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Generation Of Mismatch Negativity In A Sample Of Treatment-Resistant Schizophrenia Patients

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ABSTRACT

Generation of Mismatch Negativity in a Sample of

Treatment-Resistant Schizophrenia Patients

Denise L. Milovan

Mismatch negativity (MMN) was recorded in thirteen treatment-resistant schizophrenic patients and age- and gender-matched fourteen healthy controls. The MMN was obtained by subtracting the standard from the deviant event-related potential (ERP) brain wave. Subjects responded to infrequent visual stimulation while ignoring binaurally presented auditory input. The patient population showed a larger frequency-MMN amplitude than the normal controls. Separate analyses of the standard and deviant waveforms revealed the expected reduction in the amplitude of the MMN from frontal to central and parietal locations in the control group. In contrast, treatment-resistant patients had the largest MMN amplitudes recorded at the central-posterior electrode location. Although no cerebral lateralization was noted, the patient group displayed larger negativities at the left and right temporal sites, and at the left frontal scalp location than the normal subjects. Behavioral and ERP measures of performance to task-relevant stimuli yielded no group differences for reaction time, or P300 amplitude. The percentage of correct responses was excellent for all subjects, but controls were more accurate.

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Generation of Mismatch Negativity in a Sample of Treatment-Resistant Schizophrenia Patients

According to the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, APA, 1994), a diagnosis of schizophrenia is made when an individual is afflicted, for a minimum of six months, by at least two of the following characteristic symptoms: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, flattened or otherwise inappropriate affect, as well as diminished performance in one or more areas of functioning such as work, social relationships, self-care, and academic achievement. Lifetime prevalence rates for schizophrenia are similar throughout the world and range between 0.5 and 1% (APA, 1994). Although quite variable in its manifestations, schizophrenia tends to be a chronic disorder with a debilitating impact on the lives of the individuals affected.

In general, the severity of a psychiatric disorder is determined by taking into account several factors. These include the degree of psychosis, duration of illness, along with the length of negative psychological and social influences. Recent studies have reported that as many as 20 to 25% of the beds available in psychiatric facilities are occupied by schizophrenic patients, which account for 40% of long-duration hospitalizations (Talbott et al., 1987; Meise & Fleischhacker, 1996). Furthermore, schizophrenic patients have been found to exhibit severe impairments in their cognitive functioning levels and in their adaptability to social norms. Reports from prospective investigations suggest that five years after diagnosis, 60-70% of schizophrenic patients

continue to experience many social difficulties such as the inability to hold a job and a decrease in the number and quality of their social relationships (Meise & Fleischhacker, 1996). In addition, approximately 10-20% of all schizophrenic patients commit suicide (Winokur & Tsuang, 1975). Most studies agree that the outcome of schizophrenia may be classified as: good in 20 to 30% (complete remission of symptoms after neuroleptic treatment), intermediate in 40 to 60% (partial control of symptoms with medication), and poor in the remaining 20 to 30% (neuroleptic treatment fails to control symptom severity) of cases (Harding et al., 1987; McGlashan, 1988). This classification suggests that a large proportion of patients diagnosed with schizophrenia do not respond adequately to current pharmacological interventions.

Definitions of treatment-resistant patients range from very general to very specific. A recently published guideline for the treatment of schizophrenic patients, edited by the APA (1997), defines treatment-resistant patients as those who are either unresponsive or only partially responsive to available pharmacological treatments. These patients must continue to display positive and negative symptoms as well as bizarre behaviors and deficits in social functioning that interfere with community adaptation while medicated. A more specific definition proposes that a conclusion of treatment unresponsiveness can be drawn if a patient fails to respond to a trial of three neuroleptics of different classes using adequate doses over a standard period of administration of about 3-4 weeks (Kane et al., 1988). Lieberman (1993) argues that 30-60% of schizophrenia patients are refractory to available treatments, while Brenner et al. (1990) found that 5-25% of patients are clinically unresponsive to antipsychotic medication. The difference

in the percentages of non-responders between these investigations may be linked to the exclusion from the latter study of the patients who developed adverse effects to specific neuroleptic drugs. An additional difficulty associated with the pharmacological treatment of non-responders is that clinicians often resort to increases in antipsychotic drug dosage in an attempt to stabilize these patients. Such increases in drug levels elevate the risks of side effects associated with the administration of neuroleptics, which in turn may have a negative impact on subsequent treatment compliance. Empirical evidence has established that high dose treatments offer no advantages for patients with a history of neuroleptic refractoriness (Levinson et al, 1990; Van Putten et al., 1990; Rifkin et al., 1991; Volavka et al, 1992). Taken together, the above mentioned statistics are quite disturbing. The negative personal and social effects of their condition are especially severe. This underscores the importance of specifically investigating the neurocognitive function associated with treatment-refractory schizophrenia.

Schizophrenia and Behavioral Measures of Attention Processes

In general, attention may be defined as a gateway to a mechanism of limited capacity which selects external sensory and internal memory data that need to be integrated into coherent representations (Treisman, 1969; Öhman, 1979). Attention, however, is a multifaceted concept. Kietzman (1991), for example, has argued that there are several types of attention that are pertinent to the study of psychopathology.

Controlled and automatic attentional processes have received considerable attention as a framework into which to conceptualize and study attention in

schizophrenia. According to Posner and Snyder (1975), the automatic attention mechanisms are believed to occur without conscious volitional awareness, in parallel and without interfering with other ongoing cognitive operations. They are assumed to underlie not only highly skilled or practiced activities, but also the sensory analysis of external inputs (Posner, Snyder, & Davidson, 1980; Posner & Snyder, 1975). Sensory processes have also been termed preconscious or preattentive because they are hypothesized to occur in the absence of conscious thought, although their outcome may yield conscious representations (Strayer & Kramer, 1990). Controlled attentional processes have been interpreted as demanding conscious effort. Hence, they are believed to occur serially because they deplete large amounts of attentional capacity and interfere with the performance of other mental activities. Proponents of automatic and controlled attention theories have abandoned the view that attention processes occur in a fixed and serial progression. Instead they proposed a more flexible view according to which attention can be allocated flexibly across mental activities (Posner, Snyder, & Davidson, 1980; Posner & Snyder, 1975).

Automatic and controlled attention are core concepts of capacity theories (Allport et al., 1972; Posner and Snyder, 1975; Schneider and Shiffrin, 1977; Shaffer, 1975). Applications of capacity models to schizophrenia provide a meaningful way to explain some of the generalized performance deficits that have been associated with the disorder. Capacity theories propose that performance deficits are due to: limited task-processing resources, inability to adequately execute tasks that employ controlled processes, failure to carry out automatized processes which have become deautomatized, inappropriate

modulation of arousal, or failure to gain access to the generalized pool of attentional resources (Spring et al., 1991).

The description of schizophrenic psychopathology, put forth by Bleuler in 1908, considered that attentional deficits constitute a central feature of the disorder. Kraepelin (1919) suggested that the cognitive impairments observed in schizophrenia are consistent with difficulties in directing one's attention to relevant external stimuli. Since then, numerous experimental studies have found event-related potentials evidence that schizophrenia is associated with significant cognitive impairments, particularly on tasks that are heavily influenced by attentional demands (Michie et al., 1990; Prichard, 1986; Baribeau, 1986; Baribeau, Picton, & Gosselin, 1983). Psychiatric patients diagnosed with schizophrenia have been shown to be adversely affected by distractors (Chapman & McGhie, 1962). This impairs their ability to reach good levels of performance by effectively reducing their capacity to attend to task-relevant information (Neale & Cromwell, 1977).

Few data have been obtained to date on the pre-attentional abilities in schizophrenia and even less is known in relation to subtypes of schizophrenia (Baribeau, 1986; Hemsley, 1994). Treatment refractory patients have been excluded from many investigations because standard dosage could not be ascertained. The inability of these patients to profit from standard neuroleptic trials often constitutes an exclusion criteria for selection in pharmacological investigations (Spohn & Strauss, 1989). Consequently, there is no data on the status of pre-attentive processes in carefully selected treatment-resistant schizophrenic patients. Nevertheless, studying automatic attentional processes

in treatment-resistant schizophrenics may be highly useful for improving the understanding of the cognitive functions of this group of patients and subsequently, for increasing treatment efficacy.

Studies of automatic attentional processes using simple reaction time and binaural listening tasks showed that schizophrenics have inferior reaction times and shadowing accuracy, and display an increased variability in their responses when compared to normal control subjects (Broen, 1968; Hemsley, 1982; Lieh-Mak & Lee, 1997). Lieh-Mak & Lee (1997), interpreted these findings as suggesting that schizophrenics can not uphold a consistent cognitive readiness in order to respond adequately to stimulation. Wahl (1976) also found that schizophrenic patients were impaired in their ability to perform well a binaural listening task and concluded that schizophrenia patients are inefficient in filtering irrelevant stimuli.

Deficits of controlled attention have been repeatedly shown to be impaired in schizophrenic patients (Callaway & Naghdi, 1982; Neuchterlein & Dawson, 1984 Straube & Oades, 1992). However, these deficits do not preclude the presence of impaired pre-attentional processes in schizophrenic patients.

Event Related Potentials and Attention

Although behavioral findings point to deficits in attentional processes as a characteristic of schizophrenia, these data can not control for potentially confounding motivational and/or motor difficulties (Baribeau et al., 1983; Neuchterlein & Dawson, 1984). Furthermore, the information obtained from neuropsychological measures of

cognitive abilities can be influenced by external signals such as emotion eliciting stimuli. Thus, neuropsychological tasks often need to be analyzed in terms of the interaction between automatic activation and conscious processing strategies, which makes it difficult to disentangle controlled from automatic processes (Posner & Snyder, 1975).

Given the limitations imposed on the investigation of attentional skills through the use of behavioral cognitive batteries, new approaches to the study of the brain have become increasingly popular.

Recent advances in medical technologies and computer sciences have been instrumental in the design of more accurate techniques for the study of brain structures and functions. Some of these new techniques include: Computed Tomography (CT) which has a relatively poor time resolution (15-20 min.); Magnetic Resonance Imaging (MRI) which provides high resolution structural information, but can also provide some functional information because of a better time resolution than that of the CT (7-10 min.); Positron Emission Tomography (PET) and Single-photon Emission Computed Tomography (SPECT) which have excellent time resolution, but use invasive radioactive elements (Filipek, Kennedy, & Caviness, 1992; Lou, 1992). All these methods attempt to enhance our understanding of the correlation between the brain activity and the underlying cognitive processes. Nevertheless, high procedural costs, invasiveness, and poor time resolution constitute some important limitations that make the routine use of such techniques impractical, at the present time.

A different method of investigating the relationships between brain activity and simultaneously occurring external events is one that employs event-related potentials

(ERP). ERPs are recordings of the electrical activity of large groups of neurons that are extracted from electroencephalogram (EEG) recordings by averaging EEG samples that are time-locked to the event of interest. ERPs are advantageous because they can be obtained through noninvasive methods, have better time resolution (msec) than scans, and can be economically recorded simultaneously from different scalp locations allowing for a topographical analysis of the response pattern. An additional highly relevant advantage offered by ERPs to the study of attention is that they enable researchers to study processes which may be argued to occur with or without conscious attention, and therefore can not be readily disentangled by means of purely behavioral procedures. ERP research thus provides a popular and noninvasive methodology for the study of the brain in relation to mechanisms of attention and information processing (Näätänen & Alho, 1995a, Picton et al., 1984). These advantages notwithstanding, it is important to note that ERPs are optimal for functional explanations of cerebral events that are sufficiently well synchronized and organized to generate electrical activity that is recordable at the surface of the scalp. The ability of ERP procedures to localize the exact source of the brain activation is rather limited (Steinschneider, Kurtzberg, & Vaughan, 1992; Vaughan & Arezzo, 1988). Therefore, for a precise sub-cortical localization of the brain activation other techniques such as magnetoencephalographic recordings (MEG) are preferable.

In ERP studies peaks, waves, deflections, and components are measured. The ERP components have been conceptualized as sources of controlled and observable variability of relatively large numbers of neurons found in specific regions of the brain which are activated by specific stimulus manipulations (Baribeau & Braun, 1983;

Baribeau & Laurent, 1993; Campbell et al., 1981; Donchin, Ritter & McCallum, 1978; Näätänen & Picton, 1987; Picton et al., 1978, 1984). Näätänen (1992), argues that ERP components are best understood by means of experimental manipulations which allow researchers to uncover the underlying component structure of brain waveforms.

In ERP research some peaks have been traditionally associated with controlled attention-related tasks. They are the N100, N200b, as well as the P300 and processing negativity (PN). The N100 and the N200b are negative peaks which occur at approximately 100 msec and 200 msec, respectively, following stimulus onset. The N100 is a negative brain wave which is influenced by attention eliciting stimuli. The N100 has been found to display different scalp distributions to different experimental manipulations (Knight, Hillyard, Woods, & Neville, 1980; Näätänen & Picton, 1987). Thus the N100 can not be associated with a single cerebral event.

The N200b is a negative peak which is elicited by infrequent stimuli in tasks during which attention is directed to the input (Kline, Fruhstorfer, & Finkenzeller, 1968). The N200b appears to be related to the violation of expectations (Näätänen, 1992).

The P300 is a positive deflection peaking at about 300-400 msec after the stimulus. The P300 is an attention dependent wave and it is elicited by multiple cognitive operations associated with the detection of targets (Catts et al.,1995; Pritchard, 1986). Thus, the P300 is thought to reflect controlled attentional mechanisms associated with the detection of target stimuli.

The PN is another ERP component that was proposed to reflect another controlled attention process. It is elicited by auditory stimuli which are actively attended (Baribeau,

El Massioui, Dalbokova, & Renault, 1998; Baribeau, & Laurent, 1993; Näätänen & Alho, 1995b; Röschke et al., 1996; Ward, Catts, Fox, Michie, & McConaghy, 1991).

Early studies of information-processing in schizophrenia (Baribeau, 1983, 1986; Baribeau & Laurent, 1986, 1991; Baribeau-Braun, Picton, & Gosselin, 1983; Laurent & Baribeau, 1991, 1992; Roth et al., 1980) compared several ERP positive and negative waves elicited in patients and controls in response to experimental changes. These investigations looking at the N100 and P300 peaks provided support for controlled attentional disturbances in subtypes of schizophrenic patients. For example, the P300 was found to be significantly reduced in schizophrenic patients. The PN component was also found to be reduced in schizophrenic patients and this was interpreted to suggest difficulties in maintaining attention to relevant stimuli while effectively ignoring others (Ward et al., 1991).

The above reported abnormalities, however, do not distinguish between impairments of pre-attentive and controlled processing. It is thus possible that one or both of these mechanisms are disturbed in schizophrenia. To date, few studies have investigated preattentive mechanisms in schizophrenia. These studies used measures such as sensory gating and visual perceptual grouping (Place & Gilmore, 1980). None of the investigations of automatic attention, however, were performed with treatment-resistant patients. Therefore, the present investigation will be directed at the study of pre-attentive processes using an ERP component that is believed to reflect automatic processing.

Mismatch Negativity: An Index of Auditory Automatic Processing

The mismatch negativity (MMN) component has been argued to be an index of auditory preattentive processing (Näätänen, 1992). The MMN was initially isolated from the auditory N2 deflection. The N2 was divided into an earlier-latency MMN component and a later N2b wave using a variety of experimental manipulations (Näätänen, 1992; Näätänen, 1979; Näätänen & Gaillard, 1983). The early MMN is typically elicited by low probability deviant (target) stimuli embedded in a sequence of high probability (standard) stimuli. Näätänen (1992) proposed that automatic processing in audition yields sensory stimulus representations which lead to conscious perception and to arousal by activating the arousal mechanisms sensitive to auditory input. In this context, MMN was classified as an automatic change-detector response and is believed to provide an indirect measure of the sensory information processed by the brain. Current research focusing on the role of attention in the processing of sensory information underscores the importance of MMN data for the better understanding of auditory attentional mechanisms and their relation to sensory memory.

Two primary explanations have been proposed for the generation of the MMN: (1) it may be obtained from new afferent elements that correspond to the frequency of the deviant, but not to that of the standard tone (Thompson, Berry, Rinaldi, & Berger, 1979), and (2) is generated by a memory tracing process or echoic memory that detects changes in stimulus pattern (Näätänen, Paavilainen, Alho, et al., 1989; Näätänen, Paavilainen, & Reinkainen, 1989). The first explanatory mechanism argues that neurons responsible for the detection of deviant tones will remain activated because of long interstimulus

intervals (ISIs), while neurons responsible for standard tone frequencies and those responding to both types of stimuli will become refractory because of the short ISIs. The second explanatory mechanism implies the existence of a memory for the standard stimuli serving as a baseline against which any differences in the sequence of stimuli can be detected. According to Winkler, Reinikainen, & Näätänen (1993), a relatively constant baseline is a prerequisite for the establishment of the neural trace that is assumed to underlie the generation of the MMN.

MMN can be elicited in response to several types of stimulus discrepancies. These discrepancies include changes in frequency, intensity, spatial locus of origin, rise time, duration, phonetic structure, and partial omissions (Näätänen, 1992). Frequency (pitch) differences were found to elicit MMN even when subjects were instructed to perform visually challenging tasks, supporting the contention that MMN is elicited in the absence of conscious processing of pitch information. A possible technical limitation associated with the use of pitch differences to obtain an MMN difference wave is that when the magnitude of the deviation is increased, there is a decrease in the latency of the MMN. This increases the risk of a temporal overlap between MMN and earlier negativities (Duncan & Kaye, 1987; Novak et al., 1990; Sams et al., 1985).

Interpretations of the MMN component can also be limited by the types of tasks employed to elicit it. The amplitude of the ERP difference between standard and deviant tones is larger in conditions under which subjects are asked to actively direct their attention away from the auditory stimuli. Active ignore conditions require subjects to perform a distractor task during stimulus presentation, such as responding to visual items.

If subjects are instructed to simply ignore the tones or to read a prose passage (passive ignore) during stimulus presentation, this does not ensure that instructions have actually been followed, and the MMN may be reduced in amplitude or contaminated by other overlapping waves. Thus, active-ignore tasks are more advantageous than passive-ignore tasks because they help reduce the technical difficulties arising when subjects direct their attention to the auditory stimuli.

Although active ignore conditions have been demonstrated to elicit the clearest MMN difference waves, the MMN component has been argued to be elicited irrespective of controlled attention by numerous researchers (Winkler, Reinikainen, & Näätänen, 1993; Näätänen, 1992). Some authors have argued that the MMN is not completely independent of attention given that a strong attention focus can amplify the amplitude of the MMN difference wave and portions of the MMN may be overlapped by negativities produced by controlled attention (Woldorff, Hackley, & Hillyard, 1991). Woldorff et al. (1991) reported that attended auditory deviants elicited a larger MMN beginning at approximately 100 msec and peaking at about 200 msec while unattended targets elicited a less large negativity. Näätänen (1991), in a commentary on the influences of strong attentional focus on the amplitude of the MMN, acknowledged that there is a possibility that the intensity-MMN amplitude but not the frequency-MMN amplitude may be affected to a small extent by attentional focus. However, smaller intensity-MMN amplitudes in the absence of strongly focused attention might be simply due to dampening of the intensity-MMN amplitude generator process and not to a suppression of sensory processing in the absence of attentional focus (Näätänen, 1991).

Another factor that needs to be addressed is role of drugs on the MMN component. Näätänen (1992) reported that the MMN is increased by drugs with general activating effects and attenuated by drugs with deactivating effects on the central nervous system. As discussed below, neuroleptic medications appear to have little impact on the MMN (Catts et al. 1995; Javitt, Doneshka, Grochowski, & Ritter, 1995). In most studies, the dosage and type of neuroleptic medication were not specified, thus it is difficult to assess the validity of such data.

The relatively good understanding of what are the brain generators of the MMN difference wave increases the suitability of this component for research and clinical diagnosis purposes. As a result, MMN data have already been applied to the study of perceptual and learning capacities, the early development of the auditory system, the effects of aging on auditory sensory memory, and to patients with frontal-brain lesions, schizophrenia, and Parkinson's disease. However, topographical analyses of the MMN have been conducted mostly with normal control subjects. These investigations have demonstrated that the MMN component is maximal over the frontal-central cortical areas and may be explained, in large part, by the activity of bilateral generator sources situated in the supratemporal auditory cortex. Magnetoencephalographic recordings have provided additional support for the existence of a supratemporal auditory cortex generator of the MMN (Hari et al., 1984; Sams et al., 1985). Furthermore, the frequency-MMN generated in the supratemporal auditory cortex was found to invert it's polarity below the sylvian fissure recorded at mastoid electrode sites (Paavilainen et al., 1991; Alho et al., 1992). This inversion constitutes a useful confirmatory measure of the generation of the

MMN in studies conducted by different investigators and using different procedures. An additional MMN generator has been identified in the frontal cortex (Giard et al., 1990). Giard et al. (1990), have demonstrated that the MMN component elicited by pitch changes had a distribution that is maximal over the right frontal cerebral hemisphere. Similar right hemispheric preponderance of the MMN obtained in response to changes in frequency, intensity, or duration of the deviant stimuli were reported by Paavilienen et al. (1991). Alho et al. (1994a) evaluated the role of the dorso-lateral prefrontal cortex (DPFCx) in the generation of the MMN by recording ERPs to non-attended auditory stimuli from patients with DPFCx lesions and found an attenuation of the MMN in the patient population as compared to normal controls. This finding is compatible with the possible implication of the frontal cortex in the generation of the MMN.

Investigations of pre-attentional processes in the auditory modality are especially relevant for schizophrenia since auditory hallucinations constitute a core characteristic of the symptoms associated with the disorder. Furthermore, observations of an attenuation of the frontal MMN in schizophrenia would provide convergent evidence for the findings of frontal lobe and more specifically, of DPFCx deficits associated with the disorder (Akbarian et al., 1993; Benes et al., 1991; Zec & Weinberger, 1986). A demonstration of MMN disturbances in schizophrenia may also provide further support to the claim that this disorder is associated with disturbances of the mechanisms responsible for automatic auditory attention.

Studies of Mismatch Negativity in Schizophrenic Patients

To date only few ERP investigations of information processing in schizophrenia have evaluated the MMN. In a preliminary study conducted by Shelley et al. (1991), MMN was elicited in an active-ignore paradigm in which auditory stimuli were presented binaurally and subjects were distracted with an attention-demanding visual task. Deviant stimuli (10%) were short-duration (50 msec; short-duration condition) 633 Hz tones and standard stimuli (90%) were long-duration (100 msec; long-duration condition) 633 Hz tones and vice-versa. Patients were medicated schizophrenics. The MMN was recorded from midline and lateral sites referenced to linked ears. Only data obtained from the frontal midline electrode (Fz) was presented. The MMN component was found to be significantly attenuated in medicated schizophrenia patients as compared to normal controls in the long deviant condition but not in the short deviant condition. Shelly at al. (1991) speculated that the lack of an MMN amplitude reduction in the short deviant condition may be partly due because the short deviant stimuli are more attention capturing and elicit a P3a in controls which artificially reduces the amplitude of the MMN.

A subsequent study conducted by Javitt, Doneshka, Zylberman, Ritter, & Vaughan, (1993) studied medicated, chronic schizophrenic patients using a passive auditory oddball task. Auditory stimuli were 1000 Hz standards and 1024 Hz targets occurring with a 0.6% sequential probability. All subjects were instructed to ignore the tones, but no control measures were designed to assess subjects' compliance with instructions. ERPs were recorded from four midline electrode placements and left and

right mastoid locations. All electrodes were linked to a nose reference and the MMN was unconventionally defined as the peak negativity to deviant stimuli occurring within the 50-150 msec without subtracting them from standard tones. Group differences were reported at Fz, with smaller MMN amplitudes found in the patient population.

In a more recent investigation using a similar paradigm to the one employed in their 1993 study, Javitt et al. looked at the MMN differences in two groups of schizophrenics, one chronic-medicated and one unspecified neuroleptic-free (Javitt et al., 1995). The MMN component was obtained by subtracting the standard from the deviant waveform and the MMN amplitude was defined as the maximal negative peak in the 50-200 msec latency range at the Fz recording site. There was an amplitude reduction of the MMN in patients as compared to normal controls, however, no differences were found between medicated and drug-free schizophrenics.

Catts et al. (1995) investigated sensory processing in medicated and neuroleptic-free schizophrenic patients using an active-ignore MMN paradigm, similar to that of Shelley et al. (1991). The two schizophrenia groups were compared to a group of normal control subjects and to one of patients with bipolar affective disorder. ERPs were recorded from 16 scalp locations but the mean MMN amplitude over a 150-225 msec. epoch, was calculated for each individual subject by using only the ERPs recorded from the Fz scalp site. The MMN amplitude was reduced in schizophrenic patients irrespective of group classification when they were compared to normal controls but not to bipolar patients. Similar to the results previously reported by Shelley et al. (1991), the attenuation effects for the MMN in schizophrenic patients were stronger for the long-duration than

for the short-duration deviants. Catts et al. (1995) did not propose a formal account of this difference.

Kathmann, Wagner, Rendtorff, & Engel, (1995) compared the performance of medicated schizophrenics in stabilized condition to that of chronic alcoholics and normal controls during performance on a selective attention paradigm. Subjects were required to ignore auditory tones (20%, 1000 Hz deviants and 80%, 600 Hz standards) while tracking a luminous spot on the computer screen. Eye-tracking performance was controlled using horizontal EOG measurements. No significant differences in the amplitude of the MMN were found between the three groups, but the MMN was found to display a delayed latency in both groups of patients as compared to controls. Kathmann et al. (1995), argued that these findings may represent a slowing of automatic information processing in schizophrenia and alcoholic patients.

Investigations of Mismatch Negativity in the Current Project

The current study proposes to further investigate potential MMN abnormalities in a group of treatment-resistant schizophrenic patients whom, as previously noted, represent a significant proportion of all patients diagnosed with schizophrenia and for whom current treatment modalities are ineffective. To date, there are no reports of MMN measures in groups of treatment-resistant patients. Hence, a study of indices of pre-attentive processes using the MMN component is of particular interest. Findings of MMN deficits in treatment-resistant schizophrenia patients would support the hypothesis that automatic processing deficits represent a trait of these patients.

Previous studies which have compared the MMN amplitude in neuroleptic-free versus medicated schizophrenic patients report no differences between the two groups. However, these studies did not state whether the schizophrenic subjects were classified as treatment-refractory. Consequently, the present project will investigate the MMN in a group of treatment-resistant patients receiving progressively lower doses of medication that are nonetheless effective for patients who respond to neuroleptic medications.

The ERP task selected for this project has been found to demonstrate an MMN amplitude reduction in patients with DPFCx lesions (Alho et al, 1994a). Schizophrenia has been associated with DPFCx lesions (Akbarian et al., 1993; Benes et al., 1991; Zec & Weinberger, 1986). More specifically, the task consists of an active-ignore paradigm in which standard and deviant tones of higher frequency are presented in a binaural sequence. There are several advantages associated with this paradigm one of which being that it affords an examination of the degree to which subjects have followed the task instructions. As it has been already remarked, MMN is elicited under both passive and active-ignore conditions, but the latter paradigm is more advantageous from a technical standpoint. Measurements of reaction time and of percentage of correct responses to the visual stimuli will permit the verification that all subjects performed the ERP paradigm in a similar manner. Moreover, a comparison of the P300 deflection in response to visual stimuli between controls and patients will provide a good indication that visual targets were equally well attended to by both groups. Previous MMN studies that used frequency changes have either failed to find MMN differences between treatment-responsive patients and controls (Kathmann et al., 1995), or they employed passive-attention

paradigms that are not directly comparable to the present study (Javitt et al., 1993; Javitt et al., 1995).

Although ERPs were recorded from different scalp locations in all of the studies reviewed, none of them have reported data from topographical analyses of the MMN in schizophrenic patients. To date, demonstrations of MMN amplitude reduction at frontal electrode locations have been interpreted to support the presence of anomalous pre-attentive mechanisms in schizophrenia. However, a topographical analysis of the MMN component may further enrich our understanding of the pattern of cerebral activation in response to auditory sensory inputs displayed by schizophrenic patients. In addition, a demonstration of reversed polarity of the ERP difference waveform at lateral mastoid sites in the current paradigm will confirm the generation of the MMN component.

The negativities elicited by standard and deviant brain waves will be analyzed in the latency ranges where significant group differences in the amplitude of the MMN are found. This data will provide some indication with regards to potential overlapping effects between the pre-attentive MMN and similar latency negativities associated with controlled attentional processes.

A reduction in the amplitude of the MMN component in treatment-resistant schizophrenic patients would support the hypothesis of disturbed automatic attentional processes in the auditory modality. In addition, given the evidence of reduced MMN in treatment-responsive schizophrenics regardless of their medication status, a decreased MMN in the present patient sample would provide further support for the contention that reduced MMN may be a trait characteristic in schizophrenics.

Method

Subjects

A group of 13 medicated, treatment-resistant schizophrenic subjects (10 men, 3 women), ages 22-65 year old, were selected from patients admitted at Louis Hypolite Lafontaine Hospital. Patients fulfilled the DSM-IV (APA, 1994) criteria for schizophrenia, as determined independently by at least two psychiatrists with extensive experience with schizophrenia and blind to event-related potential data. Treatment-resistance was established by the treating physician. The minimum criteria used to determine treatment refractoriness were: (1) the current episode was treated without a significant clinical improvement for at least 6 months despite a continual neuroleptic prescription; (2) since the onset of the current episode one antipsychotic equivalent to haloperidol 30 mg was used unsuccessfully for a minimum of 6 weeks; (3) no period of good function since at least 24 months despite the use, during a sufficient period of two antipsychotics from at least two chemical classes or for the past five years despite the use of three antipsychotics. All schizophrenic patients were on a reduced medication regimen in view of a change of medication. Although neuroleptic treatment varied for each subject it was maintained within the limits of what is considered to be an effective dose for most subjects who respond to antipsychotic medications. Patients with additional active major medical or neurological illness, exposure to electro-convulsive therapy (ECT) or psychosurgery, a history of substance abuse were not included in the study. Additional clinical information was obtained on symptom severity, from ratings on the

Brief Psychiatric Rating Scale (Overall & Gorham, 1962; Appendix A); level of formal thought disorder, as determined by scores on Positive and Negative Symptom Scales (Andreasen, 1983; Andreasen, 1984; Appendix B); depressive symptoms, from rating on the Calgary Depression Scale (Addington & Addington, 1990; Appendix C); age; gender; educational background, and handedness. The presence of extrapyramidal symptoms was not considered as ground for exclusion, however, all participants were rated using the Extrapyramidal Symptom Rating Scale (Chouinard & Ross-Chouinard, 1979; Appendix D). No subject was undergoing any form of psychological treatment at the time when they were tested.

A normal control group of 14 subjects (8 men, 6 women) was selected for participation. They were solicited by word of mouth. Attempts were made to match subject groups in terms of age and gender. Controls had no lifetime or family history of any psychiatric condition, and were in good physical health as determined from answers provided on a standard demographic questionnaire devised at the Laboratory of Human Neuropsychology and Neurophysiology (LAHNN), Concordia University (see Appendix E).

Evoked Potential Recordings

Electrodes were placed on the scalp according to the 10-20 International System (see Appendix F). Electroencephalograms (EEGs) were continuously sampled (256 Hz/channel) from midline (Fz, Cz, Pz) and lateral (F3, F4, C3, C4, T3, T4, M1, M2) scalp electrode placements. For both EEG and EOG the ½ amplitude low-frequency cutoff was

set to standards of .01 Hz and the high-frequency cutoff at 100 Hz. Brain waves were digitally amplified and filtered to eliminate frequencies above 30 Hz. The signal was amplified by 100K (50 on the Grass polygraph at a programmable gain of 2). Averaging of ERPs and subtraction procedures were done using InSTEP program. InSTEP was set to continuous recording with a 75 msec prestimulus baseline and 100 msec to be recorded at the end of the task. Electrode impedance was maintained below 5 kOhm. Eye movements (EOG) were recorded from 2 electrodes, one placed above the supraorbital ridge of the right eye and one placed at the outer canthus of the left eye. A nose electrode served as reference and a scalp electrode placed 1cm posterior and to the right of C4 was used as ground. Trials on which the ERP voltage exceeded ± 100 μV were rejected from the averaging routine. Six to twelve blocks were administered in order to obtain a good resolution of the ERP.

Event-Related Potentials Test Protocol

Subjects were administered an ERP task designed to assess attention. Auditory and visual stimuli were presented in blocks of 440 stimuli, in a random order. The interstimulus interval (ISI) was kept constant at 200 msec. Auditory stimuli were 82 dB SPL pure tones lasting for 50 msec (fall and rise times of 5 msec). They were presented binaurally via headphones and consisted of standard tones of 1000 Hz occurring with a probability of 85 % and deviant tones of 1300 Hz occurring with a 10 % probability.

In addition to auditory stimuli, visual target stimuli (5 %) were presented on a computer monitor (the mean inter-target interval was 4 sec). The visual targets were a

series of four black "X"s presented on a white background (Helvetica font; Font Size 40; duration 50 msec). All visual targets appeared in the center of the computer monitor which was positioned at approximately 25 to 30 cm in front of the subject. Subjects were instructed to ignore the auditory stimuli and to respond as fast as possible when the visual targets appeared on the screen by pressing a computer keyboard (see Appendix G for verbatim instructions). Fixation was assured in the beginning of each stimulus block and subjects were required to maintain the fixation point (a small cross appearing in the middle of the computer monitor) throughout the task. Performance on the visual detection task was computer scored. Responses occurring between 80-1000 msec after stimulus onset were scored as hits, while responses occurring outside this time window were scored as misses or false alarms. All subjects completed a block of practice trials prior to the administration of the test blocks.

Procedure

Subjects were tested individually and each session lasted approximately one hour and 45 minutes. Prior to participation, each subject was explained the experimental procedures and the purpose of the study. All subjects were asked to complete a written informed consent form (see Appendix H). Subjects were instructed that they were free to withdraw their participation from the experiment at any time if they so desired, and that all data provided will be kept strictly confidential by the experimental team. Both patients and normal control subjects received a $12.00 honorarium for their participation. This research project received ethical approval from the Ethics Committee of the Louis

H. Lafontaine Hospital.

Evoked Potentials Processing and Analysis

Difference waves were obtained by subtraction of the ERP waveform elicited in the standard tone condition from the ERP waveform elicited in the deviant tone condition. ERP peak amplitudes were measured in relation to onset of stimuli, and mean voltages in reference to a 75 msec prestimulus baseline were measured over consecutive 20 msec intervals between 50 and 210 msec (50-70 msec, 70-90 msec, 90-110 msec, etc.). Averages included a sum of minimum 20 auditory deviants and 200 auditory standards per each block administered.

The results were evaluated using mixed within-subjects factorial designs and between-subjects factorial designs. Separate analyses were performed at midline electrodes (Fz, Cz, Pz), lateral electrodes (F3, F4, C3, C4, T3, T4) and mastoid locations (M1, M2). At midline electrodes data analysis for the amplitude of the MMN involved a 2 x 3 within-subjects ANOVA. At lateral electrodes data analysis involved a 2 x 2 x 3 within-subjects ANOVA. At mastoid electrodes data analysis involved a 2 x 2 between-subjects ANOVA. Significant results were adjusted using the Hundt-Feldt correction when appropriate, although the original degrees of freedom are reported. Separate analyses between the two groups were conducted at each latency interval for the MMN component as well as for the negativities elicited in response to standard and deviant auditory stimuli.

Additional analyses of variance for each group were performed for those latency

ranges where significant interactions involving the group designation were reported for the MMN component. Data analysis for the amplitude of the ERP negativities elicited by auditory stimuli involved a 2 x 2 x 3 within-subjects ANOVA and a 2 x 2 x 2 x 3 within-subjects ANOVA. Independent variables were subject groups (normal controls and schizophrenic patients); stimulus type (auditory standards and auditory deviants); cerebral hemisphere (left and right); within-hemisphere location (electrodes placed over the left and right cerebral hemispheres), and electrode site: midline (Fz, Cz, Pz) and lateral (F3, F4, C3, C4, T3, T4).

The P300 deflection of ERP wave to visual targets was identified as the largest positivity between 250 and 430 msec after stimulus onset. Amplitude and latency measurements were taken for each subject at the Pz electrode location. Group differences were evaluated using one-way ANOVA.

One-way ANOVAs were used to compare the performance of controls and patients with respect to the percentages of correct responses and the reaction times (RTs) to the visual targets.

Results

Demographics and Clinical Data

Control subjects and schizophrenic patients were group matched for age (controls M = 31.36, SD = 7.36; patients M = 39.62, SD = 12.66), t (25) = -2.05, $p < 0.06$ and gender t (25) = -1.07, $p < 0.30$. The schizophrenic subjects were individually rated on a series of clinical scales designed to assess severity of symptoms. Means and standard deviations for the scores obtained on the clinical scales by the patient group are presented in Table 1. All scores were indicative of relatively severe psychopathology with only few extrapyramidal signs.

Behavioral and P300 findings

No differences were observed between the two groups for the reaction times to the visual stimuli (controls M = 301.02, SD = 31.80; patients M = 328.40, SD = 61.70), t (18) = -1.43, $p < 0.20$. Group means for the percentage of correct responses to the visual task showed an above 90% correct level of performance for both groups. Nevertheless, control subjects responded significantly more accurately than the patient group (controls M = 98.1, SD = 1.65 %; patients M = 94.2, SD = 5.62 %), t (14) = -2.41, $p < 0.04$.

In addition, similar P300 amplitudes in response to visual targets were found in the two groups (controls M = 16.56, SD = 6.31; patients M = 18.92, SD = 9.94), F (1, 25) = 0.55, $p < 0.5$. P300 latency also failed to differentiate the groups (controls M = 367.57, SD = 34.48; patients M = 367.77, SD = 54.22), F (1, 25) = 0.0001, $p < 0.9$. Grand averages for the P300 in response to visual targets, measured at the Pz electrode location

Table 1

Summary of scores obtained on the clinical scales administered to the schizophrenic patients group

Clinical Scales (N = 10)	M	SD	Range	Severity Level
BPRS				
Total score	36	6	24 - 44	Mild to Moderate
EPSRS				
Rigidity	1	2	0 - 5	Occasional to Frequent
Tremor	2	2	0 - 8	Occasional to Frequent
Dyskinesia	2	5	0 - 15	Occasional to Frequent
PANSS				
Positive	23	3	17 - 27	Mild to Moderate
Negative	25	7	14 - 31	Mild to Moderate
General Psychopathology	46	7	36 - 53	Mild to Moderate
Calgary Depression Scale	3	2	0 - 7	Absent to Mild

Note. BPRS = Brief Psychiatric Rating Scale, EPSRS = Extrapyramidal Symptom Rating Scale, PANSS = Positive and Negative Syndrome Scale.

are presented in Figure 1. These behavioral and ERP data confirm that both groups of subjects were adept at attending to the task relevant stimuli and were following instructions.

Descriptive statistics for the ERP waveforms

Descriptive statistics for the mismatch negativity amplitude for the patient and control groups at each of the eight latency ranges defined at every 20 msec, between 50 and 210 msec are found in Appendix I. The grand averaged ERP waveforms for the MMN component for the schizophrenic patients and for the control group are presented in Figure 2.

Descriptive statistics for the amplitudes of the unsubtracted waveforms elicited in response to the deviant and standard tones are found in Appendix J. Separate analyses of variance were conducted at each of the eight latency ranges between 50 and 210 msec for the MMN.

MMN: Midline Electrodes

At midline electrode locations a significant main effect of group was found in the 190 to 210 msec range, F (1, 25) = 6.02, $p < 0.05$ (see Table 2). ERP waveforms in the schizophrenic group showed a significantly larger MNN amplitude in the 190 to 210 msec latency window than the normal controls.

A significant main effect of electrode was observed between 70 and 150 msec in the following latency ranges: 70-90 msec, F (2, 50) = 5.21, $p < 0.05$; 90-110 msec, F (2, 50) = 10.61, $p < 0.001$; 110-130 msec, F (2, 50) = 16.38, $p < 0.001$, and 130-150 msec, F

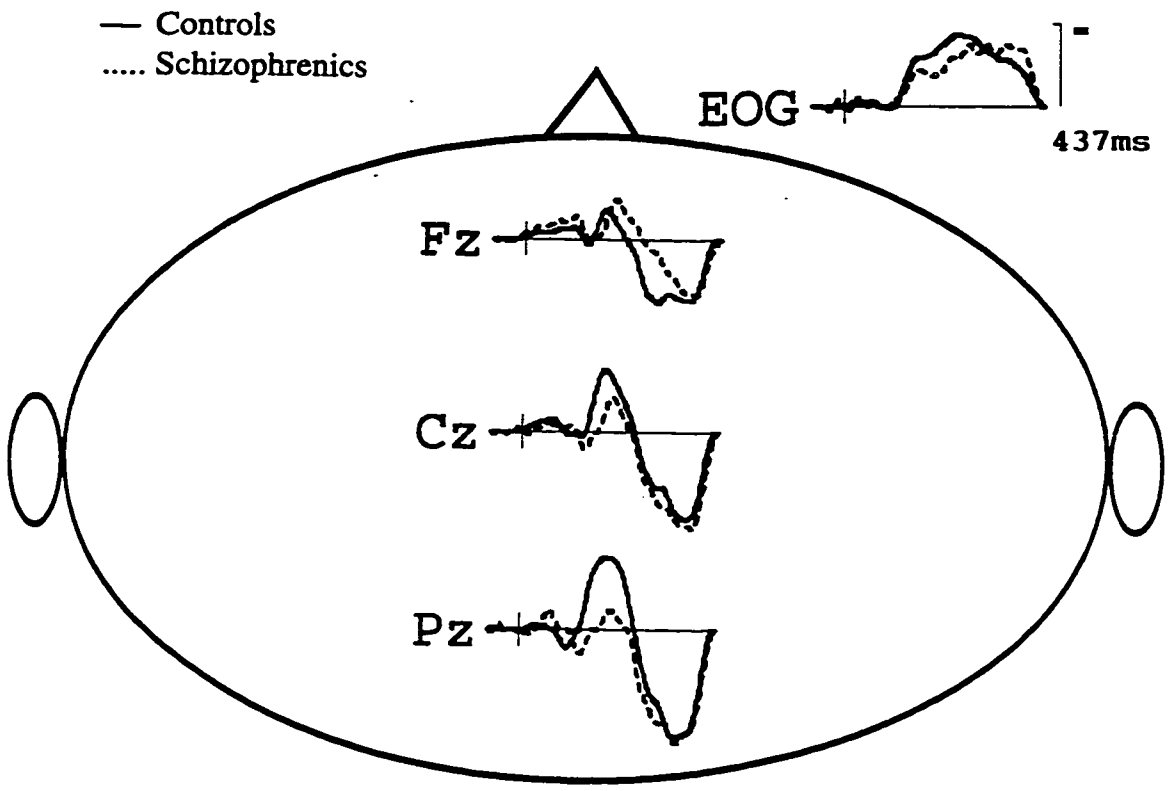

Figure 1. Grand averaged waveforms for the P300 to visual stimuli in normal controls (n = 14) and in treatment-resistant schizophrenic patients (n = 12).

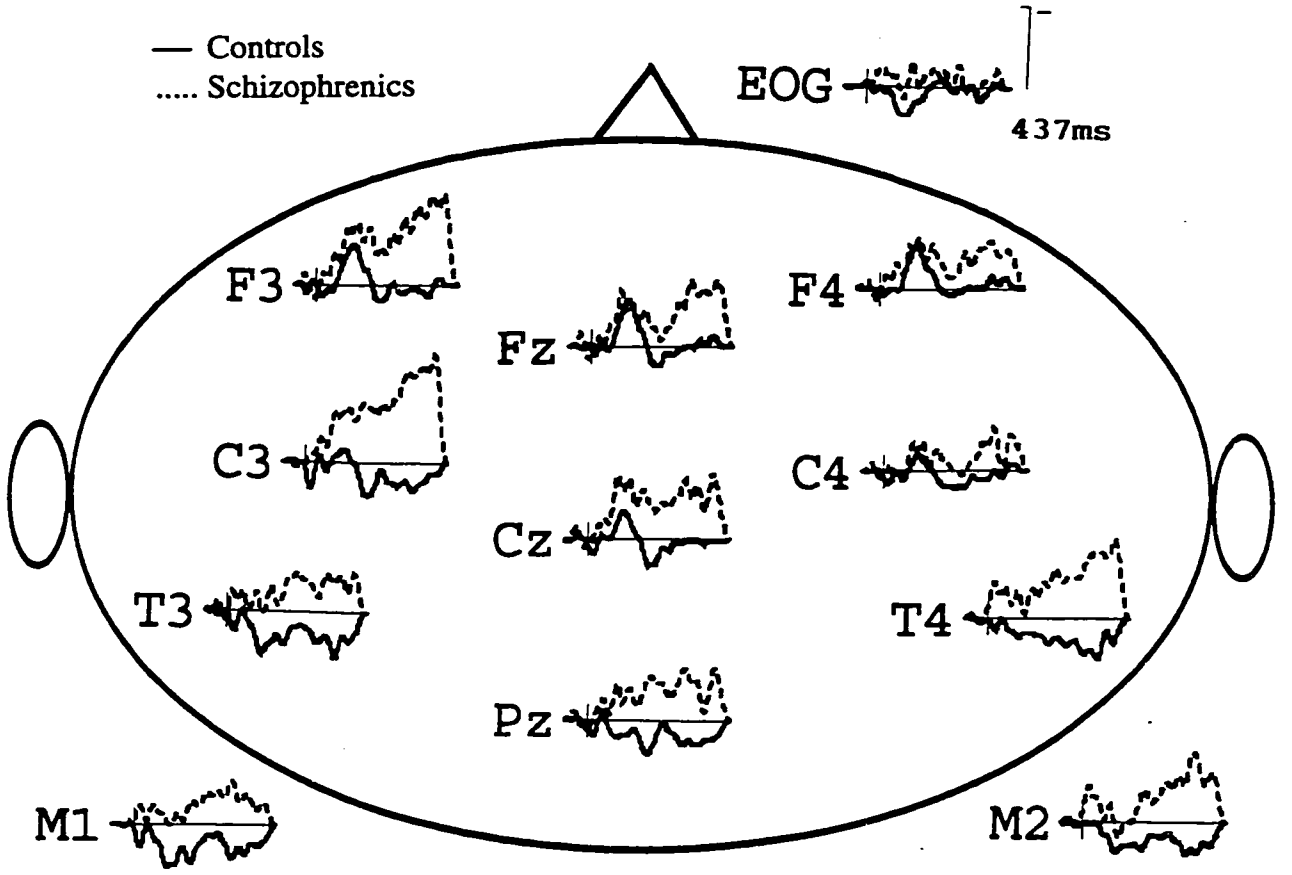

Figure 2. Grand averaged ERP waveforms for the MMN component in normal controls (n = 14) and in treatment-resistant schizophrenic patients (n = 12).

Table 2

Analyses of variance for the MMN component: midline scalp placements

Source	SS	df	MS	F
Range 50-70 msec.				
Group	27.42	1	27.42	1.27
Range 70-90 msec.				
Group	59.72	1	59.72	1.60
Range 90-110 msec.				
Group	48.18	1	48.18	1.03
Range 110-130 msec.				
Group	29.67	1	29.67	0.62
Range 130-150 msec.				
Group	34.68	1	34.68	0.72
Range 150-170 msec.				
Group	65.55	1	65.55	0.87
Range 170-190 msec.				
Group	210.78	1	210.78	3.73
Range 190-210 msec.				
Group	198.67	1	198.67	6.02*

Note. Group = controls and schizophrenia patients.

*$p < 0.05$.

(2, 50) = 3.89, $p < 0.05$ (see Table 3). These significant main effects point to an overall decrease in the amplitude of the MMN from frontal toward posterior brain locations. They confirm that the control group shows the normal topography of the MMN maximal at Fz and regressing toward the Pz electrode location.

A significant interaction between the group factor and midline electrodes was observed in the 110-130 msec range, F (2, 50) = 5.24, $p < 0.05$ (see Table 3). Follow-up analyses were performed to extricate these significant effects (see Table 4). Post hoc t-test results revealed significant differences between the two groups at Cz and Pz electrodes. The patient group displayed an increased negativity at Pz as compared to the Cz location while the control group showed an opposite pattern. These findings indicate that the MMN component in the patient population exhibits a significantly different topography from the normal control subjects.

MMN: Lateral Electrodes

At lateral electrodes, a main effect of group was found in the 190-210 msec range, F (1, 25) = 4.99, $p < 0.05$ (see Table 5), indicating that the patients had significantly larger amplitudes than the controls. Significant main effects for the electrodes placed over each hemisphere were found between 70 msec and 190 msec in the following latency windows: 70-90 msec, F (2, 50) = 4.88, $p < 0.05$; 90-110 msec, F (2, 50) = 17.18, $p < 0.001$; 110-130 msec, F (2, 50) = 28.34, $p < 0.001$; 130-150 msec, F (2, 50) = 11.96, $p < 0.001$, 150-170 msec; F (2, 50) = 7.80, $p < 0.01$; and 170-190 msec range, F (2, 50) = 3.94, $p < 0.05$ (see Table 6). These results show an overall amplitude reduction of the

Table 3

ANOVAs for the amplitude of the MMN at midline scalp electrodes: group by electrode interaction effects

Source	SS	df	MS	F
Range 50-70 msec.				
Electrode	0.5	2	0.25	0.05
Group By Electrode	2.09	2	5.05	0.20
Range 70-90 msec.				
Electrode	26.96	2	13.48	5.21*
Group By Electrode	6.22	2	3.11	1.20
Range 90-110 msec.				
Electrode	77.06	2	38.53	10.61***
Group By Electrode	14.52	2	7.26	2.00
Range 110-130 msec.				
Electrode	81.84	2	40.92	16.38***
Group By Electrode	26.19	2	13.09	5.24*
Range 130-150 msec.				
Electrode	34.88	2	17.44	3.89*
Group By Electrode	11.77	2	5.89	1.31
Range 150-170 msec.				
Electrode	33.34	2	16.67	2.46
Group By Electrode	4.34	2	2.17	0.32
Range 170-190 msec.				
Electrode	5.69	2	2.84	0.56
Group By Electrode	15.74	2	7.87	1.55
Range 190-210 msec.				
Electrode	2.83	2	1.42	0.24
Group By Electrode	15.61	2	7.81	1.31

Note. Electrode = Fz, Cz, Pz. Group = controls and schizophrenia patients.

*$p < 0.05$. ***$p < 0.001$.

Table 4

Post-hoc t-tests for the amplitude of the MMN component

Electrode	df	T-value
Range 110-130 msec		
Fz	25	-0.21
Cz	25	0.89
Pz	25	1.62
Range 190-210 msec		
Fz	25	1.65
Cz	25	2.12*
Pz	25	2.46*
Range 190-210 msec		
F3	25	1.60
F4	25	1.05
C3	25	2.32*
C4	25	0.92
T3	25	2.37*
T4	25	2.68*

Note. *$p < 0.05$.

Table 5

Analyses of variance for the MMN component: lateral electrode sites

Source	SS	df	MS	F
Range 50-70 msec.				
Group	65.23	1	65.23	2.16
Range 70-90 msec.				
Group	73.04	1	73.04	1.54
Range 90-110 msec.				
Group	83.27	1	83.27	1.67
Range 110-130 msec.				
Group	66.25	1	66.25	0.80
Range 130-150 msec.				
Group	87.87	1	87.87	1.36
Range 150-170 msec.				
Group	144.41	1	144.41	1.56
Range 170-190 msec.				
Group	316.66	1	316.66	3.52
Range 190-210 msec.				
Group	294.85	1	294.85	4.99*

Note. Group = controls and schizophrenia patients.

*$p < 0.05$.

Table 6

Analysis of variance for the MMN at lateral electrode locations: group by within location interaction effects

Source	SS	df	MS	F
Range 50-70 msec.				
Within Location	10.03	2	5.01	1.20
Group By Within Location	2.63	2	1.32	0.32
Range 70-90 msec.				
Within Location	54.76	2	27.38	4.88*
Group By Within Location	12.98	2	6.49	1.16
Range 90-110 msec.				
Within Location	206.41	2	103.20	17.18***
Group By Within Location	27.59	2	13.80	2.30
Range 110-130 msec.				
Within Location	288.60	2	144.30	28.34***
Group By Within Location	15.29	2	7.64	1.50
Range 130-150 msec.				
Within Location	112.76	2	56.38	11.96***
Group By Within Location	17.56	2	8.78	1.86
Range 150-170 msec.				
Within Location	121.25	2	60.62	7.80**
Group By Within Location	0.80	2	0.40	0.05
Range 170-190 msec.				
Within Location	39.07	2	19.54	3.94*
Group By Within Location	7.49	2	3.74	0.76
Range 190-210 msec.				
Within Location	2.29	2	1.15	0.26
Group By Within Location	13.82	2	6.91	1.58

Note. Within Location = F3, C3, T3 and F4, C4, T4 electrode placements. Group = controls and schizophrenia patients.

*$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.

MMN from frontal toward central and temporal locations, irrespective of the cerebral hemisphere and are in keeping with previous mismatch negativity findings (Näätänen, 1992). The analysis of variance performed at the mastoid locations yielded non-significant differences between the two groups of participants and confirmed the polarity inversion of the MMN component (see Appendix K). In the 110-130 msec range there was a significant interaction between the electrodes placed within each hemisphere and the two cerebral hemispheres, $\underline{F}$ (2, 50) = 4.34, $\underline{p} < 0.05$ (see Table 6). Finally, a triple interaction was found in the 190-210 msec range between the two groups, the electrodes placed within each hemisphere and the two hemispheres, $\underline{F}$ (2, 50) = 3.85, $\underline{p} < 0.05$ (see Table 7). Post hoc analyses demonstrated a significant difference between the normal controls and schizophrenic patients within the left cerebral hemisphere, at the C3 and T3 electrode sites and within the right cerebral hemisphere, at the T4 electrode site (see Table 4). For both Table 6 and Table 7, the patient group at these locations had significantly more negative MMN amplitudes than the control group. Thus, the schizophrenic patients showed a left- and right-hemisphere lateralization of the MMN component which was not reciprocated by the normal control group.

The remaining nonsignificant results obtained from the analyses of variance for the amplitude of the MMN are presented in Appendix K.

ERP Negativities Measured in the 110-130 msec Range: Midline Electrodes

The waveforms elicited by standard tones were significantly different from those elicited by deviant tones, $\underline{F}$ (1, 25) = 4.26, $\underline{p} < 0.05$ (see Table 8). As expected, the ERP negativities elicited by the deviant auditory stimuli were larger than the ones elicited by

Table 7

ANOVAs for the MMN component: interaction effects between lateral electrodes, groups and cerebral hemispheres

Source	SS	df	MS	F
Range 50-70 msec.				
Within Location By Hemisphere	5.98	2	2.99	1.43
Group By Within Location By Hemisphere	5.53	2	2.77	1.32
Range 70-90 msec.				
Within Location By Hemisphere	5.13	2	2.56	1.06
Group By Within Location By Hemisphere	3.33	2	1.67	0.69
Range 90-110 msec.				
Within Location By Hemisphere	17.34	2	8.67	3.05
Group By Within Location By Hemisphere	2.63	2	1.32	0.46
Range 110-130 msec.				
Within Location By Hemisphere	16.70	2	8.35	4.34*
Group By Within Location By Hemisphere	1.02	2	0.51	0.27
Range 130-150 msec.				
Within Location By Hemisphere	19.29	2	9.65	3.09
Group By Within Location By Hemisphere	5.73	2	2.87	0.92
Range 150-170 msec.				
Within Location By Hemisphere	15.12	2	7.56	2.41
Group By Within Location By Hemisphere	7.15	2	3.58	1.14
Range 170-190 msec.				
Within Location By Hemisphere	17.16	2	8.58	2.02
Group By Within Location By Hemisphere	19.32	2	9.66	2.28
Range 190-210 msec.				
Within Location By Hemisphere	5.87	2	2.93	0.72
Group By Within Location By Hemisphere	31.27	2	15.63	3.85*

Note. Within Hemisphere = F3, C3, T3 and F4, C4, T4 electrode locations. Hemisphere = right and left cerebral hemispheres. Group = controls and schizophrenia patients.

*$p < 0.05$.

Table 8

Analysis of variance for the ERP negativities recorded at midline electrode sites: stimulus by group interactions

Source	SS	df	MS	F
Midline Electrodes				
Range 110-130 msec.				
Stimulus	133.72	1	133.72	4.26*
Group By Stimulus	33.60	1	33.60	1.07
Range 190-210 msec.				
Stimulus	0.07	1	0.07	0.00
Group By Stimulus	125.30	1	125.30	6.62*

Note. Stimulus = auditory deviant tones and auditory standard tones. Group = controls and schizophrenia patients.

*$p < 0.05$.

Table 9

Analysis of variance for the ERP negativities recorded at midline electrode sites: electrode by group interactions

Source	SS	df	MS	F
Midline Electrodes				
Range 110-130 msec.				
Electrode	192.38	2	96.19	29.02***
Group By Electrode	12.54	2	6.27	1.89
Range 190-210 msec.				
Electrode	67.37	2	33.68	4.23*
Group By Electrode	28.29	2	14.14	1.78

Note. Electrode = Fz, Cz, Pz. Group = controls and schizophrenia patients.

*$p < 0.05$. ***$p < 0.001$.

standard tones. A significant main effect of the midline electrodes pointed to a decrease in the amplitude of the ERP negativities from frontal toward posterior locations (see Table 9).

The stimulus type factor interacted in a significant manner with the midline electrode placements, F (1, 25) = 10.83, $p < 0.001$ and a significant three-way interaction was found between the subject groups, stimulus type and scalp electrodes, F (1, 25) = 7.42, $p < 0.01$ (see Table 10). Post hoc t-tests yielded a significant difference between the two groups of subjects in response to auditory standard stimuli at the Pz electrode location. At this scalp location the patient group had significantly larger negativities than the control group (see Table 11).

ERP Negativities Measured in the 190-210 msec Range: Midline Electrodes

There was a significant two-way interaction between the groups of subjects and the auditory stimuli, F (1, 25) = 6.62, $p < 0.05$ (see Table 8). A significant difference was noted between the two groups at the Pz scalp location in the 190-210 msec range. T-test results indicated that the patient group displayed larger late negativities to standard tones than the control group (see Table 11).

ERP Negativities Measured in the 190-210 msec Range: Lateral Electrodes

A significant main effect of cerebral hemisphere, F (1, 25) = 6.45, $p < 0.05$ and a significant two-way interaction between the group variable and the two brain hemispheres, F (1, 25) = 6.42, $p < 0.05$ were observed (see Table 12). Moreover,

Table 10

Analysis of variance for the ERP negativities recorded at midline electrode sites: stimulus by electrode by group interactions

Source	SS	df	MS	F
Midline Electrodes				
Range 110-130 msec.				
Stimulus By Electrode	30.63	2	15.32	10.83***
Group By Stimulus By Electrode	20.98	2	10.49	7.42**
Range 190-210 msec.				
Stimulus By Electrode	10.78	2	5.39	1.63
Group By Stimulus By Electrode	17.40	2	8.70	2.63

Note. Stimulus = auditory deviant tones and auditory standard tones. Electrode = F3, F4, C3, C4, T3, T4. Group = controls and schizophrenia patients.

**$p < 0.01$. ***$p < 0.001$.

Table 11

Post hoc t-tests for the ERP negativities: midline electrodes

Midline Electrodes	df	T-value
Range 110-130 msec		
Fz		
Auditory deviant stimuli	25	-0.59
Auditory standard stimuli	25	-0.67
Cz		
Auditory deviant stimuli	25	0.13
Auditory standard stimuli	25	-1.94
Pz		
Auditory deviant stimuli	25	-0.25
Auditory standard stimuli	25	-2.63*
Range 190-210 msec		
Fz		
Auditory deviant stimuli	25	1.44
Auditory standard stimuli	25	0.20
Cz		
Auditory deviant stimuli	25	1.87
Auditory standard stimuli	25	-1.23
Pz		
Auditory deviant stimuli	25	1.41
Auditory standard stimuli	25	-2.48*

Note. *$p < 0.05$.

Table 12

Analysis of variance for ERP negativities recorded at lateral electrode sites: group by hemisphere interactions

Source	SS	df	MS	F
Lateral Electrodes				
Range 190-210 msec.				
Hemisphere	194.63	1	194.63	6.45*
Group By Hemisphere	193.88	1	193.88	6.42*

Note. Hemisphere = right and left cerebral hemispheres. Group = controls and schizophrenia patients.

*$p < 0.05$.

Table 13

Analysis of variance for the ERP negativities recorded at lateral electrode sites: stimulus by group interactions

Source	SS	df	MS	F
Range 190-210 msec.				
Within Location By Hemisphere	314.84	2	157.42	5.88**
Group By Within Location By Hemisphere	187.94	2	93.97	3.51*

Note. Within Location = F3, C3, T3 and F4, C4, T4 electrode locations. Hemisphere = right and left cerebral hemispheres. Group = controls and schizophrenia patients.

*$p < 0.05$. **$p < 0.01$.

stimulus type interacted significantly with the electrodes placed within each hemisphere, F (2, 50) = 5.88, $p < 0.01$ and there was a significant three-way interaction between the subject groups, the electrodes located within each hemisphere and the two brain hemispheres, F (2, 50) = 3.51, $p < 0.05$ (see Table 13).

Post hoc analyses showed a significant group difference between the ERPs elicited by auditory deviants within the left and right cerebral hemispheres, at temporal electrode sites and within the left hemisphere at the central electrode location (see Table 14). These differences were significantly larger in the patient group than in the control group. This shows that the patients failed to demonstrate a decrease in the amplitude of the ERP negative deflections elicited by auditory deviants. At the right-frontal scalp location patients displayed larger amplitudes to standard tones than the normal controls.

Remaining non-significant analyses of variance conducted at the midline and the lateral electrode placements are found in Appendix L.

MMN Within Groups Analyses

A significant main effect for the midline electrode sites was found only in the control group, in the 110-130 msec range, F (2, 50) = 20.67, $p < 0.001$ (see Table 15). The lack of significant results for the patient group notwithstanding, Figure 3 contains a graph of the group means for the MMN component at the midline electrode locations. Post hoc t-tests confirmed the expected decrease in the amplitude of the MNN from frontal toward parietal sites in the group of control subjects (see Table 16). No stimulus, electrode and within cerebral hemisphere effects were found in the patient group.

Table 14

Post hoc t-tests for the ERP negativities elicited at lateral electrode locations

Lateral Electrodes	df	T-value
Range 190-210 msec		
F3		
Auditory deviant stimuli	25	1.53
Auditory standard stimuli	25	1.78
F4		
Auditory deviant stimuli	25	-0.41
Auditory standard stimuli	25	-2.11*
C3		
Auditory deviant stimuli	25	2.37*
Auditory standard stimuli	25	1.38
C4		
Auditory deviant stimuli	25	0.60
Auditory standard stimuli	25	-0.47
T3		
Auditory deviant stimuli	25	2.34*
Auditory standard stimuli	25	0.45
T4		
Auditory deviant stimuli	25	2.23*
Auditory standard stimuli	25	0.73

Note. *$p < 0.05$.

Table 15

ANOVAs for the MMN component measured within groups

Source	SS	df	MS	F
Midline Electrodes				
Range 110-130 msec				
Controls	93.17	2	46.58	20.67***
Patients	17.65	2	8.83	3.20
Range 190-210 msec				
Controls	2.74	2	1.37	0.39
Patients	15.24	2	7.62	0.88
Lateral Electrodes				
Range 190-210 msec				
Controls				
Within Location	10.95	2	5.48	1.35
Hemisphere	4.74	1	4.74	1.17
Within Location By Hemisphere	5.75	2	2.87	2.05
Patients				
Within Location	5.37	2	2.68	0.57
Hemisphere	17.58	1	17.58	0.91
Within Location By Hemisphere	30.47	2	15.23	2.20

Note. *** $p < 0.001$.

Table 16

Post hoc t-tests for the MMN component measured within groups

	df	T-value
Midline Electrodes		
Range 110-130 msec		
Controls		
Fz vs. Cz	13	2.59*
Fz vs. Pz	13	-5.13***
Cz vs. Pz	13	-4.50***
Patients		
Fz vs. Cz	12	-1.14
Fz vs. Pz	12	-1.07
Cz vs. Pz	12	-4.24***

Note. * $p < 0.05$. *** $p < 0.001$.

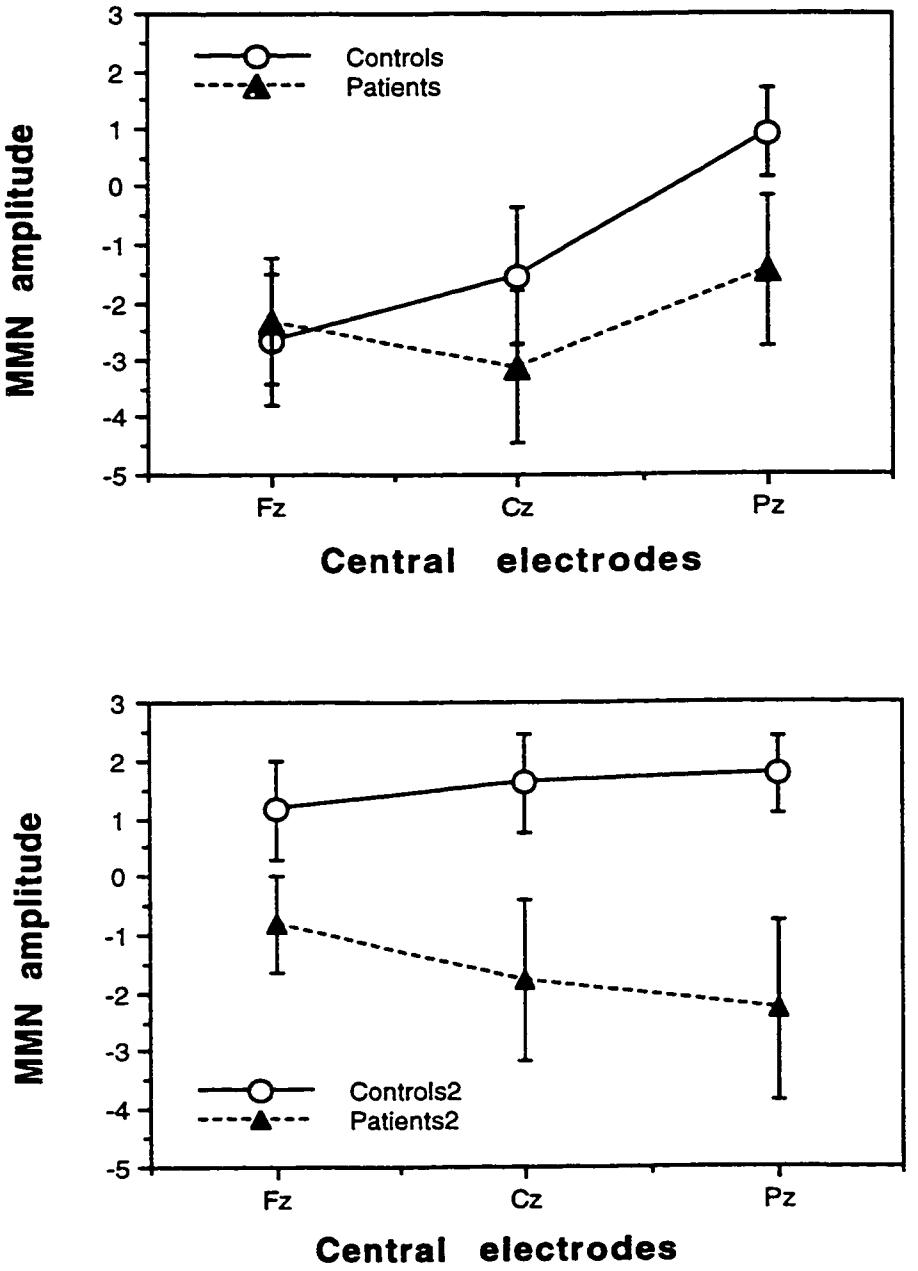

Figure 3. Group means for the MMN component measured at central electrode locations in the 110-130 msec (top panel) and 190-210 msec (bottom panel) ranges in normal controls (n = 14) and in treatment-resistant schizophrenic patients (n = 13).

Figure 4 contains an illustration of a series of superimposed ERP waveforms. These waveforms represent the ERP brain waves elicited in response to standard, deviant tones, as well as the subtracted waveforms from which the MMN component and the PN component are typically measured.

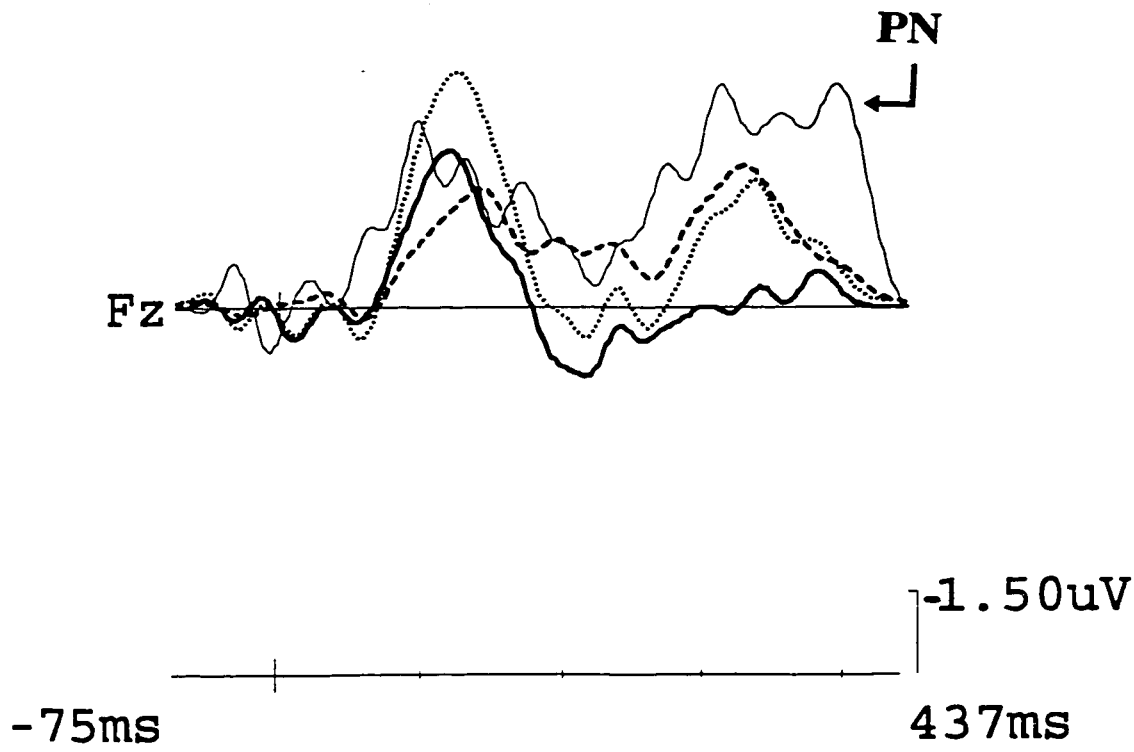

Figure 4. Superimposition of ERP raw waveforms for the standard tones (dashed line), deviant tones (dotted line) and ERP subtracted waveforms for the MMN component (continuous thick line) and a theoretical PN component (continuous thin line).

Discussion

The present study investigated an ERP index of preattentive processing in a sample of treatment refractory schizophrenia patients and healthy controls. The validity of the procedure employed was confirmed by the behavioral and visual ERP measures. All subjects followed the task instructions and provided valid responses. The normal control subjects presented the expected fronto-central topography of the MMN with a polarity reversal at the mastoid electrodes. In contrast, patients presented a lack of site differentiation for the MMN. They displayed atypical negativity peaks at parietal instead of frontal electrode locations (see Figure 3).

Behavioral and ERP indices of focused attention to visual targets

Indices of behavioral performance measured in the current project demonstrated an excellent performance of both groups to visual stimuli. The controls and the patients had comparable reaction times. Although the schizophrenic subjects were significantly less accurate than the controls, their response accuracy was still well above 90%. It appears, therefore, that all participants were equally motivated to perform the ERP task.

The evaluation of the P300 amplitude in choice RT tasks is believed to provide an ERP measure of controlled attention processes. Traditionally, the choice-RT P300 has been obtained in oddball paradigms in which an infrequent stimulus is presented in a series of standard stimuli. The P300 has been interpreted as reflecting working memory changes (Donchin & Coles, 1988). The P300 was also shown to occur in single stimulus

paradigms in which the subject is required to react to an infrequently presented stimulus (Mertens & Polich, 1997). The current study employed the latter type of paradigm and found no differences in the P300 elicited by visual stimuli in patients and controls. One explanation for this finding may be that the task demands were low and the patients could allocate sufficient attentional resources to perform it adequately. Although this possibility can not be discarded, the P300 was demonstrated to be impaired in tasks of varying levels of exigency (Levit et al., 1973; Pritchard, 1986).

Another possibility is that treatment-resistant schizophrenics have intact visual working memory capabilities. The present investigation extends earlier reports of no group differences in schizophrenia for the simple-RT P300-like component observed in the auditory modality (Oades et al., 1997). Moreover, current results also parallel those reported in a group of patients with dorso-lateral prefrontal cortex lesions by Alho et al. (1994a). Given that frontal lobe deficits have already been linked to schizophrenia (Akbarian et al., 1993), the lack of simple-RT P300 deficits to rare visual stimuli in both of these groups may reflect undiminished visual working memory processes in treatment-resistant schizophrenia.

Mismatch negativity findings

Mismatch negativity has been demonstrated to reflect automatic detection of changes in stimulus presentation because it can be elicited irrespective of whether participants attend to auditory stimuli or they perform unrelated tasks during the presentation of the tones (Alho et al., 1994a; Paavilainen et al, 1993). As such, the MMN

component is a good candidate to assess auditory sensory memory function in schizophrenia.

Contrary to the body of the evidence reporting that schizophrenia patients have a diminished MMN amplitude when compared to normal controls, the current investigation found generally larger MMN amplitudes in a sample of treatment-resistant subjects than in normal controls. Only one other study reported no reduction in the amplitude of the frequency-MMN in a group of medicated schizophrenic patients (Kathmann et al., 1995). Nevertheless, Kathmann et al. (1995), found that the amplitude of the MMN in the schizophrenic patients occurred with a significantly longer latency than in the normal control participants. These authors argued that a delay in the generation of the MMN may reflect a slowing in the ability to automatically detect changes in the frequency of a series of stimuli in schizophrenia patients. Even if the present study did not measure one MMN latency, there was no lag in the generation of the averaged MMN obtained in the 70 to 210 msec latency ranges in the patient group which included the latency period (about 145 msec after stimulus onset) where Kathmann et al. (1995), have found a delayed frequency-MMN in the patient group.

Analyses of the MMN amplitude performed at midline-electrodes revealed the expected MMN amplitude reduction from frontal (Fz) to central (Cz) and to posterior (Pz) electrode sites in the normal control group. In contrast, patient group demonstrated a reversed ERP waveform pattern in which the largest amplitude of the ERP difference wave was recorded at the Pz electrode location. No significant group differences occurred until 190-210 msec after stimulus onset. At this latency range, the

schizophrenic patients displayed significantly larger and more negative brain wave amplitudes than the normal controls at the posterior scalp location alone.

This unusual topography of the MMN amplitude in which the patient group displayed a late and markedly parietal activation pattern suggests that the current findings may reflect the generation of a processing negativity component in the schizophrenic sample in response to the auditory stimuli. The PN is a slow, endogenous, negative component which emerges in response to attended stimuli. Two attention-dependent PN components have been identified: a frontal one (Näätänen et al., 1979), and a more central one which is generated in the auditory cortex (Hansen & Hillyard, 1980; Woldorff et al., 1993, Näätänen & Michie, 1979). The earlier, frontal PN is observed in response to small pitch differences while the more central PN is usually elicited by large pitch differences (Näätänen & Michie, 1979). The PN was found to begin at about 150 msec, and to last for at least 500 msec after stimulus onset (Näätänen & Alho, 1995a; Näätänen et al., 1979). The latency, but not the amplitude of the PN was found to be influenced by the rate of presentation of the stimuli. At fast rates of presentation of stimuli, the PN occurs sooner than at long ISIs (Parasuraman, 1978). Studies of selective attention found that at short ISIs, like the ones employed in the present study, the PN latency may be shortened because the subjects have to process stimuli at faster rates in order to achieve adequate levels of performance (Hillyard et al., 1973; Näätänen & Michie, 1979). Furthermore, at fast rates of stimulus presentation the central PN component shifts in the posterior direction (Näätänen et al., 1992). The markedly parietal distribution of the difference wave observed in the present study strongly suggests that a PN component was generated

in the patient group. This negative deflection reached statistical significance for the patient group in the 190-210 msec epoch.

Although the present study proved to be well-suited to observe an MMN component in normal controls, it did not afford the discrimination of the MMN from a potential PN component that may have been elicited in the treatment-resistant patients. Therefore, the MMN amplitude may have been overshadowed by the generation of a concurrent PN component in the treatment-resistant schizophrenia patients. Further experimental manipulations are needed to explore this possibility in treatment-refractory patients. It is not unlikely that schizophrenics pay undue attention to task-irrelevant auditory input since they are prone to auditory hallucinations. Evidence in favor of this interpretation is provided by the following: larger number of omission errors in the visual task, larger variability of RTs, and larger late negativity to the tones.

Another potential explanation of the data is that the MMN is affected by focusing of attention. Oades & Dittmann-Balcar (1995), have reported a slight shift toward a posterior increase in the amplitude of the MMN during a three-tone task in which subjects were asked to passively attend to the auditory stimuli or to actively focus their attention to one of the tones. Oades & Dittmann-Balcar (1995), rejected the hypothesis that a concurrent PN may have produced an enhanced MMN in the focused attention condition. They suggested instead, that the MMN was enhanced as a result of focusing attention to one tone while ignoring two others. Although this possibility can not be dismissed yet, it remains to be determined whether strong attentional focus may modulate the amplitude of the MMN.

The MMN analyses conducted for the electrodes placed over the left and right cerebral hemispheres found no hemispheric asymmetry in the amplitude of the MMN for both groups of subjects. This notwithstanding, the patient group displayed bilaterally larger MMN amplitudes than the controls at the temporal electrode sites and unilaterally, at the left-central electrode location. As already mentioned for the midline electrode placements, this difference reached significance only in the 190 to 210 msec latency range. These results are consistent with the generation of a PN component in the schizophrenic patients. Näätänen et al. (1978, 1980) reported large PNs over the temporal cortex at the T3 and T4 electrodes. Based on these findings they suggested that the PN may be generated in the auditory cortex. Other researchers showed that the PN tended to be even larger at the C3 and C4 locations (Curry et al., 1983), consistent with the proposition that the PN has two phases, with the later being distributed more frontally than the earlier, more posterior PN.

Further exploration of the ERP negativities elicited in response to auditory stimulation

Topographical analyses of the negative ERPs obtained in response to auditory stimuli indicated that the patient group displayed significantly larger waveform amplitudes than the controls in response to standard tones at the right frontal locations (F4). Additionally, the schizophrenic patients had larger amplitudes to the auditory deviants at the C3, T3 and T4 recording sites. These data support the contention that the schizophrenic subjects have been strongly focusing their attention to the stimuli presented in the to-be-ignored auditory modality. The control group, on the other hand had no

difficulty ignoring the auditory input and focusing on the visual targets alone. The behavioral measure results and the P300 data support the assertion that both groups of subjects were able to perform well the visual distractor task. Nonetheless, the patient group was significantly less accurate than the control group in their answers. This may reflect the fact that the patient group had the time to respond well to the visual targets and to also attend to the auditory stimuli.

Conclusions

The task selected for the present experiment has manipulated the frequency of the stimuli. This task was found to be effective in demonstrating MMN reductions in patients with DPFCx lesions (Alho et al, 1992). Nevertheless, it may be that the MMN in schizophrenia is selectively affected by the physical characteristics of tone deviance. Some of the studies reporting MMN reductions in schizophrenics manipulated the duration of the tone deviance (Catts et al., 1995; Shelly et al., 1991). Other studies employed frequency differences between the deviant and standard tones. These, produced mixed results, with small pitch differences a diminished MMN in schizophrenia has been reported (Javitt et al., 1995), but when relatively large pitch differences were used no MMN amplitude deficits in schizophrenia could be demonstrated (Kathmann et al., 1995). The current study not only failed to report any MMN amplitude deficits but found larger MMN amplitudes in the treatment-resistant schizophrenics than in the control group. In light of these findings, future research is needed to ascertain if indeed, the amplitude of the MMN is shaped by the physical characteristics of the stimuli. Present

data support the contention that the MMN may be influenced by focussing of attention via the manifestation of PN.

In summary, it remains plausible that the MMN component is modulated by attentional focus in schizophrenia patients. The data obtained from this investigation point to an inability of the treatment-refractory schizophrenic patients to ignore the stimuli presented in the auditory modality. These findings support the hypothesis of an auditory cortex involvement in the psychopathology of schizophrenia. In light of these difficulties, the investigation of the MMN component in treatment-resistant schizophrenic patients remains of great interest. Future studies are required to elucidate the degree to which automatic mechanisms of attention are implicated in the disturbed symptoms observed in treatment-refractory schizophrenia patients.

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Appendix A

Brief Psychiatric Rating Scale

BRIEF PSYCHIATRIC RATING SCALE (OVERALL & GORHAM)

Period _____
Subject no _____
Sex (M=1; F=2) _____
Evaluator _____
Project _____

	Circle the column headed by the term which best describes the patient's present condition		Not Present	Very Mild	Mild	Mode rate	Mode rarely Severe	Severe	Extre mely Severe
1	Somatic Concern	Degree of concern over present bodily health. Rate the degree to which physical heath is perceived as a problem by the patient, whether complains have a realistic basis or not.	0	1	2	3	4	5	6
2	Anxiety	Worry, fear, or over-concern for present or future. Rate solely on basis of verbal report of patient's own subjective experiences. Do not infer anxiety from physical signs or from neurotic defense mechanisms.	0	1	2	3	4	5	6
3	Emotional Withdrawal	Deficiency in relating to the interviewer situation. Rate only the degree to which the patient gives the impression of failing to be in emotional contact with other people in the interview situation.	0	1	2	3	4	5	6
4	Conceptual Disorganiza-tion	Degree to which the thought processes are confused, disconnected or disorganized. Rate on the basis of integration of verbal products of the patient; do not rate on the basis of patient's subjective impression of his own level of functioning.	0	1	2	3	4	5	6
5	Guilt Feelings	Over-concern or remorse for past behavior. Rate on the basis of the patient's subjective experiences of guilt as evidenced by verbal report with appropriate affect; do not infer guilt feelings from depression, anxiety or neurotic defenses.	0	1	2	3	4	5	6
6	Tension	Physical and motor manifestations of tension "nervousness" and heightened activation level. Tension should be rated solely on the basis of physical signs and motor behavior and not on the basis of subjective experiences of tension reported by the patient.	0	1	2	3	4	5	6
7	Mannerisms and posturing	Unusual and unnatural motor behavior, the type of motor behavior which causes certain mental patients to stand out in a crowd of normal people. Rate only abnormality of movements; do not rate simply heightened motor activity here.	0	1	2	3	4	5	6

	Circle the column headed by the term which best describes the patient's present condition		Not Present	Very Mild	Mild	Mode rate	Mode rarely Severe	Severe	Extre mely Severe
8	Grandiosity	Exaggerated self-opinion, conviction of unusual ability or powers. Rate only on the basis of patient's statements about himself or self-in-relation to others, not on the basis of his demeanor in the interview situation.	0	1	2	3	4	5	6
9	Depressive Mood	Despondency in mood, sadness. Rate only the degree of despondency; do not rate on the basis of inferences concerning depression based upon general retardation and somatic complains	0	1	2	3	4	5	6
10	Hostility	Animosity, contempt, belligerence, disdain for other people outside the interview situation. Rate solely on the basis of the verbal report of feelings and not infer hostility from neurotic defenses, anxiety, nor somatic complaints. (Rate attitude toward interviewer under "Uncooperativeness").	0	1	2	3	4	5	6
11	Suspicious-ness	Belief (delusional or otherwise) that others have now, or have had in the past, malicious or discriminatory intent toward the patient. On the basis of verbal report, rate only the suspicions which are currently held whether they concern past or present circumstances.	0	1	2	3	4	5	6
12	Hallucinatory Behavior	Perceptions without normal external stimulus correspondence. Rate only those experiences which are reported to have occurred within the last week and which are described as distinctly different from the thought and imagery processes of normal people.	0	1	2	3	4	5	6
13	Motor Retardation	reduction in energy level evidenced in slowed movements. Rate on the basis of observed behavior of the patient's only; do not rate on the basis of patient's subjective impression of own energy level.	0	1	2	3	4	5	6
14	Uncooperative ness	Evidence of resistance, unfriendliness, resentment, lack of readiness to cooperate with the interviewer. Rate only on the basis of the patient's attitude and responses to the interviewer and interview situation; do not rate on basis of reported resentment or uncooperativeness outside the interview situation.	0	1	2	3	4	5	6

	Circle the column headed by the term which best describes the patient's present condition		Not Present	Very Mild	Mild	Mode rate	Mode rarely Severe	Severe	Extre mely Severe
15	Unusual Thought Content	Unusual, odd, strange, or bizarre thought content. Rate here the degree of unusualness, not the degree of disorganization of thought processes.	0	1	2	3	4	5	6
16	Blunted Affect	Reduced emotional tone, apparent lack of normal feeling or involvement.	0	1	2	3	4	5	6
17	Excitement	Heightened emotional tone, agitation, increased reactivity.	0	1	2	3	4	5	6
18	Disorientation	Confusion or lack of proper association for person, place or time.	0	1	2	3	4	5	6

Appendix B

Positive and Negative Symptoms Scales

PANSS (Positive and Negative Syndrome Scale)

Instructions:

Complete the appropriate rating for dimension following the clinical interview. Refer to the Rating Manual for item definitions, descriptions of anchoring points, scoring procedure, and norms.

Rating Key:	1 = absent	5 = moderate-severe
	2 = minimal	6 = severe
	3 = mild	7 = extreme
	4 = moderate	

Positive Scale

P1	_____	Delusions
P2	_____	Conceptual disorganization
P3	_____	Hallucinatory behaviour
P4	_____	Excitement
P5	_____	Grandiosity
P6	_____	Suspiciousness / Persecution
P7	_____	Hostility

Negative Scale

N1	_____	Blunted affect
N2	_____	Emotional withdrawal
N3	_____	Poor rapport
N4	_____	Passive / apathetic social withdrawal
N5	_____	Difficulty in abstract thinking
N6	_____	Lack of spontaneity and flow of conversation
N7	_____	Stereotyped thinking

General Psychopathology Scale

G1	_____	Somatic concern
G2	_____	Anxiety
G3	_____	Guilt feelings
G4	_____	Tension
G5	_____	Mannerisms and posturing
G6	_____	Depression
G7	_____	Motor retardation
G8	_____	Uncooperativeness
G9	_____	Unusual thought content
G10	_____	Disorientation
G11	_____	Poor attention
G12	_____	Lack of judgment and insight
G13	_____	Disturbance of volition
G14	_____	Poor impulse control
G15	_____	Preoccupation
G16	_____	Active social avoidance

Appendix C

Calgary Depression Scale

Echelle de dépression de Calgary (D. Addington & J. Addington, 1990)

Subject Code _____

Name _____

Date _____

Medical Doctor _____

	Absent	Leger	Moderé	Severe
1. Dépression	0	1	2	3
2. Désespoir	0	1	2	3
3. Auto-dépréciation	0	1	2	3
4. Idees de ref: associées a la culpabilite	0	1	2	3
5. Culpabilité pathologique	0	1	2	3
6. Dépression matinale	0	1	2	3
7. Eveil hâtif	0	1	2	3
8. Dépression observée	0	1	2	3

Appendix D

Extrapyramidal Symptom Rating Scale

EXTRAPYRAMIDAL SYMPTOM RATING SCALE (CHOUINARD & ROSS CHOUINARD, 1979)

Period _____ Evaluator _____
Subject no _____ Project _____
Sex (M=1; F=2) _____

PARKINSONISM, DYSTONIA, AND DYSKINESIA: QUESTIONNAIRE AND BEHAVIORAL SCALE
(Physician or nurse)

Inquire into the status of each symptom and rate accordingly. For nurses, rate also the behavior observed

	Absent	Mild	Moderate	Severe
1. Impression of slowness or weakness, difficulty in carrying out routine tasks	0	1	2	3
2. Difficulty in walking or with balance	0	1	2	3
3. Difficulty swallowing or talking	0	1	2	3
4. Stiffness, stiff posture	0	1	2	3
5. Cramps or pains in limbs, back or neck	0	1	2	3
6. Restless, nervous, unable to keep still	0	1	2	3
7. Tremors, shaking	0	1	2	3
8. Oculogyric crisis, abnormal sustained posture	0	1	2	3
9. Increased salivation	0	1	2	3
10. Abnormal involuntary movements (dyskinesia) of extremities or trunk	0	1	2	3
11. Abnormal involuntary movements (dyskinesia) of tongue, jaw, lips, or face	0	1	2	3
12. Dizziness when standing up (especially in the morning)	0	1	2	3

PARKINSONISM: PHYSICIAN'S EXAMINATION

1. Expressive automatic movements (facial mask/speech)
   - 0: normal
   - 1: very mild decrease in facial expressiveness
   - 2: mild decrease in facial expressiveness
   - 3: rare spontaneous smile, decreased blinking, voice slightly monotonous

2. Bradykinesia
   - 0: absent
   - 1: global impression of slowness in movements
   - 2: definite slowness in movements
   - 3: very mild difficulty in initiating movements
   - 4: mild to moderate difficulty in initiating movements
   - 5: difficulty in starting and stopping any movement, or freezing on initiating voluntary act
   - 6: rare voluntary movement, almost completely immobile

3. Rigidity
right upper limb _____
left upper limb _____
right lower limb _____
left lower limb _____

Total: _____
- 0: normal muscle tone
- 1: very mild, barely perceptible
- 2: mild (some resistance to passive movements)
- 3: moderate (definite resistance to passive movements)
- 4: moderately severe (moderate resistance but still easy to move limb)
- 5: severe (moderate resistance but still able to move limb)
- 6: extremely severe (limb nearly frozen)

4. Gait and Posture
   0: normal
   1: mild decrease of pendular arm movement
   2: moderate decrease of pendular arm movement, normal steps
   3: no pendular arm movement, head flexed, steps more or less normal
   4: stiff posture (neck back), small step (shuffling gait)
   5: more marked, festination or freezing on turning
   6: triple flexion, barely able to walk

Tremor	Total: _____					
right upper limb____	head_____	none	: 0	Occasional	Frequent	Constant or Almost So
left upper limb_____	jaw/chin____	borderline	: 1			
right lower limb____	tongue_____	small aptitude	:	2	3	4
left lower limb_____	lips_____	moderate aptitude	:	3	4	5
		large aptitude	:	4	5	6

6. Akanathisia
   0: absent
   1: looks restless, nervous, impatient, uncomfortable
   2: needs to move at least one extremity
   3: often needs to move one extremity or to change position
   4: moves one extremity almost constantly if sitting, or stamps feet while standing
   5: unable to sit down for more than a short period of time
   6: moves or walks constantly

7. Sidorrhea
   0: absent
   1: very mild
   2: mild
   3: moderate, impairs speech
   4: moderately severe
   5: severe
   6: extremely severe, drooling

8. Postural stability
   0: normal
   1: hesitation when pushed but no retropulsion
   2: retropulsion but recovers unaided
   3: exaggerated retropulsion without falling
   4: absence of postural response, would fall if not caught by examiner
   5: unstable while standing, even without pushing
   6: unable to stand without assistance

III. DYSTONIA: PHYSICIAN'S EXAMINATION

1. Acute torsion dystonia	Total _____	0: absent	4: moderately severe
right upper limb ____	head _____	1: very mild	5: severe
left upper limb _____	jaw/chin____	2: mild	6: extremely severe
right lower limb ____	tongue _____	3: moderate	
left lower limb _____	lips _____		

1. Non-acute or chronic or tardive dystonia	Total _____	0: absent	4: moderately severe
right upper limb ____	head _____	1: very mild	5: severe
left upper limb _____	jaw/chin____	2: mild	6: extremely severe
right lower limb ____	tongue _____	3: moderate	
left lower limb _____	lips _____		

IV. DYSKINETIC MOVEMENTS: PHYSICIAN'S EXAMINATION

		OCCASIONAL*	FREQUENT**	CONSTANT OR ALMOST SO
1. Lingual movements (slow lateral or torsion movement of tongue)				
none	: 0			
borderline	: 1			
clearly present, within oral cavity	:	2	3	4
with occasional partial protrusion	:	3	4	5
with complete protrusion	:	4	5	6
2. Jaw movements (lateral movement, chewing, biting, clenching)				
none	: 0			
borderline	: 1			
clearly present, small amplitude	:	2	3	4
moderate amplitude, but without mouth opening:		3	4	5
large amplitude, with mouth opening	:	4	5	6
3. Bucco-labial movements (puckering, putting, smacking, etc.)				
none	: 0			
borderline	: 1			
clearly present, small amplitude	:	2	3	4
moderate amplitude, forward movement of lips:		3	4	5
large amplitude, marked, noisy smacking of lips:		4	5	6
4. Truncal movements (rocking, twisting, pelvic gyrations)				
none	: 0			
borderline	: 1			
clearly present, small amplitude	:	2	3	4
moderate amplitude	:	3	4	5
greater amplitude	:	4	5	6
5. Upper extremities (choreoathetoid movements only: arms, wrists, hands, fingers)				
none	: 0			
borderline	: 1			
clearly present, small amplitude, movement of one limb:		2	3	4
moderate amplitude, movement of one limb or movement of small amplitude involving two limbs	:	3	4	5
greater amplitude, movement involving two limbs	:	4	5	6
6. Lower extremities (choreoathetoid movements only: legs, knees, ankles, toes)				
none	: 0			
borderline	: 1			
clearly present, small amplitude, movement of one limb:		2	3	4
moderate amplitude, movement of one limb or movement of small amplitude involving two limbs	:	3	4	5
greater amplitude, movement involving two limbs	:	4	5	6
7. Other involuntary movements (swallowing, irregular respiration, frowning, blinking, grimacing, sighing, etc.)				
none	: 0			
borderline	: 1			
clearly present, small amplitude	:	2	3	4
moderate amplitude	:	3	4	5
greater amplitude	:	4	5	6

SPECIFY .....

*when activated or rarely spontaneous; **frequently spontaneous and present when activated

Investigator's signature _____

Appendix E

Demographic Questionnaire

Personal Subject Code: _____ Date: _____

LABORATORY OF HUMAN NEUROPHYSIOLOGY AND NEUROPSYCHOLOGY
CONCORDIA UNIVERSITY & FERNARD SEGUIN RESEARCH CENTER
SUBJECT INFORMATION QUESTIONNAIRE

This questionnaire is used to gather information pertaining to your present situation and past history, as well as certain aspects of your family history. This information will assist us in understanding the results of your participation by placing it in the context of your background. Yours answers will be held in *strict confidence* by the study team and will not be revealed to anyone without your written consent.

Please write all your answers clearly and in block letters.

Family Name _____ First Name _____

Date of Birth D M Y Gender Male _____ Female_____

Home Address _____

_____

Phone Number: Work (____) _____ Home (514)_____

Current or most recent (if unemployed) occupation (please describe your occupation):

_____

_____

If you are a student and/or rely primarily on another source of income (e.g., parents), please indicate the source _____,
and their approximate average annual income:

$ 0 - 10,000	_____	$10,001 - 15,000	_____
$15,001 - 20,000	_____	$20,001 - 25,000	_____
$25,001 - 30,000	_____	$30,000 +	_____

Race (check one): Caucasian (white) ____ African-American (black) ____
Asian _____ Latin-American (Hispanic)____
Other (please specify) _____

What is your current marital status (check one)?
Married _____ Single _____ Divorced _____ Cohabiting _____

EDUCATION

How many years of education have you completed (include. kindergarten)? _____

What is the highest level of education you attained (check one)?

Grade School _____	High School_____	CEGEP _____
Bachelor _____	Master _____	Ph.D. _____
M.D. _____	Other _____	

How were your grades during the highest level you completed (check one)?

Mostly A _____ A and B's _____ Mostly B _____ B and C _____
Mostly C _____ C and D _____ Mostly D _____ Below D _____

Did you get into fights at school? Yes _____ No _____

If yes, in what academic period was this most common (check one)?

Grade School _____ High School _____ CEGEP _____ University _____

Were you ever suspended from school because of fighting? Yes _____ No _____

PRESENT MEDICAL HISTORY (only <u>within</u> the past one year)

Do you currently have any medical illness(es)? Yes _____ No _____
If yes, describe _____
_____
_____

Do you currently have allergies to any medications? Yes _____ No _____
What medication(s)? _____

Do you have any other allergies? Yes _____ No _____
If yes, describe _____
_____
_____

PAST MEDICAL HISTORY (only <u>before</u> the past one year)

Have you ever had an injury to your head? Yes _____ No _____

If yes, indicate your age at the time of each head injury experienced, in chronological order, and if you had lost consciousness, for how long have you lost consciousness?

Age ____ Loss of consciousness Yes ____ No ___ Hours _____ Minutes _____
Age ____ Loss of consciousness Yes ____ No ___ Hours _____ Minutes _____
Age ____ Loss of consciousness Yes ____ No ___ Hours _____ Minutes _____

PRESENT PSYCHIATRIC HISTORY (only within the past one year)

Are you currently hospitalized for a psychiatric illness? Yes _____ No _____
If yes, what is your diagnosis and where are you hospitalized? _____

Were you hospitalized for a psychiatric illness in the past year? Yes _____ No _____
If yes, what was your diagnosis and where were you hospitalized? _____

Are you currently receiving treatment for a psychiatric illness without being hospitalized?
Yes _____ No _____
If yes, what is your diagnosis and what type of treatment? _____

Have you received treatment for a psychiatric illness without being hospitalized in the past year?
Yes _____ No _____
If yes, what was your diagnosis and what type of treatment? _____

PAST PSYCHIATRIC HISTORY (only before the past one year)

Have you been hospitalized for a psychiatric illness? Yes _____ No _____
If yes, what was your diagnosis and where were you hospitalized? _____

Have you received treatment for a psychiatric illness without being hospitalized?
Yes _____ No _____
If yes, what was your diagnosis and what type of treatment? _____

MEDICATION AND SUBSTANCE USE

Are you currently using medication(s) (including medical and psychotropic)?
Yes _____ No _____
If yes, what medication(s) and for what purpose(s)? _____

Have you used any medication(s) in the past? Yes _____ No _____
If yes, what medication(s) and for what purpose(s)? _____

Do you drink alcohol? Yes _____ No _____

If yes, how many drinks (one drink = one glass of wine, beer or spirits), on average, per day? _____ per week? _____

How many drinks do you have, on average, per occasion of drinking? _____
How often do you get intoxicated (i.e., drunk), per week? _____ per month? ____
Have you ever been to a hospital because of drinking? Yes _____ No _____
Have you ever received treatment because of drinking? Yes _____ No _____

When was the last time you had a drink and how much did you drink? _____
_____

Do you smoke tobacco? Yes _____ No _____

If yes, how many cigarettes, on average, per day? _____ per week? _____

Have you ever used illegal drugs (e.g., cocaine, marijuana)? Yes _____ No _____

If yes, what drug(s) and how often? _____
_____

When was the last time you used an illegal drug(s) and what drug(s) was it? _____
_____

Have any of your biological relatives ever been diagnosed with a psychiatric illness (such as schizophrenia, obsessive-compulsive disorder, Tourette's syndrome, tic disorder, depression, mania, alcohol or drug abuse, panic attacks, phobias, other)?

Yes _____ No _____

If yes, please indicate which relative(s) and their diagnosis:

Children _____
Father _____
Mother _____
Brothers _____
Sisters _____
Maternal Grandmother _____
Maternal Grandfather _____
Paternal Grandmother _____
Paternal Grandfather _____
Maternal Uncles _____
Maternal Aunts _____
Paternal Uncles _____
Paternal Aunts _____
Cousins _____
Others _____

Modified Edinburgh Handedness Inventory (Oldfield, 1971)

INSTRUCTIONS: Please indicate which hand you prefer to use when completing the following activities. Some of these activities require both hands. In these cases, the part of the task, or object, for which hand preference is wanted is indicated in parentheses. For each item circle a number from one (1) to five (5), where 1 equals left hand always preferred, 5 equals right hand always preferred, and 3 equals both hands used equally often.

e.g., Holding a cup for drinking Left Always 1 2 Equal 3 4 Right Always 5

	Left Always		Equal		Right Always
1. Writing	1	2	3	4	5
2. Drawing	1	2	3	4	5
3. Throwing	1	2	3	4	5
4. Scissors	1	2	3	4	5
5. Toothbrush	1	2	3	4	5
6. Knife (without fork)	1	2	3	4	5
7. Spoon	1	2	3	4	5
8. Broom (upper hand)	1	2	3	4	5
9. Striking a match (match)	1	2	3	4	5
10. Opening a box (lid)	1	2	3	4	5

•In the past, did you prefer to use the hand that you do not prefer now? Yes ___ No ___
If Yes, explain why you changed preference _____

•Do you have any relatives, other than parents or siblings, who are left-handed?
Yes ____ No ____
If Yes, indicate which relatives and on which side of the family (i.e., maternal or paternal):

Appendix F

Evoked-potential recordings

Centre Fernard Seguin
Concordia University

MMN Protocol
ERP Testing of a Subject

INSTRUCTIONS

Pre-Hookup:

1. Ask subject or nurse of patient if he/she is allergic to any cosmetics. If YES, do not use OMNI Cream.

2. Turn on InSTEP computers and screens (master and slave), and enter into Data Acquisition on both (but enter slave first). Also turn-on the small black box located on top of the polygraph as well as the pre-amplifier on the shelf above this box (turn the knob a quarter turn, a red light will appear).

3. Retrieve the correct testing file.

4. Indicate subject's code number and date in CFS-ERP notebook.

5. Turn on polygraph and the channels that will be used.

6. Since the MMN task requires a response you must move the slave keyboard into the testing chamber. Place it such that the right side of the board is directly in front of the subject. The subject will be required to respond by pressing the "0" button.

7. There is a white wire that runs from the testing chamber to the chamber with the computers. Connect this wire to the slave keyboard wire and to the slave computer.

8. Unplug the thick black cord from the back of the computer located on the left side of the desk in the testing chamber and connect it to a slightly larger white wire coming through the wall from the computer chamber. This connects the video monitor. Only turn on this monitor, the computer itself is not needed.

9. Before the subject arrives, run the paradigm and make sure that the "XXXX" are appearing from time to time on the screen. Also, press the response button a few times and ensure that the master is registering the responses.

Polygraph:

1. It has been determined that a gain of 50 μV is good for the paradigms to be run. Thus ensure that the gain for all channels is set at 50 μV. (In InSTEP, it should be gain of 50, programmable gain at 2, and negative up).

This has been already pre-programmed.

2. Set 1/2 amp. to (low) 0.01 and (high) 100.
   AMP X 1,000 = 50
   Input Mode on USE
   The other settings do not matter.

WHAT you need:

OMNI cream (in red bottle with white lettering)
Wood stick
Gauze pad (2-3 pieces)
Electrode paste (in off-white tube)
15 gold-cup electrodes

CONSENT Form:

1. Explain the tasks to the subject and that the study looks at attention in people with problems such as theirs, respond to their questions.

2. Clearly indicate to the subject that he/she may stop their participation at any time during testing with no explanation required or asked.

3. Give informed consent to subject.

Placing Electrodes: (*For Schizophrenia MMN Studies)*

Fz, Cz, Pz, F3, F4, C3, C4, T3, T4, M1 (left mastoid), M2 (right mastoid). Nose tip (reference). Above right eye, outer canthus of left eye and a ground (placed about 1 inch to the right and behind the Cz).

1. Measure Head.

2. Put a piece of gauze on end of stick, then put a bit of OMNI cream on gauze. Rub electrode location with a bit of pressure.

3. Put some electrode paste into electrode such that cup is completely filled.

4. Holding a couple of gauze pads against the top of the electrode, place the electrode on the subject and press down.

5. Continue this procedure until all electrodes are placed. Plug each immediately into correct spot in electrode box.

LEFT EOG = O1	Right EOG = O2
M1 = Fp1	M2 = Fp2
Reference = T5	Ground = GRD

Fz, Cz, Pz, F3, F4, C3, C4, T3, T4 have their spots indicated on the electrode box.

6. **Impedance:** Set the knob located at bottom of polygraph to 5K. Press the impedance button for each electrode on the polygraph, the light should be green. If red, re-put electrode.

Calibration:

1. Set all channels on the polygraph to Ground (GND; located on the complete left side of the polygraph).
2. Put the Ground voltage at base of polygraph to 50 μV.
3. Set knob at base of polygraph currently set at 5K to AutoCal.
4. Run a paradigm (whichever you are using will do).
5. Press the Cal button of left of Input Mode repeatedly. If all channels do not appear the same at this time, something is wrong and testing may not proceed.
6. **Once calibration is done, set the Autocal to Use.**

FINISH

Once testing has been completed and subject has left the following must be done:

1. Clean the electrodes.

2. Set all polygraph channels to CAL (buttons on left most side of the polygraph). Turn off all channels and the polygraph.

3. ***Backup data onto optical disk***:

   Turn on optical disk drive and put in disk labeled J. Baribeau.
   On master, exit InSTEP and go into c:\instep\data
   Copy all the files just recorded to the optical disk using the following command:
   move c:\instep33\data\filename.* d: (a total of 6-12 files should be copied)

4. Go into the d drive and verify that all the files are there.

5. Turn off all computers, equipment, optical disk driver and video monitors.

6. Bring back the 7 electrodes that belong to Jacinthe to her office, in addition to the test binder and folder.

7. Photocopy the consent form twice and leave in E. Stip's mail box.

Appendix G

Subject test instructions

Centre Fernard Seguin
Concordia University

MMN Protocol
ERP Testing Instructions

Testing procedure:

Once all is set you may begin testing.

Place headphones on subject, ensure that left and right sides are correctly placed.

Instruct subject on the importance of not moving and blinking. tell subject that they can blink once in a while, but to try their best not to blink.

MMN:

Instructions to the subject (English version)

Give instructions for the MMN task:

"You will hear a number of beeps through the headphones and once in a while a series of Xs will appear in the middle of the screen. What I would like you to do is to try and ignore the beeps and concentrate on pressing this button *(show subject the button and press to indicate the pressure needed)* whenever you see the Xs. Respond as quickly as possible, but try to not make any mistakes. If you make a mistake, just continue the task. The Xs will always appear in the middle of the screen".

Instructions to the subject (French version)

"Vous allez entendre une series de "bips" dans les écouteurs, et de temps en temps une série de X apparaîtront au milieu de l'écran. Ce que je voudrais que vous fassiez est d'ignorer les sons et de vous concentrer à appuyer sur ce bouton (*montrer le bouton au sujet ainsi que la pression requise pour répondre*) chaque fois que vous voyez un X à l'écran. Répondez aussi vite que possible tout en essayant de ne pas faire d'erreurs. Si vous faites une erreur, ne vous en souciez pas et continuez la tâche. Les X apparaîtront toujours au centre de l'écran."

Additional instructions:

Tell the subject that the practice will only take about a minute, while the blocks themselves about 2 minutes each.

Run the MMN task first. The files are labeled as alhommn.
First give subject a practice run, the alhommn.exa. This will also give subjects a chance to get familiar with responding to the targets (XXXX). Do not save the practice.

If subject is not responding correctly, repeat the practice.

Once task is ready to start, look in binder for the order of block presentation. There are 12 alhommn.seq files (e.g., alhommnb1.seq). These are all the same but the stimuli have different randomizations. Follow the order indicated for the subject in the book, crossing out each block as it is completed.

Give the subject at least 30 seconds in between blocks to rest and always ask if they are ready to continue before you administer the next block.

Appendix H

Consent forms

PROJET SUR FONCTIONS COGNITIVES

PERSONNES RESPONSABLES:
Dr. J. Baribeau, Directrice LANNH, 848-2244 et Centre Fernand Seguin, 251-4015.
Dr. E. Stip, Psychiatre, Hôpital Louis-H. Lafontaine, 251-4015.
Robert Roth, M.A., et Denise L. Milovan, B.Sc., Coordinateur et coordinatrice, 848-2244.

FORMULAIRE DE CONSENTEMENT

Cette recherche s'intéresse au fonctionnement cognitif et à l'effet du traitement cognitif ou psychosocial sur la cognition.

(Nom; S.V.P. imprimé) _____,
j'accepte de participer à un programme de recherche conduit par le Dr. Jacinthe Baribeau du département de psychologie de l'Université Concordia et du Centre Fernand Seguin de l'Hôpital Louis-H. Lafontaine.

Si je suis choisi(e) pour participer à ce programme de recherche, je devrai participer à deux sessions de testing: une avant que je recoie un nouveau type de médicament administré par mes thérapeutes, et une après. La durée de chaque session de testing sera d'approximativement deux heures. Le testing consistera de l'enregistrement de potentiels évoqués utilisant une technique standard de EEG telle que pratiquée par l'hôpital. Des électrodes de métal seront collées sur ma chevelure, un sur mon nez, un au-dessus de mes sourcils, et un sur mon joue. Il n'y aura aucune douleur, mais peut-être seulement un léger inconfort. Je complèterai une tâche qui consiste à ignorer des sons entendus au moyen d'écouteurs et a repondre a des sitmuli visuels présentés sur un écran d'ordinateur. Le testing se poursuivera au laboratoire de l'Hôpital Louis-H. Lafontaine.

Je comprends que je suis libre d'interrompre ma collaboration à n'importe quel moment, quelle que soit la raison, et sans conséquences négatives. Les données déjà accumulées pourront être utilisées en toute confidentialité, pour des fins de recherche scientifique. Les résultats de ma performance seront donnés à mes thérapeutes sur demande, et ce, avec ma permission seulement.

On me promet que mes dossiers sont strictement confidentiels et que seules les personnes impliquées dans ce projet y ont accès. Tous mes fichiers de données seront identifiés par un code et non par mon nom. Je suis libre de participer à ce programme.

Je déclare qu'on m'a expliqué et que je comprends la procédure et les raisons de cette étude.

Signature:
(Nom)_____ (Date)_____.

(Moniteur)_____ (Date)_____.

PROJET SUR FONCTIONS COGNITIVES

PERSONNES RESPONSABLES:
Dr. J. Baribeau, Directrice LANNH, 848-2244 et Centre Fernand Seguin, 251-4015.
Dr. E. Stip, Psychiatre, Hôpital Louis-H. Lafontaine, 251-4015.
Robert Roth, M.A., et Denise L. Milovan, B.Sc., Coordinateur et coordinatrice, 848-2244.

FORMULAIRE DE CONSENTEMENT

Cette recherche s'intéresse au fonctionnement cognitif et à l'effet du traitement cognitif ou psycho-social sur la cognition.
(Nom; S.V.P. imprimé) _____,
j'accepte de participer à un programme de recherche conduit par le Dr. Jacinthe Baribeau du département de psychologie de l'Université Concordia et du Centre Fernand Séguin de l'Hôpital Louis-H. Lafontaine.

Si je suis choisi(e) pour participer à ce programme de recherche, je devrai participer à une session de testing. La durée du testing sera d'approximativement deux heures. Le testing consistera de l'enregistrement de potentiels évoqués utilisant une technique standard de EEG telle que pratiquée par l'hôpital. Des électrodes de métal seront collées sur ma chevelure, un sur mon nez, un au-dessus de mes sourcils, et un sur mon joue. Il n'y aura aucune douleur, mais peut-être seulement un léger inconfort. Je complèterai une tâche qui consiste à ignorer des sons entendus au moyen d'écouteurs et a repondre a des sitmuli visuels présentés sur un écran d'ordinateur. Le testing se poursuivera au laboratoire de l'Hôpital Louis-H. Lafontaine.

Je suis conscient(e) que je suis libre d'interrompre ma collaboration à n'importe quel moment, quelle que soit la raison, et cela, sans conséquences négatives. Les données déjà accumulées pourront être utilisées en toute confidentialité, pour des fins de recherche scientifique. Les résultats de ma performance sera donné à mes thérapeutes sur demande, et ce, seulement avec ma permission.

On me promets que mes dossiers sont strictement confidentiels et que seules les personnes impliquées dans ce projet y ont accès. Tous mes fichiers de données seront identifiés par un code et non par mon nom. Je suis libre de participer à ce programme.

Je déclare qu'on m'a expliqué et que je comprends la procédure et les raisons de cette étude.

Signature:

(Nom)_____(Date)_____.

(Moniteur)_____ (Date)_____.

Appendix I

Means and standard deviations for the MMN component

Table I1

Descriptive statistics of the mismatch negativity at midline electrode placements

		Latency ranges (msec)							
		50-70	70-90	90-110	110-130	130-150	150-170	170-190	190-210
Fz									
Controls									
	M	0.45	-1.04	-2.26	-2.66	-1.66	-0.78	0.45	1.15
	SD	1.60	3.08	3.79	4.30	3.54	4.01	3.41	3.13
Patients									
	M	-1.16	-2.04	-2.67	-2.33	-1.89	-1.96	-1.54	-0.80
	SD	3.05	3.69	4.16	3.94	3.90	3.70	3.31	2.99
Cz									
Controls									
	M	0.36	-0.44	-1.36	-1.54	-0.73	-0.02	1.18	1.62
	SD	2.42	2.70	4.47	4.39	3.77	3.79	3.79	3.18
Patients									
	M	-0.95	-2.24	-3.12	-3.12	-2.52	-2.31	-2.53	-1.78
	SD	4.09	4.68	4.91	4.83	5.49	7.50	6.31	5.00
Pz									
Controls									
	M	0.18	0.94	0.94	0.91	0.64	1.05	1.93	1.74
	SD	2.07	1.96	2.60	2.87	3.30	2.86	2.04	2.44
Patients									
	M	-0.71	-1.41	-1.52	-1.47	-1.26	-0.88	-2.05	-2.31
	SD	5.18	5.52	5.19	4.65	5.72	8.61	7.44	5.63

Table I2

Means and standard deviations for mismatch negativity at lateral electrode placements

	Latency ranges (msec)							
	50-70	70-90	90-110	110-130	130-150	150-170	170-190	190-210
F3								
Controls								
M	0.00	-1.22	-2.06	-2.38	-1.43	-0.85	0.27	0.90
SD	1.33	1.73	1.71	2.98	2.95	3.34	2.93	2.87
Patients								
M	-1.61	-2.15	-2.93	-3.25	-2.66	-2.89	-2.20	-1.70
SD	3.51	4.52	3.71	4.49	4.21	4.96	5.14	5.28
F4								
Controls								
M	0.06	-1.06	-2.14	-2.52	-1.54	-1.08	-0.31	0.27
SD	2.01	2.57	4.12	4.26	3.34	3.29	2.54	2.28
Patients								
M	-1.24	-1.46	-2.22	-2.69	-1.91	-2.42	-2.22	-0.88
SD	2.95	3.78	3.37	4.57	4.18	4.44	4.28	3.36
C3								
Controls								
M	0.20	0.01	-0.52	-0.82	-0.31	0.26	1.42	1.95
SD	1.24	2.05	3.26	3.83	3.28	3.73	3.27	2.51
Patients								
M	-1.09	-1.92	-2.75	-2.83	-2.68	-2.43	-3.26	-2.93
SD	4.90	5.47	5.62	6.18	5.85	7.94	7.26	7.19
C4								
Controls								
M	0.48	-0.16	-0.90	-0.86	-0.26	0.29	0.85	0.93
SD	2.10	2.69	4.25	4.24	3.76	3.30	2.81	3.17
Patients								
M	-0.44	-0.85	-1.35	-1.44	-0.42	-1.01	-0.73	-0.38
SD	4.00	4.49	4.24	4.55	5.47	5.83	6.41	4.21
T3								
Controls								
M	0.36	1.10	2.27	2.19	1.72	1.53	1.83	1.08
SD	1.68	1.25	2.03	1.66	1.38	1.40	1.35	1.66
Patients								
M	-0.59	-0.87	-0.53	-0.27	-0.87	-0.14	-1.18	-1.68
SD	3.42	3.40	3.39	5.28	4.08	5.57	4.51	3.89
T4								
Controls								
M	0.58	0.86	1.00	0.89	0.96	1.08	1.40	1.31
SD	1.09	1.31	2.04	2.53	2.20	1.81	1.92	2.05
Patients								
M	-1.35	-1.28	-1.18	-0.69	-1.18	-1.22	-1.72	-2.19
SD	2.95	4.00	3.96	4.70	4.11	5.84	5.82	4.28

Appendix J

Means and standard deviations for the negativities elicited separately in the standard and deviant tone conditions

Table J1

Means and standard deviation for the ERP negativities elicited by deviant auditory stimuli at midline electrode sites

		Latency range (msec)							
		50-70	70-90	90-110	110-130	130-150	150-170	170-190	190-210
Fz									
Controls									
	M	0.50	-1.33	-0.57	-4.05	-3.32	-1.82	-0.22	0.46
	SD	2.04	2.72	2.82	3.95	3.64	3.64	3.25	3.11
Patients									
	M	-0.28	-1.70	0.53	-3.23	-3.12	-3.10	-2.43	-1.58
	SD	2.78	3.93	3.03	3.20	3.56	3.17	3.18	4.18
Cz									
Controls									
	M	0.38	-0.96	-2.40	-2.64	-1.69	-0.26	1.39	1.81
	SD	2.12	2.76	5.02	4.19	3.81	3.48	3.35	3.37
Patients									
	M	0.22	-1.26	-1.64	-2.83	-2.49	-2.47	-2.24	-0.94
	SD	3.49	4.08	3.75	3.45	4.34	5.33	4.50	4.25
Pz									
Controls									
	M	-0.30	-0.26	-0.50	-0.28	-0.30	0.29	1.21	0.98
	SD	2.25	2.25	3.74	3.36	3.60	2.79	2.31	2.33
Patients									
	M	0.16	-0.55	0.18	0.01	-0.20	-0.39	-1.32	-0.74
	SD	3.85	4.40	3.85	2.64	3.49	6.23	5.81	3.90

Table J2

Means and standard deviation for the ERP negativities elicited by deviant auditory stimuli at lateral electrode sites

	Latency range (msec)							
	50-70	70-90	90-110	110-130	130-150	150-170	170-190	190-210
F3								
Controls								
M	0.42	-1.39	-2.78	-3.46	-2.84	-1.69	-0.25	0.41
SD	1.75	1.98	2.43	3.08	2.99	3.37	3.04	2.89
Patients								
M	-1.58	-2.64	-3.40	-4.58	-4.10	-4.48	-4.01	-3.37
SD	3.98	6.10	4.77	5.82	4.83	6.59	7.02	8.46
F4								
Controls								
M	0.65	-0.93	-2.44	-3.38	-2.68	-1.74	-0.26	0.08
SD	2.02	2.28	3.68	3.74	3.10	2.83	2.52	2.43
Patients								
M	0.23	-0.13	-0.82	-1.99	-1.70	-1.70	-0.63	0.57
SD	2.28	3.28	2.69	4.10	4.13	4.56	4.08	3.63
C3								
Controls								
M	-0.12	-1.28	-2.23	-2.62	-2.10	-0.95	0.65	1.12
SD	1.94	2.58	4.00	3.74	3.84	4.23	3.59	3.59
Patients								
M	-1.61	-2.78	-3.68	-4.79	-4.90	-5.17	-6.07	-5.95
SD	5.06	6.86	6.12	6.84	6.94	9.31	9.65	10.21
C4								
Controls								
M	0.35	-0.70	-1.68	-1.99	-1.49	-0.40	0.67	0.97
SD	2.16	2.58	4.06	3.95	3.60	2.68	2.49	2.82
Patients								
M	0.34	-0.73	0.77	-1.17	-1.49	-1.36	-0.74	0.31
SD	2.38	3.42	1.98	2.63	3.04	3.12	3.88	2.86
T3								
Controls								
M	-0.68	-0.07	1.05	1.36	1.11	1.07	1.38	0.80
SD	1.76	1.51	1.59	1.50	1.26	1.35	1.37	1.37
Patients								
M	-0.94	-0.73	-0.78	-0.59	-0.66	-0.74	-1.79	-2.37
SD	3.01	4.06	3.23	5.05	3.74	5.39	4.83	4.72
T4								
Controls								
M	0.04	0.21	0.17	0.12	0.04	0.54	0.84	0.51
SD	1.33	1.35	2.03	2.50	2.14	2.16	3.12	2.31
Patients								
M	-1.49	-1.34	-1.48	-9.45	-1.92	-2.53	-3.66	-3.89
SD	3.14	4.67	4.04	33.68	4.95	6.49	7.27	6.78

Table J3

Means and standard deviation for the ERP negativities elicited by standard auditory stimuli at midline electrode sites

		Latency range (msec)							
		50-70	70-90	90-110	110-130	130-150	150-170	170-190	190-210
Fz									
Controls									
	M	0.25	-0.57	-1.22	-1.70	-1.99	-1.31	-1.02	-1.10
	SD	2.18	2.82	2.64	2.63	2.94	2.56	2.84	3.26
Patients									
	M	1.07	0.53	0.88	-0.95	-1.40	-1.36	-1.30	-1.34
	SD	1.52	3.30	4.15	3.19	3.32	3.48	3.44	3.08
Cz									
Controls									
	M	-0.21	-0.57	-1.16	-1.15	-0.92	-0.17	0.14	0.13
	SD	1.60	1.76	1.55	1.19	1.46	1.08	1.98	1.62
Patients									
	M	1.37	0.68	2.30	0.77	0.42	0.28	0.61	1.18
	SD	1.57	1.59	5.12	3.51	3.49	4.10	3.74	2.72
Pz									
Controls									
	M	-0.52	-1.46	-1.72	-1.40	-1.02	-0.81	-0.88	-0.93
	SD	0.77	1.61	1.74	1.30	1.15	1.16	1.92	1.67
Patients									
	M	0.90	1.43	2.53	2.32	1.78	1.17	1.32	2.31
	SD	2.70	3.80	5.07	4.94	4.50	4.70	4.66	4.45

Table J4

Means and standard deviation for the ERP negativities elicited by standard auditory stimuli at lateral electrode sites

	Latency range (msec)							
	50-70	70-90	90-110	110-130	130-150	150-170	170-190	190-210
F3								
Controls								
M	0.46	-0.59	-0.82	-1.25	-1.24	-1.02	-0.78	-0.78
SD	1.23	1.44	1.48	1.58	2.42	1.59	1.95	2.27
Patients								
M	-0.49	-1.00	-1.15	-1.78	-1.86	-2.22	-2.99	-3.70
SD	2.52	3.22	2.89	4.05	4.85	4.57	4.78	5.51
F4								
Controls								
M	0.46	-0.39	-0.58	-1.18	-1.51	-0.92	-0.50	-0.49
SD	1.71	1.67	2.06	2.12	2.42	1.99	1.94	2.19
Patients								
M	1.64	1.92	2.37	1.52	0.82	1.32	1.60	2.19
SD	3.31	3.63	5.23	4.32	4.49	3.35	3.97	4.19
C3								
Controls								
M	-0.63	-1.84	-2.29	-2.39	-2.23	-1.79	-1.44	-1.64
SD	2.76	4.16	3.88	4.03	4.05	4.53	5.28	5.91
Patients								
M	-1.21	-2.76	-1.67	-2.96	-3.38	-4.12	-4.53	-5.04
SD	3.35	3.46	2.57	3.36	3.90	4.98	5.86	6.81
C4								
Controls								
M	-0.20	-0.69	-0.97	-1.32	-1.42	-0.82	-0.20	-0.13
SD	1.93	2.00	1.78	1.87	1.90	2.01	2.51	2.14
Patients								
M	-0.34	-0.19	0.65	-0.36	-0.91	-0.66	-0.31	0.45
SD	4.53	4.31	6.24	5.79	5.74	5.07	5.00	4.05
T3								
Controls								
M	-1.30	-1.36	-1.50	-1.08	-0.93	-0.72	-0.77	-0.58
SD	1.26	1.95	1.67	1.32	2.02	1.79	2.32	2.13
Patients								
M	-0.47	0.50	-0.14	-0.36	0.56	-0.59	-0.63	-0.93
SD	2.03	2.63	1.24	1.37	4.16	2.96	3.52	2.17
T4								
Controls								
M	-0.90	-1.14	-0.90	-1.28	-1.54	-1.15	-1.29	-1.46
SD	1.59	2.46	2.28	2.76	3.50	4.03	5.40	4.63
Patients								
M	-0.34	-0.73	-0.78	-0.93	-1.65	-2.46	-3.26	-2.98
SD	3.01	3.33	3.00	4.31	4.56	5.18	5.68	6.19

Appendix K

Analyses of variance for the amplitude of the MMN component

Table K1

Analyses of variance for the MMN component at lateral electrodes: group by hemisphere interactions

Source	SS	df	MS	F
Range 50-70 msec				
Hemisphere	1.66	1	1.66	0.36
Group By Hemisphere	0.01	1	0.01	0.00
Range 70-90 msec				
Hemisphere	1.36	1	1.36	0.42
Group By Hemisphere	2.78	1	2.78	0.86
Range 90-110 msec				
Hemisphere	0.08	1	0.08	0.01
Group By Hemisphere	11.52	1	11.52	1.06
Range 110-130 msec				
Hemisphere	0.00	1	0.00	0.00
Group By Hemisphere	10.23	1	10.23	0.96
Range 130-150 msec				
Hemisphere	3.94	1	3.94	0.38
Group By Hemisphere	14.05	1	14.05	1.37
Range 150-170 msec				
Hemisphere	0.02	1	0.02	0.00
Group By Hemisphere	2.41	1	2.41	0.21
Range 170-190 msec				
Hemisphere	0.18	1	0.18	0.04
Group By Hemisphere	14.11	1	14.11	3.02
Range 190-210 msec				
Hemisphere	2.27	1	2.27	0.20
Group By Hemisphere	20.52	1	20.52	1.80

Note. Hemisphere = right and left cerebral hemispheres. Group = controls and schizophrenia patients.

Table K2

Analyses of variance for the amplitude of the MMN at mastoid electrode locations

Source	SS	df	MS	F
Range 50-70 msec				
Electrode	0.32	1	0.32	0.16
Group By Electrode	1.08	1	1.08	0.56
Range 70-90 msec				
Electrode	0.86	1	0.86	0.27
Group By Electrode	0.24	1	0.24	0.07
Range 90-110 msec				
Electrode	2.26	1	2.26	0.35
Group By Electrode	11.16	1	11.16	1.75
Range 110-130 msec				
Electrode	0.05	1	0.05	0.01
Group By Electrode	8.39	1	8.39	1.12
Range 130-150 msec				
Electrode	0.12	1	0.12	0.04
Group By Electrode	1.66	1	1.66	0.57
Range 150-170 msec				
Electrode	0.93	1	0.93	0.22
Group By Electrode	0.22	1	0.22	0.05
Range 170-190 msec				
Electrode	1.46	1	1.46	0.31
Group By Electrode	0.31	1	0.31	0.07
Range 190-210 msec				
Electrode	0.70	1	0.70	0.15
Group By Electrode	0.01	1	0.01	0.00

Note. Electrode = M1, M2. Group = controls and schizophrenia patients.

Appendix L

Analyses of variance for ERP negativities elicited by auditory stimuli in the standard and deviant conditions

Table L1

ANOVAs for the amplitudes of the ERP negativities: midline electrode sites

Source	SS	df	MS	F
Range 110-130 msec.				
Group	60.16	1	60.16	2.52
Range 190-210 msec.				
Group	6.76	1	6.76	0.30

Note. Group = controls and schizophrenia patients.

Table L2

ANOVAs for the amplitudes of the ERP negativities: lateral electrode sites

Source	SS	df	MS	F
Range 190-210 msec.				
Group	292.77	1	292.77	2.70

Note. Group = controls and schizophrenia patients.

Table L3

ANOVAs for the amplitudes of the ERP negativities at lateral electrode sites: stimulus by group interactions

Source	SS	df	MS	F
Range 190-210 msec.				
Stimulus	12.57	1	12.57	0.46
Group By Stimulus	94.00	1	94.00	3.42

Note. Stimulus = auditory deviant tones and auditory standard tones. Group = controls and schizophrenia patients.

Table L4

ANOVAs for the amplitudes of the ERP negativities at lateral electrode sites: group by stimulus by hemisphere interactions

Source	SS	df	MS	F
Range 190-210 msec.				
Stimulus By Hemisphere	2.02	1	2.02	0.23
Group By Stimulus By Hemisphere	1.76	1	1.76	0.20

Note. Stimulus = auditory standard and deviant stimuli. Hemisphere = right and left cerebral hemispheres. Group = controls and schizophrenia patients.

Table L5

ANOVAs for the amplitudes of the ERP negativities at lateral electrode sites: group by stimulus by electrodes located within each emisphere interactions

Source	SS	df	MS	F
Range 190-210 msec.				
Stimulus By Within Location By Hemisphere	11.49	2	5.75	1.29
Group By Stimulus By Within Location By Hemisphere	18.29	2	9.15	2.06

Note. Stimulus = auditory standard and deviant stimuli. Within Hemisphere = F3, C3, T3 and F4, C4, T4 electrode locations. Group = controls and schizophrenia patients.

Table L6

ANOVAs for the amplitudes of the ERP negativities at lateral electrode sites: group by electrodes located over each cerebral hemisphere interactions

Source	SS	df	MS	F
Range 190-210 msec.				
Within Location	30.80	2	15.40	1.52
Group By Within Location	41.95	2	20.98	2.07

Note. Within Location = F3, C3, T3 and F4, C4, T4. Group = controls and schizophrenia patients.

Table L7

ANOVAs for the amplitudes of the ERP negativities at lateral electrode sites: group by stimulus by electrodes located within each hemisphere interactions

Source	SS	df	MS	F
Range 190-210 msec.				
Stimulus By Within Location	7.37	2	3.68	1.47
Group By Stimulus By Within Location	5.96	2	2.98	1.19

Note. Within Location = F3, C3, T3 and F4, C4, T4 electrode locations. Stimulus = auditory standard and deviant stimuli. Group = controls and schizophrenia patients.