UNIVERSITY OF CALIFORNIA, SAN DIEGO

SAN DIEGO STATE UNIVERSITY

Automatic Sensory Discrimination Impairment in Prodromal and Recent-Onset Schizophrenia

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy

in

Clinical Psychology

by

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2010

The Dissertation of Carol Jahchan is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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2010

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ACKNOWLEDGEMENTS

The current dissertation was supported by MH 60720, MH 76191, and MH 79777 awarded by the National Institute of Mental Health, NARSAD, and a pilot grant awarded by the VISN-22 Mental Illness Research, Education, and Clinical Center. I would like to express the deepest appreciation to my incredible advisor, Dr. Kristin Cadenhead, for her invaluable guidance and everything she has taught me throughout my graduate training. I would also like to thank Dr. Gregory Light whose patience and persistent help enabled me to learn the basic neurophysiology skills required to complete this project. I am heartily thankful to Dr. Michael Caligiuri for his constant support and interest in my professional development. Moreover, I would like to express my gratitude to Dr. Gauri Savla for being such a wonderful friend and mentor. I would like to make a special reference to everyone at the Cognitive Assessment and Risk Evaluation program for their tireless assistance with recruitment and data collection. I would also like to offer my most sincere thanks to all the study participants without whom this research would not have been possible. Lastly, I am forever indebted to my dearest parents and my loving husband for their patience and warm encouragement throughout this entire process.

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Palmer, B.W., Savla, G.N., Jahshan, C.S., & Meeks, T.W. (2009). Schizophrenia and paranoid disorders of late life. In N. Andreasen (Ed.), *The New Oxford Textbook of Psychiatry (2nd Ed.)*. New York: Oxford University Press.

Jahshan, C.S., & Sergi, M.J. (2007). Theory of mind, neurocognition, and functional status in schizotypy. *Schizophrenia Research, 89*, 278-286.

Fayyad, J.A., Jahshan, C.S., & Karam, E.G. (2001). Systems development of child mental health services in developing countries. *Child and Adolescent Psychiatric Clinics of North America, 10 (4)*, 745-762.

ABSTRACT OF THE DISSERTATION

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by

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Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2010
San Diego State University, 2010

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Deficits in automatic sensory discrimination, as indexed by mismatch negativity (MMN) and P3a, are well documented in schizophrenia patients and could underlie deficits in more complex cognitive operations, as well as clinical symptoms and real-life functioning. Although there is ample evidence to suggest that MMN is impaired in chronic schizophrenia, its reduction has not been as robust in the early stages of the disease. Moreover, MMN has not been sufficiently researched in subjects at risk for schizophrenia. The primary aim of the present study was to investigate the early stages of auditory information processing in recent-onset schizophrenia and the putative prodrome by examining the amplitude and topography of MMN and P3a. The secondary aim was to explore the relationships of MMN and P3a deficits to the severity of clinical symptoms and social functioning impairment. We assessed

26 at-risk individuals, 28 recent-onset schizophrenia patients, and 31 age-matched healthy comparison subjects on a duration-deviant MMN paradigm as well as a battery of clinical and social functioning measures. Repeated measures analyses of variance revealed large effect size MMN amplitude reductions in recent-onset patients and modest effect size MMN reductions in at-risk individuals. Additionally, both patient groups had significant P3a amplitude reductions relative to the healthy comparison group. As expected, there were no significant group differences in MMN and P3a topographic distributions. MMN was found to be independent of clinical symptomatology, whereas reduced P3a correlated with more severe negative symptoms in the at-risk group. Contrary to predictions, smaller MMN and P3a activity was associated with better social and family functioning within the patient groups, unlike the inverse association in chronic schizophrenia patients. In summary, our findings point to deviance detection abnormalities in subjects identified as putatively prodromal for schizophrenia as well as those with manifest schizophrenia. Those persons may incorrectly process auditory input or underdetect changes in their acoustic environment, failing to notice stimuli that are usually salient to most people. MMN and P3a exhibit promise as trait markers for schizophrenia as they appear to be deficient before the onset of full-blown psychosis as well as during the first two years of the illness.

1. Introduction

The current study aims to investigate the early stages of auditory information processing in recent-onset schizophrenia and the putative prodrome, using a neurophysiological paradigm. Two event-related potential components are examined, MMN and P3a. MMN measures short-term sensory memory and is the first step in a sequence of brain processes leading to the involuntary switching of attention and evaluation of the eliciting event (as indexed by P3a). (Chapman, 1966) suggested that disruption in the ability to filter out irrelevant stimuli and selectively attend to information is a fundamental symptom in early schizophrenia, which precedes the emergence of neurotic and attenuated psychotic symptoms. More specifically, the goals of the proposed study are 1) to evaluate the level of impairment in automatic sensory discrimination (as measured by the degree of reduction in MMN and P3a amplitudes) in young adults at risk to develop schizophrenia relative to demographically matched healthy comparison subjects as well as recent-onset schizophrenia patients, and 2) to determine whether MMN and P3a deficits are associated with the severity of clinical symptomatology and social functioning impairment among patients with prodromal and recent-onset schizophrenia.

The study background includes a description of the prodromal phase of schizophrenia followed by a discussion of the cognitive abnormalities in schizophrenia and a review of the findings from the few existing studies using MMN and P3a in the early stages of the illness. Next, the aims and specific hypotheses are described in detail, followed by the methods and results of the statistical analyses. The dissertation ends with a discussion of the results, strengths and limitations of the study, and its theoretical and clinical implications.

2. The Schizophrenia Prodrome

This section examines the importance of studying a population prodromal for psychosis. Section 2.1. defines the schizophrenia prodrome and is followed by a discussion of the vulnerability markers in schizophrenia research in Section 2.2. Section 2.3. comprises a description of the neurodevelopmental processes that may underlie the onset of schizophrenia in early adulthood.

2.1. Characteristics of the prodromal phase of schizophrenia

The schizophrenia prodrome is a period of rapid developmental change that predates illness onset and is characterized by a substantial functional decline together with the emergence of subthreshold psychotic symptoms (Yung & McGorry, 1996). The initial prodromal stage in schizophrenia occurs many months and up to several years prior to the onset of full-blown psychosis and represents a marked deviation from a person's normal level of functioning and previous experiences. This period is marked by the gradual development of symptoms including mood disturbance (depression, anxiety, irritability), volition changes (anhedonia, loss of drive and motivation), cognitive changes (reduced concentration and attention), physical symptoms (sleep disturbance, somatic complaints), as well as behavioral changes (social withdrawal, deterioration in school, work, or other role functioning). Those low-grade general symptoms are common in adolescence and can resolve spontaneously or they might be followed by more specific prepsychotic symptoms, such as suspiciousness, magical ideation, perceptual abnormalities, and odd behavior. Alternatively, the non-specific symptoms and behavioral changes can occur in tandem with the attenuated psychotic symptoms or in response to them. If further progression occurs, those subthreshold symptoms may evolve into frank psychotic symptoms (e.g., hallucinations, delusional thinking, disorganized speech or behavior) and mark the transition to a first psychotic episode. Nonetheless, the heterogeneous constellation of symptoms that characterizes the prodromal phase suggests a broad differential diagnosis (e.g., schizotypal personality disorder, bipolar disorder, major depressive disorder) and does not inevitably lead to schizophrenia. In fact, it

has been found that 20 to 30% of subjects presenting with an “at-risk mental state” develop psychosis within one year of ascertainment (Cannon, et al., 2008). Therefore, we will be using the term “at-risk” to refer to “prodromal”, as the latter state can only be truly diagnosed retrospectively.

2.2. Vulnerability markers and predictors of psychosis

Studying vulnerability markers in at-risk and recent-onset schizophrenia patients may shed light on the neurodevelopmental processes and dynamic changes in this beginning stage of the illness. Vulnerability markers are stable heritable traits that are present in schizophrenia probands, their non-affected relatives, as well as schizotypal subjects. It has been hypothesized that these endophenotypic traits are a predisposition to rather than a consequence of psychosis and may be more central to schizophrenia than are symptoms and DSM-IV diagnoses (Braff, Freedman, Schork, & Gottesman, 2007). In fact, endophenotypes may identify more homogeneous subsamples of patients with specific pathophysiological processes (Gottesman & Gould, 2003). The endophenotypes that have been established in schizophrenia spectrum research include neurocognitive endophenotypes, such as verbal learning and memory, working memory, and sustained focused attention, neurophysiological endophenotypes, such as sensorimotor gating or inhibitory functioning, and information processing, and neuroanatomical endophenotypes, such as brain volume and gray and white matter concentrations. Mapping genes for those quantitative endophenotypes may identify the genes that confer vulnerability for schizophrenia. Furthermore, studying biomarkers in the schizophrenia prodrome can help us identify predictors of functional outcome and psychotic conversion, while avoiding potential confounds associated with chronic illness, antipsychotic exposure, and long-term hospitalization. A number of studies that followed at-risk subjects longitudinally showed that verbal memory (Eastvold, Heaton, & Cadenhead, 2007) and visuospatial working memory deficits (Wood, et al., 2003), as well as a decline in verbal and intellectual abilities (Pukrop, et al., 2007) may be predictive of later transition to psychosis. We have found, in a previous study, that a higher than expected percentage of at-risk subjects who later converted to psychosis showed a deterioration in working memory and processing speed (Jahchan, Heaton, Golshan, & Cadenhead, 2010). Impairments in olfactory

identification ability have also been suggested to be trait markers of schizophrenia (Brewer, et al., 2003). Motor dysfunction has been found to precede the clinical onset of schizophrenia by many years. Neuromotor disturbances (Walker, Savoie, & Davis, 1994) and perspective-taking deficits (Schiffman, et al., 2004) were observed among children who later developed a schizophrenia spectrum disorder.

2.3. Neuroimaging findings in prodromal schizophrenia

Schizophrenia emerges during a critical period of neurodevelopment as a result of an interaction between environmental and genetic factors. According to the diathesis-stress model, psychosocial stressors can trigger symptoms in subjects with a preexisting genetic vulnerability (Walker & Diforio, 1997). Schizophrenia is characterized by a process of neuronal volume reduction that primarily involves the dendrites and is likely caused by glutamatergic excitotoxicity and synaptogenesis abnormalities (McGlashan & Hoffman, 2000; Rapoport, Addington, Frangou, & Psych, 2005). The neurodevelopmental hypothesis proposes that early (pre- and peri-natal) neurodevelopmental anomalies increase the risk of psychosis later in life by yielding subtle changes in brain structure and function (Lewis & Murray, 1987). Moreover, there is now evidence consistent with late, post-pubertal developmental brain alterations prior to and shortly after the onset of psychosis. Some studies suggest an acceleration of normal brain maturational processes reflected by a progressive gray matter loss involving medial temporal and orbital prefrontal regions around the time of transition to illness, in addition to dorsal prefrontal regions soon after the onset of psychosis (Pantelis, et al., 2007). The longitudinal reductions in regional cortical gray matter volume in subjects with prodromal symptoms of psychosis (Meisenzahl, et al., 2008) were found to be related to thalamic reductions in glutamate (Stone, et al., 2009). (Sun, Phillips, et al., 2009) showed greater brain contraction in the right prefrontal region in those who underwent transition to psychosis compared to those who did not. Nevertheless, the converters had increased gray matter in the occipital cortex compared to the non-converters (Borgwardt, et al., 2007). Interestingly, reductions in left parietal and occipital white matter, along with increases in the posterior cerebellum bilaterally have also been found in at-risk individuals (Walterfang, et al., 2008). It has been suggested that stress-related hormonal changes

around the time of illness onset can explain the aberrant structural changes in medial temporal and prefrontal regions (Phillips, et al., 2006).

The observed abnormalities prior to the onset of psychosis are nondiagnostic as they show considerable overlap with anatomic variation that is in the normal range. Therefore, they need to be considered in the context of normal dynamic changes – including increased myelination, synaptic proliferation and pruning, as well as subtle loss of gray matter volume – that occur in posterior regions during childhood and progress anteriorly to affect prefrontal regions during adolescence (Paus, 2005). Yet, a recently published study (Sun, van Erp, et al., 2009) that employed machine-learning-based pattern classification methods on MRI data, showed that psychotic patients can be discriminated from controls with an 86.1% accuracy, based on their distinct patterns of regional cortical gray matter changes. Furthermore, It should be noted that the neuroprogressive changes that occur after illness onset do not suggest that schizophrenia is a degenerative disorder and are not necessarily manifested in more severe cognitive impairment after illness onset (Rund, 2009). It is proposed that the brain is able to recruit alternative brain networks and compensate for some of the loss in neuropil or reduction in synaptic connections (Stern, 2002). In fact, longitudinal studies provide evidence that neurocognitive functions subsequent to a first episode of schizophrenia are relatively stable over time (Albus, et al., 2006; Hoff, Svetina, Shields, Stewart, & DeLisi, 2005) and that much of the deterioration tends to occur prior to the onset of illness (Jahchan, et al., 2010).

3. Cognitive Dysfunction in Schizophrenia

This section introduces mismatch negativity in the context of the broad array of cognitive deficits in schizophrenia. Section 3.1. discusses the cognitive abnormalities in schizophrenia and the advantages of using neurophysiological techniques to study preattentional functions. Section 3.2. defines mismatch negativity and Section 3.3. describes the neurotransmission systems involved in its generation.

3.1. The spectrum of cognitive deficits in schizophrenia

The cognitive dysfunction in schizophrenia is primary to the disorder and not due to medication or generalized psychopathology (McGhie & Chapman, 1961). The cognitive deficits of schizophrenia patients do not completely disappear when their symptoms remit (Rund, Landro, & Orbeck, 1997) and tend to predate the onset of the illness. Substantial cognitive deficits in people who go on to develop schizophrenia are apparent in childhood, exacerbate before onset of overt psychotic symptoms, and worsen with initial episode of illness (Bilder, et al., 2006). When compared to healthy controls, persons at risk for psychosis have neurocognitive deficits across multiple domains that are intermediate to those observed in first-episode patients (Eastvold, et al., 2007). The association between neurocognition (verbal memory, vigilance, and executive functioning) and functional outcome (social problem solving, skill acquisition, and community functioning) has been well established in schizophrenia (Green, Kern, Braff, & Mintz, 2000). A relationship was found between executive and attentional deficits and poor social adjustment in first-episode subjects two years after study entry (Bilder, et al., 2000). Moreover, verbal learning/memory was a significant predictor of social functioning in both a cross-sectional design involving at-risk subjects (Niendam, et al., 2007) and a 7-year longitudinal study of a first-episode sample (Milev, Ho, Arndt, & Andreasen, 2005). We have found that neurocognitive deficits, particularly executive dysfunction, and disorganized symptoms predict impaired social functioning in a sample of 22 at-risk subjects (Eslami et al., in submission).

The cognitive deficits in schizophrenia do not only include deficient performance in higher cognitive domains but also extend to early steps in cortical information processing. Therefore, they affect automatic preattentional functions as much as controlled attention-

dependent effortful information processing. Schizophrenia patients have been found to have difficulties filtering or gating trivial internal and external stimuli, as suggested by their PPI (prepulse inhibition), P50 suppression and saccadic inhibition deficits. Impairments in those elementary sensory processes could underlie clinical symptoms and deficits in more complex cognitive operations and real-life functioning (Braff & Light, 2004). It has been proposed that deficient pre-attentive, bottom-up processes indirectly contribute to the cognitive and functional decline in schizophrenia, via intellectual and sensory deprivation. The latter occurs as a result of the dampening of the automatic attention-switching function supporting the adequate reception and analysis of auditory input and speech-related information, and thus the continuous contact with the environment (Toyomaki, et al., 2008).

Neurophysiology and neuroimaging techniques have been employed to investigate the temporal and anatomical organization of functional brain activity underlying cognitive dysfunction in schizophrenia. Functional Magnetic Resonance Imaging (fMRI) is useful in localizing or identifying the specific brain regions activated while the subject is performing the respective task. Despite their indefinite spatial resolution, neurophysiological measures have the advantage of giving a precise timing of the neuronal population activity associated with a cognitive operation using event-related potentials (ERPs). ERPs are electric field patterns elicited in the brain by the summated, synchronous synaptic activity of large neuronal populations. They allow a real-time observation of the neural processes associated with sensory, perceptual, and cognitive events, with high temporal resolution (Luck, Girelli, McDermott, & Ford, 1997). The typical ERP elicited by a brief auditory stimulus consists of multiple overlapping components appearing over the interval 1.5 to 1000 ms after stimulus. Those ERP components correspond to different stages of information processing that intervene between stimulus and response (Hillyard & Kutas, 1983). Neurophysiological paradigms can be used to assess information processing at the sensory and preattentive level. They can also help quantify the biological processes underlying the higher order neurocognitive functions (e.g., complex effortful voluntary attention) assessed through classical neuropsychological tests. Understanding the impaired neural substrates at the basis of information processing deficits will help improve the pharmacologic strategies for treating those deficits in schizophrenia, which is a major step toward improving functional outcome.

3.2. What is Mismatch Negativity?

Early ERP components can be detected experimentally using a Mismatch Negativity (MMN) paradigm. MMN is a neurophysiological marker that has been studied in schizophrenia for the past 17 years. MMN is elicited in response to infrequent, physically deviant tones interspersed in the repeated presentation of a standard tone. The deviant "oddball" sounds/stimuli can differ from the standard ones in pitch, duration, intensity, timing, localization, or in more complex acoustic features. Even when consciously ignored by the subject, those features of the auditory stimuli are unconsciously analyzed and stored in short-term memory. MMN occurs as a result of a comparison process detecting a mismatch between the incoming stimulus and the sensory memory trace of the immediately preceding stimulus. The mismatching stimuli elicit a negative going wave that is largest at central midline scalp sites and typically peaks between 160 and 220 ms, although the response onset can be as early as 50ms. MMN is calculated by subtracting the waveform elicited by the frequent standard tone from that generated by the rare deviant tone (Naatanen, Paavilainen, & Reinikainen, 1989). The larger the deviation from the standard stimulus, the bigger is the MMN amplitude and the shorter its latency. In contrast to neuropsychological tests and long-latency ERP methods (e.g., N2b, P3b) that assess attention-dependent cognitive functions, MMN is passively elicited and is not under subject control or awareness. Thus, it is an index of automatic, preattentive, context-dependent information processing and a measure of auditory short-term sensory memory. The latter represents one of the simplest components of the working memory system and refers to the brain's ability to retain transient representations of the physical features (e.g., pitch, duration) of auditory stimuli over brief time periods (of approximately 30 seconds). Yet, the mere elicitation of the MMN is insufficient to prove that it occurs pre-attentively. Attention must be diverted from the deviant stimuli, which is usually achieved by asking participants to perform a task in another modality, e.g., reading a book or viewing a silent movie while being stimulated auditorily. MMN is easily tolerated, can be rapidly assessed, and yields high signal-to-noise ratios. It does not require an overt behavioral response and is uninfluenced by motivational and emotional factors, effort and level of task engagement, performance incentives, or self-monitoring (Naatanen, Paavilainen, Tiitinen, Jiang, & Alho, 1993). With MMN, there is no need to match task difficulties between

patients and healthy comparison subjects, or to control for potential attentional deficits. Nevertheless, findings regarding attentional modulation on MMN are mixed. (Haroush, Hochstein, & Deouell, 2009) found that MMN amplitude reflected momentary attentional fluctuations, suggesting possible involvement of executive inhibitory control over MMN generation. Furthermore, they showed that increasing perceptual load in the visual system (e.g., asking subjects to identify visual targets in a rapid stream of visual distractors) decreased the amplitude of the auditory MMN to frequency deviants. Most studies, however, have indicated that attention has little effect on MMN. There is evidence that MMN can be elicited during REM sleep, supporting the view that MMN operates at a pre-conscious level of processing (Sculthorpe, Ouellet, & Campbell, 2009). MMN has also been detected in comatose states and found to be useful in predicting whether or not a comatose patient will regain consciousness (Fischer, Morlet, & Giard, 2000).

MMN identifies stable deficits (test-retest reliability coefficients between .60 and .80) (Braff & Light, 2004) and is present in unaffected family members of schizophrenia patients (M. H. Hall, et al., 2006). It has not been observed in major depression, bipolar disorder, and obsessive-compulsive disorder (Umbricht, Koller, et al., 2003). Thus, MMN's reasonable specificity to schizophrenia, high heritability, and good stability over time make it an ideal endophenotype for assessing basic auditory neural network functioning in individuals at risk for psychosis. MMN may increase our understanding of the progressive pathological processes in the early stages of schizophrenia. Additionally, it could be a potential neurobiological at-risk indicator in prodromal subjects and a more sensitive predictor of psychosis. The use of MMN, along with other vulnerability markers, e.g., decline in working memory and processing speed, reduction in P50 suppression, clinical symptoms and deterioration in social functioning, may help improve the predictive power for identifying individuals at risk for schizophrenia, for early intervention. There is substantial evidence supporting the effectiveness of preventive interventions and showing that the longer the duration of untreated psychosis, the poorer the prognosis. For example, in McGorry et al.'s 2002 study, a low dose of Risperdal coupled with CBT delayed the onset and reduced the risk of early progression to first-episode psychosis in high-risk subjects.

3.3. Neurotransmission systems involved in MMN generation

MMN is primarily generated in the bilateral auditory cortex, with secondary sources in the adjacent superior temporal gyrus cortex (Alho, 1995). It has been suggested that the auditory cortex generator, underlying perceptual sound-change detection, triggers a second MMN generator in the frontal cortex, which is associated with the initiation of attention switch to sound change (Jemel, Achenbach, Muller, Ropcke, & Oades, 2002). On a neurophysiological level, deficits in MMN generation may reflect impaired neurotransmission at N-methyl-D-aspartate (NMDA)-type glutamate receptors (Krystal, et al., 1994; Strelnikov, 2007). It has been proposed that disturbances in glutamatergic functioning caused by a loss of dendritic spines, which are a primary location of NMDA receptors, may contribute to the pathophysiology of schizophrenia. In fact, cortical and thalamic glutamate function was also found to be perturbed in people at risk of developing psychosis (Stone, et al., 2009). On one hand, the administration of N-acetyl-cysteine, a glutathione precursor, to schizophrenia patients results in improved NMDA receptor function and enhanced MMN amplitude (Lavoie, et al., 2008). On the other hand, NMDA antagonists, such as Ketamine or Phencyclidine, block the generation of MMN (Javitt, Steinschneider, Schroeder, & Arezzo, 1996), induce schizophrenia-like symptoms in healthy controls, and exacerbate symptoms in schizophrenia patients (Krystal, Karper et al. 1994). However, Psilocybin, a 5-HT(2A) receptor agonist that shares similar pharmacological effects with NMDA receptor antagonists, failed to significantly reduce MMN generation in healthy subjects, suggesting that deficient MMN generation in schizophrenia may be a relatively distinct manifestation of deficient NMDA receptor functioning (Umbricht, Vollenweider, et al., 2003). In addition to the glutamatergic system, other neurotransmission systems are important in modulating CNS mechanisms of selective attention to infrequent stimuli, including GABA (Rosburg, Marinou, Haueisen, Smesny, & Sauer, 2004), norepinephrine (Turetsky & Fein, 2002), and serotonin (Kahkonen, et al., 2005).

MMN is not thought to be a fixed cortical response but one that reflects cortical plasticity (Stephan, Baldeweg, & Friston, 2006). MMN deficits may in fact reflect the glutamate-mediated loss of dendritic fields leading to progressive decline in automatic information processing in schizophrenia. A recent study showed that bilateral gray matter

reduction in Heschl's gyrus, as well as motor and executive regions of the frontal cortex, correlated with reduced MMN amplitude in schizophrenia patients (Rasser, et al., 2009). In a prospective study employing both ERP recording and magnetic resonance imaging in first-hospitalized patients with schizophrenia, (Salisbury, Kuroki, Kasai, Shenton, & McCarley, 2007) demonstrated that mismatch negativity, even when within the normal range, is correlated with the volume of the underlying left temporal auditory cortex. In longitudinal testing, a strong interrelationship was found between the progressive reductions of MMN amplitude and left hemisphere Heschl gyrus gray matter volume. MMN may therefore serve as an objective physiological index of progressive cortical deterioration in schizophrenia. This finding has important clinical implications as well and suggests that early pharmacologic interventions to halt progressive cortical gray matter reduction can be tracked via MMN amplitude measurement.

4. Review of Literature on MMN and P3a

This section summarizes findings from studies that have been conducted to date on MMN in recent-onset and prodromal schizophrenia. Section 4.1. presents those results while underscoring differences between duration and frequency MMN paradigms. Section 4.2. describes P3a and is followed by a review of the variables that may be associated with MMN and P3a, including demographic factors, clinical symptoms, and social functioning (Section 4.3.). Section 4.4. discusses the potential effects of antipsychotic medications on MMN and P3a.

4.1. MMN in Recent-Onset and Prodromal Schizophrenia

MMN has consistently been shown to discriminate between patients with schizophrenia and normal comparison subjects (e.g., (Shelley, et al., 1991). The reduced MMN amplitude in schizophrenia patients likely reflects the difficulty they have in automatically detecting changes in their acoustic environment (Michie, Innes-Brown, Todd, & Jablensky, 2002). Its prolonged latency in affected subjects might suggest a slowing of automatic information processing (Kathmann, Wagner, Rendtorff, & Engel, 1995). MMN has been consistently found to be impaired in chronic schizophrenia but it is not yet clear if MMN is deficient early in the disease process. In fact, three out of the eight studies conducted in this population found significant deficits. On one hand, one study found a reduction of duration MMN amplitude in both adolescent patients with a first episode of schizophrenia as well as patients 14 years after an adolescent illness-onset (Oades, et al., 2006). In another study, recent-onset patients (with an illness duration of approximately 3 years) showed significantly reduced MMN to both pitch and duration deviants (Umbricht, Bates, Lieberman, Kane, & Javitt, 2006). Likewise, (Javitt, Shelley, Silipo, & Lieberman, 2000) found duration MMN amplitude to be impaired in recent-onset schizophrenia patients despite normal MMN latency and topography. On the other hand, (Grzella, et al., 2001) examined novelty-elicited MMN in first- to third-episode schizophrenia and found no impairment in patients on admission. In contrast to conventional MMN paradigms, the authors used rare, non-repeated, and highly deviant novel stimuli with a long interstimulus interval. Similarly, no differences between first-episode patients and normal controls were observed in pitch-deviant MMN (Salisbury, Shenton, Griggs, Bonner-Jackson, & McCarley, 2002; Valkonen-Korhonen, et al.,

2003). (Devrim-Ucok, Keskin-Ergen, & Ucok, 2008) demonstrated that the latter is unaffected at the onset of schizophrenia but deteriorates during the post-acute illness phase. The two remaining studies did not find significant decrements in either duration or frequency MMN in first-episode patients relative to healthy controls (Magno, et al., 2008; Umbricht, et al., 2006).

While these findings appear to conflict, the type of MMN assessed may be a factor. It has been found that the MMN elicited by different classes of auditory deviance (e.g., pitch, duration, intensity) are subserved by different neuronal sources and circuits in the temporal and frontal cortex (Molholm, Martinez, Ritter, Javitt, & Foxe, 2005). Moreover, duration MMN has been suggested to be a more sensitive index of auditory system dysfunction in schizophrenia (Michie, et al., 2002). In a meta-analysis conducted by (Umbricht & Krljes, 2005), the effect size for MMN to duration deviants was about 40% larger than the effect size for frequency MMN. However, frequency MMN has been shown to be more linearly associated with the progressive pathological changes (in frontotemporal cerebral gray matter) in schizophrenia than duration MMN (Rasser, et al., 2009). In addition to the stimulus characteristics, the amount/probability of stimulus deviance (degree of standard-deviant difference) and inter-stimulus interval length may explain the inconsistencies among results. Nevertheless, the MMN abnormality in schizophrenia patients is present irrespective of those factors (Javitt, Grochowski, Shelley, & Ritter, 1998). Besides variations in the MMN paradigm across studies, differences exist in the sample characteristics. “Recent-onset” schizophrenia patients have been identified using various criteria including illness duration, acuteness of symptoms, number of psychotic episodes, and duration of pharmacological treatment. Therefore, another factor that can explain the undetectable MMN deficits in recent-onset groups is the heterogeneity of the samples that might include some patients with normal MMN, namely those who show a favorable illness course.

Only one study has been published so far on MMN before illness onset (Brockhaus-Dumke, et al., 2005). This study used a three-tone auditory oddball paradigm with duration and frequency deviants, and found that MMN peak amplitudes elicited by the duration – and not the frequency – deviants were slightly lower in prodromal subjects compared to normal controls, but this difference did not reach statistical significance. In fact, the non-significant MMN amplitude reduction in those subjects was intermediate between normal controls and

schizophrenia patients, and with a larger within-group variance. However, this study defined a prodromal state by the presence of at least two of nine self-reported subclinical cognitive disturbances on the Bonn Scale for the Assessment of Basic Symptoms. Thus, this sample would be clearly different from another that could be selected, for example, based on subsyndromal psychotic symptoms. Table 4.1. summarizes all the studies (described above) that have been conducted to date on MMN in prodromal and recent-onset schizophrenia.

Table 4.1. Study Characteristics and Results based on MMN Type

Publication	Healthy Controls			Patients				Results	
	N	m/f	Age	N	m/f	Age	Illness Duration	Pitch	Duration
Javitt et al. (2000)	15	8/7	36.3 (±9.5)	13	10/3	27.4 (±2.7)	within 3 years from first episode	S	S
Grzella et al. (2001)	21	11/10	26.3 (±7.6)	20	12/8	25.9 (±9.9)	first to third episode	NS	
Salisbury et al. (2002)	27	20/7	24.2 (±4.3)	21	18/3	24.9 (±6.2)	first hospitalization	NS	
Valkonen-Korhonen et al. (2003)	19	3/16	29 (19-43)	15	10/15	30 (15-56)	first hospitalization	NS	
Umbricht et al. (2006)	39	26/13	30.5 (±7.1)	25 26	14/12 19/7	30.3 (±6.7) 23.9 (±5.5)	3.4 (±1.5) years 0.05 (±0.1) year	S NS	S NS
Oades et al. (2006)	22	12/10	17.6 (±0.4)	28	21/7	17.5 (±0.4)	first episode		S
Devrim-Ucok et al. (2008)	34	19/15	24.5 (±6.4)	30 21	15/15 9/12	22.1 (±5.7) 21.6 (±5.6)	first hospitalization 2.5 (±2.3) months post	NS S	
Magno et al. (2008)	27	13/14	38 (±12.9)	12	9/3	24.2 (±6.2)	within 3 months from first diagnosis	NS	NS
Brockhaus-Dumke e al. (2005)	33	28/15	24.5 (±3.3)	43	29/14	25.4 (±5.8)	prodromal	NS	NS

S = Significant; NS = Nonsignificant; m/f = male/female.

Reduced MMN has been inconsistently found in subjects genetically at risk for schizophrenia. The carriers of the catechol-O-methyl transferase gene, especially the $COMT^{108/158Met}$ allele that confers a greater risk for schizophrenia, were found to have attenuated MMN amplitude to both pitch and duration deviants (Baker, Baldeweg, Sivagnanasundaram, Scambler, & Skuse, 2005). In another study, MMN to pitch deviants was reduced in offspring of schizophrenia patients but did not differentiate significantly between those high-risk children and matched controls (Schreiber, Stolz-Born, Kornhuber, & Born, 1992). MMN amplitudes to duration (Michie, et al., 2002) and frequency (Jessen, et al., 2001) deviants have been shown to be deficient in clinically unaffected family members of chronic schizophrenia patients relative to normal controls. This finding precludes illness-related factors, psychotic symptoms, medication, and hospitalization as potential explanations for the impaired MMN in patients with schizophrenia. Nonetheless, (Bramon, et al., 2004) and (Magno, et al., 2008) failed to find duration and pitch MMN impairments among first-degree relatives, suggesting that the MMN deficit seen in schizophrenia patients may be a consequence of the disease.

4.2. P3a ERP component in schizophrenia

Automatic sensory discrimination has been assessed in various studies with respect to the P3a wave, a late positive ERP that occurs between 240 and 540ms post-stimulus. The P3a is a frontally maximal ERP component elicited automatically by infrequent, task-irrelevant deviant stimuli in oddball tasks. Just like MMN, P3a has been shown to be a strongly automatic process that does not require available central capacity and is not modulated by attention (Muller-Gass, Macdonald, Schroger, Sculthorpe, & Campbell, 2007). Amplitude reductions of the P3a component have been associated with deficits in orienting to auditory stimuli that would normally be considered salient by healthy individuals (Mathalon, Ford, & Pfefferbaum, 2000).

There is evidence of reduced P3a amplitude in patients with schizophrenia (Grillon, Courchesne, Ameli, Elmasian, & Braff, 1990; Grillon, Courchesne, Ameli, Geyer, & Braff, 1990; Grzella, et al., 2001; Mathalon, et al., 2000) but few studies have examined this brain wave in the early stages of the illness. Impairment has been observed in the P3a and P3b

components in a sample of acutely psychotic, drug-naive first-episode patients (Valkonen-Korhonen, et al., 2003). Furthermore, a significant reduction in the amplitude of P300 or P3b, a component associated with attention-dependent processing of auditory information, has been found in prodromal and first-episode patients (Ozgurdal, et al., 2008).

4.3. Potential correlates of MMN and P3a

4.3.1. Demographic factors

MMN tends to get smaller with increasing age (Alain & Woods, 1999; Gaeta, Friedman, Ritter, & Cheng, 1998; Karayanidis, Andrews, Ward, & Michie, 1995). Gomot et al. (2000) demonstrated that the amplitudes of the temporal components were greater in healthy children than in adults whereas the frontal components were not affected by age. (Cooper, Todd, McGill, & Michie, 2006) found a smaller and later MMN in an elderly group (mean age = 69) relative to a young group (mean age = 21), suggesting an age-related deficit in the encoding and retention of information in auditory sensory memory. Similarly, a recent study showed that MMN amplitude declined with age in both schizophrenia patients and normal comparison subjects, whereas P3a amplitude decreased with age only in the normal comparison group (Kiang, Braff, Sprock, & Light, 2009).

There is some evidence to suggest that women have larger MMN amplitude than men, with no gender differences in MMN latency (Barrett & Fulfs, 1998). MMN also seems to differ as a function of educational level and intelligence. (Bazana & Stelmack, 2002) demonstrated an association between mental ability and speed/accuracy of auditory discrimination, i.e., the higher ability group exhibited larger P3 amplitude and shorter P3 and MMN latency. A correlation between the MMN memory trace effect and the degree of neuropsychological impairment has been reported in schizophrenia (Baldeweg, Klugman, Gruzelier, & Hirsch, 2004). Reduced duration MMN amplitude in early-onset schizophrenia patients was found to be associated with slow set shifting (Oades, et al., 2006). Although the first-episode patients in Umbricht, et al.'s 2006 study did not show a reduced MMN relative to controls, further analyses suggested that those with low premorbid educational achievement did have some abnormalities. More specifically, those with a college education showed normal MMN, whereas those who had not reached college were as impaired as chronic

patients in terms of their MMN generation. Therefore, MMN deficits may index both ongoing disease processes associated with illness progression as well as premorbid neurocognitive impairment.

4.3.2. Clinical symptomatology

MMN deficits do not seem to be related consistently to clinical symptoms. No correlations between MMN amplitudes and positive or negative symptoms were reported in (Shelley, et al., 1991) and (Kasai, et al., 1999), which is consistent with studies in which MMN remained stable despite improvement in symptoms (Schall, et al., 1998; Umbricht, et al., 1999). In fact, out of 22 studies of MMN in schizophrenia (Umbricht & Krljes, 2005), four studies found a significant relationship between MMN and positive symptoms (e.g., (Youn, Park, Kim, Kim, & Kwon, 2003), especially hallucinatory behavior (e.g., (Hirayasu, et al., 1998), while six studies reported associations with negative symptoms (e.g., (Catts, et al., 1995; Javitt, et al., 2000; Schall, Catts, Karayanidis, & Ward, 1999). Findings from first-episode samples are equally conflicting. While some studies found significant associations between smaller MMN amplitudes and higher negative symptom ratings (Oades, et al., 2006; Umbricht, et al., 2006), others did not (Salisbury, et al., 2007). In one study of first-hospitalized schizophrenia patients, there was no relationship between MMN and positive or negative symptoms at the frontal electrodes. However, larger MMN amplitudes were paradoxically associated with more pathological symptoms at the other electrode sites (Salisbury, et al., 2002), which could be attributed to the volatile pattern of symptoms during the initial stage of the illness.

4.3.3. Social functioning

By studying the neurophysiological deficits in schizophrenia, we can increase our understanding of the neurobiological disturbances that relate to the long-term dysregulation in cognition, motivation, and behavior. In a bottom-up framework, genes code for neural plasticity which bridges to neurophysiological endophenotypes via cellular pathology and dysregulation of the metabolism and activity of neurotransmitters such as dopamine. Neurophysiological measures, such as MMN, flow from the relationship of genetic variation and neural plasticity abnormalities. Sensory discrimination dysfunction, along with other

neurophysiological deficits, lead to a cascade of neurocognitive, symptomatic, and other trait abnormalities resulting in a fragmentation of functional capacity, status, and outcome (Braff, Greenwood, Swerdlow, Light, & Schork, 2008). Therefore, theoretically, MMN dysfunction should be related to poor functioning. This hypothesis was confirmed by (Light & Braff, 2005a) who reported that MMN deficits in schizophrenia patients are highly associated with patients' impairments in everyday functioning. While several studies have determined that attention-dependent neurocognitive tests are modestly associated with functioning in schizophrenia patients (e.g., with correlations of r=.30 to r=.40 accounting for 9-16% of the variance), MMN deficits were found to correlate with social functioning up to r=.68, accounting for 46% of the variance in functional status. This finding was replicated by (Kawakubo & Kasai, 2006) who demonstrated an association between MMN amplitudes and GAF scores, as well as in (Rasser, et al., 2009)'s study that showed a correlation between reduced MMN amplitude and impaired daily functioning in schizophrenia. Moreover, in a longitudinal study of schizophrenia patients (Light & Braff, 2005b), MMN deficits were highly stable, the longitudinal MMN/functional status correlation was consistent across the re-test interval, and MMN deficits at initial testing were significantly predictive of functional outcome 15 months later. Phonetic MMN was also found to be a significant predictor of social skills acquisition in a small sample of schizophrenia patients (Kawakubo, et al., 2007). MMN and P3a were both associated with higher order cognitive abilities and psychosocial functioning in normal subjects as well (Light, Swerdlow, & Braff, 2007). Nonetheless, a study of first-episode patients did not detect any associations between MMN amplitude and social functioning (Salisbury, et al., 2007).

4.4. Treatment effects on MMN and P3a

It has been shown that MMN is uninfluenced by Olanzapine (Korostenskaja, et al., 2005) and Clozapine treatment (Umbricht, et al., 1998). The latter was associated with a significant increase of P3 amplitude but did not affect deficits in MMN. Similarly, Risperidone was associated with a decrease of peak latencies, particularly pronounced for P3, but did not significantly affect abnormal MMN or P3 amplitudes (Umbricht, et al., 1999). Haloperidol did not alter MMN to frequency and duration changes but it accelerated the magnetic MMN to frequency change (Pekkonen, et al., 2002). In fact, acute D(1) and D(2) receptor stimulation

was not found to modulate MMN (Leung, Croft, Baldeweg, & Nathan, 2007). Antidepressants of the selective serotonin reuptake inhibitor class, such as Escitalopram (Oranje, Jensen, Wienberg, & Glenthoj, 2008), might however enhance MMN amplitude.

5. Current Study

5.1. Aims and Hypotheses

Aim 1: To investigate group differences in MMN and P3a amplitude.

Rationale: MMN reflects automatic auditory discrimination and plays an important role in the involuntary switching of attention to a salient stimulus change outside the focus of attention (Alho, 1995). This attentional shift to changes in the acoustic environment is captured by P3a and is supposed to occur only if the magnitude of MMN surpasses a certain threshold (Schroger, 1997). Based on this model, we expect MMN and P3a to follow the same pattern. Although there is ample evidence to suggest that MMN and P3a are impaired in schizophrenia, their reduction has not been as robust in recent-onset patients. Moreover, MMN and P3a have not been sufficiently researched in subjects at risk for schizophrenia in order to determine whether they are deficient before the full-blown illness.

Hypothesis 1a. We expect to find that MMN and P3a amplitudes will be significantly reduced in the recent-onset group relative to the normal comparison group.

Rationale: Abnormal MMN/P3a before illness onset may index a pervasive cortical pathology that is only observed in a subgroup of at-risk subjects, possibly those who are more prone to develop the illness. Thus, the effect might be subtle and hard to capture in the at-risk group, as the subset of subjects with reduced MMN/P3a – who will most likely develop schizophrenia – will be masked by the larger subset of false positives with normal MMN/P3a who will not transition to psychosis.

Hypothesis 1b. We predict that the MMN and P3a amplitude scores for at-risk subjects will lie in between those of normal comparison subjects and those with recent-onset schizophrenia.

Aim 2: To investigate group differences in MMN and P3a topography.
Rationale: MMN is generated bilaterally within the primary and secondary auditory cortices with probable contributions from bilateral dorsolateral prefrontal cortices (Deouell, Bentin, &

Giard, 1998). It is largest at fronto-central electrodes and reverses its polarity at the mastoids (Umbricht & Krljes, 2005). P3a also has a frontocentral maximum amplitude distribution as it seems to originate from stimulus-driven frontal attention mechanisms (Polich, 2007).

Hypothesis 2a. We expect that there will be no group differences in MMN and P3a topography. More specifically, MMN and P3a will be frontally distributed and there will be no hemispheric lateralization in MMN and P3a responses.

Aim 3: To examine the clinical and functional correlates of MMN and P3a within the patient groups.

Rationale: It has been postulated that 1) deficient memory-trace formation in the neurophysiological mechanisms of auditory sensory memory leads to abnormal auditory perception and discrimination, and hence could explain the auditory hallucinations in schizophrenia, and that 2) the dampened automatic attention-switching function might contribute to social withdrawal by diminishing involuntary attention switches to socially relevant auditory cues (Naatanen, Kahkonen, 2009). Therefore, theoretically, there should be a relationship between MMN/P3a deficits and both positive and negative symptoms. However, previous reports of the association between MMN and symptom severity in both chronic and first-episode schizophrenia patients have yielded inconsistent results, providing more support for an association with negative rather than positive symptoms.

Hypothesis 3a: We expect that there will be an association between both MMN and P3a deficits and negative symptoms in the at-risk and recent-onset groups.

Rationale: Deficits on neurocognitive measures have been found to predict functional outcome in schizophrenia (Green, 1996) but there are insufficient data to determine whether MMN and P3a deficits could underlie real-life functioning. It has been suggested that MMN impairment could have a detrimental effect on the ability to effectively control the focus of attention and selectively attend to relevant sounds in natural settings, and thus could

contribute to the social communication problems in schizophrenia (Matthews, Todd, Budd et al. 2007). Although a robust association has been found between MMN impairment and poor functioning in both patients with schizophrenia and nonpsychiatric subjects (Light & Braff, 2005a), only one study has examined this relationship early in the disease process (Salisbury, et al., 2007).

Hypothesis 3b. We predict that MMN and P3a dysfunction will be associated with poor social functioning in both patient groups.

5.2. Method

5.2.1. Study Design and Participants

Our patients were selected from a pool of individuals who were participating in the Cognitive Assessment and Risk Evaluation (CARE) program at UCSD. In order to be included in the CARE program, subjects had to meet the inclusion and exclusion criteria summarized in Table 5.2. Qualifying CARE participants undergo an initial clinical evaluation and are followed up longitudinally. At-risk subjects, just like recent-onset patients, are ambulatory, treatment seeking, and receive treatment as usual (pharmacological or psychosocial) according to their presenting symptoms. As part of the present study, subjects over the age of 18 years were asked to give informed consent. Those below the age of 18 (N=12) provided assent, and their guardian was asked to sign a consent form for study participation. Monetary compensation ($10 per hour) was provided to all participants. Patients were tested on the MMN/P3a paradigm and scheduled for a short clinical evaluation on the day (if possible), or within a month, of their EEG recording session. During the 30-minute evaluation, participants were assessed on a number of symptom rating measures then administered a social functioning inventory. Normal comparison subjects were selected from a sample of healthy individuals who had been previously tested on the same paradigm as part of another study. Neurophysiological testing took place at the UCSD Schizophrenia Laboratory in the Clinical Teaching Facility.

A cross-sectional, static-group comparison research design was employed in a sample of 26 at-risk individuals (AR), 28 patients with recent-onset schizophrenia (RO), and

31 normal comparison subjects (NC). The sample size required for this study was determined based on a power analysis that we performed using G*Power 3, and a meta-analysis by (D. Umbricht & Krljes, 2005) showing that the mean effect size comparing normal controls to schizophrenia patients on MMN was between .79 and 1.29. Assuming a large effect size (e.g., Cohen's d = .99) and a significance level of .05, we found that a sample size of at least 72 subjects (n = 24 per group) would be necessary in order to achieve a power of .80. The latter indicates an 80% probability of obtaining a significant result if the study is run repeatedly. The total sample (N = 85) had a good representation of both genders (60% male), was ethnically diverse (57.6% non-Hispanic White), and had a mean of 12.6 years of education (high school). Ages ranged from 12 to 30 in the NC group, 13 to 29 in the AR group, and 14 to 33 in the RO group. The majority of the at-risk subjects met criteria for at least one of the two most common prodromal syndromes (Seeber & Cadenhead, 2005; Yung, et al., 2005): "Attenuated Positive Symptom" (new onset of subsyndromal psychotic symptoms) or "Genetic Risk and Deterioration" (family history of schizophrenia in a first-degree relative or a diagnosis of schizotypal personality disorder that is associated with a recent decline in global functioning) per the Structured Interview for Prodromal Syndromes (SIPS; (Miller, et al., 2003) and established CARE criteria (described in the next section). The recent-onset patients had experienced their first psychotic episode within the last two years. Subjects who met Diagnostic and Statistical Manual of Mental Disorders (4^{th} ed.) criteria for lifetime substance abuse/dependence were not excluded from the sample unless they endorsed having used substances during the month preceding neurophysiological testing or their urine toxicology test results were positive. Two of the 26 AR individuals transitioned to psychosis during the data collection phase of the study, which lasted 20 months (October 2007 to June 2009). More specifically, one converted to psychotic mania and one to schizophrenia 25 days and one year after their ERP testing, respectively. Seven AR subjects (26.9%) and 23 RO patients (82.1%) were on at least one atypical antipsychotic with or without other psychotropic medications. 23.1% of the AR and 7.1% of the RO subjects had a first-degree relative with psychosis.

Table 5.2. Inclusion and Exclusion Criteria

Group	Inclusion Criteria	Exclusion Criteria
At-Risk Subjects (AR)	Recent onset (< 1 year) of subsyndromal psychotic symptoms	History of head injury (with loss of consciousness) or seizures
	Recent onset of frankly psychotic symptoms that are present infrequently and for short periods of time	Current substance abuse/ dependence or positive urine toxicology test
		Neurological disorder
	First-degree relative with schizophrenia or diagnosis of schizotypal personality disorder plus a recent deterioration in functioning	IQ below 80
Recent-Onset Patients (RO)	First psychotic episode within the last 2 years	(Same as AR group)
	DSM-IV diagnosis of schizophrenia	
Normal Controls (NC)	Comparable to AR and RO subjects with respect to age, sex, ethnicity, and education	(Same as patient groups)
		Personal history of mental illness or learning disability
		Cluster A personality disorder or evidence of prodromal symptoms
		Family history of psychotic illness
		History of taking psychotropic medications

5.2.2. Measures

5.2.2.1 Neurophysiological Paradigm

Electroencephalographic recordings were acquired with a Neuroscan NuAmp system. EEG was recorded from the scalp using 34 electrodes attached to an electrode cap. The following 34 equidistant electrode positions were used: Fp1, Fp2, Fz, F3, F4, F7, F8, FC1, FC2, FC5, FC6, Cz, C3, C4, CP1, CP2, CP5, CP6, Pz, P3, P4, P7, P8, O1, O2, PO9, PO10, Iz, T1, T2, T7, T8, TP9, and TP10 (Figure 5.2.) There was a reference electrode placed at the nose tip, in addition to a ground electrode at Fpz. Four additional electrodes were placed above and below the left eye as well as at the outer canthi of both eyes in order to monitor blinks and eye movements. EEG was digitally referenced off-line to linked mastoids (TP9/TP10). All impedances were kept below 4 kΩ. Signals were digitized at a rate of 1 kHz

with system acquisition filter settings at 0.5 – 100 Hz. Subjects were presented with binaural tones (1 kHz 85 dB sound pressure level, with 1 ms increase/decrease) with a fixed stimulus onset-to-onset asynchrony of 500 ms using a stimulus unit. Standard (90% probability; 50 ms duration) and deviant (10% probability; 100 ms duration) tones were presented in pseudorandom order using foam insert earphones. In order to direct attention away from the tones, subjects were asked to watch a silent cartoon videotape for 20 to 25 minutes. The testing session including electrode placement and EEG recording took approximately 75 minutes. EEG acquisition was terminated when a minimum of 225 artifact-free deviant trials were collected. Data processing was performed offline using automated procedures. Continuous recordings were mathematically corrected for eye movement artifact. Continuous data were divided into epochs relative to the onset of stimuli (-100 to 500 ms) and centered at the mean of the prestimulus baseline. Following blink correction, epochs containing more than $\pm$ 50 μV in frontal recording sites were automatically rejected. MMN waveforms were generated by subtracting ERP waveforms in response to standard tones from the ERPs generated in response to deviant tones (deviant – standard). MMN subtraction waveforms were low-pass filtered at 20 Hz (zero-phase shift, 24 dB/octave roll-off) to remove any residual high-frequency artifact. MMN and P3a amplitudes were calculated as the mean voltages across the 135 to 205 and 250 to 300 millisecond-latency ranges respectively.

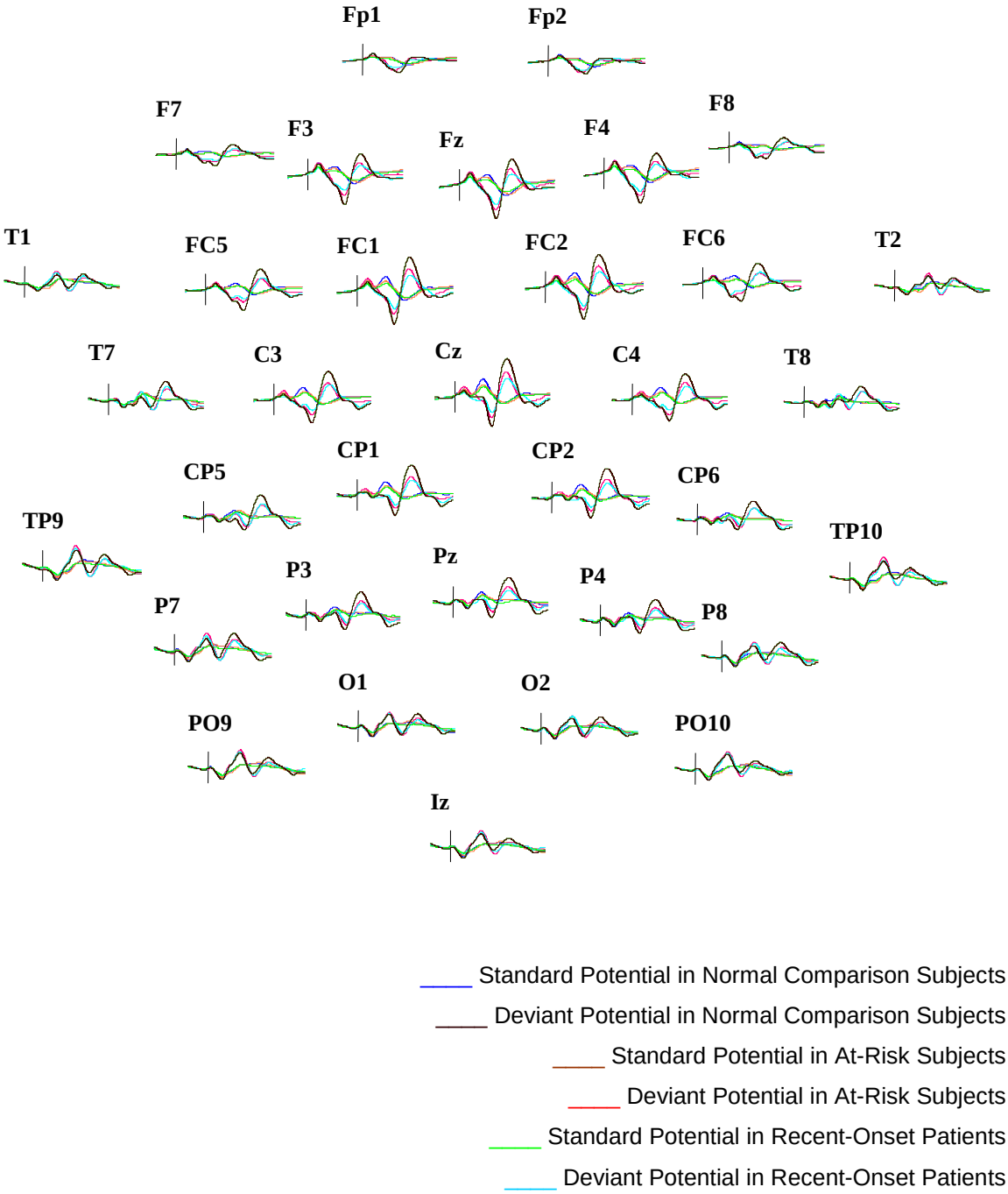


Figure 5.2. Grand Average Standard and Deviant Event-Related Potentials across all Electrodes

5.2.2.2 Clinical and Social Functioning Measures

The Structured Interview for Prodromal Symptoms (SIPS; (Miller, et al., 2003) was used to assess the level of risk for psychosis. The SIPS includes the Scale of Prodromal Symptoms (SOPS), a 19-item scale designed to measure the severity of prodromal symptoms. The SOPS contains 4 subscales: Positive, Negative, Disorganization, and General Symptoms. The three prodromal syndromes as defined by the Criteria of Prodromal Syndromes (COPS) are the “Attenuated Positive Symptom” (APS) syndrome (rating of 3 to 5 on at least one of the 5 SOPS positive items), “Brief Limited Intermittent Psychotic symptom” (BLIPS) syndrome (rating of 6 on at least one of the positive items), and “Genetic Risk and Deterioration” (GRD) syndrome (first-degree relative with a diagnosis of schizophrenia, or criteria for schizotypal personality disorder met in patient, and a 30% drop in GAF over the past year). At-risk subjects were identified according to established CARE prodromal criteria (Ballon et al., 2007) that follow the categories and symptom severity of the COPS but differ slightly in the required frequency and duration of symptoms. More specifically, for the GRD Syndrome, any decline in functioning in the last year is acceptable.

Axis I and axis II diagnoses were assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders (First, Spitzer, Gibbon, & Williams, 1996) and the Structured Interview for DSM-IV Personality Disorders (Pfohl, Blum, & Zimmerman, 1995) respectively. The Kiddie-Schedule for Affective Disorders and Schizophrenia (Chambers, et al., 1985) was administered to patients under the age of 16 (N=6). Clinical symptoms were evaluated using the Scales for the Assessment of Positive Symptoms (SAPS; Andreasen, 1983) and Negative Symptoms (SANS; Andreasen, 1984) respectively. The SAPS is a 34-item rating instrument for the assessment of the severity of positive symptoms of psychosis. It is comprised of four subscales: hallucinations, delusions, bizarre behavior, and formal thought disorder. The SANS is a 25-item scale for the assessment of negative symptoms and is divided into 5 subscales: affective flattening, alogia, apathy, asociality, and inattention. For both instruments, symptoms were rated over the last month on six-point scales (0=absent to 5=severe). Each subscale was given the same score as the highest-rated symptom in that subscale. Only the total SAPS and SANS scores (sum of subscale ratings) were used. The Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962) was used to further evaluate

general psychopathology (e.g., thinking disturbance, withdrawal, suspiciousness) and affective symptoms (e.g., anxiety, depression) within the patient groups. The BPRS is comprised of 24 items that are rated on a seven-point scale (1=not present to 7=extremely severe) on the basis of the clinician's observation (e.g., mannerisms, bizarre behavior) and the patient's self-report (e.g., somatic concern, guilt). The total BPRS score was used.

Current level of functioning was assessed with the Modified Global Assessment of Functioning (R. C. Hall & Parks, 1995). The highest GAF score from the past year was determined retrospectively for the at-risk group in order to assess any potential decline in functioning. The Social Adjustment Scale – Self Rated (Weissman & et al., 1978) was also administered to all patients > 17 years of age in order to assess instrumental and expressive role performance over the past two weeks. The following domains were examined: Work/School Role (high scores may indicate poor work performance, feelings of guilt and inadequacy, conflict with colleagues), Social and Leisure (e.g., disinterest in recreational activities, impaired peer relationships, feelings of loneliness), as well as Extended Family and Family unit (e.g., minimal contact with relatives, frequent arguments with family members, feelings of resentment). Questions in each domain are scored between 1 and 5, then a role-area mean is generated by adding the ratings in each domain and dividing the sum by the number of questions answered. The overall SAS-SR mean is calculated by dividing the sum of the domain total scores by the sum of questions answered. Family history of psychiatric illness was assessed, after receiving consent to contact a relative, using the Family History Research Diagnostic Criteria (Andreasen, Endicott, Spitzer, & Winokur, 1977).

5.2.3. Statistical Analyses

Hypotheses 1a and 1b. We expected to find that MMN and P3a amplitudes would be significantly reduced in recent-onset patients relative to age-matched controls and that the MMN and P3a amplitude scores for at-risk subjects would lie in between those of normal comparison subjects and those with recent-onset schizophrenia.

Statistical Method: A two-factor mixed model analysis of variance (ANOVA) with electrode (34 levels) as a within-subject factor and diagnostic group (3 levels) as a between-subject factor,

was performed using SPSS (version 16.0). Separate one-way ANOVAs with group (NC, AR, RO) as the independent variable and MMN amplitude as the dependent variable were conducted for each electrode site to follow up significant group by electrode interactions. The same analyses were conducted with P3a amplitude as the dependent variable.

Corollary Analysis for Hypothesis 1b: We examined whether MMN/P3a amplitudes follow a bimodal distribution in the at-risk group in order to further characterize the subsamples with normal and reduced MMN/P3a amplitudes. Additionally, we visually inspected MMN/P3a in the at-risk subjects who transitioned to psychosis over the study period.

Hypotheses 2a. We expected that there would be no group differences in MMN and P3a topography. More specifically, we predicted that MMN and P3a amplitudes would be largest at frontocentral electrodes and that there would be no left-right hemisphere differences in MMN and P3a amplitudes.

Statistical Method: A three-factor mixed model ANOVA with group as a between-subject factor, and both coronal electrode location (left versus right) and anterior-posterior electrode location (frontocentral versus centroparietal) as within-subject factors was conducted. The same analysis was repeated with P3a amplitude as the dependent variable. To further assess possible laterality effects, paired samples t-tests comparing P3a amplitudes at all 15 homotopic left-right electrode pairs were performed in each group.

Hypothesis 3a. We expected that there would be an association between both MMN and P3a deficits and negative symptoms in both patient groups.

Statistical Method: Spearman rank correlation analyses were conducted in order to assess the relationship between MMN and P3a amplitudes at frontocentral sites and clinical symptomatology as measured by the SIPS subscale scores, as well as the SAPS, SANS and BPRS total scores. Nonparametric correlations were used because the symptom rating measures are ordinal rather than continuous variables.

Hypothesis 3b. We predicted that MMN and P3a dysfunction would be associated with poor social functioning in both patient groups.

Statistical Method: Relationships between MMN and P3a amplitudes at frontocentral sites and social functioning as measured by the GAF scale ratings and SAS-SR domain and overall mean scores were investigated using Spearman rank correlations.

Exploratory Analyses: We evaluated the associations of both MMN and P3a amplitudes with age, education, and estimated premorbid IQ. The effects of gender, duration of illness, and treatment were also explored.

Statistical Method: Pearson's correlations were performed to assess relationships between MMN and P3a amplitudes at frontocentral electrodes and subjects' age, years of education, and WRAT-3 reading scores. Independent samples t-tests were conducted to examine differences in MMN and P3a amplitudes between males and females, as well as between medicated and unmedicated patients. A two-factor repeated-measures ANOVA with electrode (34 levels) as a within-subject factor and duration of illness (3 levels) as a between-subject factor was conducted, within the recent-onset group, to examine differences in MMN amplitudes between patients tested at different phases of their illness. The same analysis was repeated for P3a.

6. Results

6.1. Sample Characteristics

The at-risk group was significantly younger than both the recent-onset group and the normal comparison group ($F[2,84]=3.22$, $p=.04$), a finding which may reduce our likelihood of detecting significant group differences given that younger age has been associated with larger MMN amplitudes in both healthy controls and schizophrenia patients (Kiang, et al., 2009). There were no significant group differences in years of education ($F[2,78]=2.92$, $p=.06$), ethnicity ($\chi^2[12]=16.42$, $p=.17$), and handedness ($\chi^2[4]=7.34$, $p=.12$) but there were significantly more females than males in the normal comparison group relative to the patient groups ($\chi^2[2]=13.80$, $p=.001$) (Table 6.1a.) There were no group differences in estimated premorbid intellectual functioning ($F[2,73]=.49$, $p=.61$) as measured by the Reading Subtest of the Wide Range Achievement Test, 3rd Revision (WRAT-3; Jastak & Wilkinson, 1984). The recent-onset patients were significantly more symptomatic, in terms of their positive symptoms (SAPS), relative to the at-risk subjects. However, they were not significantly more impaired in their overall global (GAF) or social (SAS-SR) functioning (Table 6.1b.)

Table 6.1a. Baseline Demographic Characteristics

	Normal Controls (N=31)	At-Risk (N=26)	Recent-Onset (N=28)
Age (Mean/SD)	21.19 (4.24)	19.15 (3.39)	21.64 (3.73)
Gender (% Male)	35.48%	65.38%	82.14%
Ethnicity (% Caucasian)	64.52%	46.15%	60.71%
Handedness (% Right)	100%	80.77%	78.57%
Education (Mean/SD)	13.43 (3.23)	11.74 (2.38)	12.50 (1.73)
WRAT-3 Reading scores	108.86 (8.86)	105.86 (13.42)	107.54 (9.51)

Table 6.1b. Clinical and Social Functioning Ratings

	At-Risk (N=26)	Recent-Onset (N=28)	T-Test	DF	P
SIPS Positive	6.82 (5.40)	----------			
SIPS Negative	11 (7.10)	----------			
SIPS Disorganized	4.59 (3.43)	----------			
SIPS General	6.50 (5.38)	----------			
SAPS	3.81 (3.36)	6.85 (4.34)	2.65	46	.01*
SANS	7.20 (5.14)	10 (5.69)	1.74	45	.09
BPRS	14.30 (9.13)	14.74 (9.32)	.16	45	.87
GAF	51 (11.76)	45.42 (9.35)	1.81	45	.08
SAS Work Role	2.36 (.86)	2.03 (.80)	1.18	34	.25
SAS Social/Leisure	2.59 (.54)	2.65 (.68)	.34	47	.73
SAS Extended Family	2.02 (.61)	1.94 (.56)	.48	43	.63
SAS Family Unit	2.14 (1.41)	2.32 (1.72)	.36	42	.72
SAS Overall	2.36 (.47)	2.31 (.49)	.36	47	.72

* Represents significant differences between groups. On the SAS-SR (administered to 21 at-risk and 28 recent-onset patients), a higher score represents greater impairment in functioning.

6.2. Group Differences in MMN Amplitudes

Butterfly plots that overlay the grand average responses from all electrodes were generated to evaluate the mean global field power (MGFP) of the mismatch responses in each group. Figure 6.2a. shows that the grand average butterfly plots and MGFP peaks across the 100 to 300 millisecond-range were at least twice the magnitude of any activity present in the 100 milliseconds before stimulus onset, indicating that all subjects had significant MMN and P3a responses. The mismatch response peaked in the 180- to 190-millisecond range in all groups. A mixed model ANOVA with 34 electrodes as a within-subject factor, group and gender as between-subject factors, and age as a covariate was performed to assess differences in MMN amplitude among groups. Age was not a significant covariate (main effect of age: $F=1.07$, $p>.15$; electrode by age interaction: $F=.78$, $p>.15$) and was excluded from further analyses. A significant effect of electrode ($F[2.21,161.21]=166.80$, $p<.001$) indicated a frontal maxima in the mismatch negativity amplitude distribution, with the expected polarity inversion of responses at temporoparietal and other posterior electrodes. The Greenhouse-Geisser adjustment was used given that data from nearby electrodes tend to be more correlated than data from distant electrodes, which violates the sphericity or homogeneity of covariance assumption. There was a significant electrode by group interaction ($F[4.42,161.21]=3.05$, $p=.01$). The main effect of gender, as well as the electrode

by gender and electrode by group by gender interactions were not significant. However, there was a significant group by gender interaction ($F[2,73]=3.52$, $p=.03$). Females had larger mean MMN amplitude, averaged across all electrodes, than males in the normal comparison group, but smaller mean MMN amplitude than males in the recent-onset group. This finding is difficult to interpret because the mean across electrodes is not meaningful as it averages negative values from the frontocentral electrodes with positive values from the temporoparietal ones.

Separate one-way ANOVAs were conducted to follow up significant electrode by group interactions, using an alpha level of .01 to protect against type I errors. Relative to the normal comparison group, the recent-onset group had large effect size ($d=.59$ to $.94$) MMN decrements at frontocentral recording sites (Fp1, F7, F8, Fz, F3, F4, FC1, FC2, FC5, FC6, C3, Cz, C4, CP1, CP2, CP5, and T7; $p<.01$ for all) with phase reversal at posterior electrodes that was not significantly different from that of the normal comparison group (P7, P8, PO9, PO10, O1, O2, TP9, TP10, and Iz; $p>.10$ for all). Visual inspection of Figure 6.2b. suggests that patients and normal comparison subjects have nearly identical grand average ERP responses to standard, but not to deviant tones. Hence, the significant MMN differences between the recent-onset group and normal comparison group seem to be attributable to differences in deviant rather than standard waveforms. The at-risk group had significantly smaller MMN responses relative to the normal comparison group at FC5, CP5, and T7 ($p<.05$). Although no significant differences were found at other frontocentral sites, the at-risk individuals showed medium effect-size (Cohen's d values ranging from .30 to .54) MMN reductions compared with normal comparison subjects. Figure 6.2c. shows that the at-risk group's mean MMN amplitude at the frontal electrode Fz was intermediate between that of the normal comparison group and the recent-onset group. In fact, the MMN and P3a amplitudes of the at-risk sample were normally distributed at Fz (Figure 6.2d.) Descriptive statistics of mismatch responses are presented in Table 6.2. Visual inspection of Figure 6.2e. reveals that the few at-risk subjects who transitioned to psychosis (N=2) had a slightly reduced mean MMN amplitude and an earlier MMN latency relative to those (N=24) whose symptoms did not reach a psychotic level of intensity by the end of the study. Moreover, their P3a amplitude reduction was as severe as that of the recent-onset patients.

6.3. Group Differences in MMN Topography

In an analysis of group laterality differences as well as differences in MMN scalp distribution, we performed a mixed model ANOVA with group as a between-subject factor and both coronal electrode location (left [F3, FC1, FC5, CP1, CP5, P3] versus right [F4, FC2, FC6, CP2, CP6, P4]) and anterior-posterior electrode location (frontocentral [F3, F4, FC1, FC2, FC5, FC6] versus centroparietal [CP1, CP2, CP5, CP6, P3, P4]) as within-subject factors. For this analysis, only the right-handers were included (RO, n=22; AR, n=21; NC, n=31). There was a significant main effect of anterior-posterior electrode location ($F[1,71]=171.51$, $p<.001$), suggesting that averaged across groups, the mean MMN amplitude was significantly larger at the frontocentral electrodes ($M=-2.91$, $SE=.19$) relative to the centroparietal electrodes ($M=-1.25$, $SE=.15$). There was no significant main effect of coronal electrode location ($F=.06$, $p=.80$), and hence, no differences in MMN amplitude between the left and right hemisphere. Interestingly, there was a significant coronal by anterior-posterior electrode location interaction ($F[1,71]=24.48$, $p<.001$), i.e., averaged across groups, the mean MMN amplitude was slightly larger at the right side relative to the left side for the anterior electrodes, whereas the opposite pattern was found for the posterior electrodes. However, the group by anterior-posterior electrode location interaction ($F=1.25$, $p=.29$), group by side interaction ($F=2.23$, $p=.11$) and the three-way interaction ($F=.15$, $p=.86$) were not significant, suggesting no lateralized differences between groups and no differences in the topography of mismatch responses.

6.4. Group Differences in P3a Amplitudes and Topography

The mixed model ANOVA revealed a significant electrode x group interaction ($F[6.77,240.40]=3.32$, $p=.002$). A significant effect of electrode ($F[3.39,240.40]=114.21$, $p<.001$) indicated a frontal maxima in the P3a amplitude distribution. The follow-up one-way ANOVAs revealed significant group differences at Fp1, F7, Fz, F3, F4, FC1, FC2, FC5, FC6, C3, Cz, C4, CP1, CP2, CP5, P3, and T7 ($p<.01$ for all). Both patient groups had significantly smaller P3a responses at all the aforementioned recording sites ($p<.01$ for the recent-onset group; $p<.05$ for the at-risk group except for Fp1 and C4 that were not significant) relative to

the normal comparison group. There were no significant group by gender, electrode by gender, or electrode by group by gender interactions.

In an analysis of P3a topography, we found significant main effects of anterior-posterior electrode location ($F[1,67]=49.14$, $p<.001$) and coronal electrode location ($F[1,67]=8.00$, $p=.006$), suggesting that averaged across groups, the mean P3a amplitude was significantly larger at the frontocentral electrodes ($M=2.96$, $SE=.20$) relative to the centroparietal electrodes ($M=1.95$, $SE=.19$), as well as at the left hemisphere electrodes ($M=2.54$, $SE=.18$) relative to the right hemisphere electrodes ($M=2.37$, $SE=.19$). None of the interactions were significant, suggesting no lateralized differences between groups and no differences in the topography of P3a responses. In order to follow up the significant coronal electrode location main effect, paired samples t-tests comparing P3a amplitudes at all 15 homotopic left-right electrode pairs were conducted in each group. Using a conservative alpha level ($p<.01$) to reduce the probability of type I errors, this analysis revealed significant differences between FC1 and FC2 ($p=.009$) in the at-risk group, as well as between C3 and C4 ($p=.004$), CP1 and CP2 ($p=.009$), CP5 and CP6 ($p=.005$), and P3 and P4 ($p=.007$) in the normal comparison group. The P3a amplitudes on those left electrodes were slightly larger than the corresponding ones on the right.

Normal Comparison Group:

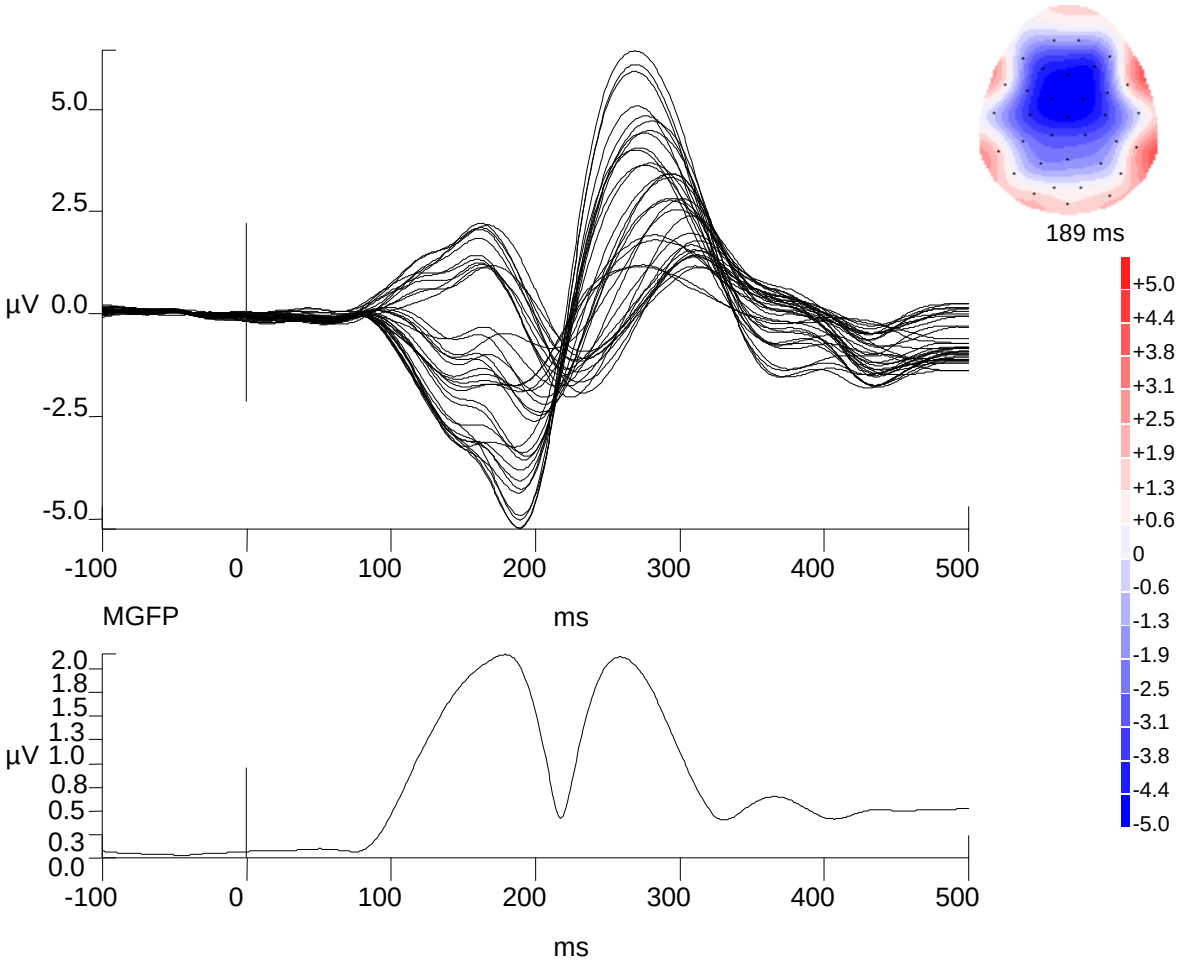


Figure 6.2a. Butterfly Plots, Two-Dimensional Scalp Topography, and Mean Global Field Power of Grand Average Mismatch Responses in each Group

At-Risk Group:

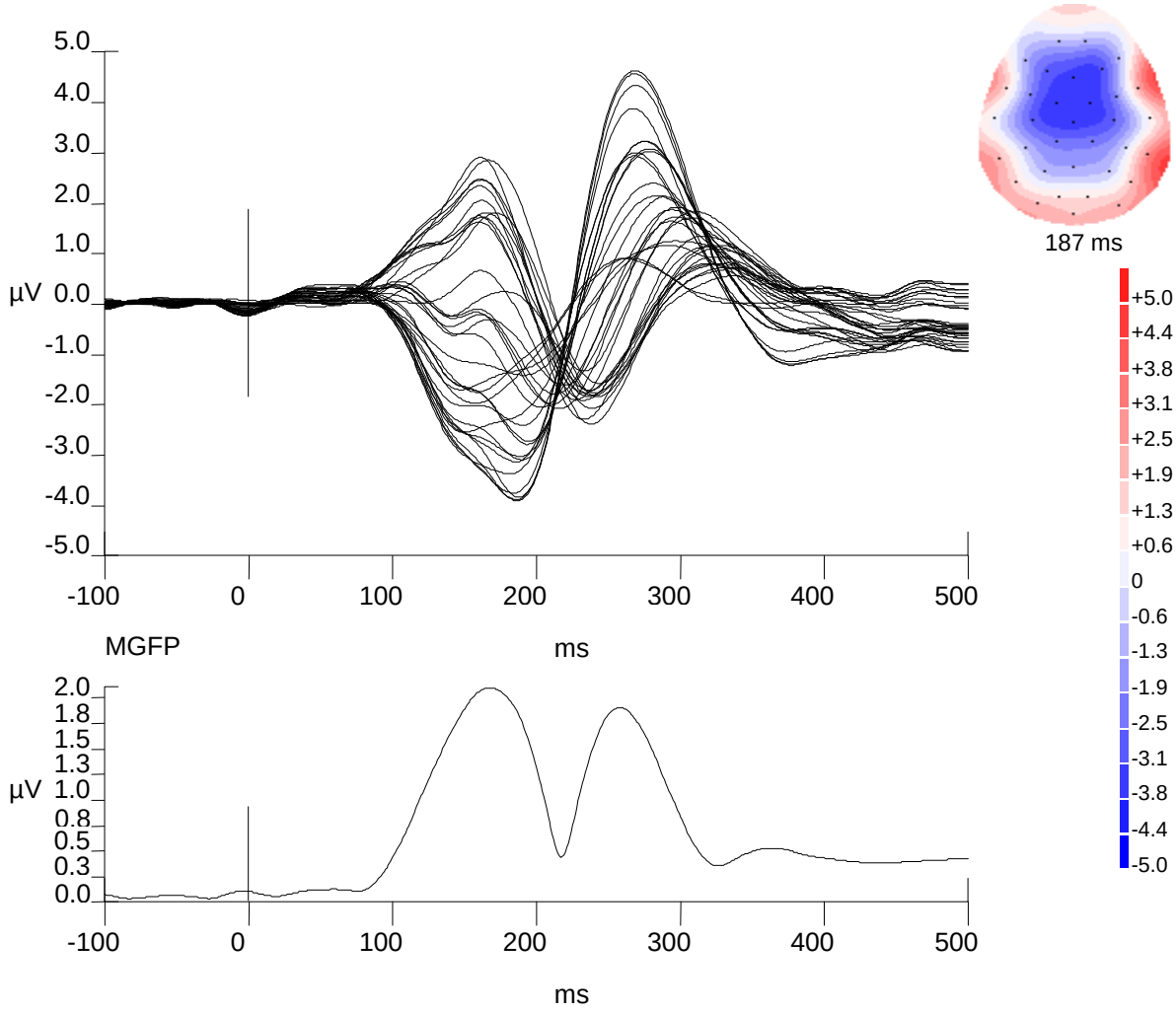


Figure 6.2a. Continued

Recent-Onset Schizophrenia Group (different amplitude scaling is used for the MGFP):

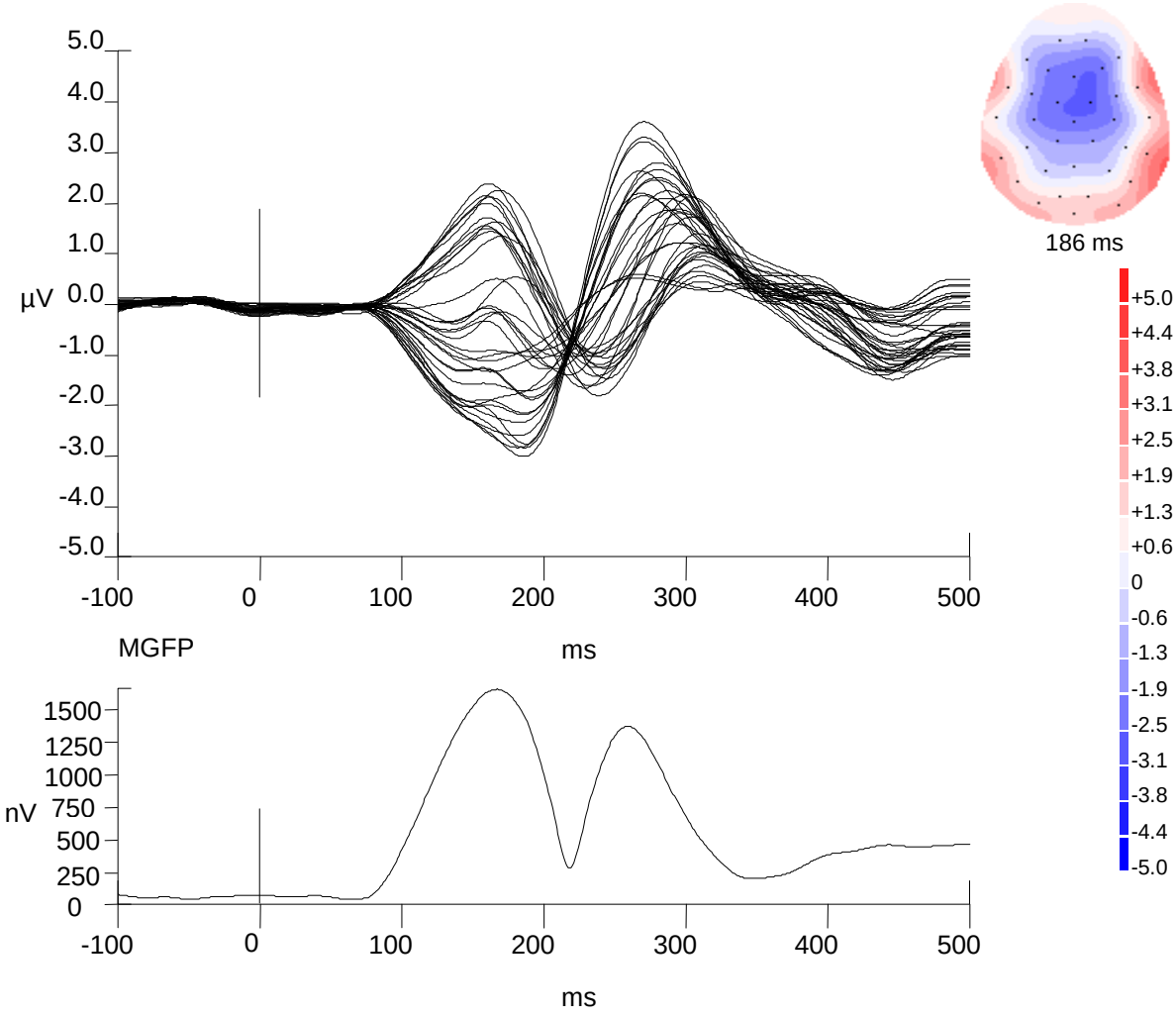


Figure 6.2a. Continued

Table 6.2. Descriptive Statistics of Mismatch Responses in all Groups

Electrode	NC (N=31)	AR (N=26)	RO (N=28)	ES (AR vs.NC)	ES (RO vs.NC)
Fp1	-1.71 (.83)	-1.41 (.77)	-.99 (.75)**	-.37	-.91
Fp2	-1.73 (.93)	-1.63 (.78)	-1.18 (.80)	-.12	-.63
F7	-1.70 (1.02)	-1.26 (.93)	-.98 (.81)**	-.45	-.78
F8	-1.81 (1.14)	-1.47 (1.14)	-1.01 (.97)**	-.30	-.76
Fz	-3.97 (1.92)	-3.29 (1.49)	-2.53 (1.58)**	-.40	-.82
F3	-3.57 (1.81)	-2.78 (1.25)	-2.16 (1.48)**	-.51	-.85
F4	-3.72 (1.79)	-3.09 (1.38)	-2.39 (1.48)**	-.39	-.81
FC1	-4.13 (2.15)	-3.30 (1.54)	-2.46 (1.75)**	-.44	-.85
FC2	-4.13 (2.11)	-3.35 (1.55)	-2.62 (1.71)**	-.42	-.79
FC5	-2.94 (1.56)	-2.15 (1.35)*	-1.63 (1.20)**	-.54	-.94
FC6	-3.02 (1.78)	-2.31 (1.47)	-1.82 (1.39)**	-.43	-.75
C3	-3.43 (1.94)	-2.67 (1.46)	-1.99 (1.45)**	-.44	-.84
Cz	-3.90 (2.12)	-3.11 (1.60)	-2.30 (1.74)**	-.42	-.82
C4	-3.25 (1.90)	-2.74 (1.51)	-2.05 (1.50)**	-.30	-.70
CP1	-2.72 (1.79)	-2.13 (1.38)	-1.55 (1.37)**	-.37	-.73
CP2	-2.59 (1.68)	-2.11 (1.36)	-1.52 (1.32)**	-.31	-.71
CP5	-1.62 (1.50)	-.76 (1.22)*	-.55 (1.17)**	-.63	-.79
CP6	-1.25 (1.54)	-.64 (1.29)	-.46 (1.09)	-.43	-.59
P7	.58 (1.50)	1.21 (1.26)	1.08 (.82)	-.45	-.41
P3	-1.41 (1.59)	-.76 (1.14)	-.53 (1.12)	-.47	-.64
Pz	-1.58 (1.53)	-1.15 (1.16)	-.75 (1.14)	-.32	-.61
P4	-1.00 (1.48)	-.62 (1.11)	-.43 (1.03)	-.29	-.45
P8	.69 (1.68)	1.24 (1.21)	1.20 (.89)	-.38	-.38
T7	-.72 (1.05)	.11 (1.34)*	.11 (.90)**	-.69	-.85
T8	-.70 (1.38)	.01 (1.45)	.16 (.99)	-.50	-.72
TP9	1.43 (1.67)	1.92 (1.19)	1.66 (.94)	-.34	-.17

Table 6.2. Continued

Electrode	NC (N=31)	AR (N=26)	RO (N=28)	ES (AR vs.NC)	ES (RO vs.NC)
TP10	1.63 (1.39)	2.22 (1.27)	1.74 (.91)	-.44	-.09
T1	.60 (.91)	1.06 (.83)	1.00 (.62)	-.53	-.51
T2	.85 (.88)	1.31 (.93)	1.05 (.65)	-.51	-.26
PO9	1.37 (1.37)	1.74 (1.15)	1.52 (.81)	-.29	-.13
PO10	1.51 (1.25)	1.85 (1.08)	1.67(.77)	-.29	-.15
O1	.65 (1.36)	1.04 (1.17)	.96 (.80)	-.31	-.28
O2	.71 (1.33)	.99 (1.07)	1.00 (.72)	-.23	-.27
Iz	1.28 (1.22)	1.65 (1.03)	1.47 (.75)	-.33	-.19

Data are given as Mean (SD) mismatch response. ** Represents significant differences between RO and NC at p<.01. * Represents significant differences between AR and NC at p<.05. Effect sizes are calculated as the standardized mean differences: ES = (Mean of NC – Mean of patient group)/Pooled SD. NC = Normal Comparison; AR = At-Risk; RO = Recent-Onset.

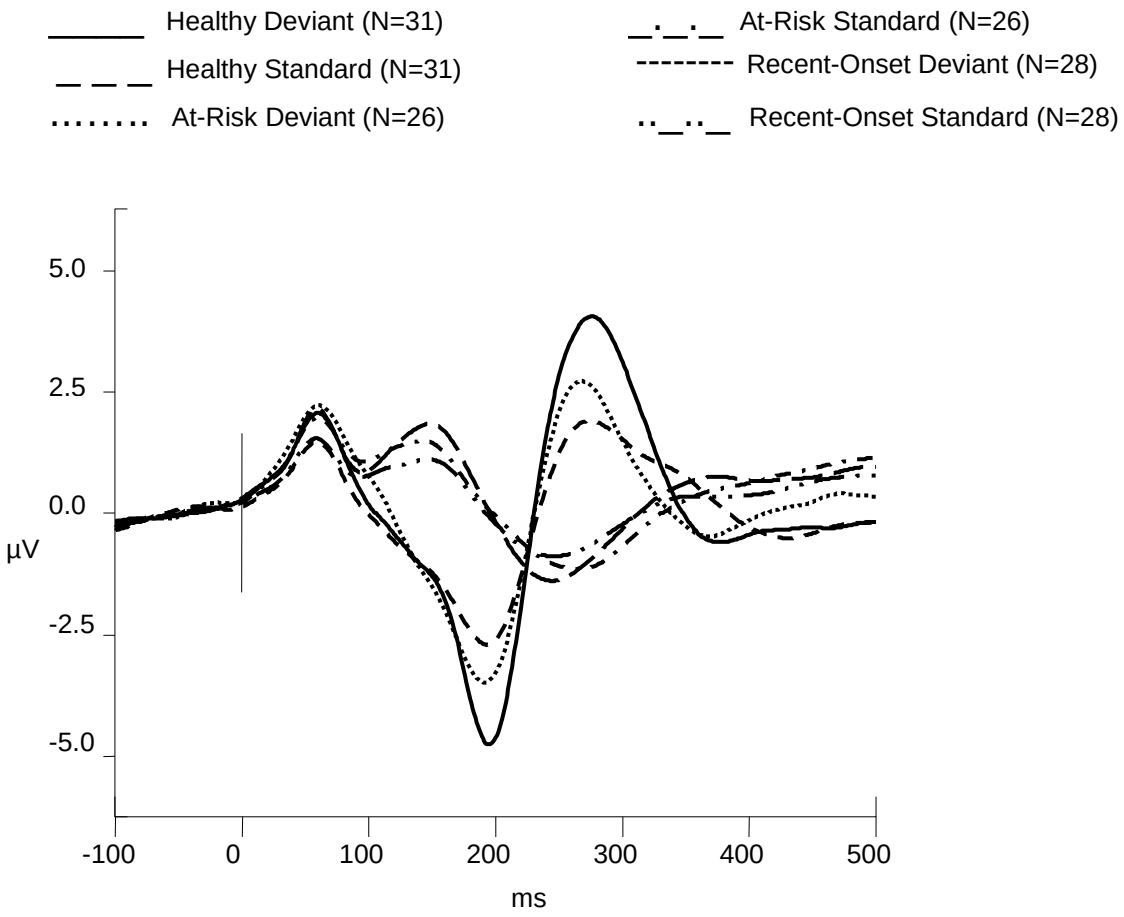


Figure 6.2b. Grand Average ERPs to Standard and Deviant Tones at Fz in each Group

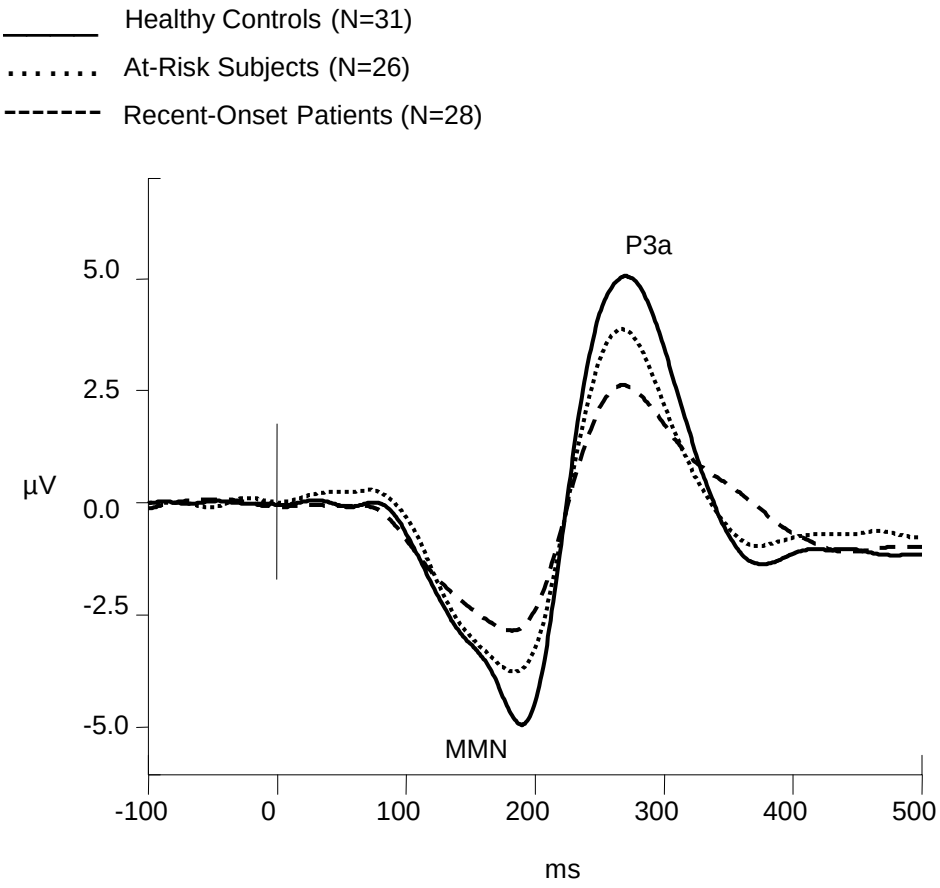
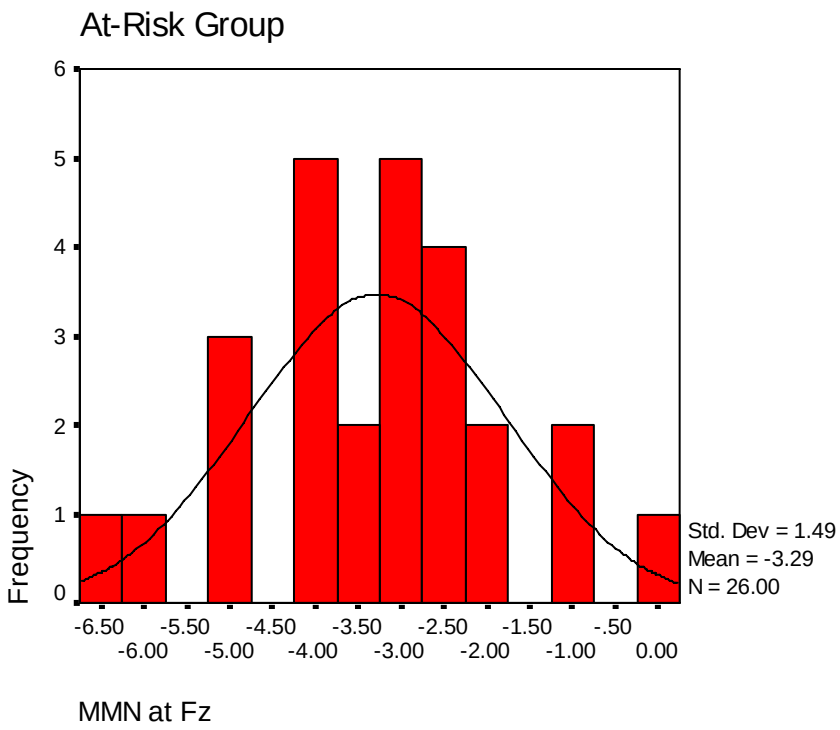


Figure 6.2c. MMN Difference Waveforms at Fz in each Group



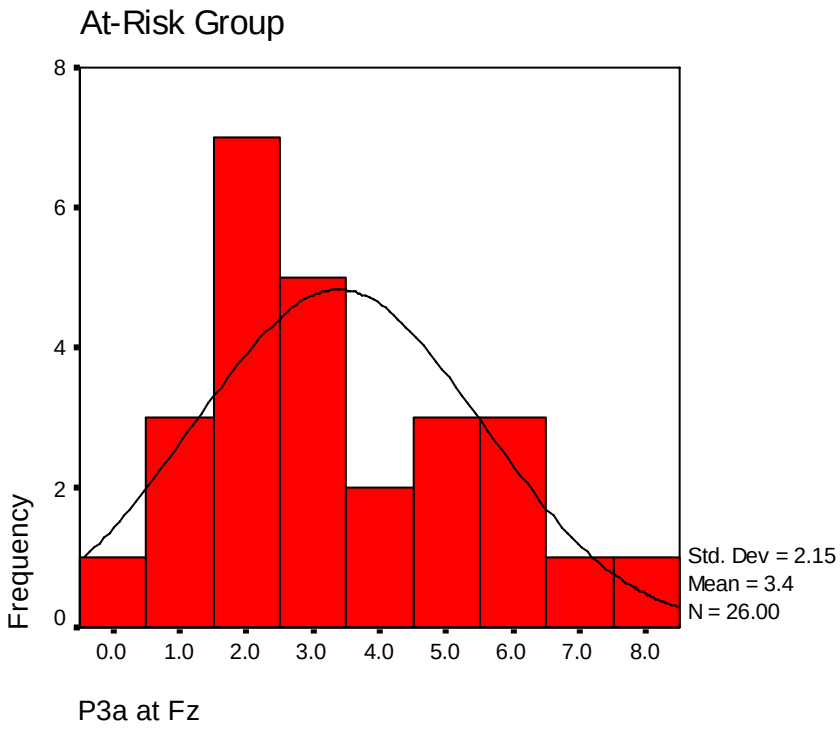


Figure 6.2d. Distributions of MMN and P3a Amplitudes at Fz in the At-Risk Group

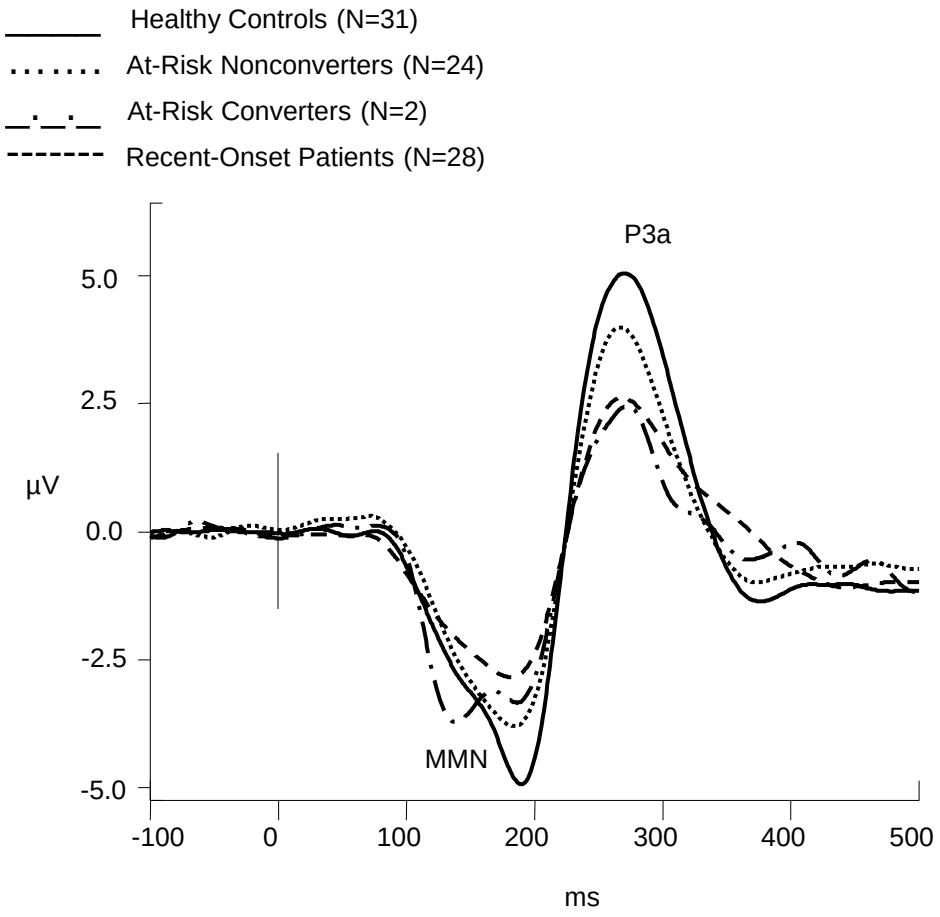


Figure 6.2e. MMN Difference Waveforms at Fz in each Group, Including the Subgroup of At-Risk Subjects that Converted to Psychosis and the One that Did Not

6.5. Relationship of MMN and P3a with Clinical Symptoms and Social Functioning

Spearman rank correlation coefficients were generated in order to assess the relationship between both MMN and P3a responses and the clinical/functional measures in the patient groups. To reduce the number of false positive findings, we report only the correlations that were significant at multiple, contiguous electrode sites.

No associations were found between mismatch responses and social functioning, as measured by the SAS-SR, or severity of positive and negative symptoms, as measured by the SIPS subscale scores, as well as the BPRS, SAPS, and SANS total scores, in any of the patient groups. There were significant Spearman rank correlations ($p<.05$) between GAF scale ratings and MMN values at frontocentral electrodes ($r_s=.39$ to $.53$; Fp1, F7, Fz, F3, F4, FC1, FC2, FC5, FC6, Cz, C3, C4) in the recent-onset group (Figure 6.5.) Contrary to our expectations, those correlations were all in the opposite direction, i.e., higher GAF scores were associated with smaller MMN amplitudes. We found no associations between GAF scores and mismatch responses in the at-risk group.

Significant Spearman rank correlations were found between P3a amplitudes and SIPS Negative in the at-risk group at Fp1, Fp2, F8, Fz, F3, F4, and FC6 ($r_s=-.43$ to $-.59$, $p<.05$). There were no significant correlations between P3a amplitudes and GAF, BPRS, SAPS, or SANS ratings in any of the patient groups. However, there were significant Spearman rank correlations ($p<.05$) between P3a amplitude and SAS-SR Extended Family ($r_s=.46$ to $.69$; Fz, F4, FC1, FC2, FC5, C3, Cz, C4, CP1, CP2, CP5, P3, Pz, P4) in the at-risk group. Those correlations are counterintuitive as they suggest that poorer social functioning (higher SAS-SR scores) is associated with larger P3a amplitudes. We found no associations between SAS-SR scores and P3a responses at the frontocentral electrodes in the recent-onset group.

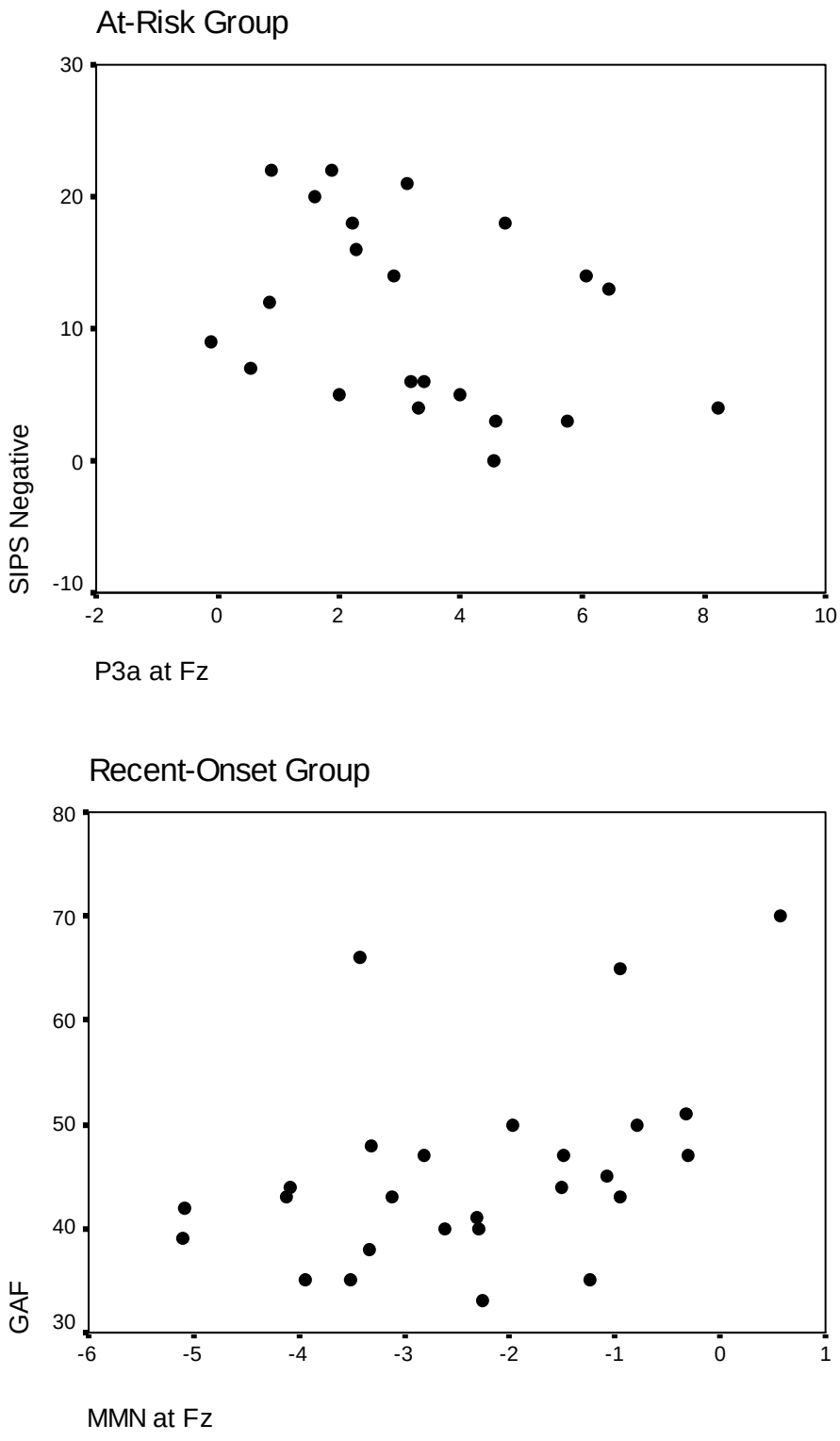


Figure 6.5. Scatterplots of the Significant Correlations between MMN/P3a Amplitudes at Fz and both Negative Symptoms and Social Functioning.

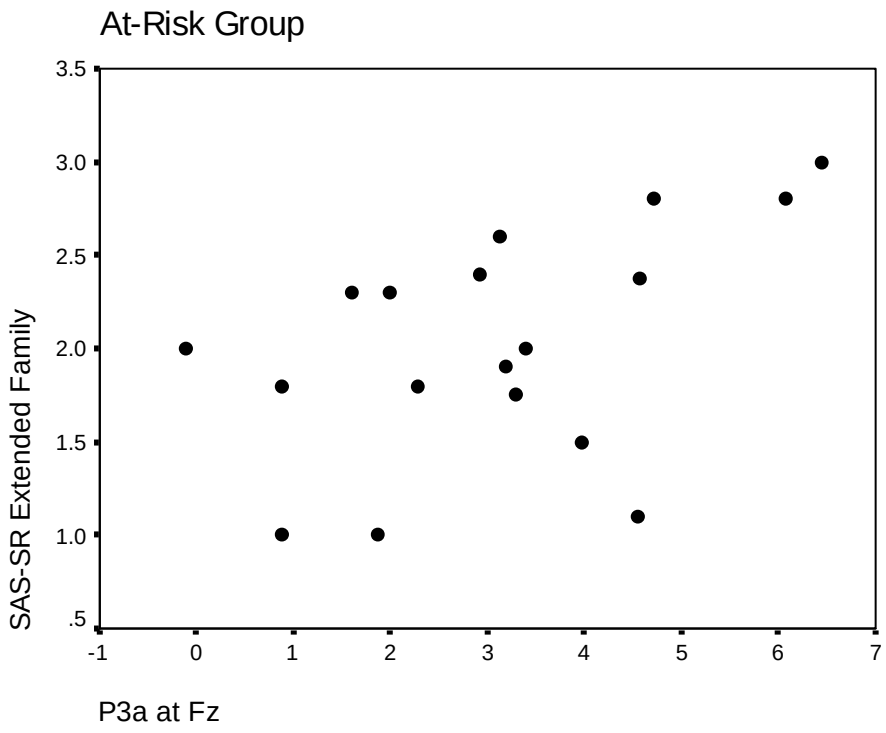


Figure 6.5. Continued

6.6. Relationship of MMN and P3a with Demographic Factors

No significant Pearson's correlations were found, in any of the groups, between age and both MMN and P3a amplitudes at the frontocentral electrodes. Moreover, years of education and premorbid IQ, as measured by the WRAT-3 Reading Subtest, were not significantly correlated with MMN amplitudes at any of the frontocentral electrodes. However, higher education was significantly associated with larger P3a amplitudes at Fp1, Fp2, F7, F8, F3, F4, FC5, FC6, CP5, P7, T7, TP9, T1, and T2 ($r=.24$ to $.39$, $p<.05$). When those analyses were performed in each group separately, education significantly correlated with P3a amplitudes at CP5, P7, P8, T7, TP9, TP10, T1, PO9, PO10, O1, O2, and Iz ($r = .41$ to $.56$, $p<.05$) in the at-risk group, and at Fp1, Fp2, and F7 ($r=.49$ to $.50$, $p<.05$) in the normal comparison group. There were no significant correlations between WRAT-3 reading scores and P3a amplitudes.

Independent samples t-tests showed that females (N=34) had larger MMN responses than males (N=51) at Cz ($t[82]=2.25$, $p=.027$), CP1 ($t[83]=2.06$, $p=.043$), and P3 ($t[83]=2.16$,

p=.034). Yet, there were no significant differences in P3a amplitudes between males and females. Upon examining gender differences in each group separately, we found that females had larger MMN amplitudes than males at Cz in the normal comparison group (t[28]=2.37, p=.025) and smaller P3a amplitudes than males at F8, F4, FC6, C4, and CP6 (p<.05) in the recent-onset group.

6.7. Influence of Treatment and Duration of Illness on MMN and P3a Responses

Independent samples t-tests within the recent-onset group revealed large effect-size differences in MMN amplitudes (d=.96 to 1.19) at frontocentral electrodes between patients who were not on antipsychotic medications (N=5) and those who were taking one or more atypical antipsychotics (N=23) at the time of testing. More specifically, the subsample that was antipsychotic-free had significantly larger MMN amplitudes at FC1, FC6, C3, Cz, C4, CP1, CP2, CP6, P4, T7, and T8 (p<.05). There were non significant, small effect-size MMN differences (e.g., d=.12 at Fz and .22 at Cz) between the at-risk subjects who were taking an atypical antipsychotic (N=7) and those who were not (N=19). Furthermore, there were no significant P3a differences between medicated and unmedicated patients in both groups.

In an attempt to explore the effects of illness duration on MMN responses, a mixed model ANOVA with electrode as a within-subject factor and duration of illness as a between-subject factor was conducted. Results revealed no significant main effect of duration of illness (F[2,23]=1.53, p=.24) or electrode by duration of illness interaction (F[4.04,46.50]=1.49, p=.22), suggesting no MMN amplitude differences among the recent-onset patients who were tested at the onset of their first psychotic break (N=9), within one year of their first break (N=9), and within two years of their first break (N=10). The same analysis conducted with P3a amplitude also yielded a nonsignificant main effect of duration of illness (F[2,23]=1.91, p=.17) and electrode by duration of illness interaction (F[6.81, 78.33]= 1.69, p=.13). There were no significant Spearman rank correlations between duration of illness (when treated as a continuous variable) and MMN or P3a amplitudes at any of the frontocentral electrodes.

7. Discussion

The main purpose of the current study was to investigate the early stages of auditory information processing in recent-onset schizophrenia and the putative prodrome, using a duration MMN paradigm. The specific aims were 1) to examine the amplitude and topography of two auditory event-related potentials, MMN and P3a, in subjects at risk to develop schizophrenia compared to recent-onset schizophrenia patients and healthy individuals; and 2) to explore the relationships of MMN and P3a deficits to the severity of clinical symptomatology and social functioning impairment within the patient groups.

Automatic sensory discrimination impairment in prodromal and recent-onset schizophrenia

Our groups were comparable with respect to ethnicity, handedness, years of education, and estimated premorbid IQ. However, there was a higher proportion of females in the normal comparison group. Moreover, the at-risk group was significantly younger than the other two groups. Despite the fact that the at-risk and normal comparison groups were not matched on age, no significant associations were found between age and MMN or P3a amplitudes at the frontocentral electrodes, in any of the groups. This finding is not congruent with previous studies showing a negative correlation between age and MMN amplitude (e.g., Kiang, et al., 2009). The absence of age effects in our sample is not surprising given our small age range (13-33) relative to those studies that encompassed a wider range (e.g., 18-65) and found more pronounced deficits in the older subjects. However, in accordance with an earlier study showing larger MMN amplitudes in women (Barrett & Fulfs, 1998), the females in our sample had larger mean MMN responses than males at a few electrode sites, i.e., Cz, CP1, and P3.

We found robust and large effect size (d=.59 to .94) MMN duration-deviant deficits at frontocentral recording sites in the recent-onset group. Consistent with our first hypothesis, subjects fulfilling criteria for a putative prodromal state, according to the SIPS, held an intermediate position between patients with recent-onset schizophrenia and normal comparison subjects. The at-risk individuals showed medium effect-size (d=.30 to .54) MMN reductions to duration deviants compared with healthy individuals. That recent-onset schizophrenia patients have significantly reduced duration MMN amplitudes relative to healthy individuals is not a novel finding, as it has been documented in two previously published

studies that tested patients within 3 years from their first episode (Javitt et al., 2000; Umbricht et al., 2006). As for the findings pertaining to our at-risk sample, they support those reported by Brockhaus-Dumke et al. (2005), mainly the fact that subjects at risk for developing schizophrenia exhibit reduced duration MMN amplitudes, though less pronounced than patients with manifest schizophrenia, prior to the onset of full-blown psychosis. The lack of a significant difference in MMN amplitude between the at-risk and normal comparison groups (except at FC5, CP5, and T7) can be attributed to the lower effect size of MMN reduction in the at-risk sample. In order to detect this moderate effect at Fz for instance (d=.40), 100 subjects in each of the two groups would have been required, at a significance level of $p<.05$ and a power of 80%. Of note, the MMN and P3a amplitude distributions of our at-risk sample revealed no bimodal distributions, precluding the possibility that the lack of significance was due to a large number of at-risk subjects with normal MMN or P3a. In fact, the normal distributions suggest that most of the at-risk subjects had some degree of preattentional processing impairment although less than half are destined to develop psychosis.

The groups had comparable MMN topographic distributions, suggesting that MMN is a reliable component that arises from the same neural generators, independently of group membership. As expected, the MMN responses were the largest at frontocentral electrodes and there was a phase reversal of MMN at posterior electrodes in all groups. There was no evidence for a hemispheric lateralization of MMN responses, which corroborates the fact that early cortical processing of auditory stimuli occurs bilaterally within the primary auditory cortex and surrounding regions of the superior temporal gyrus (Schofield, et al., 2009).

Both patient groups demonstrated significant decrements in P3a amplitudes, relative to the healthy group, at most frontocentral electrodes, indicating deficits in the orienting response to salient auditory stimuli. The P3a amplitudes were largest in normal comparison subjects, followed by at-risk subjects, and smallest in recent-onset schizophrenia patients. Just like MMN, P3a amplitude was frontally distributed in all groups, suggesting no differences in the topography of P3a responses. However, we found larger amplitudes at some of the centroparietal electrodes on the left hemisphere relative to the right one in the normal comparison group. This observation supports the notion that the normal human brain

shows a functional hemispheric asymmetry, mainly a left-hemisphere advantage for processing temporal information in sound (Devlin, et al., 2003).

The findings in this section are particularly interesting for several reasons. They indicate that abnormal MMN is present early in the disease process and is not secondary to chronicity effects. Nevertheless, it must be acknowledged that the influence of antipsychotics cannot be completely excluded since 27% of the at-risk and 82% of the recent-onset patients were receiving antipsychotic medications at the time of testing. Our preliminary analyses showed no significant MMN or P3a differences between the medicated and unmedicated at-risk subjects. Nonetheless, we found that the subsample of recent-onset patients that was on one or more atypical antipsychotics had significantly smaller MMN amplitudes at frontocentral electrodes than the subsample that was antipsychotic-free at the time of testing. Although it is hard to make any conclusions regarding treatment effects given our small sample size, it has been suggested that MMN reduction at the post-acute phase of the illness might emerge because of the initiation of antipsychotic medication (Devrim-Ucok, et al., 2008), despite contrary evidence showing that MMN is uninfluenced by Olanzapine (Korostenskaja, et al., 2005), Clozapine (Umbricht, et al., 1998), and Risperidone (Umbricht, et al., 1999).

To date, the literature regarding duration MMN's utility as an endophenotype is inconclusive. While some studies demonstrated duration MMN deficits in newly diagnosed schizophrenia patients (Oades, et al., 2006) and first-degree relatives of schizophrenia probands (Michie, et al., 2002), other studies found normal duration MMN at illness onset (Umbricht et al., 2006) and in unaffected family members (Magno et al., 2008). Our study was another attempt at investigating whether MMN and P3a could be possible markers of vulnerability to schizophrenia that might reflect premorbid neuropathology. Besides showing that MMN and P3a reductions are present in at-risk subjects, our results suggest that length of illness did not influence the extent of MMN and P3a deficits. More specifically, no significant MMN or P3a amplitude differences were observed among recent-onset patients who were tested at the onset of their first psychotic break, within one year of their first break, and within two years of their first break. We also visually inspected those components in the two at-risk subjects who converted to psychosis over the study period and found them to have a more pronounced reduction in MMN and P3a amplitudes relative to the nonconverters.

Relationships of MMN and P3a deficits with levels of psychopathology and social functioning

Contradictory to our a priori hypothesis, we found no associations between mismatch responses and negative symptoms in any of the patient groups, which is consistent with some previously reported findings in both first-episode (Salisbury, et al., 2007) and chronic schizophrenia patients (Light and Braff, 2005). Therefore, MMN seems to be relatively independent of clinical acuity or severity of positive and negative symptoms. Nonetheless, there were significant correlations between P3a amplitudes and SIPS negative symptoms at most of the frontocentral electrodes in the at-risk group. Taken together, those results suggest that levels of psychopathology have no influence on auditory sensory memory but that similar brain processes possibly underlie both negative symptoms and the involuntary switching of attention to deviant sounds in subjects at risk for psychosis.

There were significant correlations, at frontocentral electrodes, between MMN values and GAF scale ratings in the recent-onset group, as well as between P3a amplitudes and SAS-SR Extended Family in the at-risk group. Those correlations are paradoxical as they suggest that smaller MMN and P3a activity is associated with better social and family functioning, unlike the inverse association in patients with chronic schizophrenia (Light & Braff, 2005a). It may be argued that the more severely impaired at-risk patients are less insightful into their interpersonal difficulties, which causes them to endorse less problems on the SAS-SR. However, this explanation does not hold when one takes into account the opposite relationship between MMN and the clinician-rated GAF in the recent-onset group. Given that severity of symptoms contributes to the overall GAF score, the difficulty in finding understandable correlations may be attributed to the volatile and constantly changing pattern of symptoms in the early stages of the illness.

MMN was not significantly associated with subjects' reading level or number of years in school, in any of the groups. Although WRAT-3 reading scores did not correlate with P3a amplitudes at any of the frontocentral electrodes, having more years of education significantly correlated with larger P3a amplitudes in the at-risk and normal comparison groups. Therefore, unlike MMN, P3a seems to be reflective of both negative symptoms and educational level in the at-risk group, and could be an indicator of premorbid educational attainment in at-risk subjects.

Limitations of the Study

To our knowledge, this is the first study to examine both MMN and P3a in at-risk and recent-onset schizophrenia patients. However, several limitations about the present study should be noted. Foremost, its naturalistic cross-sectional design and modest sample sizes require special consideration. The low conversion rate in our at-risk sample (14% after one year and 30% after three years of ascertainment) did not yield sufficient statistical power to employ a longitudinal design and assess the potential role of MMN/P3a as predictors of conversion to psychosis, social or global functioning. However, we included a newly diagnosed schizophrenia group in an attempt to alleviate this problem and examine potential changes in MMN and P3a deficits with illness progression. We also conducted a preliminary inspection of our few at-risk subjects who transitioned to psychosis after they were tested. Additionally, concern about the heterogeneity of the at-risk group has to be taken into account. Given that our study did not follow the putatively prodromal subjects over time, we cannot consider those who did not convert to psychosis during the study “false-positives”, as we would have expected additional subjects to convert had they been followed beyond the study duration. Moreover, it is impossible to predict who will develop schizophrenia versus another kind of psychotic disorder (e.g., bipolar disorder, psychotic depression). Nonethess, the similarities between the MMN/P3a aberrations in the at-risk group and the recent-onset schizophrenia group indicate that the observed decrease of MMN/P3a amplitude is most likely associated with an enhanced risk of schizophrenia. In order to investigate whether MMN and P3a amplitudes truly reflect the progression from a prodromal stage to schizophrenia, following at-risk subjects over time and testing them repeatedly on this paradigm, before and after they convert, is necessary. It will be valuable to determine whether the size of the MMN/P3a amplitude can differentiate between subjects at various stages of the prodrome and identify those for whom psychosis is imminent.

Perhaps a more serious caveat of the study design was its lack of control over treatment effects that likely confounded our results. Testing the effect of treatment on MMN/P3a in this highly unstable period was not feasible given that patients had various acuteness levels and had been on antipsychotics for different lengths of time. Moreover, the CARE Program offers treatment as necessary, which may have delayed the transition to

psychosis, explaining our low conversion rate. As we previously mentioned, we found more pronounced MMN reductions in the medicated recent-onset patients relative to the unmedicated ones. Yet, when we included treatment (on versus off antipsychotics) as another grouping factor in the repeated measures ANOVA, we found no significant treatment by group by electrode interaction. As McGorry et al. (2008) highlighted, early psychosis researchers have often allowed treatment to vary widely in their studies, minimizing this major weakness of the naturalistic design. Therefore, larger samples and randomized controlled trials that include placebo and different antipsychotics are needed to carefully assess treatment effects on preattentional processing impairments in the prodrome and initial stages of schizophrenia.

Another potential limitation is that this study was partly based on secondary analyses of existing data from 23 healthy subjects who were previously tested at the UCSD Schizophrenia Laboratory. Given that the patient and control data were not collected in parallel (although we prospectively collected data from 8 additional young controls who were participating in the CARE program), the possibility of cohort effects cannot be completely ruled out. However, the same MMN/P3a paradigm was used and testers adhered to the same instructions. Furthermore, the at-risk and recent-onset patients were treatment seeking and were willing to participate in the research studies conducted at CARE. The effects of this sampling source on potential ascertainment bias are uncertain. Thus, our results need replication with other samples.

Our inability to find clear-cut correlations between MMN/P3a and functioning may be partly explained by the fact that we employed a self-report measure that is not as reliable as performance-based measures of functional capacity or in- vivo assessments of everyday functioning. Another factor that might have contributed to the absence of relationships with the other SAS-SR domains could be the limited range of scores on this measure. Moreover, the SAS-SR and GAF ratings may not have fully reflected patients' functioning across multiple domains. Similarly, the WRAT-3 reading subtest may not have been the best measure for capturing intellectual functioning. A better estimate of IQ might combine both verbal (e.g., vocabulary) and visuospatial (e.g., block construction) tasks. Finally, it would have been informative to examine relationships between MMN/P3a and neurocognitive variables, such

as attention, memory, and executive functioning, as well as other demographic variables, such as socioeconomic status.

Implications of the Study

The current study has theoretical and pragmatic implications. Preattentive processes are vital to the optimal detection of changes in the auditory environment. The findings from the two ERP components that we studied point to deviance detection abnormalities in subjects identified as putatively prodromal for schizophrenia as well as those with manifest schizophrenia. Those persons may incorrectly process auditory input or underdetect changes in their acoustic environment, failing to notice stimuli that are usually salient to most people. In other words, they have difficulty organizing sensory stimulations from their surrounding environment and effectively responding to them. Those sensory processing problems may result in poor self-regulation, inattentiveness, and disorganization, causing significant disruption to everyday functioning.

On a theoretical level, the clarification of the extent of MMN/P3a deficits in an at-risk population contributes to the overall efforts to identify potential markers of vulnerability to schizophrenia, and to link those deficits to the underlying pathology in neurological systems. Our results suggest that MMN and P3a exhibit promise as trait markers for schizophrenia as they appear to be deficient before the onset of full-blown psychosis – especially during the more advanced stage of the prodrome that shortly precedes conversion – as well as during the first two years of the illness. Given the observation that P3a was significantly reduced in both at-risk and recent-onset patients relative to normal comparison subjects, and did not seem to be affected by antipsychotic treatment, it may be argued that P3a is a more robust risk marker than MMN, and potentially a more fundamental preattentive process required for higher order integrative processes.

On a clinical level, this study emphasizes the importance of designing and implementing psychosocial interventions that would treat the underlying neurophysiological deficits in newly diagnosed individuals while concurrently addressing the more observable behaviors interfering with higher-level functional goals. Sensory integrative treatment has been used in autism spectrum disorders and shown to be helpful in increasing patients' ability

to generate responses that are appropriately graded in relation to incoming sensations, resulting in more adaptive social behaviors (Hodgetts & Hodgetts, 2007). Although there is not much empirical support for the efficacy of this treatment approach in schizophrenia (Reisman & Blakeney, 1991), it might be beneficial to combine sensory integration and modulation techniques with more traditional treatment strategies including cognitive behavioral therapy, social skills training, and cognitive remediation.

Future Directions

The years of extensive research that have been devoted to advance our understanding of schizophrenia have not yet unraveled its mystery, mainly because of the lack of adequate methodology to study its heterogeneous clinical presentation. Schizophrenia remains a complex disorder with a variable expression and poorly defined pathophysiology. Furthermore, no laboratory test for psychotic illness currently exists and no objective diagnostic biomarker has been identified in order to accurately predict the level of risk for psychosis. In this study, we attempted to assess one elementary aspect of cognition in the early stages of schizophrenia, namely auditory sensory discrimination. It is now well documented that the cognitive impairment in schizophrenia is a hallmark of the disorder (e.g., (Elvevag & Goldberg, 2000) and a better predictor of overall functioning than overt symptomatology (Puig, et al., 2008). Therefore, studying preattentive information processing is a first step toward improving the long-term functional outcome of affected individuals.

Longitudinal neurophysiological assessment in prodromal samples is quite challenging and large studies of this type are currently lacking. Progress in this particular line of research therefore requires incremental contributions of long-term multisite studies that should be able to address many important questions that our cross-sectional study failed to answer. For instance, based on our results, we cannot confidently assert that preattentive auditory processing deficits are trait-related and not affected by disease duration. Longitudinal designs are needed to determine whether the MMN and P3a abnormalities observed in the early course of schizophrenia worsen with illness progression, as well as to delineate the rate of change in those risk indicators in subjects who convert to psychosis. Additionally, it will be useful to ascertain whether MMN can be a vulnerability marker for functional disability in at-

risk individuals and those with recent-onset schizophrenia, that is, whether it can predict medication adherence, academic or vocational functioning, and other instrumental activities of daily living. Future research might also benefit from combining brain imaging and neurophysiological techniques in order to test whether the MMN reduction in at-risk subjects is associated with the regional cortical gray matter loss that occurs around the time of transition to psychosis (Wood, et al., 2008). It will be useful to determine whether any of the abnormal structural changes observed in this population, such as the reduced gray matter volume in medial temporal and prefrontal regions, can serve as a mediator of the relationship between sensory discrimination deficits and social functioning impairment. Another important question has to do with the extent to which sensory discrimination impairment improves sensitivity and predictive accuracy relative to other known risk factors of conversion to psychosis, such as functional decline, severity of subsyndromal psychotic symptoms (Haroun, Dunn, Haroun, & Cadenhead, 2006), and cannabis abuse (Kristensen & Cadenhead, 2007). If found to have a good predictive validity in determining which individuals are at greatest risk for schizophrenia, MMN could potentially be added to the risk prediction algorithm developed by the North American Prodromal Longitudinal Studies (NAPLS) consortium (Cannon et al., 2008). Yet, one should consider the feasibility of using event-related potentials as a clinical diagnostic tool.

On another note, there continues to be a debate about whether certain characteristics of the MMN paradigm can capture the severity of the deficits differently and impact the results obtained. For instance, it has been postulated that MMN to duration change is more impaired in schizophrenia and more sensitive to the pathophysiology of the disorder than MMN to frequency change (Michie, et al., 2002). The paradigm that we used in our study employed one type of deviant stimuli and did not allow us to substantiate that statement. Therefore, future studies should attempt to manipulate the factors that might be contributing to the inconsistencies in previous reports, i.e., the type of auditory deviance, the time interval between the tones, and the amount or probability of stimulus deviance.

Recently, an increasing number of studies have been employing more sophisticated approaches to the analysis of EEG data, which provide a more detailed account of the brain's event-related neurooscillatory activity, relative to the conventional analysis of amplitudes. One

of those methods is time-frequency analysis (Makeig, Debener, Onton, & Delorme, 2004), which could be an ideal tool for elucidating the role of frequency-specific neuronal oscillations and their synchronization in automatic sensory processing. Deconstructing event-related brain activity into different frequency bands will permit to examine, for instance, if the MMN reduction in the early stages of the illness is characterized by a specific high-frequency oscillation pattern or accompanied by an altered synchronization in the gamma band response (Roach & Mathalon, 2008). Using spectral decomposition methods may therefore provide more information about the true nature of the neuropathophysiological processes underlying schizophrenia.

8. References

Alain, C., & Woods, D. L. (1999). Age-related changes in processing auditory stimuli during visual attention: evidence for deficits in inhibitory control and sensory memory. *Psychol Aging, 14*(3), 507-519.

Albus, M., Hubmann, W., Mohr, F., Hecht, S., Hinterberger-Weber, P., Seitz, N. N., et al. (2006). Neurocognitive functioning in patients with first-episode schizophrenia : results of a prospective 5-year follow-up study. *Eur Arch Psychiatry Clin Neurosci, 256*(7), 442-451.

Alho, K. (1995). Cerebral generators of mismatch negativity (MMN) and its magnetic counterpart (MMNm) elicited by sound changes. *Ear Hear, 16*(1), 38-51.

Andreasen, N. C., Endicott, J., Spitzer, R. L., & Winokur, G. (1977). The Family History Method Using Diagnostic Criteria: Reliability and Validity. *Archives of General Psychiatry, 34*(10), 1229-1235.

Baker, K., Baldeweg, T., Sivagnanasundaram, S., Scambler, P., & Skuse, D. (2005). COMT Val108/158 Met modifies mismatch negativity and cognitive function in 22q11 deletion syndrome. *Biol Psychiatry, 58*(1), 23-31.

Baldeweg, T., Klugman, A., Gruzelier, J., & Hirsch, S. R. (2004). Mismatch negativity potentials and cognitive impairment in schizophrenia. *Schizophr Res, 69*(2-3), 203-217.

Barrett, K. A., & Fulfs, J. M. (1998). Effect of gender on the mismatch negativity auditory evoked potential. *J Am Acad Audiol, 9*(6), 444-451.

Bazana, P. G., & Stelmack, R. M. (2002). Intelligence and information processing during an auditory discrimination task with backward masking: an event-related potential analysis. *J Pers Soc Psychol, 83*(4), 998-1008.

Bilder, R. M., Goldman, R. S., Robinson, D., Reiter, G., Bell, L., Bates, J. A., et al. (2000). Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. *Am J Psychiatry, 157*(4), 549-559.

Bilder, R. M., Reiter, G., Bates, J., Lencz, T., Szeszko, P., Goldman, R. S., et al. (2006). Cognitive development in schizophrenia: follow-back from the first episode. *J Clin Exp Neuropsychol, 28*(2), 270-282.

Borgwardt, S. J., Riecher-Rossler, A., Dazzan, P., Chitnis, X., Aston, J., Drewe, M., et al. (2007). Regional gray matter volume abnormalities in the at risk mental state. *Biol Psychiatry, 61*(10), 1148-1156.

Braff, D. L., Freedman, R., Schork, N. J., & Gottesman, II (2007). Deconstructing schizophrenia: an overview of the use of endophenotypes in order to understand a complex disorder. *Schizophr Bull, 33*(1), 21-32.

Braff, D. L., Greenwood, T. A., Swerdlow, N. R., Light, G. A., & Schork, N. J. (2008). Advances in endophenotyping schizophrenia. *World Psychiatry, 7*(1), 11-18.

Braff, D. L., & Light, G. A. (2004). Preattentional and attentional cognitive deficits as targets for treating schizophrenia. *Psychopharmacology (Berl)*.

Bramon, E., Croft, R. J., McDonald, C., Virdi, G. K., Gruzelier, J. G., Baldeweg, T., et al. (2004). Mismatch negativity in schizophrenia: a family study. *Schizophr Res, 67*(1), 1-10.

Brewer, W. J., Wood, S. J., McGorry, P. D., Francey, S. M., Phillips, L. J., Yung, A. R., et al. (2003). Impairment of olfactory identification ability in individuals at ultra-high risk for psychosis who later develop schizophrenia. *Am J Psychiatry, 160*(10), 1790-1794.

Brockhaus-Dumke, A., Tendolkar, I., Pukrop, R., Schultze-Lutter, F., Klosterkotter, J., & Ruhrmann, S. (2005). Impaired mismatch negativity generation in prodromal subjects and patients with schizophrenia. *Schizophr Res, 73*(2-3), 297-310.

Cannon, T. D., Cadenhead, K., Cornblatt, B., Woods, S. W., Addington, J., Walker, E., et al. (2008). Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. *Arch Gen Psychiatry, 65*(1), 28-37.

Catts, S. V., Shelley, A. M., Ward, P. B., Liebert, B., McConaghy, N., Andrews, S., et al. (1995). Brain potential evidence for an auditory sensory memory deficit in schizophrenia. *Am J Psychiatry, 152*(2), 213-219.

Chambers, W. J., Puig-Antich, J., Hirsch, M., Paez, P., Ambrosini, P. J., Tabrizi, M. A., et al. (1985). The assessment of affective disorders in children and adolescents by semistructured interview. Test-retest reliability of the schedule for affective disorders and schizophrenia for school-age children, present episode version. *Arch Gen Psychiatry, 42*(7), 696-702.

Chapman, J. (1966). The early symptoms of schizophrenia. *British Journal of Psychiatry, 112*(484), 225-251.

Cooper, R. J., Todd, J., McGill, K., & Michie, P. T. (2006). Auditory sensory memory and the aging brain: A mismatch negativity study. *Neurobiol Aging, 27*(5), 752-762.

Deouell, L. Y., Bentin, S., & Giard, M. H. (1998). Mismatch negativity in dichotic listening: evidence for interhemispheric differences and multiple generators. *Psychophysiology, 35*(4), 355-365.

Devlin, J. T., Raley, J., Tunbridge, E., Lanary, K., Floyer-Lea, A., Narain, C., et al. (2003). Functional asymmetry for auditory processing in human primary auditory cortex. *J Neurosci, 23*(37), 11516-11522.

Devrim-Ucok, M., Keskin-Ergen, H. Y., & Ucok, A. (2008). Mismatch negativity at acute and post-acute phases of first-episode schizophrenia. *Eur Arch Psychiatry Clin Neurosci, 258*(3), 179-185.

Eastvold, A. D., Heaton, R. K., & Cadenhead, K. S. (2007). Neurocognitive deficits in the (putative) prodrome and first episode of psychosis. *Schizophr Res, 93*(1-3), 266-277.

Elvevag, B., & Goldberg, T. E. (2000). Cognitive impairment in schizophrenia is the core of the disorder. *Crit Rev Neurobiol, 14*(1), 1-21.

Eslami, A., Jahchan, C., & Cadenhead, K.S. (in submission). Disorganized symptoms, along with neurocognitive deficits, predict impaired social functioning in subjects at risk for psychosis.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. (1996). Structured Clinical Interview for DSM-IV Axis I Disorders - Non-Patient Edition (SCID-I/NP, Version 2.0). New York: Biometrics Research Department, New York State Psychiatric Institute.

Fischer, C., Morlet, D., & Giard, M. (2000). Mismatch negativity and N100 in comatose patients. *Audiol Neurootol, 5*(3-4), 192-197.

Gaeta, H., Friedman, D., Ritter, W., & Cheng, J. (1998). An event-related potential study of age-related changes in sensitivity to stimulus deviance. *Neurobiol Aging, 19*(5), 447-459.

Gottesman, II, & Gould, T. D. (2003). The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry, 160*(4), 636-645.

Green, M. F. (1996). What are the functional consequences of neurocognitive deficits in schizophrenia? *American Journal of Psychiatry, 153*, 321-330.

Green, M. F., Kern, R. S., Braff, D. L., & Mintz, J. (2000). Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? *Schizophr Bull, 26*(1), 119-136.

Grillon, C., Courchesne, E., Ameli, R., Elmasian, R., & Braff, D. (1990). Effects of rare non-target stimuli on brain electrophysiological activity and performance. *Int J Psychophysiol, 9*(3), 257-267.

Grillon, C., Courchesne, E., Ameli, R., Geyer, M. A., & Braff, D. L. (1990). Increased distractibility in schizophrenic patients. Electrophysiologic and behavioral evidence. *Arch Gen Psychiatry, 47*(2), 171-179.

Grzella, I., Muller, B. W., Oades, R. D., Bender, S., Schall, U., Zerbin, D., et al. (2001). Novelty-elicited mismatch negativity in patients with schizophrenia on admission and discharge. *J Psychiatry Neurosci, 26*(3), 235-246.

Hall, M. H., Schulze, K., Rijsdijk, F., Picchioni, M., Ettinger, U., Bramon, E., et al. (2006). Heritability and reliability of P300, P50 and duration mismatch negativity. *Behav Genet, 36*(6), 845-857.

Hall, R. C., & Parks, J. (1995). The modified global assessment of functioning scale: addendum. *Psychosomatics, 36*(4), 416-417.

Haroun, N., Dunn, L., Haroun, A., & Cadenhead, K. S. (2006). Risk and protection in prodromal schizophrenia: ethical implications for clinical practice and future research. *Schizophr Bull, 32*(1), 166-178.

Haroush, K., Hochstein, S., & Deouell, L. Y. (2009). Momentary Fluctuations in Allocation of Attention: Cross-modal Effects of Visual Task Load on Auditory Discrimination. *J Cogn Neurosci*.

Hillyard, S. A., & Kutas, M. (1983). Electrophysiology of cognitive processing. *Annu Rev Psychol, 34*, 33-61.

Hirayasu, Y., Potts, G. F., O'Donnell, B. F., Kwon, J. S., Arakaki, H., Akdag, S. J., et al. (1998). Auditory mismatch negativity in schizophrenia: topographic evaluation with a high-density recording montage. *Am J Psychiatry, 155*(9), 1281-1284.

Hodgetts, S., & Hodgetts, W. (2007). Somatosensory stimulation interventions for children with autism: literature review and clinical considerations. *Can J Occup Ther, 74*(5), 393-400.

Hoff, A. L., Svetina, C., Shields, G., Stewart, J., & DeLisi, L. E. (2005). Ten year longitudinal study of neuropsychological functioning subsequent to a first episode of schizophrenia. *Schizophr Res, 78*(1), 27-34.

Jahchan, C., Heaton, R. K., Golshan, S., & Cadenhead, K. S. (2010). Course of neurocognitive deficits in the prodrome and first episode of schizophrenia. *Neuropsychology, 24*(1), 109-120.

Javitt, D. C., Grochowski, S., Shelley, A. M., & Ritter, W. (1998). Impaired mismatch negativity (MMN) generation in schizophrenia as a function of stimulus deviance, probability,

and interstimulus/interdeviant interval. *Electroencephalogr Clin Neurophysiol, 108*(2), 143-153.

Javitt, D. C., Shelley, A. M., Silipo, G., & Lieberman, J. A. (2000). Deficits in auditory and visual context-dependent processing in schizophrenia: defining the pattern. *Arch Gen Psychiatry, 57*(12), 1131-1137.

Javitt, D. C., Steinschneider, M., Schroeder, C. E., & Arezzo, J. C. (1996). Role of cortical N-methyl-D-aspartate receptors in auditory sensory memory and mismatch negativity generation: implications for schizophrenia. *Proc Natl Acad Sci U S A, 93*(21), 11962-11967.

Jemel, B., Achenbach, C., Muller, B. W., Ropcke, B., & Oades, R. D. (2002). Mismatch negativity results from bilateral asymmetric dipole sources in the frontal and temporal lobes. *Brain Topogr, 15*(1), 13-27.

Jessen, F., Fries, T., Kucharski, C., Nishimura, T., Hoenig, K., Maier, W., et al. (2001). Amplitude reduction of the mismatch negativity in first-degree relatives of patients with schizophrenia. *Neurosci Lett, 309*(3), 185-188.

Kahkonen, S., Makinen, V., Jaaskelainen, I. P., Pennanen, S., Liesivuori, J., & Ahveninen, J. (2005). Serotonergic modulation of mismatch negativity. *Psychiatry Res, 138*(1), 61-74.

Karayanidis, F., Andrews, S., Ward, P. B., & Michie, P. T. (1995). ERP indices of auditory selective attention in aging and Parkinson's disease. *Psychophysiology, 32*(4), 335-350.

Kasai, K., Okazawa, K., Nakagome, K., Hiramatsu, K., Hata, A., Fukuda, M., et al. (1999). Mismatch negativity and N2b attenuation as an indicator for dysfunction of the preattentive and controlled processing for deviance detection in schizophrenia: a topographic event-related potential study. *Schizophr Res, 35*(2), 141-156.

Kathmann, N., Wagner, M., Rendtorff, N., & Engel, R. R. (1995). Delayed peak latency of the mismatch negativity in schizophrenics and alcoholics. *Biol Psychiatry, 37*(10), 754-757.

Kawakubo, Y., Kamio, S., Nose, T., Iwanami, A., Nakagome, K., Fukuda, M., et al. (2007). Phonetic mismatch negativity predicts social skills acquisition in schizophrenia. *Psychiatry Res, 152*(2-3), 261-265.

Kawakubo, Y., & Kasai, K. (2006). Support for an association between mismatch negativity and social functioning in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry, 30*(7), 1367-1368.

Kiang, M., Braff, D. L., Sprock, J., & Light, G. A. (2009). The relationship between preattentive sensory processing deficits and age in schizophrenia patients. *Clin Neurophysiol, 120*(11), 1949-1957.

Korostenskaja, M., Dapsys, K., Siurkute, A., Maciulis, V., Ruksenas, O., & Kahkonen, S. (2005). Effects of olanzapine on auditory P300 and mismatch negativity (MMN) in schizophrenia spectrum disorders. *Prog Neuropsychopharmacol Biol Psychiatry, 29*(4), 543-548.

Kristensen, K., & Cadenhead, K. S. (2007). Cannabis abuse and risk for psychosis in a prodromal sample. *Psychiatry Res*.

Krystal, J. H., Karper, L. P., Seibyl, J. P., Freeman, G. K., Delaney, R., Bremner, J. D., et al. (1994). Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in

humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry, 51*(3), 199-214.

Lavoie, S., Murray, M. M., Deppen, P., Knyazeva, M. G., Berk, M., Boulat, O., et al. (2008). Glutathione precursor, N-acetyl-cysteine, improves mismatch negativity in schizophrenia patients. *Neuropsychopharmacology, 33*(9), 2187-2199.

Leung, S., Croft, R. J., Baldeweg, T., & Nathan, P. J. (2007). Acute dopamine D(1) and D(2) receptor stimulation does not modulate mismatch negativity (MMN) in healthy human subjects. *Psychopharmacology (Berl), 194*(4), 443-451.

Lewis, S. W., & Murray, R. M. (1987). Obstetric complications, neurodevelopmental deviance, and risk of schizophrenia. *J Psychiatr Res, 21*(4), 413-421.

Light, G. A., & Braff, D. L. (2005a). Mismatch negativity deficits are associated with poor functioning in schizophrenia patients. *Arch Gen Psychiatry, 62*(2), 127-136.

Light, G. A., & Braff, D. L. (2005b). Stability of mismatch negativity deficits and their relationship to functional impairments in chronic schizophrenia. *Am J Psychiatry, 162*(9), 1741-1743.

Light, G. A., Swerdlow, N. R., & Braff, D. L. (2007). Preattentive sensory processing as indexed by the MMN and P3a brain responses is associated with cognitive and psychosocial functioning in healthy adults. *J Cogn Neurosci, 19*(10), 1624-1632.

Luck, S. J., Girelli, M., McDermott, M. T., & Ford, M. A. (1997). Bridging the gap between monkey neurophysiology and human perception: an ambiguity resolution theory of visual selective attention. *Cogn Psychol, 33*(1), 64-87.

Magno, E., Yeap, S., Thakore, J. H., Garavan, H., De Sanctis, P., & Foxe, J. J. (2008). Are auditory-evoked frequency and duration mismatch negativity deficits endophenotypic for schizophrenia? High-density electrical mapping in clinically unaffected first-degree relatives and first-episode and chronic schizophrenia. *Biol Psychiatry, 64*(5), 385-391.

Makeig, S., Debener, S., Onton, J., & Delorme, A. (2004). Mining event-related brain dynamics. *Trends Cogn Sci, 8*(5), 204-210.

Mathalon, D. H., Ford, J. M., & Pfefferbaum, A. (2000). Trait and state aspects of P300 amplitude reduction in schizophrenia: a retrospective longitudinal study. *Biol Psychiatry, 47*(5), 434-449.

McGhie, A., & Chapman, J. (1961). Disorders of attention and perception in early schizophrenia. *Br J Med Psychol, 34*, 103-116.

McGlashan, T. H., & Hoffman, R. E. (2000). Schizophrenia as a disorder of developmentally reduced synaptic connectivity. *Arch Gen Psychiatry, 57*(7), 637-648.

Meisenzahl, E. M., Koutsouleris, N., Gaser, C., Bottlender, R., Schmitt, G. J., McGuire, P., et al. (2008). Structural brain alterations in subjects at high-risk of psychosis: a voxel-based morphometric study. *Schizophr Res, 102*(1-3), 150-162.

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

Milev, P., Ho, B. C., Arndt, S., & Andreasen, N. C. (2005). Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. *Am J Psychiatry, 162*(3), 495-506.

Miller, T. J., McGlashan, T. H., Rosen, J. L., Cadenhead, K., Ventura, J., McFarlane, W., et al. (2003). Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophr Bull, 29*(4), 703-715.

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

Muller-Gass, A., Macdonald, M., Schroger, E., Sculthorpe, L., & Campbell, K. (2007). Evidence for the auditory P3a reflecting an automatic process: elicitation during highly-focused continuous visual attention. *Brain Res, 1170*, 71-78.

Naatanen, R., Paavilainen, P., & Reinikainen, K. (1989). Do event-related potentials to infrequent decrements in duration of auditory stimuli demonstrate a memory trace in man? *Neurosci Lett, 107*(1-3), 347-352.

Naatanen, R., Paavilainen, P., Tiitinen, H., Jiang, D., & Alho, K. (1993). Attention and mismatch negativity. *Psychophysiology, 30*(5), 436-450.

Niendam, T. A., Bearden, C. E., Zinberg, J., Johnson, J. K., O'Brien, M., & Cannon, T. D. (2007). The course of neurocognition and social functioning in individuals at ultra high risk for psychosis. *Schizophr Bull, 33*(3), 772-781.

Oades, R. D., Wild-Wall, N., Juran, S. A., Sachsse, J., Oknina, L. B., & Ropcke, B. (2006). Auditory change detection in schizophrenia: sources of activity, related neuropsychological function and symptoms in patients with a first episode in adolescence, and patients 14 years after an adolescent illness-onset. *BMC Psychiatry, 6*, 7.

Oranje, B., Jensen, K., Wienberg, M., & Glenthoj, B. Y. (2008). Divergent effects of increased serotonergic activity on psychophysiological parameters of human attention. *Int J Neuropsychopharmacol, 11*(4), 453-463.

Ozgurdal, S., Gudlowski, Y., Witthaus, H., Kawohl, W., Uhl, I., Hauser, M., et al. (2008). Reduction of auditory event-related P300 amplitude in subjects with at-risk mental state for schizophrenia. *Schizophr Res, 105*(1-3), 272-278.

Pantelis, C., Velakoulis, D., Wood, S. J., Yucel, M., Yung, A. R., Phillips, L. J., et al. (2007). Neuroimaging and emerging psychotic disorders: the Melbourne ultra-high risk studies. *Int Rev Psychiatry, 19*(4), 371-381.

Paus, T. (2005). Mapping brain maturation and cognitive development during adolescence. *Trends Cogn Sci, 9*(2), 60-68.

Pekkonen, E., Katila, H., Ahveninen, J., Karhu, J., Huotilainen, M., & Tiihonen, J. (2002). Impaired temporal lobe processing of preattentive auditory discrimination in schizophrenia. *Schizophr Bull, 28*(3), 467-474.

Pfohl, B., Blum, N., & Zimmerman, M. (1995). The Structured Interview for DSM-IV Personality (SIDP-IV). Iowa City, Iowa: Department of Psychiatry, University of Iowa.

Phillips, L. J., McGorry, P. D., Garner, B., Thompson, K. N., Pantelis, C., Wood, S. J., et al. (2006). Stress, the hippocampus and the hypothalamic-pituitary-adrenal axis: implications for the development of psychotic disorders. *Aust N Z J Psychiatry, 40*(9), 725-741.

Polich, J. (2007). Updating P300: an integrative theory of P3a and P3b. *Clin Neurophysiol, 118*(10), 2128-2148.

Puig, O., Penades, R., Gasto, C., Catalan, R., Torres, A., & Salamero, M. (2008). Verbal memory, negative symptomatology and prediction of psychosocial functioning in schizophrenia. *Psychiatry Res, 158*(1), 11-17.

Pukrop, R., Ruhrmann, S., Schultze-Lutter, F., Bechdolf, A., Brockhaus-Dumke, A., & Klosterkotter, J. (2007). Neurocognitive indicators for a conversion to psychosis: comparison of patients in a potentially initial prodromal state who did or did not convert to a psychosis. *Schizophr Res, 92*(1-3), 116-125.

Rapoport, J. L., Addington, A. M., Frangou, S., & Psych, M. R. (2005). The neurodevelopmental model of schizophrenia: update 2005. *Mol Psychiatry, 10*(5), 434-449.

Rasser, P. E., Schall, U., Todd, J., Michie, P. T., Ward, P. B., Johnston, P., et al. (2009). Gray Matter Deficits, Mismatch Negativity, and Outcomes in Schizophrenia. *Schizophr Bull*.

Roach, B. J., & Mathalon, D. H. (2008). Event-related EEG time-frequency analysis: an overview of measures and an analysis of early gamma band phase locking in schizophrenia. *Schizophr Bull, 34*(5), 907-926.

Rosburg, T., Marinou, V., Haueisen, J., Smesny, S., & Sauer, H. (2004). Effects of lorazepam on the neuromagnetic mismatch negativity (MMNm) and auditory evoked field component N100m. *Neuropsychopharmacology, 29*(9), 1723-1733.

Rund, B. R. (2009). Is schizophrenia a neurodegenerative disorder? *Nord J Psychiatry, 63*(3), 196-201.

Rund, B. R., Landro, N. I., & Orbeck, A. L. (1997). Stability in cognitive dysfunctions in schizophrenic patients. *Psychiatry Res, 69*(2-3), 131-141.

Salisbury, D. F., Kuroki, N., Kasai, K., Shenton, M. E., & McCarley, R. W. (2007). Progressive and interrelated functional and structural evidence of post-onset brain reduction in schizophrenia. *Arch Gen Psychiatry, 64*(5), 521-529.

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

Schall, U., Catts, S. V., Chaturvedi, S., Liebert, B., Redenbach, J., Karayanidis, F., et al. (1998). The effect of clozapine therapy on frontal lobe dysfunction in schizophrenia: neuropsychology and event-related potential measures. *Int J Neuropsychopharmacol, 1*(1), 19-29.

Schall, U., Catts, S. V., Karayanidis, F., & Ward, P. B. (1999). Auditory event-related potential indices of fronto-temporal information processing in schizophrenia syndromes: valid outcome prediction of clozapine therapy in a three-year follow-up. *Int J Neuropsychopharmacol, 2*(2), 83-93.

Schiffman, J., Lam, C. W., Jiwatram, T., Ekstrom, M., Sorensen, H., & Mednick, S. (2004). Perspective-taking deficits in people with schizophrenia spectrum disorders: a prospective investigation. *Psychol Med, 34*(8), 1581-1586.

Schofield, T. M., Iverson, P., Kiebel, S. J., Stephan, K. E., Kilner, J. M., Friston, K. J., et al. (2009). Changing meaning causes coupling changes within higher levels of the cortical hierarchy. *Proc Natl Acad Sci U S A, 106*(28), 11765-11770.

Schreiber, H., Stolz-Born, G., Kornhuber, H. H., & Born, J. (1992). Event-related potential correlates of impaired selective attention in children at high risk for schizophrenia. *Biol Psychiatry, 32*(8), 634-651.

Schroger, E. (1997). On the detection of auditory deviations: a pre-attentive activation model. *Psychophysiology, 34*(3), 245-257.

Sculthorpe, L. D., Ouellet, D. R., & Campbell, K. B. (2009). MMN elicitation during natural sleep to violations of an auditory pattern. *Brain Res, 1290*, 52-62.

Seeber, K., & Cadenhead, K. S. (2005). How does studying schizotypal personality disorder inform us about the prodrome of schizophrenia? *Curr Psychiatry Rep, 7*(1), 41-50.

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

Stephan, K. E., Baldeweg, T., & Friston, K. J. (2006). Synaptic plasticity and dysconnection in schizophrenia. *Biol Psychiatry, 59*(10), 929-939.

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *J Int Neuropsychol Soc, 8*(3), 448-460.

Stone, J. M., Day, F., Tsagaraki, H., Valli, I., McLean, M. A., Lythgoe, D. J., et al. (2009). Glutamate Dysfunction in People with Prodromal Symptoms of Psychosis: Relationship to Gray Matter Volume. *Biol Psychiatry*.

Strelnikov, K. (2007). Can mismatch negativity be linked to synaptic processes? A glutamatergic approach to deviance detection. *Brain Cogn, 65*(3), 244-251.

Sun, D., Phillips, L., Velakoulis, D., Yung, A., McGorry, P. D., Wood, S. J., et al. (2009). Progressive brain structural changes mapped as psychosis develops in 'at risk' individuals. *Schizophr Res, 108*(1-3), 85-92.

Sun, D., van Erp, T. G., Thompson, P. M., Bearden, C. E., Daley, M., Kushan, L., et al. (2009). Elucidating a Magnetic Resonance Imaging-Based Neuroanatomic Biomarker for Psychosis: Classification Analysis Using Probabilistic Brain Atlas and Machine Learning Algorithms. *Biol Psychiatry*.

Toyomaki, A., Kusumi, I., Matsuyama, T., Kako, Y., Ito, K., & Koyama, T. (2008). Tone duration mismatch negativity deficits predict impairment of executive function in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry, 32*(1), 95-99.

Turetsky, B. I., & Fein, G. (2002). Alpha2-noradrenergic effects on ERP and behavioral indices of auditory information processing. *Psychophysiology, 39*(2), 147-157.

Umbricht, D., Javitt, D., Novak, G., Bates, J., Pollack, S., Lieberman, J., et al. (1998). Effects of clozapine on auditory event-related potentials in schizophrenia. *Biol Psychiatry, 44*(8), 716-725.

Umbricht, D., Javitt, D., Novak, G., Bates, J., Pollack, S., Lieberman, J., et al. (1999). Effects of risperidone on auditory event-related potentials in schizophrenia. *Int J Neuropsychopharmacol, 2*(4), 299-304.

Umbricht, D., Koller, R., Schmid, L., Skrabo, A., Grubel, C., Huber, T., et al. (2003). How specific are deficits in mismatch negativity generation to schizophrenia? *Biol Psychiatry, 53*(12), 1120-1131.

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

Umbricht, D., Vollenweider, F. X., Schmid, L., Grubel, C., Skrabo, A., Huber, T., et al. (2003). Effects of the 5-HT2A agonist psilocybin on mismatch negativity generation and AX-

continuous performance task: implications for the neuropharmacology of cognitive deficits in schizophrenia. *Neuropsychopharmacology, 28*(1), 170-181.

Umbricht, D., Bates, J. A., Lieberman, J. A., Kane, J. M., & Javitt, D. C. (2006). Electrophysiological indices of automatic and controlled auditory information processing in first-episode, recent-onset and chronic schizophrenia. *Biol Psychiatry, 59*(8), 762-772.

Valkonen-Korhonen, M., Purhonen, M., Tarkka, I. M., Sipila, P., Partanen, J., Karhu, J., et al. (2003). Altered auditory processing in acutely psychotic never-medicated first-episode patients. *Brain Res Cogn Brain Res, 17*(3), 747-758.

Walker, E. F., & Diforio, D. (1997). Schizophrenia: a neural diathesis-stress model. *Psychol Rev, 104*(4), 667-685.

Walker, E. F., Savoie, T., & Davis, D. (1994). Neuromotor precursors of schizophrenia. *Schizophr Bull, 20*(3), 441-451.

Walterfang, M., McGuire, P. K., Yung, A. R., Phillips, L. J., Velakoulis, D., Wood, S. J., et al. (2008). White matter volume changes in people who develop psychosis. *Br J Psychiatry, 193*(3), 210-215.

Weissman, M. M., & et al. (1978). Social Adjustment by Self-Report in A Community Sample and in Psychiatric Outpatients. *Journal of Nervous & Mental Disease, 166*(5).

Wood, S. J., Pantelis, C., Proffitt, T., Phillips, L. J., Stuart, G. W., Buchanan, J. A., et al. (2003). Spatial working memory ability is a marker of risk-for-psychosis. *Psychol Med, 33*(7), 1239-1247.

Wood, S. J., Pantelis, C., Velakoulis, D., Yucel, M., Fornito, A., & McGorry, P. D. (2008). Progressive changes in the development toward schizophrenia: studies in subjects at increased symptomatic risk. *Schizophr Bull, 34*(2), 322-329.

Youn, T., Park, H. J., Kim, J. J., Kim, M. S., & Kwon, J. S. (2003). Altered hemispheric asymmetry and positive symptoms in schizophrenia: equivalent current dipole of auditory mismatch negativity. *Schizophr Res, 59*(2-3), 253-260.

Yung, A. R., & McGorry, P. D. (1996). The prodromal phase of first-episode psychosis: Past and current conceptualizations. *Schizophrenia Bulletin, 22*(2), 353-370.

Yung, A. R., Yuen, H. P., McGorry, P. D., Phillips, L. J., Kelly, D., Dell'Olio, M., et al. (2005). Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. *Aust N Z J Psychiatry, 39*(11-12), 964-971.