instead of all of them in the same ear or in both ears simultaneously, may have interfered with the formation of a strong memory trace for the standard stimulus. Näätänen and Winkler (1999) established that the brain retains the different features (such as frequency and location) of the same stimulus as a functionally integrated "whole" stimulus representation and not as a set of independent feature traces. As
a result, manipulations of one feature may affect or even eliminate the MMN elicited by
deviance in another feature (Naätänen & Winkler). It is therefore possible that varying the
standard stimulus by location (left and right ear) may have diminished or even prevented a
deviance effect that would otherwise have occurred following the presentation of rare
frequency deviants. In the usual Schröger and Wolff paradigm, the duration of the standard
stimuli varies from trial to trial, but all the stimuli are presented in the same physical
location.

The muting of the distraction and deviance effects in this experiment may also have
been a result of the special character of the location stimulus dimension. According to
Naätänen, Porkka, Merisalo and Ahtola (1980), spatial differences have a privileged status in
selective attention. Kahneman (1970) wrote that "there seems to be no doubt that the best
performance in selective attention is achieved when spatial orientation is possible (p. 124)."
Several studies (Spieth, Curtis, & Webster, 1954; Treisman, 1964) found that the
discriminability of spatially distinct auditory channels was not improved when a frequency
difference was added to further separate these channels. Naätanen, Porkka et al.'s (1980) own
research confirmed that spatial difference (left vs. right ear) leads to much faster
discrimination than even large differences in frequency in the same ear. If spatial differences
are so powerful in enhancing discrimination, it is conceivable that spatial discrimination is
highly resistant to distraction effects. This hypothesis is supported by the complete lack of
effect of the deviants on accuracy (hits) in this experiment, even though the large deviant
elicted a significant P3a and caused a significant prolongation in RT. Another indication of
the special character of spatial differences is that RTs were distinctly shorter in this location-
discrimination study than in Schröger and Wolff's duration-discrimination study (1998b): in
this study, the RTs of controls were 388 ms to the small deviant and 402 ms to the large
deviant, compared with 505 ms to the small deviant and 545 ms to the large deviant in the
Schröger and Wolff experiment.

The conclusion of this comparison of the results obtained with the S-W duration-
discrimination paradigm and with this study's location-discrimination paradigm is that the
choice of a location-discrimination substitute task may not have been suitable for comparing
distraction-related group differences between schizophrenic patients and controls. For
reasons that could not easily be foreseen, the substitute paradigm produced much weaker
effects than had been anticipated. This is unfortunate since weaker effects diminished the
capacity of this experiment to gain a better understanding of abnormal deviance processing in
schizophrenic patients and of the effect of nicotine on these abnormalities.

3.3.2 Behavioural differences between controls and patients in the placebo condition

The behavioural location-discrimination task produced no significant differences in
RTs between controls and patients in the placebo condition. However, controls had a higher
hit rate (about 95%) than the patients (about 87%). Patient impairments on this task were
consistent with previous findings that individuals with schizophrenia exhibit deficits in
identifying sound location (Balogh & Leventhal, 1982; Guterman & Klein, 1992). The cause
of this deficit is believed to be a problem with the encoding of temporal information that is
similar to the encoding problem in these patients discussed in Experiment 1. The three
primary cues the auditory system uses to locate sounds are interaural differences in the
arrival time (interaural differences in timing, or ITD), interaural differences in the ongoing
phase of the sound wave reaching the two ears (interaural differences in phase, or IPD), and
interaural difference in the loudness (ILD) at the two ears (Middlebrooks & Green, 1991).
Matthews, Todd, Budd, Cooper and Michie (2007) examined these factors in schizophrenic
patients by measuring hit rates, RTs and MMN to targets and deviants defined by their ITD,
IPD, or ILD. The results revealed a selective impairment in the use of temporal cues to
sound lateralization in schizophrenia, as opposed to a global deficit in auditory processing.

Task-irrelevant frequency deviance had no significant effect on the hit rates of either
controls or patients who took placebo. This is consistent with the theory presented above that
spatial discrimination is highly resistant to distraction effects. However, irrelevant large
frequency deviances elicited significantly prolonged RTs in both controls and patients
compared with their RTs to standard stimuli. These RT prolongations amounted to 20 ms in
controls compared with 12 ms in the patients. They indicate that the task-irrelevant frequency
changes produced a switch in attention away from the location-discrimination task and
toward the deviant frequencies. Processing the deviant frequencies caused distraction which
is evidenced by a deterioration in performance on the task (longer RTs).
3.3.3 MMN differences between controls and patients in the placebo condition

Although patients who ingested the placebo did not exhibit a significant MMN component to the small deviant, ANOVAs found no significant differences between the MMN amplitudes or latencies of controls and patients in the placebo condition. This suggests that the MMN components of patients were within normal limits and that their pre-attentive acoustic change detector was as sensitive to task-embedded frequency deviants as the MMN of controls. Although many studies have consistently reported an attenuated MMN in schizophrenic patients, Umbricht & Krljes (2005) indicated that their MMN amplitudes to frequency deviants are not always smaller than those of controls. This was confirmed in the present experiment. The failure to find significant group differences in MMN amplitudes could also be due to lack of statistical power (.18 for the comparison of controls and patients who took placebo) because of the small number of participants.

On the other hand, the MMN amplitudes and latencies of controls and patients were affected in different ways by the manipulation of the extent of deviance. Patients' MMN amplitudes were greater to the large deviant than to the small deviant, but their MMN latencies were not affected. In contrast, controls' MMN latencies were faster to the large deviant than to the small deviant, while their MMN amplitudes were unaffected by the degree of stimulus deviance. These results are unusual because a common finding in MMN research in schizophrenia is that patients' MMN amplitudes show a diminished sensitivity to the extent of stimulus deviance compared with controls (Umbricht & Krljes, 2005). In addition, Javitt et al. (1998) demonstrated that patients' MMN were less sensitive than controls' to changes from smaller-deviant to larger-deviant stimuli. In this case, the main reason why the MMN amplitudes of patients were larger to the large deviant than to the small deviant is that the MMN amplitude of patients to the small deviant was so minuscule (-0.28 µV) as to be no greater than the zero baseline.

A possible cause of the non-significant MMN amplitude of patients to the small deviant may have been differences in the attentional capacities of patients and controls. In the original Näätänen (1990) model, the MMN was claimed to be unaffected by manipulation of attention. In their most recent reformulation, Näätänen et al. (2007) now indicate that while the MMN can be elicited independently of attention, it may also be modified by it. It is therefore elicited relatively independently of attention. The diminished attentional resources
of patients (vs. those of controls) may have reduced their MMN to small deviants, thereby creating an abnormal stimulus deviance effect by psychologically increasing the difference in amplitude between their MMN to small and large deviants. This would be consistent with the findings of Muller-Gass, Stelmack and Campbell (2006). They concluded that MMN amplitudes can be affected by attention because attention might enhance the discriminability of deviant stimuli. This effect is strongest for the detection of smaller deviants because larger deviants do not need attention to be discriminated. It is also possible that attention has a larger effect in a Schröger-like task than in the usual auditory oddball task. Schröger tasks require that subjects actively attend to the auditory channel in which irrelevant deviant features are presented, because irrelevant features are embedded in task-relevant stimuli.

Javitt et al. (1998) suggested that schizophrenic abnormalities in detecting stimulus features likely reflect the failure of the early encoding of stimulus features; the quality of the sensory memory trace is thus flawed. Abnormalities in processing feature-specific stimulus information are associated with impairments in temporal lobe generators (Shalgı & Deouell, 2007). These abnormal MMN results for schizophrenic patients confirm previous findings that these patients do not process potentially-distracting stimuli in a normal manner (Braff, 1993; Umbricht & Krljes, 2005). The shortening of the MMN latencies of controls to increases in stimulus deviance also supports theories suggesting that normals are more efficient than schizophrenic patients in the processing of stimulus changes (Birkett et al., 2006; Gooding et al., 2005).

In patients who ingested the placebo (and in those who ingested nicotine), smaller MMN amplitudes were correlated with longer reaction times. This confirms the existence of a strong ($r=-.63$) relationship between MMN amplitudes and behaviour which was found in previous research (see review in Kujala et al., 2007).

### 3.3.4. P3a differences between controls and patients in the placebo condition

The P3a amplitudes of patients to the large deviant were reduced compared with the P3a amplitudes to the large deviant of controls. The P3a amplitudes to the small deviant of the two groups were not significantly different. All of the patients' P3a amplitudes were very small in this experiment, to the point where none was significantly different from the zero baseline. It is not surprising to find a very small P3a to the small deviant in patients since
Nicotine and schizophrenia

their MMN to the small deviant was also too small to be statistically significant. As reviewed in Näätänen et al. (2007), only deviant stimuli that are large enough to surpass a certain threshold of magnitude elicit an attention-switching P3a. The presence of a P3a signals the activation of the neural processes that orient attention away from the task at hand and toward a new and distracting stimulus.

This finding of diminished P3a amplitude in schizophrenic patients replicates the results of many previous studies described at the beginning of this report. These reductions in the P3a were associated with dysfunction of the anterior cingulate (Mathalon et al., 2000; Turetsky et al., 1998) and with prefrontal and medial temporal lobe lesions (Knight et al., 1998) in these patients. On the basis of their fMRI study of the P3a in schizophrenic patients, Laurens et al. (2005) suggested that several areas of their brains were less engaged by deviant novel stimuli than in controls, with the result that they were less able to effectively assess their potential significance for ongoing behaviour. Valkonen-Korhonen et al. (2003), who found normal N1 and MMN components and diminished P3a and P3b components in schizophrenic patients, suggested that many neural deficits are involved, including a deficit in sensory memory trace formation, alterations in deviance detection processes and deficits in attentional processes. Unlike a healthy brain, in which deviance detection processes instantly update its model of the sensory input as the changes occur (Sussman & Winkler, 2001; Sussman et al., 2002), the brains of schizophrenic patients appear to have imbalanced processes of temporospatial deviance detection. According to Valkonen-Korhonen et al., such imbalanced processes are consistent with the well-documented abnormalities in temporoprontal functions of schizophrenic patients.

The most unusual aspect of the results of Experiment 2 that were described so far is that schizophrenic patients had a significant MMN component to the large deviant and a significant prolongation in reaction time to the task without having a significant P3a. These results suggest that the generally-accepted model of auditory processing based on Näätänen's model of central auditory processing may not apply to schizophrenic patients. Under Näätänen's model, the attention-orienting process starts with an MMN-indexed detection of change in the environment. If the change is of sufficient magnitude, a subsequent significant P3a signals a switch in the orienting of attention away from the location task and toward the processing of the irrelevant deviant stimulus. This switch of attention produces a
deterioration in performance on the original task. In this experiment, however, schizophrenic patients produced a significant MMN to the large deviant and evidence of deterioration in performance (RT prolongation) following presentation of that deviant without having a significant P3a. On the other hand, it may be possible to reconcile these results to Nääätänen's (1990, 1992) model because this model specifies that the threshold for the switching of attention may vary across individuals and groups. Perhaps even very small change-related MMN are sufficient to trigger an attention switch and consequent behavioural distraction in schizophrenic patients without an enhanced P3 component.

The MMN amplitudes to the small deviant of patients who took placebo were strongly (.77) positively correlated with their P3a amplitudes to the small deviant, but there were no significant correlations between their MMN and P3a amplitudes to the large deviant, nor between the MMN and P3a amplitudes of controls. Also in patients who took placebo, larger P3a amplitudes to the small deviant were associated with shorter P3a latencies to the small deviant, while larger P3a amplitudes to the large deviant were associated with longer P3a latencies to the large deviant.

3.3.5 RON differences between controls and patients in the placebo condition

There were no differences in RON components between patients and control participants. The only significant RON components in this experiment (only to the large deviant) were in patients who took nicotine. This is discussed further in the next section dealing with the effects of nicotine. Even though the RON components of controls and patients who ingested placebo were not significantly greater than zero, there were many significant correlations between the RON and behavioural results. In patients who took placebo, larger RON amplitudes were associated with higher hit rates. In controls, larger RON components were associated with shorter reaction times and higher hit rates. These associations confirm the link between the RON and refocusing of attention toward the task at hand (Schröger, Giard et al., 2000).

3.3.6 Nicotine effects

The main nicotine effect in this experiment was on the MMN amplitude. Specifically, nicotine altered differences between MMN amplitude to small deviance versus MMN amplitude to large deviance. The MMN amplitude of patients who ingested placebo,
unlike the MMN amplitude of controls, was larger to the large-deviant stimulus than to the small-deviant stimulus. This deviance-related effect was not observed when comparing controls and patients who ingested nicotine. Nicotine achieved this change by increasing the MMN amplitudes of patients to the small deviant to a greater degree than it increased their MMN amplitudes to the large deviant. As a result, nicotine effects on the MMN in patients were manifested in two related ways: their MMN component to the small deviant became significantly larger than zero; and their MMN amplitudes to the small and the large deviant were no longer significantly different from each other.

Kassell (1997) suggested that nicotine may improve cognition in two ways: by increasing the attentional resources allocated to the task-relevant stimuli (Kahneman, 1973) and by narrowing the brain's internal stimulus filter that inhibits the processing of irrelevant stimuli (see Broadbent, 1958). In this experiment, nicotine's effect was probably not achieved by increasing attentional resources to task-relevant stimuli: it did not improve patients' accuracy on the location-discrimination task, nor did it prevent the deterioration in performance induced by distractors. However, nicotine might have enhanced the detection of small stimulus change by increasing the attentional resources allocated to all stimuli, including the small deviant. Again, Muller-Gass et al (2006) indicate that attention might benefit the detection of small stimulus change but will have little effect on the detection of large stimulus change.

The mechanism through which nicotine might have normalized the MMN processes of schizophrenic patients remains speculative, in part because the causes of the MMN deficits of these patients are not well understood. As mentioned earlier, Javitt et al. (1998) suggested that MMN abnormalities in detecting stimulus failures may reflect inaccurate encoding of stimulus features. Baldeweg et al. (2006) demonstrated that nicotine can improve stimulus encoding and memory trace formation. They suggested that this improvement is achieved though nicotine's effect on acetylcholine, which plays a role in the early stages of stimulus encoding (Miranda & Bermudez-Rattoni, 1999).

Postmortem studies have revealed that the schizophrenic brain is characterized by increased cell density, reductions in the dendritic spines in the frontal cortex, and smaller somal size in the temporal cortex. One of the main mechanisms suggested for the reduction in dendrites has been glutamatergic excitotoxicity (Coyle, 1996; McCarley et al., 1996;
Nicotine activates nicotinergic \( \alpha_7 \) brain receptors, which affect NMDA by modulating the release of dopamine, glutamate, GABA, serotonin and acetylcholine (Berman et al., 2007). Nicotine may therefore have normalized patients' MMN to frequency deviants by glutamatergic release following activation of \( \alpha_7 \) receptors co-localized on NMDA terminals. Alternately, nicotine's effect on the MMN may have been mediated through the muscarinic acetylcholine system, since antagonists of this system attenuated frequency MMN in healthy controls (Pekkonen et al., 2001). Nicotine could achieve this indirectly, by causing the release of acetylcholine that would activate muscarinic acetylcholine receptors.

Nicotine appears to have had no effect in altering patients' diminished P3a amplitudes. This contradicts the findings of Polich et al. (2006), who found that nicotine had increased P3a amplitudes in healthy subjects. However, their paradigm was very different from the one employed in the present study. Nicotine treatment produced the only significant appearance of the RON component (to large deviants) in this experiment. The RON amplitude effect to large deviants is particularly interesting because nicotine has been shown to improve selective attention (Jacobsen et al., 2004) and RON is associated with frontally-generated refocusing of attention back to the task at hand following distraction (Schröger, Giard et al., 2000). Enhanced RON amplitudes and latencies in patients might mean that because of their reduced attentional capacities, patients require more top-down "effort" than controls to return to the task. Nicotine may enable this.

While the RON amplitudes of patients in the placebo condition were correlated with their accuracy results, the larger RON amplitudes of patients in the nicotine condition were associated with faster reaction times but were not associated with hit rates. This is consistent with previous findings that nicotine is particularly good at improving response speed (reviewed in Heishman et al., 1994).

3.3.7 Correlations with medication, clinical ratings and withdrawal symptoms

There were no correlations between patients' medication status and any of the results in this experiment. There were also no associations between patients' results and their TWSC
ratings, or between their nicotine-induced "change" scores for MMN amplitudes and their nicotine-induced "change" ratings for the TWSC. This lack of association suggests that the patients' tobacco withdrawal symptoms did not affect their ERP and behavioural results. Light and Braff (2005) found a strong correlation between the Global Assessment of Functioning (GAF) ratings of schizophrenic patients and their MMN amplitudes. This correlation was replicated 1-2 years later, indicating a stable association. This experiment replicated previous studies reviewed by Umbricht and Krljes (2005) which found associations between smaller MMN amplitudes and having more hallucinations. Smaller MMN amplitudes were also associated with longer reaction times. In addition, larger P3a amplitudes were associated with higher scores on the negative symptoms subscale of the PANSS.

3.4 Limitations and conclusion of Experiment 2

The limitations of this experiment were similar to the ones described for Experiment 1. Sample size was even smaller in this case (one fewer patient) because of task demands. This experiment was the first to use a Schröger-style paradigm (with task-irrelevant deviant features embedded in task-relevant stimuli) to examine whether nicotine could normalize the diminished pre-attentive and attention-dependent neural processing of distracting events in schizophrenic patients. It found that nicotine appeared to normalize patients' detection of small stimulus deviance, as indexed by the MMN, and may have improved their re-orienting to the task following distraction, reflected in the RON. On the other hand, nicotine did not affect attentional switching to distractors or behavioural distraction.

The modified study paradigm adapted from Schröger and colleagues proved useful in elucidating some of the early-stage neural mechanisms which may be impacted by nicotine, especially concerning MMN deficits to small distractor deviants. However, the link between this effect and the enhanced distractibility of schizophrenic patients remains unclear. The absence of robust ERP indicators of attentional switching with this task also made it difficult to examine how nicotine or smoking may influence this crucial stage of distractor processing. Experiment 3 which follows used an auditory-visual paradigm that was more successful at allowing an examination of the effects of nicotine over the full range of distraction-related ERP components.
EXPERIMENT 3
Auditory-Visual Distraction Paradigm

4.0 Introduction

4.0.1 The auditory-visual distraction paradigm

The auditory-visual distraction paradigm used in Experiment 3 is similar to the paradigm developed by Escera, Alho, Winkler and Näätänen (1998), whose work is associated with that of Schröger and colleagues (see for example, Escera, Alho, Schröger, & Winkler, 2000). This test paradigm resembles the classic Schröger-Wolff (1998a) auditory-auditory paradigm in that it combines behavioural and ERP measures of distraction and uses small as well as large task-irrelevant auditory distractor stimuli. Unlike the classic Schröger-Wolff paradigm, however, the task-relevant and task-irrelevant stimuli are in different modalities: a visual discrimination task is paired with task-irrelevant auditory distractor stimuli. A paradigm employing different physical modalities for the targets (to be detected) and the distractors (to be ignored) results in wider "channel separation." As a result, the extent of distraction is much reduced. In other words, it is easier to ignore the irrelevant auditory deviant when it is presented in a different modality (Schröger and Wolff, 1998a).

This is demonstrated by the results of studies that used these different types of paradigms. In the Schröger and Wolff (1998b) auditory-auditory paradigm, the small-deviant stimuli (standards and deviants with frequencies of 700 and 750 Hz, for a deviance of 7%) distracted attentional resources away from the target detection task with the following results: a significant reduction in hit rate of 4% to target stimuli of small-deviant frequency relative to targets of standard frequency, and prolongations of about 50 ms in RT to target stimuli of small-deviant frequency relative to targets of standard frequency. By comparison, Escera, Alho, Winkler, and Näätänen (1998), whose visual target stimulus was preceded by an auditory stimulus (standards and deviants of 600 and 700 Hz, for a deviance of 17%), observed a significant hit rate decrease of 2.3%, and their deviant tones did not significantly affect the RT. San Miguel, Corral and Escera (2008, p. 3) nevertheless point out that there are advantages to employing inter-modality tasks:

This paradigm is particularly well suited to test the independence of the involuntary attentional mechanisms from endogenous factors because distraction here is thought to be purely exogenous and involuntary as the sounds are completely irrelevant to the
task, and they are presented on a different sensory modality that is explicitly asked to be ignored.

One reason why this auditory-visual paradigm was chosen for Experiment 3 is that most of the behavioural studies that found uncontradicted enhancing effects of nicotine/smoking on attention and working memory in schizophrenic patients used paradigms with visual tasks (Barr et al., 2008; Dépatie et al., 2002; Levin, Wilson et al., 1996; Smith et al., 2002). In addition, a review of the effects of nicotine on ERPs by Pritchard et al. (2004) found more evidence of nicotine effects in the visual modality than in the auditory modality. As a result, it was felt that nicotine might have a stronger effect within a paradigm using a visual task than within a similar paradigm using an auditory task.

In Experiment 3, each participant was presented with a task-irrelevant auditory stimulus followed by a task-related visual target that required a (mouse-clicking) response. On most trials, the irrelevant auditory stimulus was of the same frequently-occurring frequency. At rare and unpredictable times, the frequency of the auditory stimulus was changed. This auditory "deviance" was irrelevant to the visual detection task. However, if the magnitude of the deviance surpassed a certain threshold, the subject's attention could be switched away from the visual task and toward the auditory deviant. This sometimes resulted in distraction, evidenced by a deterioration in the performance of the visual task.

Experiment 3 had the same two specific objectives as Experiment 2. The first was to compare schizophrenic and control smokers with respect to the pre-attentive detection of task-irrelevant, potentially distracting auditory frequency-deviant stimuli and the possible consequent involuntary switching of attention. The second objective of Experiment 3 was to examine the effects of nicotine on the behavioural performance and the MMN, P3a and RON components of schizophrenic smokers. The extent of deviance was also manipulated by presenting small and large frequency deviants. Distractor processing was examined by both performance (behavioural) and electrophysiological measures. Performance was assessed by two measures: RT and correct responses. Distraction was inferred to have occurred if RTs were prolonged or correct responses were decreased following presentation of the deviant relative to the standard. Distraction was also measured electrophysiologically by examining the pre-attentive detection of the distractors, as evidenced by the MMN, and the involuntary switching and re-orienting of attention, as measured by the P3a and RON, respectively.
The N1 ERP to standard stimuli was also evaluated to determine whether any group differences or nicotine effects were related to early encoding of sensory features.

Given previous research findings in healthy controls with this paradigm, it was predicted that rare deviant sounds would impair behavioural performance in controls, as evidenced by slower reaction times and reduced rates of correct detections, with greater impairment to larger (vs. smaller) deviants. Based on previous reports of greater behavioural distractibility in schizophrenic patients, greater performance impairments were predicted in patients than in controls. It was also predicted that rare deviant sounds would elicit MMN, P3a and RON components in controls, and that these components would be attenuated in patients (vs. controls). Finally, on the basis of the apparent discrepancies between previous nicotine-performance and nicotine-ERP studies, it was predicted that nicotine (vs. placebo) would improve the behavioural performance of patients (i.e. shorter RT prolongations and smaller decreases in hit rates induced by distractors), but that nicotine would increase the pre-attentive detection of distractors as indexed by greater MMN amplitudes, and may decrease involuntary distraction and re-orienting as shown by smaller P3a and consequent smaller RON component amplitudes. As an additional objective, the experiment examined the relationships between patients' clinical symptoms, including smoking withdrawal symptoms, and ERP and behavioural indices, and between patients' medication and ERP and behavioural indices.

4.1 Method

4.1.1. Participants

Twelve male controls and 12 male outpatients from the Experiment 1 participant pool took part in Experiment 3. The inclusion/exclusion criteria, symptoms ratings by treating psychiatrists and the auditory screening were the same as in Experiment 1. To ensure that controls and patients were matched on intelligence and smoking-related factors, they completed the North American Reading Test (NART; Blair & Spreen, 1989; see Appendix A), which is an approximate measure of intelligence, the 8-item 15-point Modified Fagerstrom Test for Nicotine Dependence (FTND: Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991; see Appendix B), and the Modified Reasons for Smoking Scale (MRSS;
Berlin et al., 2003; see Appendix C). All subjects received an honorarium for their participation.

4.1.2. General procedure

Testing took place between 12:00 and 17:00 at the Clinical Neuroelectrophysiology and Cognitive Research Laboratory of the Royal Ottawa Mental Health Centre. All participants were instructed to abstain overnight from alcohol, caffeine and any drug other than the patients' medication, and were requested to refrain from smoking for three hours before the tests. Control participants were required to attend one test session lasting approximately 2.5 hours while patients were required to perform the same tests twice, in two separate sessions lasting approximately 3-3.5 hours each. Patients' sessions were longer because they involved a nicotine-or-placebo administration procedure. Upon their first arrival at the lab, adequacy of all participants' hearing was tested at 750 Hz, 1000 Hz and 1500 Hz, using a descending method-of-limits procedure, before EEG recording commenced. All thresholds were at or below 20 dB (SPL). Participants were then questioned about their abstinence from smoking, alcohol and drugs. Carbon monoxide (CO) levels were also assessed by means of an instrument measuring their expired-breath CO level (Vitalograph Breath CO instrument, Vitalograph Inc., Lenexa, Kansas). Participants were then taken into a sound-attenuated, electrically-shielded recording chamber and sat in a comfortable chair while electrodes were applied. During this application, patients were administered nicotine or a placebo (see nicotine procedure below). The drug conditions were not administered to the controls. Following electrode placement and nicotine or placebo absorption (in patients), electrophysiological data were acquired over a 30-40 minute interval which allowed for several 2-3 minute breaks. Frequent rest periods were required to maintain patient cooperation. At the end of the recordings, participants completed the Tobacco Withdrawal Symptom Checklist (TWSC; Hughes & Hatsukami, 1986; see Appendix D and description below).

4.1.3. Nicotine and placebo administration

Nicotine was administered within a randomized, double-blind, placebo-controlled, cross-over design with half of the patients receiving nicotine in the first session and placebo in the second session, and the remaining half receiving nicotine and placebo in the reverse
order. Nicotine was administered orally as two 4-mg pieces of Nicorette Plus polacrilex gum (Hoechst Roussel). The placebo gum (containing no nicotine) was a commercial gum similar in size, shape and texture. To reduce any perceptual and sensory differences between the two, patients wore a blindfold while putting the gum pieces in their mouths. Also, a drop of mint oil was placed on each gum and participants wore nose plugs throughout the chewing period. During that period, which lasted 25 minutes as specified by the Nicorette Plus guidelines, patients heard a taped voice every minute asking them to chew ("bite twice"). After each bite, they "parked" the gum between their teeth and gums. After the chewing period, the gum was discarded and patients were given a strong commercial mint gum to chew for five minutes to help disguise any placebo-nicotine difference.

Cigarette smoking yields a rapid delivery of nicotine to the bloodstream, resulting in sharp peaks in blood nicotine concentration. The peak of plasma nicotine concentration achieved within ten minutes of smoking an average-nicotine-yield cigarette is approximately 35 nanograms per milliliter, followed by a trough at 15 nanograms per milliliter within 30 minutes (Russell, 1988). After chewing one piece of 4-mg nicotine gum for 30 minutes, blood concentration reaches a peak of about 18 nanograms per milliliter of nicotine (Russell, Raw & Jarvis, 1980). Chewing two pieces of 4-mg nicotine gum results in peak blood levels of about 36 nanograms per milliliter within 30 minutes after the initiation of chewing, which approximates the effect achieved ten minutes after smoking a cigarette. The elimination half-life of nicotine is approximately 120 minutes (Benowitz, Jacob, Jones, & Rosenberg, 1982; Feyerabend, Ings, & Russel, 1985).

4.1.4. Stimulus paradigm

Participants sat on a comfortable chair approximately 50 cm from a computer monitor. The task involved the discrimination of one of two categories of visual stimuli presented every 1300 ms (onset-to-onset). The visual stimuli were presented at the centre of a computer monitor. Half of the visual stimuli were single letters (uppercase A, E, J, P, R, S, U, or Y) and half were single digits (2 to 9). The stimuli were black on a white background. The duration of the visual stimulus was 200 ms. Subjects were instructed to respond as quickly and as accurately as possible with a right mouse button press for a letter and a left mouse button press for a digit, using the index and middle fingers of their right hand. Each
visual stimulus was preceded by an irrelevant auditory stimulus which the participants were instructed to ignore. The time between the onset of the auditory and visual stimuli was 300 ms. For each of the two visual stimulus categories, the preceding auditory stimulus was either a standard tone (1200 Hz, $p = .80$), a small-deviant tone (1025 Hz, $p = .10$) or a large-deviant tone (700 Hz, $p = .10$). All auditory stimuli were presented at an intensity of 80 dB SPL, having a duration of 150 ms and a rise-and-fall time of 5 ms. The auditory stimuli were presented binaurally through headphones. The auditory and visual pairs were presented in random order, with the exception that two deviant stimuli could not be presented on consecutive trials. An equal number of auditory standards and deviants preceded both the visual letters and digits. A practice block was presented prior to the start of testing. It included 100 auditory-visual pairs: 40 standard tones followed by a letter and 40 standard tones followed by a digit; 5 small-deviant tones followed by a letter and 5 small-deviant tones followed by a digit; and 5 large-deviant tones followed by a letter and 5 large-deviant tones followed by a digit. The practice session was repeated until a participant obtained 60% correct responses. If a participant was unable to reach that level of proficiency after three practice runs, the test was terminated. Practice was followed by five testing blocks. Each testing block included 200 auditory-visual pairs.

4.1.5. EEG recording and measures

The EEG was recorded with tin electrodes placed on midline frontal (Fz), central (Cz) and parietal (Pz) scalp positions according to the international 10-20 system (Jasper, 1958; Cooper, Osselton, & Shaw, 1969). Scalp electrical activity was recorded in a monopolar manner, the reference being to linked earlobes. Two additional electrodes, one on the left supra-orbital ridge and one on the external canthus of the left eye, recorded electro-oculographic (EOG) activity in one channel, with a mid-forehead electrode serving as ground. Electrode impedances were kept below 5 kOhms. The EEG and EOG signals were recorded continuously with an analog-to-digital sampling rate of 256 Hz, using amplifier bandpass filters set at 0.1-30.0 Hz. Digital data were stored on hard disk for off-line ERP processing and analysis. Off-line, the continuous EEG signals were reconstructed into 950 ms epochs (or "trials"), beginning 50 ms prior to stimulus onset. Eye movements and blink artifact were removed from the EEG signals using an algorithm operating in the time and
frequency domains (Woestenburg, Verhaten & Slangen, 1983). Ocular-corrected trials with amplitudes exceeding +/-100 \mu V were excluded from further analyses. For each participant and drug condition, trials were averaged separately for correctly-detected standard, small-deviant and wide-deviant stimuli and sorted according to scalp recording site. A minimum of 65 artifact-free correctly-detected deviant stimulus trials was required to retain a participant's ERP averages in the final analysis.

Amplitudes and latencies of the ERP components were based on latency windows taken from grand-average waveforms. All ERP components were measured relative to the average of all data points in the pre-stimulus baseline. N1 latency to standard stimuli was defined at Fz (where it was largest) as the latency corresponding to the peak negativity occurring within the 50-150 ms latency range. N1 amplitude was defined as the average of the amplitude points (relative to the average pre-stimulus voltage) within a 50 ms window around each individual's the peak negativity, i.e. 25 ms pre-peak and 25 ms post-peak. The MMN was measured in the difference wave, calculated by subtracting point-by-point the ERP to the standard from that of the deviant. The difference wave removes processing that is common to both the standard and the deviant, leaving only the difference in processing (for example, the MMN). MMN latency was defined at Fz as the latency corresponding to the peak negativity occurring during the 80-220 ms latency range, and MMN amplitudes were defined as averages of the amplitude points within a 50 ms window around each individual's peak negativity. P3a and RON amplitudes and latencies were derived from difference waveforms in the same manner as MMN amplitudes and latencies, but for the P3a, latency was defined as the latency corresponding to the peak positivity occurring within the 225-350 ms latency range at Cz, and for the RON, latency was defined as the latency corresponding to the peak negativity occurring within the 450-600 latency range at Fz.

4.1.6. Behavioural measures

Trials with a correct button press occurring 100 to 900 ms after the onset of the visual stimulus were considered to be hits. Reaction times (ms) and correct detection rates (%) were determined separately for the visual stimuli following the presentation of standard tones, small-deviant tones and large-deviant tones for control participants and for patients in the
placebo and nicotine conditions. Missed responses were not analyzed as they were minimal in number and were not different between groups or between stimuli or drug conditions.

4.1.7. Smoking withdrawal ratings

Smoking withdrawal symptoms were assessed at the end of each session with the TWSC to determine whether alterations in behaviour and in ERPs by nicotine were related to withdrawal relief. The items of the self-report TWSC questionnaire, which are derived from the DSM-IV list of withdrawal symptoms (American Psychiatric Association, 1994), are irritability, frustration or anger, difficulty concentrating, restlessness, anxiety or nervousness, hunger, depressed mood, and desire to smoke. For each item, participants were asked to choose on a four-point scale (0=not present, 1=mild, 2=moderate, 3=severe) the answer that best described how they felt. Scores for each symptom rating were summed to form a single TWSC index.

4.1.8. Analysis

Statistical analyses were performed using SPSS (Statistical Package for Social Sciences, 15th Edition). Analyses of variance (ANOVAs) were run on behavioural measures (reaction times, correct detection rates) and on ERP amplitudes and latencies (N1, MMN, P3a and RON). Separate mixed-design ANOVAs compared the behavioural measures and ERPs of controls with those of patients in the placebo condition, and the behavioural measures and ERPs of controls with those of patients in the nicotine condition, using one between-subjects factor with two levels (group: controls vs. patients) and one within-subjects factor with three levels for the behavioural measures (stimulus: standard vs. small-deviant vs. large-deviant) and with two levels for the MMN, P3a and RON (stimulus: small-deviant vs. large-deviant). Repeated-measures ANOVAs compared the behavioural measures and ERPs of patients in the placebo condition with those of patients in the nicotine condition, using two within-subjects factors (condition: placebo vs. nicotine; stimulus: small-deviant vs. large-deviant). Greenhouse-Geisser corrections were applied when appropriate to compensate for sphericity (equal covariance) violations. Since all the effects were the subject of specific a priori hypotheses based on previous research findings, a .05 level of significance was used in all analyses.
Confidence intervals of the means were examined to determine whether MMN, P3a and RON mean amplitudes were significantly different from the zero baseline. T-tests were used to determine whether control and patient participants differed on personal characteristics including age, education, BMI, number of cigarettes smoked per day, breath CO level, scores on the NART, FTND, and MRSS; whether the TWSC scores of patients with placebo differed from those of controls and patients with nicotine; and to compare the numbers of EEG trials analysed for each group, condition and paradigm. Pearson Product Moment Correlation or non-parametric equivalents were used to assess the relationships between behavioural and ERP measures and PANSS scores, TWSC ratings and patients' medication.

4.2 Results
4.2.1. Participant Characteristics

Demographic and clinical characteristics of the participants are shown in Table 20, as well as results of independent-samples t-tests comparing patients and controls. No significant differences were found between control and patient participants for any personal characteristic, including age, schooling, body-mass index, number of cigarettes per day, CO levels, intelligence (excluding four patients whose English was poor), degree of nicotine dependence or reasons for smoking. Scores on the FTND (12 for patients and 11 for controls) indicated that both groups were heavily dependent on nicotine (7 points or more = heavy dependence). Controls and patients did not differ with respect to tobacco withdrawal symptoms, nor was there any difference in withdrawal symptoms between patients in the placebo (M=8.08; SE=1.4) and the nicotine conditions (M=10.08; SE=1.5) [t(11) = 1.17, p<.27].

PANSS scores for the patients averaged 53 (14 + 14 + 25) and ranged from 34 to 77. According to a recent study (Leucht et al., 2005) that translated PANSS scores into ratings on the Clinical Global Impressions Scale (CGI; Guy, 1976), which is used by psychiatrists to obtain a global picture of patients' overall clinical state, the CGI ratings of this experiment's patient participants were roughly as follows: none at score 1 = normal, not at all ill; 2 at score 2 = borderline mentally ill; 5 at score 3 = mildly ill; 4 at score 4 = moderately ill; 1 at score 5 = markedly ill; none at score 6 = severely ill; and none at score 7 = extremely ill.
Table 20. Means (SE) of Characteristics of Patients and Control Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n = 12)</th>
<th>Controls (n = 12)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>41 (2.5)</td>
<td>42 (2.5)</td>
<td>-0.31</td>
<td>.76</td>
</tr>
<tr>
<td>Years of schooling</td>
<td>12 (0.4)</td>
<td>13 (0.2)</td>
<td>-0.78</td>
<td>.44</td>
</tr>
<tr>
<td>BMI</td>
<td>25 (1.5)</td>
<td>24 (0.9)</td>
<td>0.49</td>
<td>.84</td>
</tr>
<tr>
<td>Cigarettes per day</td>
<td>27 (2.8)</td>
<td>23 (1.3)</td>
<td>1.30</td>
<td>.21</td>
</tr>
<tr>
<td>CO level</td>
<td>17 (1.3)</td>
<td>18 (1.9)</td>
<td>-0.27</td>
<td>.79</td>
</tr>
<tr>
<td>NART*</td>
<td>107 (1.7)</td>
<td>112 (2.2)</td>
<td>-1.77</td>
<td>.09</td>
</tr>
<tr>
<td>TWSC**</td>
<td>8 (1.4)</td>
<td>8 (0.9)</td>
<td>0.15</td>
<td>.88</td>
</tr>
<tr>
<td>FTND</td>
<td>12 (0.7)</td>
<td>11 (0.7)</td>
<td>1.14</td>
<td>.27</td>
</tr>
<tr>
<td>MRSS-addiction</td>
<td>6 (0.6)</td>
<td>5 (0.6)</td>
<td>0.09</td>
<td>.92</td>
</tr>
<tr>
<td>MRSS-pleasure</td>
<td>9 (0.7)</td>
<td>8 (0.5)</td>
<td>1.65</td>
<td>.11</td>
</tr>
<tr>
<td>MRSS-relaxation</td>
<td>7 (0.9)</td>
<td>7 (0.8)</td>
<td>0.13</td>
<td>.90</td>
</tr>
<tr>
<td>MRSS-social</td>
<td>4 (0.5)</td>
<td>3 (0.4)</td>
<td>1.22</td>
<td>.23</td>
</tr>
<tr>
<td>MRSS-stimulation</td>
<td>5 (0.9)</td>
<td>5 (0.5)</td>
<td>0.00</td>
<td>1.00</td>
</tr>
<tr>
<td>MRSS-habit</td>
<td>3 (0.7)</td>
<td>4 (0.7)</td>
<td>-0.71</td>
<td>.49</td>
</tr>
<tr>
<td>MRSS-sensorimotor</td>
<td>4 (0.8)</td>
<td>6 (0.8)</td>
<td>-1.56</td>
<td>.13</td>
</tr>
<tr>
<td>PANSS (positive)</td>
<td>14 (1.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS (negative)</td>
<td>14 (1.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS (general pathology)</td>
<td>25 (2.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine equivalents (mg)</td>
<td>107 (43.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Three patients were excluded from this analysis because of poor knowledge of English.
** The TWSC score for patients is an average of the scores for their two sessions.

4.2.2. Behavioural performance

Means and standard errors for performance indices are shown in Table 21. There were no significant differences in overall RT between controls, patients with placebo and patients with nicotine. There was a significant main effect of type of stimulus in the analysis of controls and patients with placebo \([F(1,22)=5.67, p<.008, \eta^2=.19]\). Planned follow-up comparisons indicated that RTs were slower to large-deviant stimuli than to standard stimuli for both controls (prolonged by 17 ms, \(p<.02\)) and patients with placebo (prolonged by 14 ms, \(p<.04\)), but not for patients with nicotine \((p<.66)\). Reaction times also tended to be longer for controls (13 ms) following presentation of the small deviant compared to the standard, but the difference failed to attain significance \((p<.07)\).
### Table 21. Mean Reaction Times and Hit Rates to Visual Stimuli Preceded by Auditory Standards and Small and Large Deviants

<table>
<thead>
<tr>
<th></th>
<th>RT (SE) ms</th>
<th>Hits (SE) %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Controls (n=12)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>standard stimulus</td>
<td>510(12.7)</td>
<td>91(1.2)</td>
</tr>
<tr>
<td>small-deviant stimulus</td>
<td>523(12.8)</td>
<td>93(1.3)</td>
</tr>
<tr>
<td>large-deviant stimulus</td>
<td>527(12.6)</td>
<td>92(1.3)</td>
</tr>
<tr>
<td><strong>Patients with Placebo (n=12)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>standard stimulus</td>
<td>515(19.0)</td>
<td>78(4.5)</td>
</tr>
<tr>
<td>small-deviant stimulus</td>
<td>518(19.9)</td>
<td>78(4.9)</td>
</tr>
<tr>
<td>large-deviant stimulus</td>
<td>529(19.8)</td>
<td>80(3.8)</td>
</tr>
<tr>
<td><strong>Patients with Nicotine (n=12)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>standard stimulus</td>
<td>516(18.3)</td>
<td>79(3.8)</td>
</tr>
<tr>
<td>small-deviant stimulus</td>
<td>522(18.3)</td>
<td>81(3.7)</td>
</tr>
<tr>
<td>large-deviant stimulus</td>
<td>519(18.9)</td>
<td>80(3.3)</td>
</tr>
</tbody>
</table>

Controls had significantly higher correct detection rates than patients in both conditions [controls vs. placebo: $F(1,22)=8.57, p<.01, \eta^2=.23$; controls vs. nicotine: $F(1,22)=10.51, p<.004, \eta^2=.32$]. There were no significant main effects of type of stimulus in the analyses of controls and patients with placebo [$F(1,22)=1.23, p<.30, power=.24$] and of controls and patients with nicotine [$F(1,22)=1.79, p<.19, power=.32$]. Planned comparisons confirmed that accuracy of visual detection had not been affected by the type of auditory stimulus that preceded it.

#### 4.2.3. EEG Results - General

Table 22 displays the number of EEG trials to standard and deviant stimuli included in the analyses for each group and condition. Control participants had significantly more trials than patients with nicotine for all three stimuli [standard: $t(12) = -3.70, p<.00$; small deviant: $t(12) = 3.29, p<.00$; large deviant: $t(12) = 4.41, p<.00$]. There were no differences in trials between controls and patients with placebo or between patients in the two conditions.
Table 22. Means (SE) Trials per Average ERP to Standard and Deviant Stimuli

<table>
<thead>
<tr>
<th></th>
<th>Standard stimulus</th>
<th>Small-deviant stimulus</th>
<th>Large-deviant stimulus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>740(12.5)</td>
<td>93(1.6)</td>
<td>93(1.7)</td>
</tr>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>placebo</td>
<td>716(60.2)</td>
<td>88(8.1)</td>
<td>89(7.4)</td>
</tr>
<tr>
<td>nicotine</td>
<td>620(29.8)</td>
<td>78(4.1)</td>
<td>77(3.2)</td>
</tr>
</tbody>
</table>

Grand-averaged ERPs. Grand-averaged "raw" ERPs following presentation of the auditory standard and deviant stimuli are presented in Figure 9. Note that in this figure, the ERPs to both the auditory stimuli and the visual stimuli (presented 300 ms after the onset of the auditory stimuli) are illustrated. A negative deflection peaking at about 150 ms (i.e. at about 450 ms following the onset of the auditory stimulus) and a positive deflection peaking at about 200-250 ms are apparent following the onset of the visual stimulus. A parietal maximum late positivity peaking at about 450-500 ms after onset of the visual stimulus is also apparent. This is probably the P3b (or P300), associated with the overt detection of the visual target. However, processing associated with the visual stimuli should be different depending on whether they are preceded by an auditory standard or a deviant. The subtraction of the ERPs following presentation of the standard from the ERPs following the deviant stimulus removes this common processing. This is apparent in the difference waves, presented in Figure 10.

Raw ERPs are usually larger than those observed in the difference wave. Thus the vertical amplitude scale is 2.8 µV for the raw ERPs (Fig. 1) while for the difference waves (Fig. 2), the same scale reflects a deflection of only 1.05 µV. Thus the ERPs illustrated in the raw ERPs are more than 2.5 times the amplitude of those in the difference waves. The two scales shown in Figures 9 and 10 also indicate when each of the two paired stimuli began and ended for each stimulus cycle. The first stimulus, which was a standard or a deviant tone, started at 0 ms (at the vertical bar on the left) and lasted 150 ms. The visual target, which was a number or a letter, appeared 150 ms after the end of the tone and lasted 200 ms.
Figure 9. Grand-Averaged Raw Waveforms, Auditory-Visual Distraction Paradigm

Figure 10. Difference Waveforms to Small-Deviant and Large-Deviant Stimuli, Auditory-Visual Distraction Paradigm
4.2.4 N1 event-related potentials to standard stimuli

Means and standard error values for N1 ERPs to standard stimuli derived at Fz are provided in Table 23. There were no significant differences in N1 amplitudes or N1 latencies to standard stimuli between control participants, patients in the placebo condition and patients in the nicotine condition.

Table 23. Mean (SE) N1 Amplitudes and Latencies at Fz to Standard Auditory Stimuli

<table>
<thead>
<tr>
<th></th>
<th>Amplitude (µV)</th>
<th>Latency (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (n=12)</td>
<td>-1.99(0.3)</td>
<td>101.50(2.2)</td>
</tr>
<tr>
<td>Patients with Placebo (n=12)</td>
<td>-1.59(0.2)</td>
<td>100.20(2.4)</td>
</tr>
<tr>
<td>Patients with Nicotine (n=12)</td>
<td>-1.44(0.2)</td>
<td>100.52(2.9)</td>
</tr>
</tbody>
</table>

4.2.5 MMN event-related potentials

Table 24 shows the means and standard errors of MMN amplitudes and latencies derived at Fz from the small-deviant-minus-standard difference waveform and the large-deviant-minus-standard difference waveform. As the asterisks indicate, only controls had significant MMN components to both deviants. Patients in both conditions had significant MMN only to the large deviant.

The MMN amplitudes of controls were larger than those of patients with placebo, but this difference just failed to reach significance \( F(1,22)=3.96, p<.06, \eta^2=.15 \). Planned follow-up analyses of this group difference showed that the MMN amplitudes of controls to small-deviant stimuli were larger than those of patients with placebo \( F(1,22)=7.10, p<.01, \eta^2=.24 \). A main effect for type of deviant was also found in all main analyses [controls and patients-placebo: \( F(1,22)=15.23, p<.001, \eta^2=.41 \); controls and patients-nicotine: \( F(1,22)=6.20, p<.02, \eta^2=.22 \); patients in both conditions: \( F(1,11)=9.18, p<.01, \eta^2=.46 \)].
Table 24. Mean (SE) MMN Amplitudes and Latencies at Fz to Small- and Large-Deviant Stimuli, with Significance of MMN Amplitudes Compared with Zero Baseline

<table>
<thead>
<tr>
<th></th>
<th>MMN Amplitude</th>
<th>MMN Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Small Deviants</td>
<td>Large Deviants</td>
</tr>
<tr>
<td></td>
<td>μV</td>
<td>μV</td>
</tr>
<tr>
<td>Controls (n=12)</td>
<td>-0.76(0.1)**</td>
<td>-1.18(0.1)**</td>
</tr>
<tr>
<td>Patients with Placebo (n=12)</td>
<td>-0.26(0.1)</td>
<td>-0.93(0.1)**</td>
</tr>
<tr>
<td>Patients with Nicotine (n=12)</td>
<td>-0.47(0.1)</td>
<td>-0.73(0.2)**</td>
</tr>
</tbody>
</table>

**p<.01

Planned follow-up comparisons of these type-of-deviant effects indicated that controls and patients with placebo had greater MMN amplitudes to large deviants than to small deviants [controls: $F(1,22)=4.53$, $p<.045$, $n^2=.17$; placebo: $F(1,22)=11.5$, $p<.003$, $n^2=.34$]. The MMN amplitudes of patients with nicotine did not differ for the two deviants. To sum up, all three MMN components to large deviants were significant, but only controls had a significant MMN to small deviants. The only difference between the groups and conditions was that the MMN amplitudes to small deviants of controls were larger than the MMN amplitudes to small deviants of patients with placebo. The MMN amplitudes of controls and of patients with placebo were affected by stimulus deviance: they were greater following large deviants than following small deviants. The MMN amplitudes of patients with nicotine were not affected by stimulus deviance.

MMN latencies did not differ significantly between controls, patients with placebo and patients with nicotine. Main effects of type of deviant were found in the analyses of controls and patients with placebo [$F(1,22)=10.31$, $p<.004$, $n^2=.32$] and of controls and patients with nicotine [$F(1,22)=6.44$, $p<.02$, $n^2=.23$]. Planned follow-up analyses of these type-of-deviant effects indicated that the MMN latencies of controls were shorter to large deviants than to small deviants [$F(1,22)=7.83$, $p<.01$, $n^2=.26$]. To sum up, there were no
differences in latencies between the groups and conditions. Only the MMN latencies of controls were affected by stimulus deviance; they were shorter to large deviants than to small deviants.

4.2.6 P3a event-related potentials

Means and standard errors for P3a amplitudes and latencies derived at Cz from difference waveforms are provided in Table 25. The asterisks in the table indicate that only controls had significant P3a components to both deviants. The P3a components of patients in both conditions were not significant for either type of deviant. ANOVA results indicated that there was no significant group difference between the P3a amplitudes of controls and patients with placebo to either deviant [small: $F(1,22)=0.09, p<.09,\text{ power}=.06$; large: $F(1,22)=1.51, p<.23,\text{ power}=.22$]. The overall P3a amplitudes of controls and patients with nicotine were significantly different [$F(1,22)=4.63, p<.04, n^2=.17$]. Planned follow-up comparisons of this group effect revealed that controls had a larger P3a amplitude to large deviants than patients with nicotine [$F(1,22)=5.89, p<.02, n^2=.21$], but that their P3a amplitudes to small deviants were not different.

Table 25. Mean (SE) P3a Amplitudes and Latencies at Cz to Small- and Large-Deviant Stimuli, with Significance of P3a Amplitudes Compared with the Zero Baseline

<table>
<thead>
<tr>
<th></th>
<th>P3a Amplitude</th>
<th>P3a Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Small Deviants</td>
</tr>
<tr>
<td></td>
<td>$\mu V$</td>
<td>$\mu V$</td>
</tr>
<tr>
<td>Controls (n=12)</td>
<td>0.46(0.3)*</td>
<td>0.95(0.2)**</td>
</tr>
<tr>
<td>Patients with Placebo (n=12)</td>
<td>0.38(0.2)</td>
<td>0.55(0.3)</td>
</tr>
<tr>
<td>Patients with Nicotine (n=12)</td>
<td>0.20(0.2)</td>
<td>0.32(0.3)</td>
</tr>
</tbody>
</table>

*p < .05; **p < .01
The analysis of controls and patients with placebo indicated that they were affected by stimulus deviance, but this effect failed to attain significance \[ F(1,22)=3.72, p<.067, n^2=.15 \]. Planned follow-up analyses of this type-of-deviant effect revealed that controls had a larger P3a amplitude to large deviants compared to small deviants \[ F(1,22)=4.10, p<.055, n^2=.16 \]. To sum up, controls had significant P3a components to both deviants, but patients in both conditions did not have significant P3a components for either the small or the large deviants. The only difference between the groups and conditions was that controls had a greater P3a amplitude to large deviants than patients with nicotine. The only effect of stimulus deviance was for controls, who had greater P3a amplitudes to large deviants than to small deviants. None of the analyses of P3a latencies found significant effects.

4.2.7 RON event-related potentials

Means and standard errors of RON amplitudes and latencies at Fz from difference waveforms are provided in Table 26. The asterisks in the table indicate whether the RON amplitudes were significantly different from the zero baseline. Only controls had significant RON components to both deviants, while patients in both conditions had significant RON components only to large deviants. None of the ANOVAs of RON amplitudes and latencies found significant effects.

4.2.8 Correlations

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

4.2.8.1. RT, accuracy, ERP, PANSS, medication and TWSC ratings of patients

Longer reaction times of patients in the placebo condition to small-deviant stimuli were associated with higher scores on the excitement item of the positive-symptoms subscale of the PANSS [Kendall's tau(12)=.51, p<.04]. Smaller MMN amplitudes to small deviants of patients with placebo were associated with higher scores on the anxiety sub-item of the general psychopathology scale of the PANSS [Kendall's tau(12)=-.51, p<.04]. Larger MMN amplitudes of patients with placebo to large deviants were associated with higher scores on the "stereotyped thinking" sub-item of the negative scale of the PANSS [Kendall's tau(12)=-.60, p<.02]. Smaller RON amplitudes in patients with placebo to small deviants were
Table 26. Mean (SE) RON Amplitudes and Latencies at Fz to Small- and Large-Deviant Stimuli, with Significance of RON Amplitudes Compared with Zero Baseline

<table>
<thead>
<tr>
<th></th>
<th>RON Amplitude</th>
<th>RON Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Small Deviants</td>
<td>Large Deviants</td>
</tr>
<tr>
<td>MV</td>
<td>μV</td>
<td>μV</td>
</tr>
<tr>
<td>Controls (n=12)</td>
<td>-0.49(0.2)*</td>
<td>-0.39(0.2)**</td>
</tr>
<tr>
<td>Patients with Placebo (n=12)</td>
<td>-0.32(0.3)</td>
<td>-0.65(0.2)**</td>
</tr>
<tr>
<td>Patients with Nicotine (n=12)</td>
<td>-0.39(0.2)</td>
<td>-0.64(0.2)**</td>
</tr>
</tbody>
</table>

*p<.05; **p<.01

associated with higher scores on the General Psychopathology Scale of the PANSS \[r=-.61, p<.03\]. There were no significant correlations between the ERPs of patients and their TWSC ratings. There were no significant correlations between nicotine-induced "change" scores for ERPs and nicotine-induced "change" ratings for the TWSC. Patients' doses of antipsychotic medication (measured in chlorpromazine equivalents; Bezchlibnyk-Butler & Jeffries, 2006) were not correlated with their ERPs or behavioural results.

4.2.8.2. Correlations between ERPs

In patients with placebo, greater MMN amplitudes to small-deviant stimuli were associated with larger P3a amplitudes to small-deviant stimuli \[r=.64, p<.03\] and to large-deviant stimuli \[r=.67, p<.02\]. Greater MMN amplitudes in patients with placebo to large-deviant stimuli were associated with greater P3a amplitudes to large-deviant stimuli \[r=.71, p<.01\]. In patients who ingested placebo, greater RON amplitudes to large-deviant stimuli were correlated with greater MMN to small deviants \[r=.66, p<.02\] and large deviants. \[r=.69, p<.01\]. In patients who ingested placebo, larger P3a amplitudes to large deviants were associated with longer P3a latencies to wide deviants \[r=.69, p<.01\]. In patients who
took placebo, larger RON amplitudes to small deviants were associated with shorter RON latencies to small deviants \( r=-.60, p<.04 \).

4.3 Discussion

This experiment tested the hypothesis that minimally-deprived schizophrenic smokers would show behavioural and electrophysiological evidence of abnormal distractor processing, with performance measures indicating greater responsivity to task-irrelevant acoustic deviants, but with ERP measures showing less responsivity with respect to pre-attentive detection, involuntary attentional switching and attentional re-orientation. It was also hypothesized that these abnormalities might be altered with acute nicotine intake. For both controls and patients, reaction times to visual targets were slightly but significantly prolonged when they were preceded by a rare auditory deviant compared to when they were preceded by a frequent auditory standard. There was thus evidence that the processing of the irrelevant auditory deviant did have a detrimental effect on the visual detection task. However, accuracy of detection of the visual target was not affected by the prior presentation of the auditory deviant. Patients had a lower accuracy, demonstrating that the task was more difficult for them. Many reasons could account for this difference in accuracy, including deficits in sensory encoding and perception of the visual stimuli and/or inability to sustain attention.

The MMN was attenuated in the patient group following presentation of the small deviant stimuli. This replicates many previous studies. The MMN following presentation of the large deviant was slightly but not significantly reduced in the patients compared to the controls. Muller-Gass et al. (2006) noted that attention to the auditory train of stimuli can increase the amplitude of the MMN elicited by small deviants. One reason for this is that attention might improve the discriminability of the standard and deviants, or perhaps alter the sensory memory for the standards. Attention did not alter the MMN elicited by the large deviant because it was already easy to discriminate from the standard. It is possible that controls were able to attend to both the auditory and visual stimuli, thereby increasing their MMN to the small deviant. Patients may not have had the attentional capacity to attend both stimuli, with the result that their MMN to small deviants was attenuated compared with controls'.
P3a amplitudes and latencies did not differ for patients and controls, but only controls had greater P3a amplitudes to large deviants than to small ones. There were no differences between the RON components of patients and controls. As in Experiment 2, patients in Experiment 3 exhibited significant distraction effects (prolongation in RT following presentation of the large deviant) without showing a significant P3a. This is not consistent with Näätänen's (1990, 1992) model of auditory processing, which seemed to require that behavioural distraction be preceded by a switching of attention accompanied by a significant P3a. However, since Näätänen specified that the threshold for the switching of attention may vary across groups, it is possible that very small MMN and P3a components may be sufficient to trigger an attention switch and consequent distraction in schizophrenic patients.

Nicotine exerted important effects on patients' behavioural and electrophysiological measures. Unlike controls and patients in the placebo condition, patients who took nicotine did not show prolonged reaction times in response to task-irrelevant frequency deviants. Unlike the MMN amplitudes of patients in the placebo condition, the MMN amplitudes of patients in the nicotine condition to small deviants did not differ from that of controls. Also unlike patients who were administered placebo, patients who received nicotine had smaller P3a amplitudes to large deviants than control participants. A possible mechanism through which nicotine may have changed patients' MMN amplitudes is by nicotine's activation of nicotinergic α7 brain receptors, which affect NMDA by modulating the release of many neurotransmitters. All the effects described above were independent of early sensory processing, as N1 amplitudes and latencies to standard stimuli were similar in patients and controls and were not affected by nicotine administration. The nicotine effect appears to reflect an absolute effect of nicotine since it was not related to smoking withdrawal intensity or to nicotine-induced withdrawal relief.

4.3.1 Results for healthy subjects in this experiment vs. results in Escera-type studies

Part of the objectives of this experiment was to use an auditory-visual distraction paradigm similar to that of Escera and colleagues (see review in Escera, Alho, Schröger, & Winkler, 2000) because this paradigm had been successful in eliciting small but significant behavioural and ERP distraction effects in healthy subjects. Did this experiment obtain
similar results? This is determined by comparing the results of Escera-type studies with the results obtained by this experiment's control participants.

Starting with behavioural performance, the results for control subjects in this experiment indicate that hit rates were not affected by task-irrelevant changes in frequency in unattended auditory stimuli. On the other hand, RTs were significantly prolonged by 12 ms following presentation of large (42%) frequency deviances. They were also prolonged by 13 ms following small (15%) frequency deviances, but that difference was not statistically significant (\(p<.07\)). Similar results have been found in other Escera-type studies. In Yago, Corral and Escera (2001), for example, a 10% frequency deviance significantly prolonged RT to visual stimuli by 8 ms. In contrast, when the extent of deviance was very small (5%), RT was reported to decrease and when deviance was large (65% to 80%), no effect on RT was observed. The same study found no deviance effect on hit rates to any of its six frequency deviants, some of which were almost identical to the ones in this study (15% and 40%). Reviews of Escera-type studies (Escera, Alho, Schröger, & Winkler, 2000; Escera, Alho, Winkler, & Näätänen, 1998) reported that relatively minor changes in frequencies such as the ones used in this experiment produced reductions in accuracy (hit rates) of about 2%, and RT reductions of about 5 ms, while obtrusive novel sound deviants produced RT prolongations of 20 ms and longer.

Table 27 presents the ERPs obtained in this experiment to those obtained in Yago, Corral, & Escera (2001). The Yago et al. study was chosen for this comparison because it included stimuli with almost the same degrees of deviance. Even more important, it is among the few studies of this type that published detailed ERP results. In Yago et al., the auditory stimuli were a 600 Hz standard tone (\(p = .82\)) and six deviant tones (\(p = .03\) each) which differed in frequency by 5% (630 Hz), 10% (660 Hz), 15% (690 Hz), 20% (720 Hz), 40% (840 Hz) and 80% (1080 Hz). This experiment used a 1200 Hz standard one (\(p = .80\)) and two deviant tones (\(p = .10\) each) which differed in frequency by 15% (1025 Hz) and 42% (1200 Hz). Table 27 only shows the Yago et al. results for the 15% and 40% deviant frequencies.
Table 27. ERP Amplitudes in this Experiment and in Yago, Corral and Escera (2001)

<table>
<thead>
<tr>
<th></th>
<th>MMN (μV)</th>
<th>P3a (μV)</th>
<th>RON (μV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yago, Corral, &amp; Escera (2001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15% deviant</td>
<td>-0.93*</td>
<td>0.58</td>
<td>-1.23**</td>
</tr>
<tr>
<td>40% deviant</td>
<td>-0.72*</td>
<td>1.02*</td>
<td>-1.62**</td>
</tr>
<tr>
<td>Experiment 3, results for controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15% deviant</td>
<td>-0.76**</td>
<td>0.46*</td>
<td>-0.49*</td>
</tr>
<tr>
<td>42% deviant</td>
<td>-1.18**</td>
<td>0.95**</td>
<td>-0.39**</td>
</tr>
</tbody>
</table>

*p < .05; **p < .01

The results in Table 27 indicate that there are many similarities between the two sets of results. The gaps between the MMN and P3a amplitudes of the two studies are almost all relatively small: 0.17 μV for the MMN amplitudes to the 15% deviant, 0.42 μV for the MMN to the 40-42% deviant, 0.12 μV for the P3a to the 15% deviant and 0.07 μV for the MMN to the 40-42% deviant. The only difference in significance relative to the zero baseline is that the P3a to the 15% deviant is significantly greater than zero in this experiment, but not significant in the Yago et al. study. On the other hand, Yago et al. reported significant P3a amplitudes to their 10% and 20% deviants. Differences in RON amplitudes between the two studies are greater (0.74 μV for small deviants and 1.23 μV for large) than for the MMN and the P3a, but this could be due to differences between the tasks. Subjects in this experiment discriminated between letters and numbers, while subjects in the Yago et al. experiment discriminated between even and odd numbers. Overall, this comparison of the results of the Yago et al. experiment and of this experiment suggests that Experiment 3 was quite successful in replicating the results of Escera-type distraction experiments.

4.3.2 Behavioural differences between controls and patients in the placebo condition

The behavioural discrimination task did not produce significant differences in RTs between controls and patients in the placebo condition. However, controls had a higher hit rate than the patients. This finding of diminished accuracy in the patients is consistent with
previous findings of impairment in sustained attention (vigilance) in schizophrenia (Green, 1996; Sharma & Antonova, 2003). Sustained attention is often assessed with the Continuous Performance Test, in which subjects monitor a series of numbers or letters and are asked to press a button when they detect a specified target. Schizophrenic patients typically miss more targets than healthy controls, even in the absence of distraction (Nestor & O'Donnell, 1998). The fact that patients required much more frequent breaks (rest periods) than controls in this experiment in order to maintain adequate performance in this experiment suggests that sustaining attention on the task was more difficult for the patients.

Frequency deviances had no significant effect on the hit rate of either controls or patients who took placebo. These results are not consistent with the predictions formulated for Experiment 3. It was predicted that both controls and patients would experience deviance-related decreases in hit rates, with greater decreases in patients than in controls. The RTs of both patients and controls were affected by irrelevant stimulus deviance. Large-deviant frequencies prolonged the RTs of controls by 17 ms and the RTs of patients by 14 ms. The RTs of controls to small deviants were also prolonged by 13 ms, but this result did not reach statistical significance ($p=.07$). These RT prolongations confirm that the frequency deviants distracted patients and controls away from the discrimination task and toward the deviant stimuli.

The lack of a deviance effect on the hit rates of the patients, and the lack of difference between patients and controls in deviance-associated performance alterations, are unexpected given previous reports of increased patient vulnerability to distraction (Braff, 1993). This result is particularly surprising since healthy subjects have shown distraction effects on accuracy measures with similar paradigms (see review in Escera et al., 2000). A possible explanation for the patients' results is the lack of representativity of the sample of patients who participated in this experiment. As described earlier, these patients did not differ from controls in intelligence or in years of schooling. Schizophrenic patients typically perform one to two standard deviations below the general population on neuropsychological tests (Bilder, 1997). The problem is that only "high functioning" (the psychiatrists' term) patients can be enrolled in studies with this type of paradigm because less "high functioning" patients are unable to perform the task adequately.
4.3.3 MMN differences between controls and patients in the placebo condition

The MMN was attenuated in the patient group following presentation of the small deviant stimulus. This replicates many previous studies (reviewed by Umbricht & Krljes, 2005). The MMN following presentation of the large deviant was slightly but not significantly reduced in the patients compared to the controls. One possible reason for the difference in MMN to small deviants may be due to reduced attentional capacities in the patients. Muller-Gass, Stelmack and Campbell (2006) have noted that attention to the auditory train of stimuli can increase the amplitude the MMN elicited by small deviants. One reason for this is that attention might improve the discriminability of the standard and deviants or perhaps alter the sensory memory for the standards. Attention to the auditory stimuli was not necessary to alter the MMN elicited by a large deviant because it was already easy to discriminate from the standard. It is thus possible that controls were able to attend to both the auditory and visual stimuli. This benefited the processing of the small deviant but not the large deviant. The patients may not have been as attentive as the controls given their reduced attentional resources. This would not have affected the MMN elicited by the large deviant but would have resulted in an attenuated MMN following presentation of the small deviant.

The other significant MMN effect in Experiment 3 was that the MMNs of controls and patients both showed stimulus deviance effects: both groups had greater MMN amplitudes to large deviants than to small deviants. This is a well-known effect of "bottom up" processes, that is an effect of the magnitude of the irrelevant deviances (Berti, Roeber, & Schröger, 2004). "Bottom up" mechanisms react to raw sensory input, shifting attention quickly and automatically to potentially important changes in our environment. The greater the change, the greater the reaction. In addition, controls had shorter MMN latencies to large deviants than to small deviants, while the MMN latencies of patients did not distinguish between the two types of deviants. The shortening of the MMN latencies of controls to increases in stimulus deviance, which was also found in Experiment 2, is compatible with theories suggesting that healthy people are more efficient than schizophrenic patients at processing irrelevant information (Birkett, Brindley, Norman, Harrison, & Baddeley, 2006; Gooding, Braun, & Studen, 2006; Wang et al., 2005).
4.3.4 P3a differences between controls and patients in the placebo condition

There were no statistically significant differences between the P3a amplitudes of patients and controls. This is surprising because the P3a components of patients to both deviants, unlike those of controls, were so small that they were not significantly different from the zero baseline. This lack of group difference does not appear to be due to a reduction in the P3a amplitudes of controls, since their P3a amplitudes were not much smaller than the ones obtained with similar stimuli in the study by Yago, Corral and Escera (2001; see comparison in Table 27). The ANOVA results suggest that the lack of a significant group difference may be related to low statistical power, at least for group differences in P3a amplitudes to small deviants, and possibly also to large deviants (power = .06 for P3a amplitude to small deviants; .22 to large deviants). The cause of these statistical difficulties, apart from the small number of subjects, is that these components are very small and that the deviance in patient's results is relatively large. The P3a amplitudes of controls, unlike those of patients, were greater to large deviants than to small deviants.

Although the lack of group differences between patients and controls on the P3a was unexpected, the small size of patients' P3a components (neither was different from the zero baseline) is consistent with previous findings of reduced P3a components in schizophrenic patients (see review earlier in this thesis). Reductions of the P3a component in schizophrenia were associated with many brain regions (Laurens et al., 2005). According to Valkonen-Korhonen et al. (2003), who found normal MMN components and diminished P3a components in schizophrenic patients, no single neural dysfunction is responsible. Instead, they suggested that many impairments are involved, including a deficit in sensory memory trace formation, alterations in deviance detection processes and deficits in attentional processes. The result is that unlike a healthy brain, in which deviance detection processes instantly update its model of the sensory input as the changes occur (Sussman et al., 2001, 2002), the brains of schizophrenic patients appear to have imbalanced processes of temporospatial deviance detection.

In Experiment 3, as in Experiment 2, schizophrenic patients had a significant MMN to large deviants, and a prolongation in reaction time to large deviants, despite not having a significant P3a component to large deviants. As mentioned in the discussion for Experiment 2, these results do not necessarily contradict Näätänen's model of auditory processing, which
seemed to require that a significant P3a accompany behavioural distraction. Since Näätänen (1990, 1992) specified that the threshold for the switching of attention may vary across individuals and groups, perhaps even very small MMN and P3a components are capable of provoking an attention switch and consequent behavioural distraction in schizophrenic patients.

In controls, but not in patients, larger P3a amplitudes were associated with shorter reaction times. In patients with placebo, greater MMN amplitudes were associated with greater P3a amplitudes and longer P3a latencies to large deviants.

4.3.5 RON differences between controls and patients in the placebo condition

There were no statistically significant differences between the RON amplitudes of patients and controls, even though the RON component to small deviants of patients was not significantly different from zero. In Figure 6, however, the RON components of controls and the RON components to large deviants in patients in both conditions are clearly visible.

RON correlation results for controls are consistent with the Schroger-Wolff theory that this component is associated with the reorienting of attention back to the task after distraction. There was a strong association ($r=.62$) between larger RON amplitudes and longer reaction times to standard and large-deviant stimuli. This is the reverse of the pattern for the P3a, where larger P3a amplitudes were associated with shorter reaction times. In patients who took placebo, larger RON amplitudes were associated with larger MMN amplitudes.

4.3.6 Nicotine effects

Nicotine administration was associated with important effects in patients in this experiment. Most importantly, nicotine appears to have changed behaviour: nicotine-treated patients were less distractible than controls. Unlike controls and patients in the placebo condition, whose reaction times were prolonged in response to irrelevant large frequency deviants, patients who ingested nicotine showed no prolongation in reaction times following these deviants. Unlike the MMN amplitudes of patients in the placebo condition, the MMN amplitudes to small deviants of patients in the nicotine condition did not differ from that of controls. Nicotine may have changed patients' MMN amplitudes by activating nicotinergic
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α7 brain receptors, which affect NMDA by modulating the release of dopamine, glutamate, GABA, serotonin and acetylcholine (Berman, Talmage, & Role, 2007). Several studies have found links between NMDA receptor hypofunction and deficits in the MMN (reviewed in Umbricht & Krljes, 2005). NMDA antagonists have been shown to induce patterns of symptoms similar to those of schizophrenia (Javitt, 2007).

Finally, nicotine administration in patients was associated with reduced P3a amplitude to large deviants such that it became significantly smaller than the P3a of controls. Indeed, this nicotine-altered P3a did not significantly vary from the zero baseline. The absence of the P3a suggests that ingestion of nicotine prevented the inappropriate switching of attention from the visual task to the processing of the irrelevant auditory deviant. Since the P3a is believed to have frontal generators (Friedman, Cycowicz et al., 2001), this effect may reflect frontal lobe inhibitory action to regulate the control of attention (Lewis, Cruz, Eggan, & Erickson, 2004; Volk & Lewis, 2002). Nicotine may therefore have served to prevent the behavioural distraction seen in patients in the placebo condition. The P3a is consistent with the performance data. RTs to the visual task preceded by the large auditory deviants were prolonged in patients following ingestion of the placebo. They were not prolonged following ingestion of nicotine.

Nicotine affected the distraction-related ERPs of schizophrenic patients both by increasing some (MMN to small deviants) and by decreasing others (P3a to large deviants). This suggests a moderating function resembling the executive "top-down" control that is attributed to working memory functions based in the prefrontal cortex. San Miguel, Corral and Escera (2008) argue that a clear link between attentional control and working memory is emerging, with the evidence pointing toward a role of working memory in controlling the balance between the exogenous (involuntary) and endogenous (voluntary) mechanisms of attention. This experiment's results suggest that, under specific conditions, nicotine may improve attention and reduce distraction by bolstering deficient working memories. This is consistent with the theory of Newhouse, Potter and Singh (2004) to the effect that nicotine enhances cognition in smokers and in patients with cognitive problems, but would not improve and may even impair cognitive functioning in people who are already at or near their optimal cognitive level.
4.3.7 Relations between medication, clinical ratings, tobacco withdrawal and results

There were no correlations between medication status and any of the results in this experiment. There were no associations between patients' behavioural or ERP results and their tobacco withdrawal symptoms. Smaller MMN and RON amplitudes were associated with higher scores on the general psychopathology scale of the PANSS. Smaller MMN amplitudes were also associated with positive symptoms including delusions, suspiciousness and hostility.

5.0 SUMMARY AND CONCLUSION

The purpose of this thesis was to use behavioural performance measures (hit rates, RT) and distraction-related ERPs (MMN, P3a, RON) to gain a better understanding of the cerebral processes related to distractor processing in schizophrenia, and a better understanding of the effects of nicotine on this processing in schizophrenic smokers. To accomplish this, three double-blind, placebo-controlled experiments with different paradigms were performed. The subjects were minimally-nicotine-deprived (3 hours) schizophrenic smokers and healthy smokers.

Study 1 used a passive (non-task) paradigm in which subjects watched a silent video while they heard (and were instructed to ignore) frequent and rare deviant tones. The results replicated many previous studies showing that patients had diminished MMN amplitudes following presentation of both frequency and duration deviants. Contrary to previous findings that MMN components associated with duration deviants were more diminished in schizophrenia than MMN components associated with frequency deviants (see review by Umbricht and Krljes, 2005), this study found larger patient deficits in MMN components elicited by frequency deviants than by duration deviants. Strong correlations between the frequency and duration MMN amplitudes of schizophrenia patients suggested that even though the acoustic change detection processes underlying the frequency and duration MMNs are different, they are closely connected in the patients. As reduced frequency MMNs are seen in late but not in early schizophrenia, and attenuated duration MMNs are seen regardless of disease progression, the current findings raise hopes that the MMN, and the frequency MMN in particular, might offer a biological marker of post-onset progressive cognitive deterioration in schizophrenia (Todd et al., 2008; Umbricht & Krljes, 2005). If that
were the case, it would have profound theoretical and clinical implications for understanding and treating schizophrenia (van der Stelt & Belger, 2007).

Relative to controls, patients treated acutely with nicotine still exhibited diminished frequency MMNs but not duration MMNs. Given that the initiation of smoking behaviour precedes symptom expression in young schizophrenic patients (Gurpegui et al., 2005; Riala, Hakko, Isohanni, Pouta, & Räsänen, 2005) and that reduced duration, but not frequency MMNs, are exhibited in first-episode patients and early schizophrenia (Salisbury et al., 2002; Todd et al., 2008), nicotine effects on MMN elicited by duration properties may reflect actions on vulnerability mechanisms predisposing to schizophrenia.

It is not easy to speculate on the specific mechanism through which nicotine might have effected these changes since the causes of the differences between the MMN of schizophrenic and healthy individuals are still unclear. Current theories include deficits in the encoding of stimulus features preventing the formation of precise memory traces against which deviant stimuli can be compared; possible problems with the frontal-lobe attention switching mechanism that the MMN may initiate; or a failure of coordination between different brain regions, in particular between the temporal and frontal lobes. According to Jacobsen et al. (2004), whose schizophrenic patient subjects underwent fMRI scanning while they performed a selective attention task with and without nicotine, nicotine enhanced functional brain connectivity in the patients. Since this increased functional connectivity included a network of regions including the frontal cortex, nicotine may activate an auditory-cortex-frontal lobe network responsible for the automatic processing of sound duration changes. Considerable evidence has implicated deficient NMDA receptor functioning in MMN deficits in schizophrenia (Krystal et al., 2003) and in functional disconnectivity in schizophrenia in particular (Nestor et al., 2001). Given that NMDA receptors are indirectly activated by nicotine (Purves et al., 1997), these nicotine-related functional changes may be one factor underlying smoking-schizophrenia co-morbidity.

Study 2 of this thesis used the novel auditory distraction paradigm of Schröger and Wolff (1998b) that embeds task-irrelevant deviant features within task-related stimuli. The Schröger-Wolff paradigm had to be modified for this study because most schizophrenia patients were unable to adequately perform the required tone-duration discrimination task. Instead, an easier location-discrimination task was used in which subjects detected the ear of
delivery of the tones. Unfortunately, the location-discrimination task produced much weaker behavioural and electrophysiological effects than the conventional Schröger and Wolff task. One possible reason for the difference in results was that the presentation of half of the stimuli in each ear, instead of all in the same ear or in both ears simultaneously, interfered with the formation of a strong memory trace for the standard stimulus. Another possibility is that spatial selection, which is a fundamental and powerful form of selective attention, may be highly resistant to distraction effects.

In spite of this drawback, the results of Study 2 included prolongations in reaction times to deviant stimuli, indicating that the deviants had caused some deterioration in performance in both patients and controls. Patients' MMNs did not differ from those of controls but they were greater to large deviants than to small. The cause of this stimulus deviance effect was a very small (non significant) patients' MMN to the small deviant. More importantly, patients in this study also had diminished (non-significant) P3a and RON components to both deviants. The finding of such a small P3a component, which is an electrocerebral index of attentional switching, was unexpected given the evidence of distraction provided by the prolongations in the reaction times of patients. These results appeared to suggest that the Näätänen model of auditory processing may not apply to schizophrenic patients. Under Näätänen's model, the attention-orienting process starts with an MMN-indexed detection of change in the environment. If the change is of sufficient magnitude, a subsequent significant P3a signals a switch in the orienting of attention away from the task and toward the processing of the irrelevant deviant stimulus. This switch of attention then produces a deterioration in performance on the original task. However, it is suggested that the results of Study 2 may be reconciled to Näätänen's model. The model proposed a threshold for the switching of attention that may vary across individuals and groups. Perhaps the threshold required for schizophrenia patients is lower than for healthy controls.

The main nicotine effect in Study 2 was on patients' MMN amplitude to the small deviant. The gap between the MMN to the small and the large deviant that was observed in patients who ingested placebo was not observed in patients who took nicotine. This nicotine effect was achieved by increasing the MMN amplitudes of patients to the small deviant to the point where they became statistically significant. One possible reason why this MMN was so
small may be related to differences in the attentional capacities of patients and controls. The original Naätänen model (1990) had claimed that the MMN was unaffected by manipulations of attention, but Naätänen et al. (2007) now state that the MMN can sometimes be modified by attention because attention might enhance the discriminability of deviant stimuli (Muller-Gass et al., 2006). This effect is strongest for the detection of small deviants, since large deviants do not need help to be discriminated. It is also possible that attention plays a greater role in a paradigm where deviants are embedded in the task-relevant stimuli, since subjects actively attend to the auditory channel in which irrelevant deviant features are presented. As a result, it is possible that the greater attentional capacities of controls, by increasing their MMN to the small deviant, prevented them from having a stimulus-deviance effect like the one observed in the patients. Kassel (1997) suggested that nicotine improves cognition in two ways: by increasing the attentional resources allocated to the task-relevant stimuli, and by narrowing the brain's internal stimulus filter that inhibits the processing of irrelevant stimuli. In Study 2, nicotine appears to have increased the attentional resources of the patients to all stimuli, including the small deviants.

Study 3 used a visual task with auditory frequency deviants. These deviants caused patients and controls to have prolongations in reaction time to the task. The MMN of patients to the small deviant were non-significant and reduced compared to those of controls. The P3a amplitudes of patients and controls did not differ but the P3a to both deviants of the patients were so small that they were not significant. Once again, patients were exhibiting an MMN and evidence of behavioural distraction without having a significant P3a.

Nicotine exerted important behavioural and ERP effects in this experiment. Patients who were administered nicotine were less distractible than controls. Unlike controls and patients who ingested placebo, patients who ingested nicotine did not exhibit prolongations in their reaction times following the presentation of deviant tones. These same patients who were administered nicotine also exhibited smaller P3a amplitudes than controls, suggesting that nicotine dampened the frontal attention-switching function contributing to behavioural distraction. In addition, nicotine caused the MMN of patients to the small deviant to increase to the point where it was no longer significantly different from that of controls. In this study, nicotine affected the ERPs of patients by increasing some (MMN to small deviants) and decreasing others (P3a to large deviants). These effects suggest that nicotine is playing a
moderating role that resembles the executive "top-down" control that is attributed to working memory functions based in the prefrontal cortex. These results give support to theories suggesting that, under specific conditions, nicotine may improve attention and reduce distraction by bolstering deficient working memories.

These nicotine-related attentional/cognitive actions in patients are consistent with recent findings on DMXB-A, a novel partial α7 nAChR agonist that is currently undergoing clinical trials in schizophrenia and has been shown to improve sensory gating (Olincy et al., 2006). According to the most recent report (Freedman et al., 2008), DMXB-A improved patients' scores on attention/vigilance and working memory and reduced their negative symptoms. These findings provide support to the theory that schizophrenic patients smoke as self-medication to relieve early sensory processing deficits that may mediate their cognitive and clinical symptoms (Lasser et al., 2000). Since intact cognitive processes are crucial to the capacity of schizophrenia patients to lead normal social and professional lives, it is highly desirable that more research be devoted to this promising field. Perhaps even more important for schizophrenic patients who smoke to self-medicate their cognitive symptoms, the development of nicotine drugs that could take the place of cigarettes could also reduce the harmful health consequences associated with smoking.

The experiments performed for this thesis had limitations. Their main weakness was the small number of participants. It was mentioned several times in reporting these experiments that surprising non-statistically-significant differences may have been due to too-low statistical power. This study would also have been enriched by using multiple nicotine doses and routes of nicotine administration which more closely mimic smoking (e.g. nicotine inhaling) and by having both patients and controls take acute nicotine, instead of only patients, and having non-smoking as well as smoking participants. The study would have gained by using a larger number of electrodes, especially electrodes positioned at mastoid and frontal sites using nose reference, in order to be able to examine the separate effects of nicotine at these different sites (Kujala et al., 2007). There is of course an ethical concern when nicotine is administered to non-smoking participants. On the other hand, the decision to investigate the effects of nicotine on patients and control subjects who smoke was justified. Researchers who use nonsmoking subjects, such as Barr et al. (2008) in a recent study, for example, must then qualify their findings as follows:
We chose to investigate the effects of nicotine in nonsmokers and excluded smokers to avoid the confounding effects of nicotine withdrawal and reversal effects on outcome measures. Findings in nonsmokers with schizophrenia may not generalize to smokers with schizophrenia because smokers with schizophrenia may have pathophysiological differences compared with nonsmokers, including more severe disease.

The objectives pursued by Barr et al. (2008) are legitimate ones but they are not the ones that were pursued in this thesis. One of the objectives of this thesis was to gain a better understanding of the reasons why schizophrenic smokers have such a high rate of smoking (while keeping in mind that smoking involves more than ingesting nicotine; see Forchuk et al., 2002). This could not have been achieved with a sample of nonsmoking patients.

Another main problem with this study was that the patients were not typical schizophrenia patients. They had to be exceptionally "high-functioning" (the psychiatrists' term) to be able to perform the relatively complex tasks required for these experiments. As a result, this study must also specify that its results cannot be generalized to all smokers with schizophrenia. This poses a challenge to future researchers, who must find paradigms that can examine the cognitive effects of nicotine without requiring that the patient subjects be exceptionally competent. Finally, the fact that all the patients were taking antipsychotic medication was not considered a problem since previous studies found no effect of typical or atypical antipsychotics on the MMN (Schall et al., 1998; Umbricht et al., 1998, 1999), and since no correlation was found between patients' dosage of antipsychotic medication and any of their behavioural or ERP results. A recent study by Rezvani et al. (2007) found that clozapine had impaired attentional function in rats, but only one patient who participated in this study was taking that medication.

Given the pivotal role of NMDA receptor hypofunction in schizophrenia, future studies may wish to examine the separate and combined effects of nicotine and NMDA agonists on attentional processing in these patients.
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NART SCORE SHEET

Subject Name: ________________________________
Group: ________________________________
Code No. ________________________________

APPENDIX A

 Column 1

— DEBT
— DEBRIS
— AISLE
— REIGN
— DEPOT
— SIMILE
— LINGERIE
— RECIPE
— GOUGE
— HEIR
— SUBTLE
— CATACOMB
— BOUQUET
— GAUGE
— COLONEL

 Column 2

— SUBPOENA
— PLACEBO
— PROCREATE
— PSALM
— BANAL
— RAREFY
— GIST
— CORPS
— HORSE D'OEUVRE
— SIEVE
— HIATUS
— GAUCHE
— ZEALOT
— PARADIGM
— FACADE

 Column 1

— CELLIST
— INDICT
— DENTE
— IMPUGN
— CAPON
— RADIX
— AEON
— EPITOME
— EQUIVOCAL
— REIFY
— INDICES
— ASSIGNATE
— TOPIARY
— CAVEAT
— SUPERFLUOUS

 Column 2

— LEVIATHAN
— PRELATE
— QUADRUPED
— SIDEREAL
— ABSTEMIOUS
— BEATIFY
— GAOLED
— DEMESNE
— SYNCOPE
— ENNUI
— DRACHM
— CIDEVANT
— EPERGNE
— VIVACE
— TALIPES
— SYNECDOCHE

VLQ = 128.7 - .89 (x errors) = ________________________________
PIQ = 119.4 - .42 (x errors) = ________________________________
FSIQ = 127.8 - .78 (x errors) = ________________________________
APPENDIX B
MODIFIED FAGERSTROM TEST FOR NICOTINE DEPENDENCE

Please answer one answer for each question.

1. How many cigarettes a day do you usually smoke?
   - 0 1 - 10
   - 0 11 - 20
   - 0 21 - 30
   - 0 31 or more

2. What type of cigarette do you smoke?
   - Low nicotine (0.9 mg or less)
   - Medium nicotine (1.0 to 1.2 mg)
   - High nicotine (1.3 mg or more)

3. How often do you inhale the smoke from your cigarette?
   - Never
   - Sometimes
   - Always

4. How soon after you wake up do you smoke your first cigarette?
   - Within less than 5 minutes
   - Within 6 - 30 minutes
   - Within 31 - 60 minutes

5. Do you smoke more during the first two hours of the day than during the rest of the day?
   - No
   - Yes

6. Which cigarette would you most hate to give up?
   - The first cigarette in the morning
   - Any cigarette other than the first one

7. Do you find it difficult to refrain from smoking in places where it is forbidden, such as public buildings, on airplanes or at work?
   - No
   - Yes

8. Do you still smoke when you are so ill that you are in bed most of the day?
   - No
   - Yes
APPENDIX C

Date_________________________ ID#_________________________

Modified Reasons for Smoking Scale

Using the scale below, write the number that most accurately indicates how you feel about the statement on the blank line.

1 = Never
2 = Seldom
3 = Occasionally
4 = Frequently
5 = Always

1. I smoke cigarettes to keep myself from slowing down. /_____/
2. Handling a cigarette is part of the enjoyment of smoking it. /_____/
3. Smoking cigarettes is pleasant and relaxing. /_____/
4. I light up a cigarette when I feel angry about something. /_____/
5. When I have run out of cigarettes, I find it almost unbearable until I can get one. /_____/
6. I smoke cigarettes automatically without even being aware of it. /_____/
7. It is easier to talk and get along with other people when smoking. /_____/
8. I smoke cigarettes to stimulate me, to perk myself up. /_____/
9. Part of the enjoyment of smoking a cigarette comes from the steps I take to light up. /_____/
10. I find cigarettes pleasurable. /_____/
11. When I feel uncomfortable or upset about something, I light up a cigarette. /_____/
12. I am very much aware of the fact when I am not smoking a cigarette. /_____/
13. I light up a cigarette without realizing I still have one burning in the ashtray. /_____/
14. While smoking I feel more confident with other people. /_____/
15. I smoke cigarettes to give me a «lift». /_____/
16. When I smoke a cigarette, part of the enjoyment is watching the smoke as I exhale. /_____/
17. I want a cigarette most when I am comfortable and relaxed. /_____/
18. When I feel «blue» or want to take my mind off cares and worries, I smoke cigarettes. /_____/
19. I get a real gnawing hunger for a cigarette when I haven't smoked in a while. /_____/
20. I've found a cigarette in my mouth and did not remember putting it there. /_____/
21. I smoke much more when I am with other people. /_____/

TOBACCO WITHDRAWAL SYMPTOM CHECKLIST

Date: ___________________________ ID # ___________________________
Test session: ___________________________

Below are a list of symptoms that may occur following abrupt cessation or reduction in the amount of cigarettes smoked. Please fill in the circle beside the answer that best describes how you are feeling right now.

1. Irritability, frustration or anger
   - ○ not present
   - ○ mild
   - ○ moderate
   - ○ severe

2. Difficulty concentrating
   - ○ not present
   - ○ mild
   - ○ moderate
   - ○ severe

3. Restlessness
   - ○ not present
   - ○ mild
   - ○ moderate
   - ○ severe

4. Anxiety, nervousness
   - ○ not present
   - ○ mild
   - ○ moderate
   - ○ severe

5. Hunger
   - ○ not present
   - ○ mild
   - ○ moderate
   - ○ severe

6. Depressed mood
   - ○ not present
   - ○ mild
   - ○ moderate
   - ○ severe

7. Desire to smoke
   - ○ not present
   - ○ mild
   - ○ moderate
   - ○ severe

SCORE: ___________________________