DIFFERENTIAL RELATIONSHIPS OF MISMATCH NEGATIVITY AND VISUAL P1 DEFICITS TO PREMORBID CHARACTERISTICS AND FUNCTIONAL OUTCOME IN SCHIZOPHRENIA

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Abstract

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Sensory deficits have been consistently observed in patients with schizophrenia, and previous studies have explored relationships between either auditory or visual deficits and various clinical characteristics and patients' global functioning. The present dissertation is the first to assess with EEG both auditory and visual deficits in the same patient sample and to relate each type of deficit to symptoms, present functioning, and premorbid functioning. The first study assessed visual deficits associated with schizophrenia during the concurrent presentation of auditory and visual stimuli. Patients with schizophrenia and healthy controls were presented with both parvocellularly-biased and magnocellularly-biased stimuli while passively listening to an auditory paradigm intended to elicit mismatch negativity responses. By comparing the present visual results to those of a very similar study, which included different visual stimuli, we underscore the importance of utilizing appropriate stimuli in assessing visual deficits in patients with schizophrenia. The purpose of the second study was to assess auditory deficits associated with schizophrenia. Duration, frequency, and intensity deviants were embedded in the auditory mismatch negativity paradigm to which the participants listened during the visual task. Mismatch negativity deficits were assessed, relative to each of the three deviants. We demonstrate that the mismatch negativity results are characteristic of patients with schizophrenia, regardless of the

simultaneous visual task in which the participants are engaging. The third study relates the findings of the auditory and visual deficits in patients with schizophrenia to clinical characteristics, including symptoms, present, and premorbid functioning. Differential relationships suggest that different underlying pathophysiological mechanisms may account for impaired visual and auditory neurophysiological dysfunction. This knowledge could help in the treatment and management of schizophrenia.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

GENERAL INTRODUCTION

In a textbook designed for students and physicians, Kraepelin, a psychiatrist, described "dementia praecox" as a syndrome, which, although highly heterogeneous in presentation, seemed to have certain common symptoms. The common symptoms included cognitive and executive dysfunction, which continued to decline until a "terminal state" was reached. He used the name "dementia praecox" (translated from German as "precocious dementia"), as the condition was observed in younger adults, unlike Alzheimer's disease, which is typically seen in the elderly. Because, aside from the cognitive and executive dysfunction, the rest of the symptoms, such as hallucinations and delusions, were so varied in presentation, he determined that there were likely several forms of the disorder. Kraepelin did not strongly consider the etiology of "dementia praecox"; rather, his focus was on clinical observations (Kraepelin, 1899).

Bleuler later introduced the name "schizophrenia," literally meaning "splitting of the mind" that is used today. He further refined the conceptualization of the syndrome by referring to "basic" symptoms and "accessory" symptoms. He considered the basic symptoms to be what today are considered the negative and cognitive symptoms (described below) and the accessory symptoms to be the positive ones. Bleuler was also convinced that schizophrenia was really several diseases, since the etiology was unknown and unaccounted for. The unifying factor was the presence of the basic symptoms. Bleuler also disagreed with the inevitable "terminal state" following progressive mental deterioration to which Kraeplin referred, arguing that some cases involved recovery (Bleuler, 1920).

Jablensky (Jablensky, 2010) reviewed the history of the progression of schizophrenia. He concluded that despite the years of research and hundreds of research articles published on areas of schizophrenia, the etiology still remains unsure. His suggestion for future research was to focus on relating clinical symptoms to different areas of brain dysfunction associated with schizophrenia to eventually gain a better understanding of the true source of schizophrenia (Jablensky, 2010). That is the general aim of the present dissertation. By assessing both the auditory and visual deficits associated with schizophrenia in the same patient sample and relating each individually to clinical characteristics, such as symptoms, premorbid functioning, and global functioning, the goal was to learn more about schizophrenia and its etiology.

Schizophrenia Background

Schizophrenia affects approximately 1% of the population (Saha, Chant, Welham, & McGrath, 2005). The onset is typically in young adulthood; patients rarely experience a first episode before adolescence or after middle age. Men usually experience the initial onset at a younger age than women (Howard, Rabins, Seeman, & Jeste, 2000), but by the end of the risk period, both men and women are equally affected (Leung & Chue, 2000).

Patients with schizophrenia suffer from difficulties in many areas, from early sensory processing (Javitt, 2009a) to higher-order cognitive functioning (Dickinson, Ramsey, & Gold, 2007; Heaton et al., 2001; Heinrichs & Zakzanis, 1998). They often experience difficulty with independent living, functioning at work, or engaging in social interactions (Wynn, Sugar, Horan, Kern, & Green, 2010).

Schizophrenia Symptoms

Schizophrenia is associated with three basic clusters of symptoms, including positive, negative, and cognitive symptoms. Positive symptoms refer to when the patient experiences an altered reality and include symptoms such as hallucinations, delusions, and agitation. Negative symptoms refer to when the patients' experiences are diminished and include symptoms such as blunted affect, lack of motivation to do even the most basic things, and withdrawal. Finally, cognitive symptoms include abstract thinking, looseness of association, and difficulty concentrating, among other difficulties (A. Association, 2000). Schizophrenia presents heterogeneously, with varying degrees of severity and varying symptoms from individual to individual (Peralta & Cuesta, 2001).

Cognitive Dysfunction

Cognitive deficits associated with schizophrenia refer to deficits with information processing. As mentioned above, they manifest in a variety of ways, and have been identified in nearly every cognitive function, from sensory processing, which will be discussed further below, to early attention (indexed, for example, by the P300 potentials), to higher levels of cognition. The higher levels include, but are not limited to attention, working memory, and problem solving (Dickinson & Harvey, 2009). Not only are deficits present in many domains of cognition, but they are present in patients at all stages of the disease. They are observed at the patient's first episode (Censits, Ragland, Gur, & Gur, 1997; Mohamed, Paulsen, O'Leary, Arndt, & Andreasen, 1999; E. M. Riley et al., 2000; Saykin et al., 1994; Schuepbach, Keshavan, Kmiec, & Sweeney, 2002; Townsend, Malla, & Norman, 2001) and their severity tends to remain fairly constant until the patient reaches approximately 65 years old (Albus et al., 2002; Hughes et al., 2003).

Although the general population is most likely to associate schizophrenia with positive symptoms, since they are the most overt to others, the negative and cognitive symptoms should not be underestimated in their effects on the patients. More and more, research is demonstrating that the cognitive symptoms are a core feature of schizophrenia and have a profound effect on individuals' abilities to engage in daily life and function overall (Green, Kern, & Heaton, 2004).

Neurochemical Models of Schizophrenia

There are two basic approaches to the underlying neurochemical basis of schizophrenia. The earlier approach is often referred to as the dopamine or localized model. Essentially, this approach attributes schizophrenia to excessive dopaminergic activity in the brain (Sayed & Garrison, 1983). For decades, this was the dominant approach. It was largely accepted because it was supported by what seemed to be convincing evidence. Dopaminergic agents, such as amphetamine, administered to healthy controls could induce the positive symptoms generally exhibited by patients with schizophrenia (i.e. hallucinations and delusions). Further, dopaminergic antagonists could reverse those symptoms. However, there remain several problems with the dopaminergic model of schizophrenia.

The first glaring problem is that although amphetamine was able to reproduce the positive symptoms, patients with schizophrenia suffer from negative and cognitive symptoms, as well, both of which are debilitating and important to consider. The dopaminergic agents were unable to reproduce those types of symptoms. It is hard to accept a model of schizophrenia that does not account for the disease as a whole, but can only explain certain parts of it.

Another problem with the dopaminergic/localized model is that dopamine is only found in specific areas of the brain, mostly in the frontal and limbic brain regions. However, as described above, schizophrenia affects many different parts of the brain, much more than just the frontal and limbic regions. The sensory deficits, for example, could not be explained by the localized model, nor could other forms of cognitive dysfunction associated with schizophrenia.

Researchers considered dysfunction of transmission of the neurotransmitter glutamate as a possible underlying cause of deficits associated with schizophrenia after it was shown that phencyclidine (PCP) could induce behaviors similar to those seen in patients with schizophrenia. This effect was achieved by blockage of the N-methyl-D-aspartate-type glutamate receptors (NMDAR) (Javitt, 1987). Unlike the dopaminergic agents, which were unable to reproduce the negative and cognitive schizophrenic symptoms, NMDAR antagonists, such as ketamine and PCP, were able to simulate all the different types of symptoms, including positive, negative, and cognitive (Javitt & Zukin, 1991). When ketamine was administered to both animals and humans, it reproduced the dopaminergic deficits in a manner similar to that seen in schizophrenia. This suggests that the dopaminergic deficits might be "downstream" to underlying disturbances in glutamatergic function (Javitt, 2007).

The glutamatergic model of schizophrenia is supported by the diffused nature of the disease. Unlike dopamine, which is localized to very specific areas of the brain, glutamate is present throughout the cerebral cortex. It is the main excitatory neurotransmitter in humans and is utilized by approximately 60% of the neurons in the brain (Nieuwenhuys, 1994). Because it is involved in most of the activity in the cortex, and because schizophrenia effects are present throughout the brain, glutamate dysfunction is a likely candidate for the symptoms of

schizophrenia. Studies have pointed even more specifically to the NMDA (N-methyl-D-aspartate)-type glutamate receptors (Javitt, 2007).

Method for Assessing Symptoms in Schizophrenia

The PANSS (the Positive and Negative Syndrome Scale) is the most commonly used tool to measure patients' symptom severity (Kay, Fiszbein, & Opler, 1987; Van den Oord et al., 2006). Trained clinicians use a scale to rate each patient on each item (symptom) from 1-7. 1=absent, 2=minimal, 3=mild, 4=moderate, 5=moderate severe, 6=severe, and 7=extreme (Kay et al., 1987).

Studies have shown it to have very good internal reliability, construct validity, and to be sensitive to change. An item response analysis demonstrated that the five factor PANSS is overall very good at assessing patients' symptoms' severity levels, though some items were better than others (Santor, Ascher-Svanum, Lindenmayer, & Obenchain, 2007).

Methods for Assessing Global Functioning in Schizophrenia

Schizophrenia can be so debilitating that the patients often have difficulty engaging in basic daily functioning. Many patients with schizophrenia are forced to move to special residential facilities, while others manage to live in their own homes, with varying degrees of assistance.

Several tools were created to assess patients' functional abilities. These include the Independent Living Scales (ILS) (Loeb, 1996) and the Global Assessment of Functioning (GAF) (A. Association, 2000), both of which were used for the present dissertation.

Independent Living Scale

The ILS was originally designed to determine the level of supervision needed for individuals with dementia who were in a residential facility, based on their cognitive skills. Essentially, it assesses the individual's ability to engage in daily activities and to care of him or herself. It assesses how well the patient is likely to succeed living independently. This tool has been shown to be reliable and valid for use with patients with schizophrenia (Revheim & Medalia, 2004).

The ILS (Loeb, 1996) includes five subscales and two factor-analyzed subscales, which comprise 70 items. The five subscales include: (1) memory orientation, (2) managing money, (3) managing home and transportation, (4) health and safety, and (5) social adjustment. Of the two factor subscales, the present study focused on the problem-solving factor subscale (ILS-PB) rather than the performance information factor. It includes 33 items across all subscales, assesses the patient's reasoning skills for engaging in daily living, and takes approximately 20-25 minutes to administer. An example of a question from the ILS-PB might be: "What would you do if your lights and television went out simultaneously?" The patient would need to demonstrate that s/he would take a logical course of action.

Green et al. (2011) demonstrated that the ILS-PB serves as a proxy measure for "functionally meaningful" cognition in schizophrenia by correlating it with the MATRICS Consensus cognitive battery MCCB), a measure of cognitive performance. The ILS-PB and the MCCB had 26% shared variance (Green et al., 2011).

Global Assessment of Functioning

The GAF (A. Association, 2000) was designed to assess psychiatric patients' overall psychosocial functioning in both outpatients and inpatients. It is administered by a trained clinician, and includes 10 mini-scales that assess different areas of functioning, such as psychological and social. The clinician scores the patient 0-10 on each mini-scale and adds them all up. The overall score could be anywhere from 1-100 with 100 being the highest level of functioning and 1 the lowest. The scores are generally based on an interview and mental status exam, but assigning the actual score on the GAF usually only requires about 5-15 minutes (Liberman et al., 1998). It has been shown to be reliable in patients with schizophrenia (Startup, Jackson, & Bendix, 2002). The validity of the GAF used for functional status is somewhat mixed, and some researchers argue that it may correlate more strongly with clinical symptoms than functioning (Mausbach, Moore, Bowie, Cardenas, & Patterson, 2009). However, it is a very commonly used scale for assessing functioning and is therefore used for the present study.

Sensory Dysfunction

Prior to the early 1960s, minimal to no attention was paid to schizophrenic patients' sensory function. However, researchers began to document patients' reports of sensory distortions (McGhie & Chapman, 1961) and later technology was utilized to explore sensory dysfunction in patients with schizophrenia more objectively (Adler et al., 1982; Holzman, 1972; Saccuzzo & Braff, 1981). ERPs and fMRI have since been used in many studies to demonstrate visual and auditory deficits. ERPs are very useful for studying patients' early responses, since they have excellent temporal resolution; and fMRIs are used for their spatial resolution, to pinpoint locations in the brain involved in the different responses (Javitt, 2009a).

Although all of schizophrenic patients' senses have been shown to be affected by the disease, even including olfactory (Atanasova et al., 2008; Moberg et al., 1999) and somatosensory systems (Javitt, Liederman, Cienfuegos, & Shelley, 1999), the auditory and visual systems have been studied much more extensively. The present paper focuses on the electrophysiological measures of auditory mismatch negativity (MMN) and of the early visual ERP component P1.

Methods for Assessment of Auditory Dysfunction in Schizophrenia

The Auditory System

The ear consists of three distinct parts: the outer ear (pinna), the middle ear, and the inner ear. The outer ear helps to determine the origin or location of the sound by reflecting and attenuating the sound waves when they hit the pinna, which are the folds of cartilage surrounding the ear canal. The sound then travels down the auditory canal, where it is amplified. The middle ear includes the ear drum and the tiny bones adjacent to it called ossicles. The ossicles attach to the cochlea, which is part of the inner ear. The basilar membrane runs down the center of the cochlea and supports the Organ of Corti.

Vibrations transmit from the ear drum through the ossicles to the cochlea. The ossicles amplify the sound pressure from the ear drum before the sound enters the cochlea. There, they are converted from mechanical displacement into electrochemical signals via hair cells of the Organ of Corti. Primary sensory neurons in the spinal ganglion send their axons into the cochlear part of the eight cranial nerve to reach the cochlear nuclei. The pathway then bifurcates through the brainstem and travels to the inferior colliculi of the midbrain, the thalamus (specifically the

medial geniculate nuclei), and ultimately the primary auditory cortex, which lies on Heschl's gyri.

Mismatch Negativity (MMN)

The auditory MMN is an event-related potential that is generated within the primary auditory cortex when a stimulus does not match the stimuli produced in the recent past (Javitt, Steinschneider, Schroeder, & Arezzo, 1996; Naatanen, 1995). The mismatch negativity response represents a form of echoic memory. The individual compares the stimulus presented with the memory trace of the previous stimuli presented and if it is different in any way, it generates a different waveform (Naatanen, Jacobsen, & Winkler, 2005).

Naatanen et al. (Naatanen et al., 2005) reviews several pieces of evidence in support of the concept that MMN reflects a memory trace. First, the MMN does not follow the first stimulus presented in a sequence (Cowan, Winkler, Teder, & Naatanen, 1993; Sams, Hamalainen et al., 1985), nor does it appear following stimuli with very long inter-stimulus intervals (ISIs) (Sokolov, Spinks, Naatanen, & Lyytinen, 2002). This demonstrates that it is not that the MMN is in response to a particular tone, but rather in response to a tone relative to other tones. A second piece of evidence that the MMN reflects a comparison process and is not simply a different response to a different stimulus is that the MMN can be elicited by reduced stimulus duration (Kaukoranta, Sams, Hari, Hamalainen, & Naatanen, 1989; Naatanen, Paavilainen, & Reinikainen, 1989; Paavilainen, Alho, Reinikainen, Sams, & Naatanen, 1991), ISI (Ford & Hillyard, 1981; Hari et al., 1989; Naatanen, Jiang, Lavikainen, Reinikainen, & Paavilainen, 1993; Nordby, Roth, & Pfefferbaum, 1988; Russeler, Altenmuller, Nager, Kohlmetz, & Munte, 2001), or stimulus intensity. Those MMNs, which are longer and larger, could not reflect a fresh

neuronal population. Third, the MMN responds differently than afferent responses to the administration of NMDAR antagonists; therefore, it is different from an afferent response (Javitt et al., 1996). Fourth, the MMN, unlike the N1, an afferent response, can be observed in utero (Draganova et al., 2005; Huotilainen et al., 2005) and in newborns (Alho, Sainio, Sajaniemi, Reinikainen, & Naatanen, 1990). Among other arguments, Naatanen also provides the difference in the MMN and N1 generators and the fact that the generators underlying the MMN activity are similar to the generators activated when certain cognitive tasks relating to memory as support for the memory trace argument (Naatanen et al., 2005; Pulvermuller & Shtyrov, 2006).

Several studies have demonstrated that N1 and MMN have differences generators. Scherg used dipole mapping to explore the generators of different auditory components and found that the N1 generator was posterior to the MMN generator, though both on the supratemporal plane (Scherg, Vajsar, & Picton, 1989). He repeated the analysis two years later with the same results (Scherg & Berg, 1991). Sams et al. also sought to distinguish between the sources for the N1 and the MMN, since the N1 can sometimes overlap with MMN and be elicited in response to similar stimuli. Using magnetoencephalography (MEG) with seven healthy subjects, the researchers were able to tease apart the sources of the two different components. Similar to Scherg et al.'s findings, they confirmed that both the MMN and the N1 were generated in the supratemporal cortex, but that the N1 source was posterior to that of MMN (Sams, Kaukoranta, Hamalainen, & Naatanen, 1991).

The "mismatch" could be in a variety of ways. For example, the stimulus could be deviant in duration (Shelley et al., 1991), frequency (Javitt, Doneshka, Zylberman, Ritter, & Vaughan, 1993), or intensity. It could also deviate in other ways, such as location or from other

abstract rules (Bendixen, Prinz, Horvath, Trujillo-Barreto, & Schroger, 2008; Schroger & Wolff, 1996). The present study included duration, frequency, and intensity deviants to elicit mismatch negativity. Those specific deviants were selected because they (especially duration and frequency) have been established in the literature as eliciting robust MMN responses (Umbricht & Krljes, 2005).

Schroger argued that it is not necessary to have a random order of deviants to produce MMN. Whether the standards and deviants are presented in a random or fixed order should not affect the mismatch negativity (Schroger, 1998). He provided specific examples of studies in which fixed order paradigms were used and mismatch negativity was unaffected. Scherg et al. served as an early example of researchers who used a fixed order paradigm. In their paradigm, every fifth stimulus was a deviant, and MMN was still observed and unimpaired, relative to studies in which a random order was used (Scherg et al., 1989). As will be mentioned below, the present study utilized a paradigm which included a fixed order presentation of the deviants. This purpose of this was to eliminate the possibility of a confounding p3a, which generally appears in response to random, task-irrelevant infrequent deviant stimuli (Ford & Hillyard, 1981; Ford, Roth, & Kopell, 1976).

Importantly, the MMN is produced pre-attentively, i.e. attention is not required to elicit the MMN (Kane, Curry, Butler, & Cummins, 1993; Paavilainen, Simola, Jaramillo, Naatanen, & Winkler, 2001). In fact, it can sometimes be confounding, since other components, such as the N200 (Naatanen & Gaillard, 1983) or P300, can appear during attention that involves focused attention. MMN can be elicited even if the subject is not consciously aware of the stimuli

presented. For example, as mentioned above, the MMN can be generated in sleeping babies (Cheour-Luhtanen et al., 1996) and even some people in a coma (Fischer et al., 1999).

Because it is best if the MMN is produced without attention to the auditory input and it is still elicited when engaging in another task (Alho, Woods, & Algazi, 1994; Woldorff, Hillyard, Gallen, Hampson, & Bloom, 1998), subjects are generally instructed to engage in a separate "distracting" visual activity simultaneously. For example, the subject is usually given headphones, from which the standard (significant majority of the tones) and deviant tones are emitted, and is given a silent movie to watch, books to read, or a visual discrimination task to accomplish (as was the case for this project) at the same time. That helps to ensure that the subject will not be focusing on the auditory stimuli and that the MMN will indeed be obtained pre-attentively.

The MMN is a difference waveform created from subtracting the standard response waveform from the deviant response waveform. It is possible and often best to use an optimized design for the MMN paradigm, in which several deviants are included. For example, one tone (the standard) would be presented the vast majority of the time, and at different points, duration, frequency, and intensity deviants would each be presented. Upon analysis, it would be possible to get an MMN waveform for each of the deviants by subtracting each type of deviant waveform from the standard separately (Todd et al., 2008). It is important because different deviants may be sensitive to different conditions. Furthermore, Umbricht et al. discovered in their meta-analysis that certain deviants are more deficient in patients with schizophrenia than others. For example, they found that the effect size of the duration deviant was 40% greater than that of the frequency deviant (Umbricht & Krljes, 2005).

The MMN latency is approximately 100-250 ms from change onset (Sams, Paavilainen, Alho, & Naatanen, 1985). However, it varies based on the type of deviant. The MMN for the duration deviant generally occurs significantly later than that for the intensity or frequency, simply because the subject needs to have heard the entire length of the stimulus to detect that it is different from the standard.

MMN and Schizophrenia

In schizophenia, deficits in the auditory system are observed both in behavioral tasks, such as difficulty in matching tones following a brief delay (Holcomb et al., 1995; Strous, Cowan, Ritter, & Javitt, 1995) and in the generation of ERPs, such as MMN (Javitt et al., 1993; Shelley et al., 1991; D. S. Umbricht, J. A. Bates, J. A. Lieberman, J. M. Kane, & D. C. Javitt, 2006). A meta-analysis (Umbricht & Krljes, 2005) revealed a particularly strong effect size of .99 for MMN deficits in patients with chronic schizophrenia.

Although attenuated MMNs can be exhibited by patients with other neurological conditions, there is a pattern of MMN deficits that is specific to schizophrenia (Javitt, Grochowski, Shelley, & Ritter, 1998). For example, patients with Alzheimer's disease exhibit reduced MMNs with longer inter-stimulus intervals (3 seconds), but they exhibit normal MMNs at shorter ISIs (Pekkonen, Jousmaki, Kononen, Reinikainen, & Partanen, 1994). MMN in patients with schizophrenia is unaffected by ISI (Javitt, Strous, Grochowski, Ritter, & Cowan, 1997). Stroke patients also exhibit reduced MMNs, under certain conditions, but, unlike patients with schizophrenia, the reduced MMNs are generally accompanied by increased P1s (Alho, Woods, Algazi, Knight, & Naatanen, 1994). Alcohol-intoxicated individuals also exhibit reduced MMNs, but they are not accompanied by attention-dependent component reductions (P3, for

example) (Jaaskelainen et al., 1995), as is the case in schizophrenia, nor are they accompanied by deficits in tone matching or reaction times, as they are in patients with schizophrenia. MMN deficits have not been observed in patients with other types of psychiatric disorders, such as bipolar disorder or major depression (Catts et al., 1995; Umbricht et al., 2003).

MMN has been linked to structural (Rasser et al., 2011; Salisbury, Kuroki, Kasai, Shenton, & McCarley, 2007; Salisbury, Shenton, Griggs, Bonner-Jackson, & McCarley, 2002) and functional (Javitt, 2000; Javitt et al., 1996) impairment within the auditory sensory cortex. In addition, as mentioned above, deficits have been linked to impaired tone matching ability (Javitt, Shelley, & Ritter, 2000; Todd, Michie, & Jablensky, 2003), which, in turn, correlates with impairments in processes such as auditory emotion recognition (Leitman, Laukka et al., 2010) or attentional allocation (Leitman, Laukka et al., 2010; Leitman, Sehatpour et al., 2010). Correlations with persistent negative and cognitive symptoms (Kiang et al., 2007; Turetsky, Bilker, Siegel, Kohler, & Gur, 2009; Umbricht & Krljes, 2005) in schizophrenia, and impaired social and global function in both schizophrenia patients (Light & Braff, 2005; Wynn et al., 2010) and normal controls (Light, Swerdlow, & Braff, 2007) have also been reported. Thus, MMN appears to index neural processes critical for psychosocial success across diagnostic groups.

Methods for Assessment of Visual Dysfunction in Schizophrenia

The Visual System

An image enters the eye through the lens and forms an image on the retina. The area of the visual field where light causes excitation or inhibition of a cell is the receptive field.

Photoreceptors (cones or rods) in the retina respond to light in their receptive fields and form excitatory or inhibitory synapses onto bipolar cells. Bipolar cells synapse onto ganglion cells, whose axons are sent into the optic nerve. Two dominant types of retinal ganglion cells are M cells and P cells. M cells have large diameter fibers and project to the magnocellular layers of the lateral geniculate nucleus (LGN) of the thalamus, while P cells have smaller receptive fields and project to the parvocellular layers of the LGN of the thalamus. The magnocellular and parvocellular systems comprise the subcortical level of the visual system and project to the dorsal and ventral streams of the cortex. The magnocellular system relays information more quickly to the cortex, but the information relayed tends to be of lower resolution and with minimal detail (Norman, 2002). Essentially, the magnocellular system works to direct the individual's attention to the object on a global level, to see the whole object, albeit somewhat superficially at first. The parvocellular system supplements the magnocellular system. Once the latter directs the viewer's attention to the object and allows the viewer to determine what the object is, the former enables the person to see the item more closely and in more depth. It enables the individual to see the details, including the color, of the object. Although the parvocellular system relays the information more slowly to the cortex and only engages limited portions of the object at a time, the resolution is very high. The interaction of the magnocellular and parvocellular systems is often described as "frame and fill". The magnocellular system frames the object and the parvocellular system fills in the details within the frame (Doniger, Foxe, Murray, Higgins, & Javitt, 2002; Vidyasagar, 1999).

As mentioned above, both the magnocellular and parvocellular pathways begin at the retina. They each project to different layers of the visual cortex (V1) via the LGN. Although the pathways are mostly separate early on, there is some interaction between the two and even more

later on, in the dorsal and ventral streams. The magnocellular neurons project primarily to layers 4Ca and 4B, and from there, projections are sent to the dorsal visual stream, including the middle temporal visual area and the inferior parietal cortex. The parvocellular neurons project primarily to layer 4Cb and superficial layers of V1. From there, projections are sent to the ventral visual stream, including the lateral occipital complex and inferior temporal (Lund, 1973; Merigan & Maunsell, 1993; Schroeder, Mehta, & Givre, 1998).

Because, early on, the magnocellular and parvocellular pathways are, for the most part, separate, it is possible to activate one or the other by presenting stimuli that bias one or the other. For example, presenting low contrast stimuli would mainly activate the magnocellular system; while high contrast stimuli would activate the parvocellular system (Kaplan, 1991; Tootell, Silverman, Hamilton, Switkes, & De Valois, 1988). Spatial frequency is used for this study to activate one or the other. Specifically, the magnocellular system responds to low spatial frequency stimuli (such as stimuli with larger, fewer horizontal lines); while the parvocellular system responds to high frequency stimuli (smaller and more horizontal lines) (Derrington & Lennie, 1984; Tootell et al., 1988). Finally, the parvocellular pathway is engaged by color; while the magnocellular is not (Kaplan, 1991).

Visual P1

Visual evoked potentials (VEPs), i.e. visual event-related potentials, have been used to study visual deficits associated with schizophrenia. When subjects are presented with visual stimuli, a predictable set of components are generated. Certain components of patients with schizophrenia can then be compared with normal controls' to explore schizophrenia-related deficits.

The visual P1 is a positive deflection that generally peaks between approximately 75-100 ms (Murray, Foxe, Higgins, Javitt, & Schroeder, 2001). It has two underlying generators in the brain, one in the dorsolateral cortex, which is driven primarily by the magnocellular system, and one in the ventrolateral cortex, which is driven primarily by the parvocellular system (Di Russo, Martinez, Sereno, Pitzalis, & Hillyard, 2002; Martinez et al., 1999).

Visual P1 and Schizophrenia

Deficits in early visual processing have become increasingly well-documented over the past decade (Butler et al., 2007; Butler et al., 2001; Foxe, Doniger, & Javitt, 2001; Schechter et al., 2005). Studies have explored the visual P1 when elicited by magnocellularly-biased stimuli and the visual P1 when elicited by parvocellularly-biased stimuli and compared the components in patients with schizophrenia and normal controls. Butler et al. utilized luminance contrast to bias towards the different subcortical systems. As discussed above, low luminance contrast tends to activate the magnocellular system, while higher luminance contrast tends to engage the parvocellular system. Patients exhibited reduced responses, relative to controls, from magnocellularly-biased stimuli, and normal responses to parvocellularly-biased stimuli (Butler et al., 2005). Another study examined patients' v. controls' responses to low v. high spatial frequency stimuli. As mentioned above, the former tends to engage the magnocellular system, while the latter engages the parvocellular system. As expected, patients exhibited reduced P1 potentials in response to the low spatial frequency stimuli (Butler et al., 2007). Numerous studies were conducted that led researchers to conclude that schizophrenia was associated with visual deficits mostly related to the magnocellular pathway (Butler & Javitt, 2005; Yeap et al., 2008).

By comparison to MMN, deficits in early visual processing have been observed in unaffected family members of schizophrenia probands (Yeap et al., 2006). Furthermore, within schizophrenia, deficits are not highly linked to symptoms or global outcome, although they are related to specific impairments in more complex forms of cognitive processing including stimulus encoding, perceptual closure (Leitman, Sehatpour et al., 2010), reading (Revheim, Butler et al., 2006), and face emotion recognition (Butler et al., 2009).

Premorbid Function

The present study also examines the relationship between auditory and visual deficits associated with schizophrenia and patients' premorbid functioning. Thus far, no studies have explored the relationship between visual deficits and premorbid function.

MMN and premorbid functioning has been examined. Studies have looked at MMN in patients at different points in the illness. For the most part, researchers have consistently observed reduced MMN in both chronic and recent-onset schizophrenia (Umbricht & Krljes, 2005). However, MMN deficits are variably observed in unaffected family members of schizophrenia probands (Bramon et al., 2004; Jessen et al., 2001; Magno et al., 2008; Michie, Innes-Brown, Todd, & Jablensky, 2002). This may lead to the conclusion that MMN is not present at illness onset and that it develops as the disease progresses (Magno et al., 2008; Salisbury et al., 2007; Salisbury et al., 2002). Interestingly, though, recent studies found that individuals at symptomatic high risk for schizophrenia exhibited reduced MMNs (Brockhaus-Dumke et al., 2005; Shin et al., 2009). This would seem to indicate quite the opposite conclusion: that reduced MMN is inherent and is present prior to illness onset, at least in a subset of patients.

Umbricht et al. conducted a study in which they assessed MMN in three groups of patients: chronic, recent, and first-episode. In the two former groups, MMN was reduced, consistent with prior research. The first-episode group as a whole was not reduced, but the researchers divided the group further, based on premorbid function. Since minimal objective information is available on patients' premorbid function, researchers relied on patients' educational achievements. They ultimately divided the first-episode group into two parts: those with some college (good premorbid function) and those with none (poor premorbid function). They discovered that MMN was reduced in those first-episode patients with poor premorbid function, but not in the good premorbid function group (D. S. Umbricht et al., 2006).

Trait v. State Measures in Schizophrenia

The difference between the MMN and visual P1with respect to unaffected family members relates to the distinction between trait and state measures. Chen et al. neatly summarizes the distinction between the two. A trait marker associated with schizophrenia is generally present prior to the overt onset of symptoms and may play a causal role in the condition. A state marker reflects the manifestation of symptoms at that time. It is useful to distinguish between the two types of measures when attempting to determine the etiology of a disease, since teasing them apart can tell researchers what was there prior to symptoms and may be related to causality (trait markers) and what can definitely not have been a contributing source (state markers)(Chen, Bidwell, & Norton, 2006). Since it has been demonstrated that the visual P1 deficit can be found in unaffected family members, in addition to the patients themselves (Yeap et al., 2006), it is a trait measure. Based on the study by Umbricht et al. that demonstrated that reduced MMN was only found in patients with poor premorbid function (D. S. Umbricht et

al., 2006), it appears that MMN may be a trait marker for that subset of patients, but not for all patients with schizophrenia.

ERPs and Brain Function

The present study utilized event-related potentials (ERPs) to assess the auditory and visual deficits associated with schizophrenia. ERPs involve presenting different stimuli to the subject while running an electroencephalogram (EEG), so that researchers can assess the brain's responses to the stimuli presented. Once the data is collected, the ERPs can be extracted from the EEGs by averaging the EEG activity that followed each of many stimulus repetitions. The EEG is an excellent tool to utilize in cognitive neuroscience research, and especially in patients with schizophrenia. This entirely non-invasive tool involves a generally painless application of electrodes to the subject's head. Many paradigms require no attention. It is also relatively inexpensive to run EEG sessions, relative to running an MRI, for example. The main expense is the initial investment in the lab equipment, but thereafter, running the individual sessions is not too expensive (Light et al., 2010).

ERPs have excellent temporal resolution. This enables researchers to determine when the earliest response to a stimulus occurs. It is possible to study the sensory responses; they generally occur much earlier on than the more complex cognition.

Finally, ERPs can serve as objective, biological measures of cognition. The ability to quantify deficits in patients with schizophrenia can be very useful in clinical research (Javitt, Spencer, Thaker, Winterer, & Hajos, 2008). It is possible to quantify to what extent a particular

drug has an effect on schizophrenia sensory deficits by referring to the average changes in latency and amplitude of the waveforms generated by certain stimuli presented.

Although ERPs are very useful, there are also some limitations, the main one being that EEGs have poor spatial resolution. Determining the neural generators of the components observed can be very difficult to do on EEGs alone; it is often most effective to conduct a cross-study with fMRI. Even with the source analysis that is available today, the signal could have been produced from an infinite number of combinations of sources.

Critical Questions

Both auditory and visual findings have been observed consistently in schizophrenia across patient samples, and have been reported to show differential association with demographic and clinical patient characteristics (Javitt, 2009b). To date, however, the two sets of deficits have yet to be studied within the same patient sample, leaving open interrelationship between measures. For the present dissertation, auditory and visual ERP deficits were assessed simultaneously in a group of chronic, stabilized individuals with schizophrenia v. controls. Relative relationships with symptoms, premorbid function, and functional outcome were also assessed. Specifically, the three primary goals include the following:

Aim 1: To assess visual deficits associated with schizophrenia. Hypothesis: that patients with schizophrenia will generate normal visual C1and P1 amplitudes in response to the high spatial frequency stimuli (those that are parvocellularly-biased). However, in response to the low spatial frequency stimuli (magnocellularly-biased), there will be a marked reduction in the amplitudes, relative to controls.

Aim 2: To assess auditory deficits associated with schizophrenia. Hypothesis: that patients with schizophrenia will exhibit reduced MMN amplitudes to each of three deviant stimuli (including duration, frequency, and intensity deviants) in an oddball paradigm, relative to controls

Aim 3: To assess the differential relationships of auditory and visual ERP measures with symptoms, premorbid function, and functional outcome. Hypothesis: that associations with both premorbid, present functioning, and symptoms will differ. Specifically, within auditory measures, we predict associations not only to premorbid function but also to illness duration and global outcome. In contrast, we predicted that such associations would be absent for visual measures.

Limitations of Previous Studies

Despite the extensive literature on MMN and visual ERP deficits individually, no studies have yet obtained both auditory and visual measures within the same patient samples.

Many studies have included the MMN paradigm, and substantial and interesting research has been published on the topic. However, few studies have included several different types of deviants. This is important, since different deviants have been shown to produce different MMN effects. This indicates a sensitivity of one deviant over another, depending on the circumstances.

Significance of this Thesis

Assessing both auditory and visual modalities in the same patient sample allows for comparison of associations of each modality with demographic and clinical features. Per the hypothesis, if associations with both premorbid and present functioning differ for auditory and visual ERPs, it would suggest differential contribution to disease etiopathogenesis, and hence different utility in the diagnosis, management, and etiological investigation of schizophrenia.

Additionally, the present study utilized an optimized design, including three different types of deviants. This allows for assessing relationships between various deviants and premorbid and present functioning.

Finally, the design used for this dissertation allowed for collection of both auditory and visual data simultaneously, thereby enabling researchers to collect more data in a shorter period of time.

CHAPTER 1

Mismatch negativity (MMN) is an event-related potential that is generated in response to a deviation in a pattern of standard tones (Naatanen, 1979; Naatanen, Gaillard, & Mantysalo, 1978; Naatanen & Michie, 1979). The MMN has been replicated many times in patients with schizophrenia (Javitt, 2009b; Naatanen & Kahkonen, 2009; Umbricht & Krljes, 2005). The deficits have been so consistently observed, that a meta-analysis conducted on 62 studies involving MMN through 2003 reported an effect size of .99 (Umbricht & Krljes, 2005).

The present study involves collection and analysis of data in the auditory and visual domains simultaneously. Alain et al. conducted a study similar to the present one, in which both the auditory and visual stimuli were presented simultaneously and data were analyzed in both domains. The purpose of their study was to assess the MMN outside the focus of attention. For one of the experiments included in their study, researchers instructed patients with schizophrenia and controls to engage in a "challenging" visual discrimination task while ignoring the auditory stimuli. The visual task involved pressing a button each time a set of five thin lines appeared, and the auditory stimuli consisted of a paradigm designed to elicit MMN, utilizing pitch and pattern deviants (Alain et al., 1998).

Alain et al. reported reduced MMN amplitudes in patients following the pitch deviants; however, they found that following the pattern deviants, the patients' and controls' MMN amplitudes were not significantly different. They discredited the theory that patients with schizophrenia have deficits relating to pitch deviants, but have an intact ability to detect patterns, by providing evidence from a second experiment. In a second experiment, when subjects were instructed to actively respond to deviants, including pattern deviants, patients did exhibit a deficit

(Alain et al., 1998). Since amplitudes were only reduced following the pitch deviant, the question remains of whether reduced MMN amplitudes exhibited in the patients can be observed following other deviants while data is being collected for a simultaneous challenging visual task.

Because responses can vary, depending on the deviant, it is important to utilize several deviants. Many previous studies have used only one deviant and have generalized about MMN based on it. Umbricht et al. compared the effect sizes of the duration and frequency deviants in 23 previous studies that included only frequency deviants and 14 studies that included only duration deviants. They found the duration deviant's effect size to be larger, though not statistically significant. Next, the researchers compared three studies that included both frequency and duration deviants (Umbricht & Krljes, 2005).

In one of the studies that included both types of deviants, Javitt et al. assessed MMN in patients with chronic schizophrenia, patients with recent-onset schizophrenia, and controls, while the subjects were engaged in a behavioral task. They reported that MMN amplitudes were reduced in both groups of schizophrenia patients, relative to controls, across both frequency and duration MMN conditions (Javitt, Shelley, Silipo et al., 2000).

Michie et al. also conducted a study that included both duration and frequency deviants. They presented small but discernible frequency deviants, large frequency deviants, and duration deviants to a group of schizophrenia patients and control subjects. The patient group exhibited a significantly reduced MMN to the duration deviants, there was a similar trend for the large frequency deviants, but they did not exhibit significantly reduced MMNs in response to the small frequency deviants (Michie et al., 2000).

The final study included in the meta-analysis for the purpose of distinguishing between the different deviants was originally conducted to assess how specific MMN deficits are to

schizophrenia. Umbricht et al. presented an MMN paradigm that included both frequency and duration deviants to patients with schizophrenia or schizoaffective disorder, patients with bipolar disorder, patients with major depression, and control subjects. Researchers found that only the schizophrenia group exhibited reduced MMNs, relative to the other groups. When analyses were conducted across groups, only MMN to duration was considered significantly reduced. However, more detailed analyses revealed that both duration and frequency deviants elicited reduced MMNs in the schizophrenia patients (Umbricht et al., 2003).

Umbricht et al. also addressed the issue of deviance probability in the MMN paradigm in their meta-analysis. They found that although the results did not reach significance, the smaller the probability of the deviant among the standards, the bigger the effect size of the study. Using two studies that systematically varied the probability of the frequency deviant, they did find a significant correlation between effect size and the probability of the deviant (Umbricht & Krljes, 2005).

Finally, the MMN meta-analysis addressed the issue of the "degree of deviance", i.e. how much the deviant should deviate from the standard to elicit the best MMN response. The results did not reach significance, but an interesting trend did emerge. The researchers found that for the frequency deviant, the studies that used deviants with smaller levels of difference had larger effect sizes. However, for duration, the larger the deviation employed for the study, the greater the effect size (Umbricht & Krljes, 2005).

The present study, utilizing an optimized design, aimed to determine whether the concurrent presentation of both visual and auditory stimuli produced MMN deficits characteristic of patients with schizophrenia following pitch, duration, and intensity deviants. We hypothesized that the present study would demonstrate that the MMN deficits characteristic of patients with

schizophrenia can be observed in all types of deviants while patients are engaged in a challenging task for the purpose of visual data collection. Because the MMN is pre-attentive (Kane et al., 1993; Paavilainen et al., 2001), the visual task should not interfere with the auditory stimuli presentation. In fact, many other MMN studies have intentionally included some kind of visual distraction. Those forms of "distraction" included providing the subject with reading material, like magazines or books, or a silent movie. Some studies have included visual tasks, as well, although not necessarily challenging.

Provided that schizophrenia patients exhibit deficits in response to all three types of deviants, per our hypothesis, this test battery should enable researchers to collect a large amount of data in a short period of time. Efficiency is important, especially when working with certain types of patients, such as those with mental illnesses, or young children, who might have difficulty sitting still for long periods of time. Further, a more efficient paradigm could be useful for any form of ERP research, given that research budgets are often very limited and subjects and technicians are often paid by the hour.

Methods and Materials

Participants: Participants were recruited from inpatient and chronic residential care settings associated with the Nathan Kline Institute (Orangeburg, New York) and from community and staff volunteers. Informed consent was obtained from 26 patients diagnosed with either schizophrenia (n=14) or schizoaffective disorder (n=12) and 19 controls (**Table 1)**. Individuals with organic brain disorders, mental retardation, past drug or alcohol dependence, current drug or alcohol abuse or hearing/vision impairments were excluded. All procedures were approved by

the Nathan Kline Institute Institutional Review Board. All subjects provided written informed consent.

Procedure: During the visual task (see Chapter 1), auditory stimuli were presented passively though headphones and consisted of a sequence of four complex tones (1 standard tone and duration, intensity, and frequency deviants) presented in random order at SOAs of 500-505 ms. The standard stimulus (70% sequential probability) was a harmonic tone composed of three superimposed sinusoids (500, 1000, and 1500 Hz) as suggested by (Zion-Golumbic, Deouell, Whalen, & Bentin, 2007) to maximize MMN amplitude, and was 100 ms in duration, approximately 85 dB, and with 5 ms rise and fall time. Duration, pitch and intensity deviants (10% probability each) were 150 ms in length, 10% lower in pitch, or 10 dB lower in intensity, respectively, relative to standards, each presented with sequential probability of 10%. At the beginning of each run, the first 15 auditory stimuli were standards.

Data Acquisition: Continuous EEG data, along with digital timing tags for both auditory and visual stimuli, were acquired using a 168-channel BioSemi Active II system (BioSemi, Amsterdam, The Netherlands) with custom, evenly spaced electrodes on a cap using standard reference and ground procedures (http://www.biosemi.com/faq/cms&drl.htm). Data were filtered with a zero-phase shift 40 Hz low-pass filter (48 dB/octave). No highpass filter was applied. Epochs (-100 to 750 ms) were created off-line and were baseline-corrected from 80 ms pre-stimulus to 20 ms post-stimulus onset and artifact-rejected at ± 100 μV. Epochs were then averaged off-line for each participant for each stimulus type. Similar numbers of sweeps were included in patient and control averages (**Table 2).** MMN was defined as deviant minus standard difference waves.

ERP Components: Auditory components of interest consisted of MMN to the three deviant types. The latency ranges for the duration, intensity, and frequency deviants were 200-250 ms post-stimulus onset, 140-200 ms, and 100-190 ms, respectively. Amplitudes were measured at frontocentral electrodes relative to average mastoids. For each component, the primary dependent measures were amplitude and latency within pre-specified latency ranges. Amplitudes were determined as peaks within each specified latency window.

Statistical analysis: Repeated measures multivariate analyses of variance (rmMANOVAs) were conducted for amplitude and latency. Deviant type (pitch/duration/intensity) was included as a within-subjects factor. Split-half reliability was computed for key measures using Cronbach's alpha across the 8 separate acquisition runs.

Results

Auditory Analyses:

MMN showed a typical distribution, with peak amplitude at frontocentral electrodes across groups and conditions (**Figure 1**). Patients showed a highly significant reduction in MMN amplitude relative to controls across all deviants ($F(1,43)=14.2$, $p<.0001$), with no significant deviant-type X group interaction ($F(2,42)=1.04$, $p=.36$). Moreover, deficits were significant for each deviant type considered individually (**Figure 2**). Effect size of reduction was somewhat larger for duration ($d=1.29$) and pitch ($d=1.17$) than intensity ($d=.77$) deviants. Split-half reliability across the 8 acquisition runs was similar across deviant types (.92, .90 and .91 for duration, pitch and intensity, respectively).

Average MMN latency was comparable between groups ($F(1,43) = 2.24$; $p = 0.14$) for each deviant type (**Table 3**). For duration deviants, an early MMN component was also observed. Both the amplitude (-2.54 and -4.09 μV for patients and controls, respectively) and the latency (171.67 and 180.19 ms from stimulus onset for patients and controls, respectively) were significantly different across groups. ($t = 3.83$, $p < .0001$ and $t = -2.21$, $p = .03$, respectively)

Medication: No significant relationship with medication dose, as reflected in CPZ equivalents, was observed for any of the experimental measures.

Comment

Per our hypothesis, patients exhibited MMN deficits when presented with all three deviants, including duration, frequency, and intensity. Regardless of the visual task in which the patients were engaging simultaneously during the auditory presentation, they exhibited the deficits characteristic of patients with schizophrenia. Thus, utilizing a paradigm that assesses sensory deficits in two domains simultaneously has been shown to be effective in demonstrating the typical mismatch negativity deficits across deviants in schizophrenia.

CHAPTER 2

For decades, researchers have been reporting reduced visual evoked potentials (VEPs) in patients with schizophrenia. Buchsbaum et al., in an article on event-related potentials and schizophrenia, provided a comprehensive table of eleven visual studies from the mid-1960s to the mid-1970s, the vast majority of which reported reduced components in patients with schizophrenia (Buchsbaum, 1977). Mukundan et al. further supported the concept of attenuated VEPs in patients with schizophrenia. In their experiment, both patients with schizophrenia and normal controls were presented with a series of flashes approximately every 3 seconds and the event-related potentials following them were analyzed in both groups. They reported that the visual P1, among other early components, was significantly reduced in patients with schizophrenia (Mukundan, 1986). Visual evoked potential studies have since multiplied, knowledge about early-stage visual P1 deficits and other early components has advanced tremendously, and the way in which visual experiments are conducted has been refined (Yeap et al., 2008).

The visual P1 is an early positive-deflecting component with peak latency at approximately 100 ms. It can be elicited when subjects are presented with very simple stimuli, such as a set of straight lines or a checkerboard. Previous studies have explored the underlying generators of the evoked response components; however Di Russo et al. conducted one of the most thorough investigations, where he focused on the early components. The researchers included a combination of electrophysiological recordings, source analysis, anatomical MRI scans, and fMRI to probe the sources of the components (Di Russo et al., 2002).

Their first step was to conduct electrophysiological (EEG) recordings while presenting visual stimuli to elicit the visual potentials. Their first improvement over previous studies was to utilize a higher density electrode array of 64 electrodes, so that dipole mapping could be more precise. The stimuli consisted of high spatial frequency checkerboards presented to the subjects at different locations on a screen before them. Di Russo et al. used the EEG data to conduct dipole mapping using Brain Electrical Source Analysis (BESA) (Di Russo et al., 2002).

A subset of the participants who engaged in the VEP experiment also underwent anatomical MRI scans, and a subset of those participants engaged in the fMRI portion of the study. For the fMRI recordings, the same stimuli (with an altered order and duration of presentation) were presented to the subjects while blood oxygen level dependent (BOLD) signals were recorded. The dipoles found from the source analysis were projected onto the anatomical MRI scans and the BOLD signals from the fMRI were used to further localize the source of the early components on the MRI scans (Di Russo et al., 2002).

The C1, the earliest component, typical appears between 40-70 ms following stimulus presentation (Jeffreys & Axford, 1972). Di Russo et al. determined that the C1 generator arose from the primary visual cortex. They concluded that to be the case based on the fact that the C1 reversed polarity for the upper v. lower visual stimulation. This is a feature of the calcarine fissure (Jeffreys & Axford, 1972), which includes the primary visual cortex. Further, the dipole mapping in conjunction with the MRI and fMRI all pointed to a location within V1 for the C1 generator (Di Russo et al., 2002).

The P1 component generally appears following the C1, with a typical onset latency of 65-80 ms following stimulus presentation (V. P. Clark & Hillyard, 1996). Based on the dipole mapping, Di Russo et al. divided the P1 into two phases: an early P1 that was observed from 80-

110 ms following stimulus presentation and a late P1 that was observed between 110-140 ms following stimulus presentation. The early P1 was localized to the areas V3, V3a, and the middle occipital gyrus; while the late P1 was localized to area V4 in the fusiform gyrus (Di Russo et al., 2002).

Although the P1 has been shown repeatedly to be reduced in patients with schizophrenia, there is some variability in the literature. Yeap et al. reported that 8 out of the 26 papers that examined the visual P1 in patients with schizophrenia did not find the P1 deficit (Yeap et al., 2008). One possibility for the variability may be the stimuli that the other studies included to elicit the visual P1.

The visual system includes both cortical and subcortical levels. The cortical level includes the dorsal and ventral stream, and the subcortical level includes the magnocellular and parvocellular system (Ungerleider & Mishkin, 1982). Certain very simple stimuli have been shown to bias either the magnocellular or parvocellular system. Although there is an array of stimuli from which to choose, the present study included stimuli that biased each system based on spatial frequency. The magnocellular system, the system that spotlights an object and enables the individual to focus on it, is generally activated when a subject is presented with low spatial frequency stimuli, while the parvocellular system is activated in response to high spatial frequency stimuli (Kaplan, 1991; Tootell et al., 1988). Studies have shown that patients with schizophrenia have reduced P1 amplitudes when presented with magnocellularly-biased stimuli (Butler & Javitt, 2005; Butler et al., 2007).

Alain et al. conducted a study that was very similar to the present one and included concurrent presentation of auditory and visual paradigms in patients with schizophrenia and controls. The participants were instructed to attend to a visual task and ignore the auditory

stimuli, which included an MMN paradigm with pitch and pattern deviants. For the visual task, the subjects were randomly presented with five thin bars or five thick bars. They were instructed to press on a button each time they saw five thin bars (the target) appear on the screen. The evoked potentials following the target were analyzed, and the patients' and controls' visual P1 amplitudes' were not significantly different (Alain, Hargrave, & Woods, 1998).

The stimulus that is used to elicit the visual P1 is crucial in demonstrating the reduced amplitudes generally characteristic of patients with schizophrenia. Because the visual P1 deficit is usually observed in response to magnocellularly-biased stimuli and less regularly (or weaker) in response to parvocellularly-biased stimuli (Butler et al., 2007), it is important to incorporate the appropriate stimuli in the study. The present study included stimuli that discriminated between the two systems by including large low spatial frequency gratings (1 cycle per degree) that biased the magnocellular system as one type of stimulus. The other type of stimulus, small high spatial frequency gratings (5 cycles per degree), targeted the parvocellular system. Evoked potentials following each of the two stimuli were analyzed.

Molholm et al. demonstrated that perfectly simultaneous presentation of auditory and visual stimuli has been shown to modulate the event-related potentials, when compared to the ERPs to auditory or visual stimuli presented at different times. When subjects were presented with a tone and an image of a disc on a screen simultaneously, the visual P1s were reduced, relative to when the visual stimulus was presented separately from the tone (Molholm et al., 2002). For that reason, the present study was designed to prevent stimulus overlap of the auditory and visual stimuli, although both auditory and visual paradigms were run concurrently.

The purpose of the present study is to demonstrate that a simultaneous presentation of auditory and visual paradigms should still generate reduced visual P1 components in patients

with schizophrenia, regardless of the auditory stimuli. We hypothesize that the fact that Alain et al. and several other studies did not report a reduced visual P1 in patients with schizophrenia may be a function of the stimulus that they used, rather than the fact that auditory stimuli were presented simultaneously in the case of Alain et al. The fact that the researchers only analyzed the evoked potentials following the high spatial frequency stimuli could explain their results. Five thin lines may not be the most effective stimulus to bias the magnocellular system, which is what has shown to be more affected by schizophrenia (Butler et al., 2007). We hypothesize that when using stimuli that truly discriminate between the magnocellular and parvocellular systems, the visual P1 deficit will be reduced in patients with schizophrenia during a concurrent presentation of auditory and visual stimuli.

Methods and Materials

Participants: Participants were recruited from inpatient and chronic residential care settings associated with the Nathan Kline Institute (Orangeburg, New York) and from community and staff volunteers. Informed consent was obtained from 26 patients diagnosed with either schizophrenia (n=14) or schizoaffective disorder (n=12) and 19 controls (**Table 1)**. Individuals with organic brain disorders, mental retardation, past drug or alcohol dependence, current drug or alcohol abuse or hearing/vision impairments were excluded. All procedures were approved by the Nathan Kline Institute Institutional Review Board. All subjects provided written informed consent. Subjects were corrected to near-normal visual (20/32 or better) prior to participation.

Procedure: ERPs were collected in a single session. During auditory stimulus presentation (see Study 2), subjects were asked to attend to a sequence of visual stimuli and to mouse-press in response to a pre-designated target stimulus (a schematic picture of an animal) that occurred on

11% of trials while ignoring all other stimuli. A distractor animal (an animal that resembled the target animal) appeared on another 11% of the trials. Additional visual stimuli consisted of high (HSF, 5 cycles/degree) and low (LSF, 1 cycle/degree) spatial frequency, 100% contrast horizontal gratings (39% sequential probability each). At a viewing distance of 114 cm, the stimulus field subtended 6.1 · 4.6 degrees of visual angle. All stimuli were presented centrally against a 50% gray background that was isoluminant with the mean luminance of the sine-wave gratings. The stimulus onset asynchronies were 875 ms ± 25 ms. Sequences were timed to prevent stimulus overlap. Auditory and visual stimuli were presented simultaneously in 250 s blocks, with brief pauses in between.

Eight blocks were collected per participant.

Data acquisition: Continuous EEG data, along with digital timing tags for both auditory and visual stimuli, were acquired using a 168-channel BioSemi Active II system (BioSemi, Amsterdam, The Netherlands) with custom, evenly spaced electrodes on a cap using standard reference and ground procedures (http://www.biosemi.com/faq/cms&drl.htm). Data were filtered with a zero-phase shift 40 Hz low-pass filter (48 dB/octave). No highpass filter was applied. Epochs (-100 to 750 ms) were created off-line and were baseline-corrected from 80 ms pre-stimulus to 20 ms post-stimulus onset and artifact-rejected at ± 100 μV. Epochs were then averaged off-line for each participant for each stimulus type. Similar numbers of sweeps were included in patient and control averages (**Table 2).**

ERP Components: Visual components were measured relative to nose reference and consisted of early (90-125 ms) and late (125-160 ms) P1 to LSF stimuli, and C1 (90 - 125 ms) and P1 (125 - 160 ms) to HSF. The electrodes for each component were chosen based upon visual inspection of

the data and published distributions of auditory and visual ERPs (Butler et al., 2007; Javitt, Shelley, Silipo, & Lieberman, 2000). For each component, the primary dependent measures were amplitude and latency within pre-specified latency ranges. Amplitudes were determined as peaks within each specified latency window.

Statistical analysis: Separate repeated measures multivariate analyses of variance (rmMANOVAs) were conducted for amplitude and latency of identified components. For the visual P1, latency range and hemisphere were included as within-subjects factors. For C1, only a single latency range was used. Since it was a midline component, hemisphere was not included as a factor. For visual components, visual acuity was included as a covariate. Split-half reliability was computed for key measures using Cronbach's alpha across the 8 separate acquisition runs.

Results

Visual ERPs:

***Low spatial frequency (LSF)*:** LSF responses consisted of bilateral dorsal early and late P1 components (Figure 3). P1 was significantly reduced in patients across both early and late latency ranges ($F(1,43)=7.19$, $p=.01$) (Figure 4). Differences remained strongly significant following covariation for visual acuity ($F(1,39)=7.62$, $p=.009$). There were no significant main effects of hemisphere ($F(1,43)=.88$, $p=.35$), group X hemisphere ($F(1,43)=.11$, $p=.7$) or group X latency range ($F(1,43)=1.73$, $p=.2$) interactions (Table 3). Split half reliability for P1 across runs was .91.

P1 latency was similar across groups (F(1,43)= 0.13 p=0.7) (**Table 3**). There was a significant main effect for hemisphere (F(1,43)= 10.03; p=.003). The hemisphere x group interaction was not significant (F(1,43)= 1.18; p=.28).

High Spatial Frequency (HSF): As expected, C1 amplitude was comparable between groups (F(1,43) = 0.93; p =0.34). P1 amplitude was significantly reduced before covariation for visual acuity (F(1,43)=4.75, p=.035) (Figure 4), but not significant following covariation (F(1,40)=4.04, p=.088). There was a significant main effect of hemisphere (F(1,43)=18.9, p<.001), but no significant group X hemisphere interaction (F(1,43)=1.41, p=.24). C1 latency was marginally significant between groups (F(1,43)=4.05, p=.05), but became non-significant following covariation for visual acuity (F(1,39)=2.90, p=.1) P1 latency to HSF stimuli was not significantly different between groups (F(1,43)= .04; p=.84) (**Table 3**).

Medication: No significant relationship with medication dose, as reflected in CPZ equivalents, was observed for any of the experimental measures.

Discussion

Despite the concurrent presentation of both auditory and visual stimuli, the results obtained in the present experiment are generally consistent with previous studies involving the visual P1 in patients with schizophrenia. The P1 amplitude in response to the low spatial frequency stimuli was reduced in patients with schizophrenia, relative to healthy controls. This study underscores the importance of utilizing stimuli that properly bias the magnocellular system, since the magnocellular system has been shown to be more affected in schizophrenia than the parvocellular one (Butler et al., 2007). If an ambiguous stimulus is used, patients' responses may appear to be artificially similar to that of controls.

Although the P1 amplitude in response to the high spatial frequency stimuli was initially significantly reduced in patients, the difference became non-significant following covariation for visual acuity. This highlights the importance of considering visual acuity in studies including visual evoked potentials. Studies generally report that the subjects' vision was corrected to normal. However, most studies fail to include the specific visual acuity values. Patients with schizophrenia tend to have worse vision overall. One factor contributing to this may be that they do not get the best optometric care. They may be less vigilant about going to the optometrist to keep up with the prescription or may not have the means with which to pay for new glasses. Another factor that may be a contributing factor to their poorer eyesight is that some of the medication that they take for schizophrenia may affect their vision. Anticholinergic medication can have a detrimental effect on vision. Even the antipsychotics that are not expressly anticholinergic have intrinsic anticholinergic activity.

Patients' reduced visual acuity may be particularly important when relating to high spatial frequency stimuli or parvocellularly-biased stimuli. The ability to view smaller, more detailed objects is more difficult with impaired eyesight than larger figures. The components following HSF stimuli may be artificially reduced in patients because of visual acuity. Therefore, when conducting studies, researchers should be vigilant about reporting the actual visual acuity measures associated with the patients and controls and covarying for visual acuity when analyzing the visual data, especially with high spatial frequency stimuli.

CHAPTER 3

Substantial progress has been made with etiological models of schizophrenia since Kraepelin's time; however, the perfect treatment for patients with this debilitating disease has yet to be found (Kantrowitz & Javitt, 2010). Exploring links between neurophysiological deficits and clinical characteristics has been suggested as a road to learn more about the source of schizophrenia (Jablensky, 2010), so that information can be applied to a better treatment. Previous studies have examined the relationships between individual sensory deficits and symptoms and premorbid and present functioning (Umbricht & Krljes, 2005; Yeap et al., 2008). However, the present study is the first to assess relative relationships with symptoms, premorbid function, and functional outcome in both sensory modalities in the same patient sample.

Umbricht et al. conducted a meta-analysis, which included studies that related to MMN in schizophrenia. They explored the relationship between the MMN and both positive and negative symptoms and found that of the twenty-two studies on MMN in schizophrenia that included correlations between MMN and symptoms, only one study found a significant correlation between positive symptoms (as determined by the Positive and Negative Symptom Scale) and MMN (Umbricht & Krljes, 2005). Utilizing both MRI and high-density electrophysiology, Youn et al. explored hemispheric asymmetry of the MMN equivalent current dipole (ECD) power in patients with schizophrenia and controls. They found that the left MMN ECD power and the positive symptoms of the PANSS were negatively correlated (Youn, Park, Kim, Kim, & Kwon, 2003). Six of the twenty-two studies that correlated MMN and symptoms reported a significant relationship between negative symptoms and MMN (Umbricht & Krljes, 2005).

Kiang et al. and Turetsky et al. found significant correlations between MMN and certain higher-order cognitive deficits (Kiang et al., 2007; Turetsky et al., 2009). Kiang et al. explored the source of impaired proverb interpretation in schizophrenia. They hypothesized that it was either related to disorganized semantic associations or working memory deficits. They recruited patients with schizophrenia and controls and tested their abilities to accurately interpret proverbs. The researchers then correlated the subjects' proverb interpretation abilities with both disorganized symptoms and auditory working memory (i.e. MMN). They found that there was no correlation with disorganized symptoms, but that there was a significant relationship between proverb interpretation and MMN (Kiang et al., 2007). Turetsky et al. found that MMN and N100 were closely associated with formal thought disorder and alogia (Turetsky et al., 2009).

Umbricht et al. found 17 MMN studies in which illness duration was considered. The researchers then examined the relationships between the effect size of each study and illness duration. Initially, they did not find a significant relationship. However, they separated the frequency and duration deviants and found a significant correlation with frequency and (after removing one outlier study), found a significant correlation with duration. Thus, it appears that there is a significant relationship between the two (Umbricht & Krljes, 2005).

Premorbid function, defined for the present study as education level, has been shown to be related to MMN. Umbricht et al. found that first-episode patients with poor premorbid function (no college) exhibited reduced MMN amplitudes, while those with good premorbid function exhibited normal MMN amplitudes at first episode (Umbricht et al., 2003). MMN has also been shown to be related to global functioning, as assessed by the Global Assessment of Functioning (GAF) and another tool that is meant to determine level of independence in a community living situation (Light & Braff, 2005).

Since the visual P1 deficit was discovered later than the MMN, relatively fewer studies (although at least upwards of 26) have been conducted on it. Few have attempted to correlate the visual P1 with clinical characteristics. Yeap et al. examined the relationships between the visual P1 and illness duration, medication, and symptomatology, among other things (Yeap et al., 2008). In contrast to the MMN, the vast majority of studies, most of which used either the Brief Psychiatric Rating Scale (BPRS), the Scale for Assessment of Negative Symptoms (SANS), and/or various neuropsychological tests, did not find any significant relationship between any of the symptoms associated with schizophrenia and the visual P1 (Bruder et al., 1998; Butler et al., 2005; Schechter et al., 2005). Yeap et al. did find a very weak positive correlation between the visual P1 amplitude and both the BPRS and the SANS. However, it is an unusual finding and highly counterintuitive, since it seems to indicate that the higher the P1 amplitude (i.e. closer to that of controls'), the more severe the symptoms. This finding has yet to be replicated. In further contrast to the MMN, Yeap et al. did not find any relationship between patients' ages or illness duration with the visual P1 (Yeap et al., 2008). No relationship between the visual P1 and education was observed (Bruder et al., 1998).

Thus, quite a few studies examined the relationships between global functioning, premorbid functioning, illness duration, and symptoms with either auditory or visual sensory deficits. MMN was found to be associated with those clinical characteristics, while the visual P1 did not seem to correlate with them overall. As mentioned above, the present study assesses the relationships between functioning and symptomatology and both auditory and visual deficits in the same patient sample.

Methods and Materials

Participants: Participants were recruited from inpatient and chronic residential care settings associated with the Nathan Kline Institute (Orangeburg, New York) and from community and staff volunteers. Informed consent was obtained from 26 patients diagnosed with either schizophrenia (n=14) or schizoaffective disorder (n=12) and 19 controls (**Table 1)**. Individuals with organic brain disorders, mental retardation, past drug or alcohol dependence, current drug or alcohol abuse or hearing/vision impairments were excluded. All procedures were approved by the Nathan Kline Institute Institutional Review Board. All subjects provided written informed consent. Subjects were corrected to near-normal visual (20/32 or better) prior to participation.

Procedures:

Clinical measures: Symptoms were analyzed using a 5-factor model (Kay, 1990). Current functional level was assessed using the GAF (A. P. Association, 2000) and ILS problem solving scale (Loeb, 1996). Premorbid function was assessed by dividing subjects into poor (12 or fewer years of education) and good (more than 12 years of education) premorbid groups (D. Umbricht, J. Bates, J. Lieberman, J. Kane, & D. Javitt, 2006). Clinical measures were evaluated by centrally trained and certified raters with interrater reliability maintained at ≥.8).

Statistical Analysis: Relationship of ERP amplitudes to clinical measures was assessed using multivariate regression vs. indicated measures. For regressions across group, a stepwise approach was used with group entered at step 1 and additional variables (e.g. MMN, P1) entered at subsequent steps. Overall regression significance was assessed based upon multivariate regression coefficient (*R*) values, while significance of individual variables was evaluated based upon partial correlation taking into account group membership. Correlations were analyzed

hierarchically in that multivariate regressions were performed first, and individual correlations were reported only if the multivariate regression showed significance. Correlations with symptoms, medication, and functional outcome were based upon uncorrected Pearson correlations and were considered exploratory.

Results

Premorbid function

Premorbid function was characterized based upon educational achievement. Patients as a group showed significantly lower educational achievement ($t=5.35$, $p<.001$) and individual SES ($t=6.17$, $p<.001$) than controls despite similar parental SES ($t=.65$, $p=.6$) (**Table 1**). Patients who did not progress beyond high school were otherwise demographically and symptomatically similar to those who did, although medication doses were much higher among patients with poor premorbid function (**Table 4**).

For both groups, the time between end of formal education and first hospitalization was similar and >2 yrs, suggesting that education was not interrupted by overt symptom onset, but may have been influenced by prodromal symptomatology. MMN amplitudes correlated significantly and strongly with premorbid educational achievement ($r=.73$, $p<.0001$) (**Figure 5)**. This correlation remained strongly significant in a MANCOVA incorporating group as well as premorbid function ($F(3,37)=5.79$, $p=.002$). Furthermore, the group X premorbid function interaction was non-significant ($F(3,37)=.78$, $p=.5$), suggesting similar relationship across groups.

When assessed categorically across 3 groups (poor vs. good premorbid patients vs. controls), there was not only a significant main effect of group ($F(2,41)=13.7$, $p<.0001$), but also a group X MMN-type interaction ($F(4,82)=3.79$, $p=.007$), reflecting smaller duration vs. pitch ($p<.002$)

and duration vs. intensity ($p<.002$) in patients with poor premorbid educational achievement but not in the other two groups (**Figure 6**).

For visual measures, there was no significant relationship between visual measures to LSF stimuli and educational status ($r=.33$, $p=.46$). Although there was a weak correlation between premorbid education status and P1 to HSF stimuli ($r=.30$, $p=.045$), the correlation became non-significant once group was included in the model ($r=.14$, $p=.23$). No significant correlations were observed between visual measures and illness duration.

Duration of illness

Across deviant types, there was a marginal correlation between MMN amplitude and illness duration ($R=.54$, $F(3,21)=2.91$, $p=.06$). However, significant correlations were observed with illness duration and both duration- ($r=.53$, $p=.007$) and intensity- ($r=.41$, $p=.04$) MMN independently, with longer illness durations predicting smaller MMN amplitude. Despite the correlation with illness duration, no significant correlation was observed with age at time of testing (all $p>.08$).

When premorbid education achievement and duration of illness were considered simultaneously, both were significant independent predictors (education: partial $r= -.48$, $p=.018$; illness duration: partial $r=.57$, $p=.004$) (**Figure 7**). When analyses were stratified by premorbid education, a significant group x MMN-type interaction was observed in patients with poor premorbid function ($F(2,31)=8.19$, $p=.001$) with greater reduction in MMN to duration ($t=5.72$, $p<.0001$) than to pitch ($t=3.05$, $p=.005$) or intensity ($t=3.51$, $p=.001$) deviants. In contrast, no significant relationship between illness duration and MMN was observed in this group ($R=.45$, $F(3,11)=.95$, $p=.45$). Patients with good premorbid status showed no differential reduction across MMN types

(F(2,26)=0.55, p=.58), but a significant reduction with increasing illness duration (*R*=.90, F(3,6)=8.40, p=.014).

Clinical correlations

Symptoms: In addition to being associated with premorbid educational status, MMN amplitude across deviant types correlated significantly with degree of cognitive symptoms, which were measured using the PANSS (r=.70, p=.003). Significant independent correlations were observed between MMN to pitch (r=.61, p=.002) and intensity (r=.63, p=.001) deviants, with no significant correlation with MMN to duration deviants (r=.24, p=.26). No significant correlations with positive or negative symptoms were observed for any of the MMN types. No significant correlations were observed with symptoms and visual measures to either LSF or HSF stimuli.

Functional capacity: Functional capacity was assessed using both ILS and GAF. Across deviant types, reduced MMN amplitude was significantly associated with reduced score on the ILS (r=.62, p=.02), with significant independent correlation for duration- (r=-.45, p=.021) and intensity- (r=-.41, p=.047), but not pitch- (r=-.18, p=.4), MMN. In contrast, no significant correlation was observed between MMN and GAF. No significant correlation was observed between any visual measures and either ILS or GAF.

Medication: No significant relationship with medication dose, as reflected in CPZ equivalents, was observed for any of the experimental measures.

Conclusion

Consistent with previous research, a relationship between MMN and premorbid functioning was observed, but there was no significant relationship between the visual P1 and premorbid functioning. The present study also found a stronger relationship between duration MMN and premorbid function than the other deviants.

Similarly, in the present study, no relationship between duration of illness and visual P1 was observed. The present study did find a relationship between MMN and illness duration, consistent with previous research. However, in Umbricht et al.'s meta-analysis, they found relationships between frequency and duration deviants and illness duration (Umbricht & Krljes, 2005); in the present study, no relationship between illness duration and frequency deviant was observed.

The clinical correlations in the present study were also similar to those in previous literature. In the present study, relationships between cognitive symptoms and MMN were observed, but no relationship between negative and positive symptoms and MMN were found. No relationship between symptoms and visual P1 were observed. It is worth noting that in the meta-analysis, some studies did find relationships between MMN and negative symptoms. However, those studies were in the minority (Umbricht & Krljes, 2005).

The present study found a relationship between MMN and global functioning, but did not find one between visual P1 and global functioning, which is mostly consistent with current literature. However, the relationship between MMN and global functioning was demonstrated via the Independent Living Scale (ILS) and not the Global Assessment of Functioning (GAF). Although another study found a relationship between the GAF and MMN (Light & Braff, 2005), this was not the case in the present study.

Thus, the pattern of correlations observed in the present study is, for the most part, consistent with existing literature on the relationships between sensory dysfunction and premorbid and present functioning, symptoms, and illness duration. It shows differential relationships between MMN and visual P1 and clinical characteristics, premorbid and present functioning. This indicates that there are likely different etiologies for each of the sensory deficits.

CHAPTER 4

Sensory deficits, as revealed by behavior, ERP and fMRI, have become increasingly well established in schizophrenia over recent years (Javitt et al., 2008). The present study evaluates two sensory neurophysiological measures – auditory MMN and visual P1 - that are now widely used in schizophrenia research (Butler & Javitt, 2005; Javitt et al., 2008; Naatanen & Kahkonen, 2009) with the goal of assessing their relative association with clinical features of the disorder. Primary findings are that, within the same patient sample, both auditory and visual ERP measures are reduced, but are differentially associated with demographic and clinical features. In particular, the study confirms our prior report of a significant association between poor premorbid educational achievement and MMN generation (D. S. Umbricht et al., 2006), while differentiating relative contributions of premorbid and disease related factors in overall MMN generation. Finally, the study adds to the growing list of social/occupational measures that have been linked to impaired MMN generation in schizophrenia.

Deficits in MMN generation have been reported consistently in chronic schizophrenia patients relative to age-matched controls. In a prior study, we noted the post-hoc observation that among first-episode subjects, MMN deficits were observed only in individuals who had failed to progress beyond high school, whereas in chronic patients deficits were observed among patients both with and without college education (D. S. Umbricht et al., 2006). In the present study, an extremely strong association between premorbid educational status and MMN was again observed, not only within schizophrenia subjects, but also across patients and controls (**Figure 6**). Furthermore, once the patient group was divided by premorbid function, differential patterns of dysfunction were observed. Thus, only for patients with poor premorbid function, was a greater deficit to duration than other deviant types observed (**Figure 7**). This may be

particularly relevant given that reports of normal premorbid MMN derive primarily from studies which utilized pitch deviants (Salisbury et al., 2007; Salisbury et al., 2002), whereas more recent studies showing relationship of MMN to prodromal status have utilized duration deviants (Bodatsch et al., 2010; Shin et al., 2009).

Salisbury et al. presented stimuli to generate MMNs using pitch deviants in four groups of subjects: patients with chronic schizophrenia, older control subjects, patients with first-episode schizophrenia, and younger control subjects. Researchers found that MMN was very significantly reduced in patients with chronic schizophrenia, but that they were normal in the three remaining groups, including the group with the first-episode patients (Salisbury et al., 2002).

Bodatsch et al. used duration deviants to explore MMN in subjects at risk for schizophrenia. They assessed MMN in subjects at risk for schizophrenia and conducted a follow-up assessment 2-3 years later. The researchers reported that MMN was reduced in at-risk subjects that ultimately "converted" to patients with schizophrenia (i.e. experienced their first episodes of schizophrenia). However, MMN was comparable to the healthy controls' in the "non-converters", who although at risk for the condition, were still not diagnosed a minimum of 24 months after baseline (Bodatsch et al., 2010).

Shin et al. reported consistent results with duration deviants for MMN. They utilized magnetoencephalography (MEG) to assess MMN in 16 subjects who were at ultra-high risk for schizophrenia and 18 matched healthy control subjects. Researchers reported that the high-risk group exhibited a reduced MMNm dipole, relative to the control group (Shin et al., 2009).

Such findings emphasize the need to use "optimized" MMN paradigms with independent pitch, duration and other deviant types per run, and to consider deviant type when discussing discrepancies within the MMN literature. In addition, this study demonstrates the need to consider potential neurodevelopmental and neurodegenerative factors independently, with a discrepancy between MMN to duration vs. pitch deviance serving as a potential marker for a form of schizophrenia most associated with poor premorbid function. For both groups of patients, reductions were observed across MMN type, with increased deficit within increasing illness duration.

In the present study, a significant correlation was also observed between MMN and ILS. ILS measures problem solving ability for daily living, and is a proxy measure for ability to live independently. ILS has previously been shown to be related to impaired sensory processing, as reflected in impaired tone matching ability (Revheim, Schechter et al., 2006). There was no significant relationship between the GAF and MMN in the present study despite a prior report of significant association (Light & Braff, 2005), suggesting that such correlations may be variable across cohorts (Umbricht & Krljes, 2005). The present findings thus suggest that MMN may be most strongly associated with trait cognitive deficits and functional impairments, and less strongly with more labile symptom clusters and medication-sensitive variables.

In the present study, deficits in P1 generation to magnocellular-biased (LSF) stimuli were observed as in prior studies. Consistent with prior research, P1 was unrelated to premorbid function, symptoms, illness duration or functional outcome. However, this is the first study to demonstrate absence of these associations in the same cohort where associations with MMN were independently observed. The present study also demonstrates that both active visual and

passive auditory ERP can be obtained within the same session, further optimizing ERP acquisition in neuropsychiatric research.

Structural brain issues in Schizophrenia

One potential explanation for the dissociation between auditory and visual findings relates to the time course of structural brain alterations in schizophrenia. Alterations in brain structure in schizophrenia were initially reported based upon postmortem tissue. More recent studies have utilized imaging based approaches focused on both grey and white matter to delineate regional changes. In addition, diffusion tensor imaging (DTI) provides a measure of white matter connectivity between regions. These measures help elucidate potential underlying causes of schizophrenia, as well as differential relationships of visual and auditory dysfunction to premorbid functioning in schizophrenia.

Several studies have demonstrated structural abnormalities in the occipital region of patients with schizophrenia. Ardekani et al. examined neuroanatomical differences between 14 patients with schizophrenia and 14 healthy controls by utilizing diffusion tensor imaging. They found reduced white matter fractional anisotropy in various regions of the brain, including the superior temporal gyrus (auditory-related) and the medial occipital lobe (visual-related). The researchers used voxel-wise analysis for this study, which is a statistical imaging tool that allows for comparison between patients and controls at each point in the brain. Therefore, researchers do not need to limit themselves to regions of interest. They can explore differences in the entire brain (Ardekani, Nierenberg, Hoptman, Javitt, & Lim, 2003).

Butler et al. also conducted a study that utilized diffusion tensor imaging, but they focused on the visual regions of the brain. The researchers examined white matter in 17 patients

and 21 controls at four levels of the visual system, including the optic radiations (very early stage of visual processing), the striate cortex, the inferior parietal lobule, and the fusiform gyrus (late stage of visual processing). They found that fractional anisotropy was only decreased in the optic radiations and not at any other level. Based on that finding, researchers concluded that the visual dysfunction associated with schizophrenia occurs at a very early stage in visual processing (Butler et al., 2006).

One study that was not consistent with previous literature was designed to compare cell number and volume in the lateral geniculate nucleus of the thalamus in patients with schizophrenia and controls. Nissl-stained sections were examined in 15 patients and 15 controls. The researchers utilized a particular sampling method to determine whether or not there were differences between the groups, and discovered that there were, in fact, no significant differences in the neuronal number and volume (Selemon & Begovic, 2007).

Studies have also explored structural deficits in the auditory region. Shenton et al. explored differences in the temporal lobe between 15 patients with schizophrenia and 15 controls. Both groups underwent magnetic resonance imaging, and differences were determined by researchers that were blind to the subjects' diagnoses. They determined that there was a 15% decrease in gray matter in the superior temporal gyrus of patients with schizophrenia. They also found reductions in the anterior hippocampus-amygdala and the left parahippocampal gyrus (Shenton et al., 1992).

Schlaepfer et al. also utilized magnetic resonance imaging, but they were specifically interested in the heteromodal association cortex. They included the dorsolateral prefrontal cortex, inferior parietal lobule, and superior temporal gyrus as their regions of interest. For their study, they compared those regions in patients with schizophrenia and patients with bipolar disorder.

They found that all three regions were reduced in patients with schizophrenia, but not in patients with bipolar disorder. The researchers had also assessed occipital and sensorimotor regions of the brain, as comparison regions that they hypothesized would not differ between groups. They found that although the gray matter of the regions of interest were reduced in patients with schizophrenia, relative to those with bipolar disorder, there was not a significant difference in the comparison regions (Schlaepfer et al., 1994).

Hirayasu et al. compared the MRI images of the planum temporale and Heschl's gyrus in 20 first-episode patients with schizophrenia, 24 first-episode patients with manic psychosis and 22 controls. They found that the patients with schizophrenia had reduced gray matter in both areas, relative to the patients with manic psychosis and the controls (Hirayasu et al., 2000).

Hazlett et al. assessed cortical gray and white matter in unmedicated patients with schizophrenia and schizotypal disorder. Magnetic resonance images were assigned Brodmann areas using a postmortem histological atlas. The researchers then conducted a MANOVA to determine group differences between the two groups of patients and the controls. They found that the patients with schizophrenia had reduced gray matter most markedly in the frontal and temporal regions, though there was overall gray matter reduction across the cortex (Hazlett et al., 2008).

Lee et al. focused on the white and gray matter differences in the superior temporal gyrus between patients with schizophrenia and controls. The researchers utilized magnetic resonance imaging and diffusion tensor imaging to assess gray and white matter, respectively. 21 patients with schizophrenia were compared with 22 controls. They found increased mean diffusivity in both white and gray matter in the superior temporal gyrus of patients with schizophrenia. They suggested that this likely indicates loss of organization in white matter tracts (such as loss of

myelin, axonal fibers, etc.). The increased mean diffusivity in the gray matter also reflects decreased integrity of gray matter in the brain. Further, the researchers reported that the decreased gray matter in the superior temporal gyrus correlated with duration of illness (Lee et al., 2009).

Rasser et al. investigated temporal and frontal cortical volume loss in patients with schizophrenia. They were interested in the relationship of cortical deficits to patients' mismatch negativity ERPs. The researchers conducted high resolution magnetic resonance images on patients with schizophrenia and age-matched controls, utilizing cortical pattern matching, a technique which allows for statistical comparisons across subjects. They found that the patients exhibited reduced gray matter in Heschl's gyrus, which along with reductions in certain frontal regions, was associated with reduced ERPs to frequency deviants. Reductions on the right Heschl's gyrus was associated with reduced ERPs to duration deviants, as well (Rasser et al., 2009a).

Smiley et al. utilized postmortem tissue to explore deficits in the auditory cortices of schizophrenia brains. The researchers found thinning of the upper layers of the caudal planum temporal and of the rostral planum temporal and Heschl's gyrus, whichwill be discussed in greater detail below (Smiley et al., 2009).

Thus, both auditory (Javitt, 2000; Rasser et al., 2009b; Smiley et al., 2009; Sweet, Pierri, Auh, Sampson, & Lewis, 2003) and visual (Butler et al., 2006; Butler et al., 2005; Dorph-Petersen, Pierri, Wu, Sampson, & Lewis, 2007) ERP deficits in schizophrenia are linked to anatomical and histological changes within underlying generator regions. However, little progressive change has been reported in occipital gray matter over the course of schizophrenia,

suggesting that reductions in occipital volume likely predate onset of illness and play a permissive role in illness onset.In contrast, progressive volume reduction occurs in auditory regions over the course of the illness (Salisbury et al., 2007; Salisbury et al., 2002) and thus may be more related to illness onset and disease progression.

Kasai et al. investigated changes in the auditory region of the brain after the first 1.5 years following the onset of schizophrenia symptoms. Their study included 13 patients hospitalized for their episode of schizophrenia, 15 patients hospitalized for their first episode of affective psychosis, and 14 healthy controls. The researchers focused on the superior temporal gyrus and hippocampal-amygdala complex when conducting the magnetic resonance imaging scans. They demonstrated that patients with schizophrenia exhibited reductions in the left superior temporal gyrus, relative to the other group of patients and controls 1.5 years following the first hospitalization (Kasai et al., 2003). Lee et al.'s study exploring white and gray matter of the superior temporal gyrus is consistent with the change over time, since they found the decreased gray matter to be associated with duration of illness (Lee et al., 2009).

Neeltje et al. performed yet another MRI study that assessed change in cortical thickness over the course of schizophrenia. They compared patients with schizophrenia with healthy controls on cortical thickness change after five years. The patients with schizophrenia in this study did not have a standard baseline duration of illness, rather they were heterogeneous in this regard. The researchers still found more thinning in the frontal and temporal regions of the patients, relative to controls at the five-year follow-up (Neeltje et al., 2011).

Salisbury et al. conducted a similar longitudinal study that extended Kasai et al.'s findings. It included patients at their first hospitalization for schizophrenia, patients with bipolar

disorder with psychosis, and healthy control subjects. Researchers conducted both electrophysiologic testing and magnetic resonance imaging (MRI) on each subject at the patients' first hospitalization (for patients with schizophrenia and bipolar disorder) and approximately 1.5 years later as a follow-up. The electrophysiologic testing was used to assess MMN amplitude at each time point. The regions of interest for the MRI were the Heschl's gyrus and planum temporale. At the first assessment, groups were not significantly different in terms of MMN amplitude, and the patients exhibited normal gray matter volume. At the follow-up testing, the patients with schizophrenia, unlike the other groups, exhibited MMN deficits. They also exhibited, unlike the other groups, reduced left hemisphere Heschl's gyrus gray matter, which correlated strongly with the MMN (Salisbury et al., 2007).

Whitford et al. used voxel-based morphometry to compare structural brain differences in 41 patients with first-episode schizophrenia and 47 healthy controls. The first MRI was administered to patients with first-episode schizophrenia within the first 3 months following the initial onset of psychosis. This initial MRI provided the researchers with evidence of differences between the groups in various regions of the brain. There was decreased grey matter in the frontal, parietal, and temporal cortices of the patients, relative to the controls. They also reported increased grey matter in the occipital lobe (Whitford et al., 2006).

Following the baseline study, the researchers conducted a longitudinal study with 25 of the initial first-episode patients. For the longitudinal study, they utilized tensor-based morphometry, which they determined was more sensitive to changes over time than voxel-based morphometry. 2-3 years following the baseline MRI, the patients underwent a second MRI and the two MRI results were compared. They reported decreased grey matter at the 2-3 year follow-

up in several regions, including the superior temporal gyrus, but did not report significant changes in the occipital region (Whitford et al., 2006).

In histological studies, differential involvement of primary (core) vs. secondary (belt, parabelt) auditory cortex has been reported (Smiley et al., 2009; Sweet et al., 2003). Specifically, as mentioned above, Smiley et al. measured the volume asymmetry of the planum temporale in 19 schizophrenia and 18 control autopsy brains. Then, they used 11 of the schizophrenia brains and 10 of the control brains to measure the widths and fractional volumes of the upper and lower layers. In the brains of schizophrenia patients, they found very pronounced thinning of the upper layers of the caudal planum temporal (secondary auditory cortex) in the left hemisphere, but significantly less pronounced changes in the rostral planum temporale and Heschl's gyrus (primary auditory cortex). These findings may potentially account for the differential association of pitch/intensity vs. duration deviants in patients with poor premorbid function (Smiley et al., 2009).

Molholm et al. utilized fMRI to determine the locations of the generators for both pitch and duration deviants. They presented twenty healthy control subjects with a paradigm that included both types of deviants, while subjects were in the bore of the magnet, watching a movie silently. Within auditory regions, pitch MMN was localized to the superior temporal gyrus of the primary auditory cortex, whereas duration MMN is generated primarily within secondary auditory regions which may mature later (Molholm, Martinez, Ritter, Javitt, & Foxe, 2005), also potentially accounting for the differential association of pitch/intensity vs. duration MMN with premorbid function in schizophrenia.

Differential genetic architecture may also be important. For example, the dysbindin gene is located on chromosome 6p22.3 and has been shown to be associated with an increased risk for schizophrenia (B. Riley & Kendler, 2006; Sun, Kuo, Riley, Kendler, & Zhao, 2008). The mutations reported on the dysbindin gene have included both a six-marker (Funke et al., 2004) and a three-marker haplotype (Williams et al., 2004). Donohoe et al. recruited 18 patients with three-marker dysbindin risk haplotypes and 20 non-risk haplotype patients. They then explored whether the haplotype was associated with reduced gray matter. They reported that the dysbindin risk haplotype was associated with reduced occipital and frontal gray matter, but it did not affect the temporal brain regions(Donohoe et al., 2010). This may potentially account for the impaired visual ERP findings observed in carriers vs. non-carriers of the risk haplotype (Donohoe et al., 2008).

Another study seems to support the concept that genetics may affect gray matter reductions in schizophrenia. Byun et al. compared gray matter in three groups of participants: 31 individuals who did not have schizophrenia, but had a high genetic risk for it; 29 healthy controls; and 31 patients with schizophrenia. All the participants underwent magnetic resonance imaging, and gray matter was compared based on the scans. The individuals who had a high genetic risk for schizophrenia had significantly greater cortical thinning than the healthy controls in various regions of the brain, including the right anterior cingulate cortex (ACC), left paracingulate and posterior cingulate regions; bilateral frontal regions including frontal pole and ventromedial prefrontal cortex; bilateral temporal regions including the left parahippocampal gyrus; and bilateral inferior parietal and occipital regions. Patients with schizophrenia had more thinning in the fronto-tempero-parietal regions than the individuals with high genetic risk, but no

diagnosis of schizophrenia. For the high genetic risk group, those with two or more first-degree relatives that had the disease had more cortical thinning in the right anterior cingulated cortex and in the left paracingulate cortex than those with only one first-degree relative with schizophrenia (Byun et al., 2012).

Phillips et al. compared superficial white matter in four groups of participants: patients with schizophrenia, their relatives, healthy controls, and their relatives. The patients exhibited reduced fractional anisotropy most prominently in the occipital and temporal regions, relative to the healthy controls. Also, it did appear that the fractional anisotropy was reduced in certain areas in the patients' relatives, relative to the controls' relatives, it did not come out entirely significant, once statistical corrections were made (Phillips et al., 2011).

Clark et al. did find statistically significant reductions in both patients' and their relatives' white matter in specific areas of the brain, when compared to controls and their relatives. They utilized diffusion tensory imaging and high-resolution structural data to examine the major white matter pathways of the participants (K. A. Clark et al., 2011).

Although both auditory and visual deficits have been linked to underlying glutamatergic dysfunction, particularly at N-methyl-D-aspartate (NMDAR)-type glutamate receptors (Javitt et al., 2008), the paths to NMDAR dysfunction are unknown and may differ across brain regions. Auditory and visual ERPs may therefore serve as biomarkers for different forms of schizophrenia and may help elucidate convergent pathological processes and risk mechanisms.

There are specific limitations to the study. First, all patients were receiving medication at the time of testing, so potential effects of medication cannot be discounted. Furthermore,

patients with poor premorbid function, as assessed by education achievement, were receiving markedly high doses of antipsychotics despite similar levels of symptoms. Nevertheless, no correlation of medication dose with sensory function was observed either within or across patient groups. Thus, the greater MMN deficits observed in poor premorbid patients is unlikely to be a direct result of higher medication dosage.

Second, our division of patients into good vs. poor premorbid function was based on education achievement alone. In a prior study (D. S. Umbricht et al., 2006), we observed that other measures, such as retrospective assessment of social function, were not predictive of MMN. Objective data regarding premorbid patient status can be observed for limited patient samples (e.g. army database registries), suggesting need for future studies investigating such patients. Educational achievement can also be obtained objectively, but may be confounded by educational opportunities. At present, the specific premorbid features (including premorbid IQ) related to MMN deficits at illness onset (or prior) remain to be determined, and will be an important area of research.

In sum, although auditory MMN and visual P1 deficits are reliably associated with schizophrenia and are both present in the same subject sample, these measures have distinct functional correlates. MMN shows significant correlation with both premorbid and current functional status and illness duration, whereas visual P1, especially to LSF stimuli, shows deficits irrespective of these measures. In addition, present findings provide the first evidence for separate neurodevelopmental and neurodegenerative “paths” to impaired MMN generation in schizophrenia, with duration MMN most specifically linked to poor premorbid, presumed neurodevelopmental dysfunction. Overall, present findings demonstrate that sensory

dysfunction, while reliably present, is not a unitary phenomenon in schizophrenia, suggesting that these measures may index differential underlying functional and neurogenetic mechanisms.

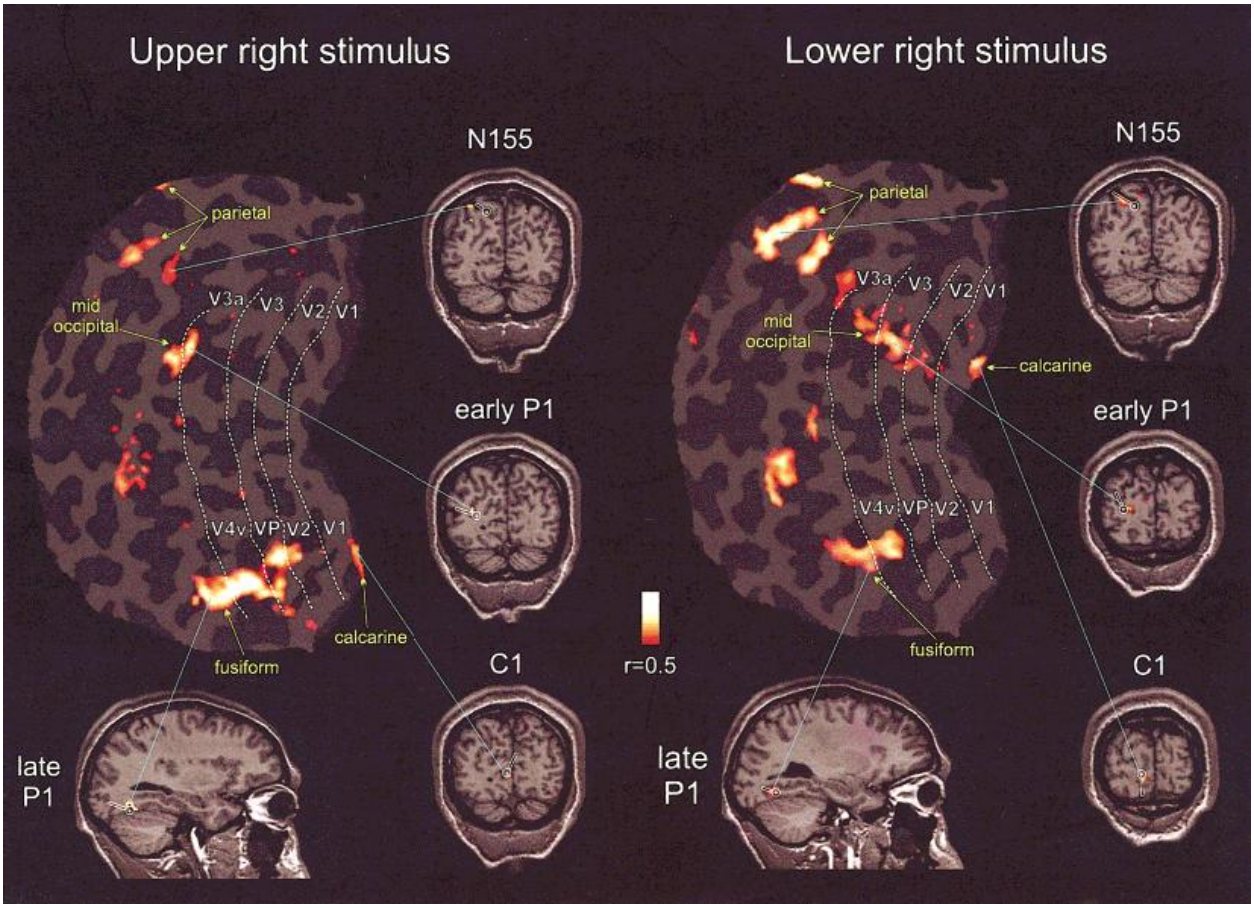


Figure A (from Di Russo et al., 2002). Spatial correspondence between dipole models fitted to the grand average VEP and fMRI activations in a single subject (KD). fMRI activations and retinotopic mappings of visual areas for upper and lower right field stimuli were projected onto a flattened cortical representation of the left hemisphere. Dashed white lines represent the boundaries of visual areas traced from visual field sign maps (sulcal cortex, dark gray; gyral cortex, light gray). Coronal and saggital sections display the same activations before flattening. The circles with pointers indicate the fitted dipoles from the grand-average VEP model in response to the same stimuli.

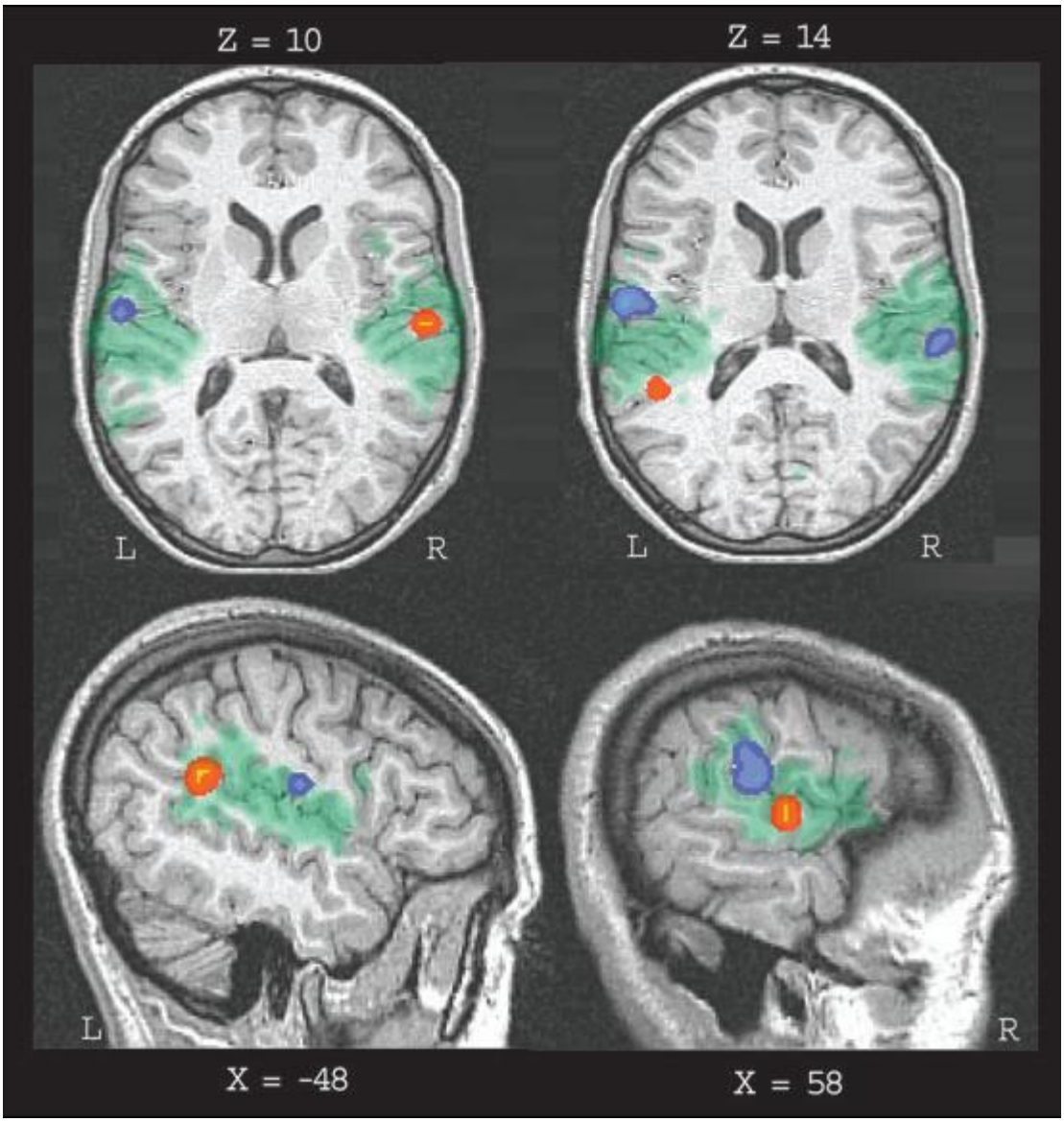


Figure B (from Molholm et al., 2005). MMN generators in auditory cortices: significant duration-related MMN activations are shown in blue and frequency MMN activations are shown in orange. The larger extent of auditory cortices activated by simple sensory stimulation is shown in the shaded green. This region served as the region of interest (ROI) within which subsequent tests for MMN activity were conducted. For both this and Figure 3, the functional data have been transformed into Talairach and Tournoux coordinates and are displayed on the brain of an individual subject that has been similarly transformed.

Table 1. Demographics and Clinical Characteristics of Patients and Controls

Characteristic	**Mean, SD**	
	Controls	**Patients**
Age	35.8 ± 9.9	36.0 ± 10.5
Gender (M/F)	16/3	25/1
Parental socioeconomic status (SES)	42.2 ± 12.8	42.8 ± 18.8
Education	16.1 ± 2.8	12.5 ± 2.2*
Individual SES	46.8 ± 13.8	27.2 ± 10.0*
Visual Acuity, Near	0.96 ± 0.1	0.98 ± 0.1
Visual Acuity, Far	1.3 ± 0.2	0.99 ± 0.2
PANSS-positive	----	10.6 ± 2.8
PANSS-negative	----	14.8 ± 4.5
PANSS-cognitive	----	11.5 ± 3.2
Independent Living Scale (ILS-PB)	----	38.3 ± 12.1
GAF	----	41.4 ± 7.6

* $p<.001$

Table 2. Mean Number of Accepted Sweeps

Mismatch Negativity

Deviant Type	Controls (n=19) Mean ± SD	Patients (n=26) Mean ± SD
Duration	367.3± 59.3	333.2± 51.6
Frequency	361.6 ± 59.5	329.0 ± 49.4
Intensity	361.9 ± 58.8	329.3 ± 48.3
Standard	1087.6 ± 177.4	987.8 ± 151.9

Visual Measures

High Spatial Frequency	771.2 ± 119.5	700.4 ± 111.9
Low Spatial Frequency	775.8 ± 118.7	696.4 ± 114.5

Table 3. Latencies of Patients and Controls

Mismatch Negativity

Deviant Type	**Controls (n=19) Mean ± SD (ms)**	**Patients (n=26) Mean ± SD (ms)**
Duration	237.3 ± 13.5	233.8 ± 16.8
Frequency	144.3 ± 23.6	133.8± 25.7
Intensity	175.4 ± 12.4	172.9 ± 16.3

Visual Measures

Spatial Frequency	**Component**		
High	**C1**	105.9 ± 9.8	111.1 ± 7.4*
	Late P1	152.5 ± 7.1	151.9 ± 10.2
Low	**Early P1**	103.1 ± 2.8	104.4 ± 2.4
	Late P1	146.1 ± 9.3	148.05 ± 11.5
	N1	189.7 ± 7.5	188.7 ±10.6

* p=.05

Table 4. Demographics and Clinical Characteristics of Poor vs. Good Premorbid Patients

Characteristic	Mean ± SD	
	Poor Premorbid	**Good Premorbid**
Age	34.5 ± 11.2	38.3 ± 9.3
Gender (M/F)	16/0	9/1
Parental socioeconomic status (SES)	39.6 ± 21.1	49.4 ± 11.7
Education (yrs)	11 ± 1.2	14.8 ± 1.3*
Individual SES	21.9 ± 7.6	35.2 ± 7.8*
Age at first hospitalization (yrs)	18.3 ± 4.4	22.3 ± 5.7
Time: end of education to onset (yrs)	1.3 ± 4.7	2.6 ± 4.4
Duration of illness (yrs)	16.3 ± 9.6	15.2 ± 9.1
PANSS-positive	11.6 ± 2.3	9.3 ± 3.4
PANSS-negative	15.6 ± 4.7	13.7 ± 4.6
PANSS-cognitive	11.4 ± 2.9	10.8 ± 2.4
Independent Living Scale (ILS-PB)	36.6 ± 11.6	43.0 ± 11.6
GAF	37.9 ± 5.7	46.8 ± 7.7*
Medication dose (mg CPZ equiv)	1426.2 ± 965.9	527.4 ± 354.6*

* $p<.05$. Patients were included in the "poor premorbid" group if they completed 12^{th} grade or below and in the "good premorbid" group if they completed any education beyond 12^{th} grade.

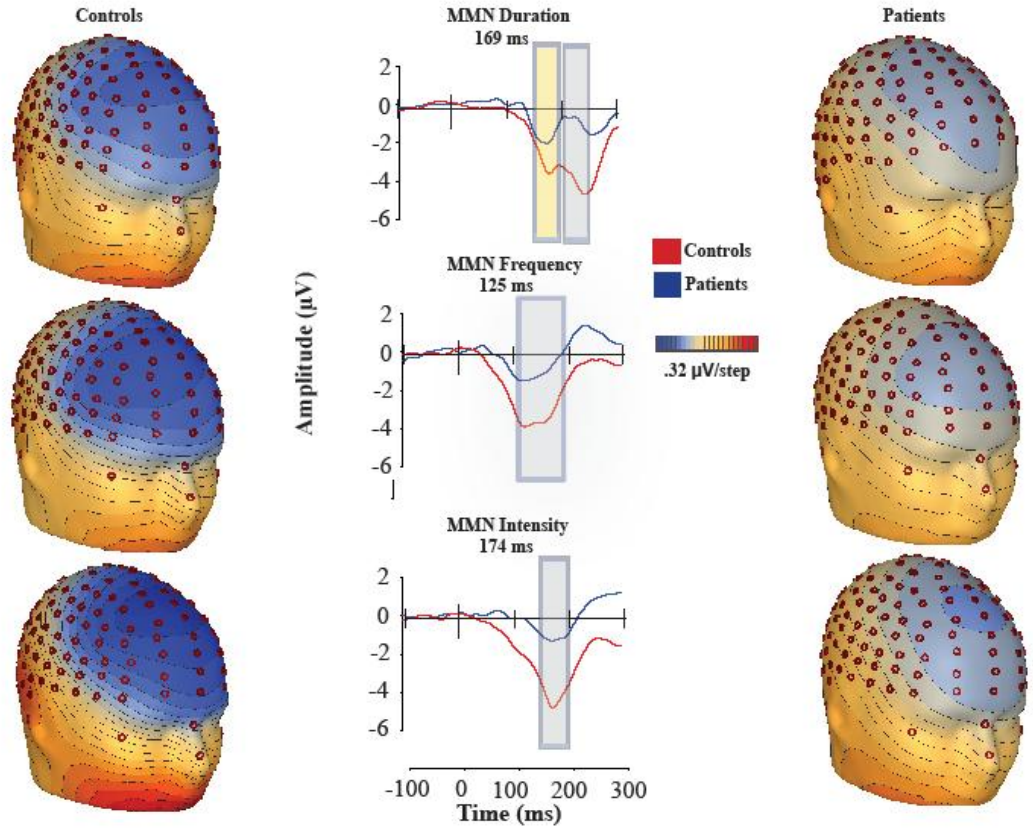


Figure 1. Voltage topography maps and group-averaged MMN waveforms for controls and patients. High-density electrodes were selected from the vicinity of Fz, FCz, and Cz.

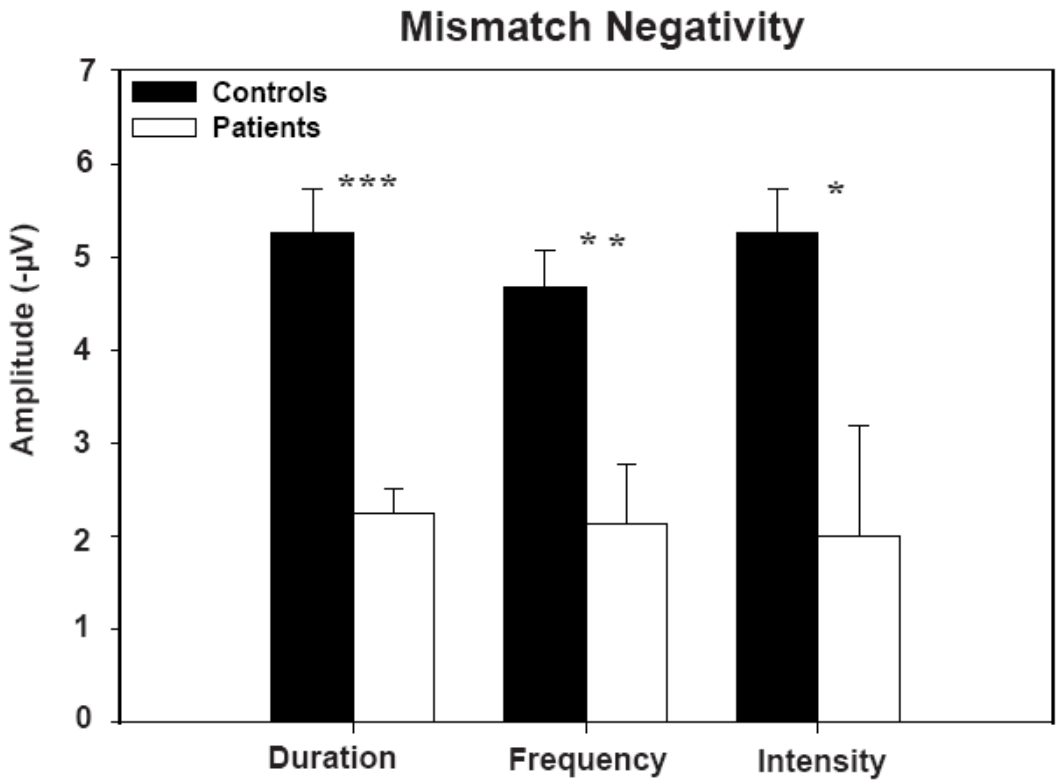


Figure 2. Patients' v. controls' MMN amplitudes in response to duration, frequency, and intensity deviants. Error bars represent the standard error of the mean for patients and controls.

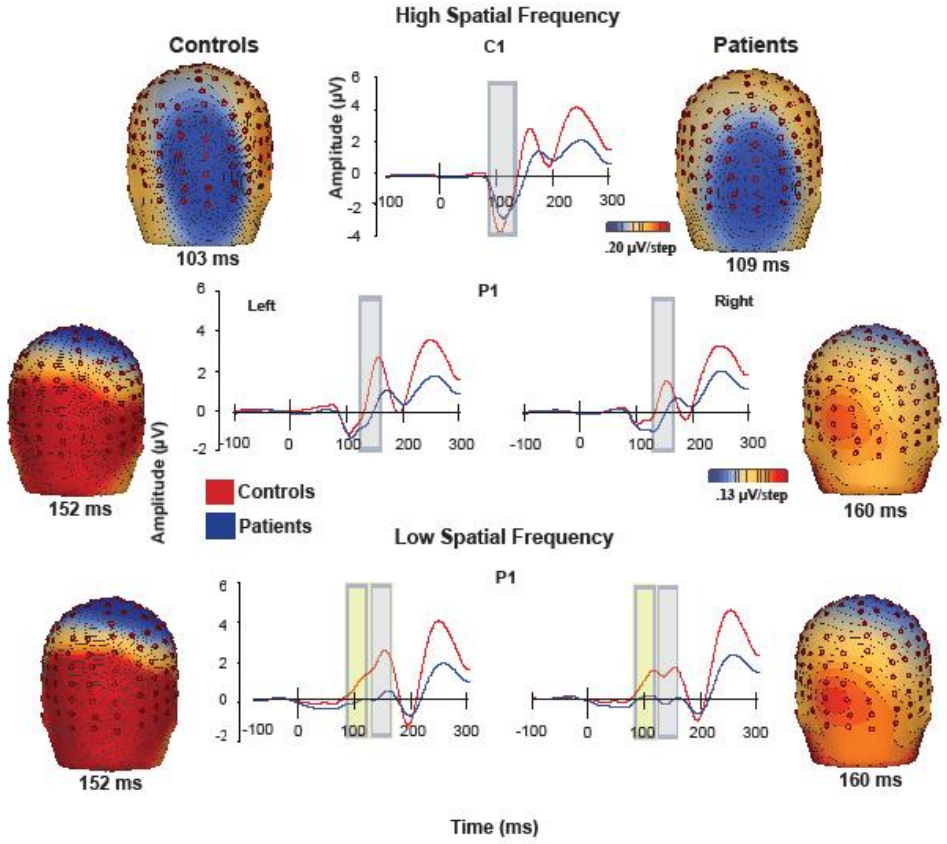


Figure 3. Voltage topography maps and group-averaged waveforms of responses of controls and patients to low and high spatial and frequency gratings. High-density electrodes were selected from the vicinity of PO3, PO7, P5, and PO9 for the waveforms for the left hemisphere P1 and from PO4, PO8, P6, and PO10 for the right hemisphere

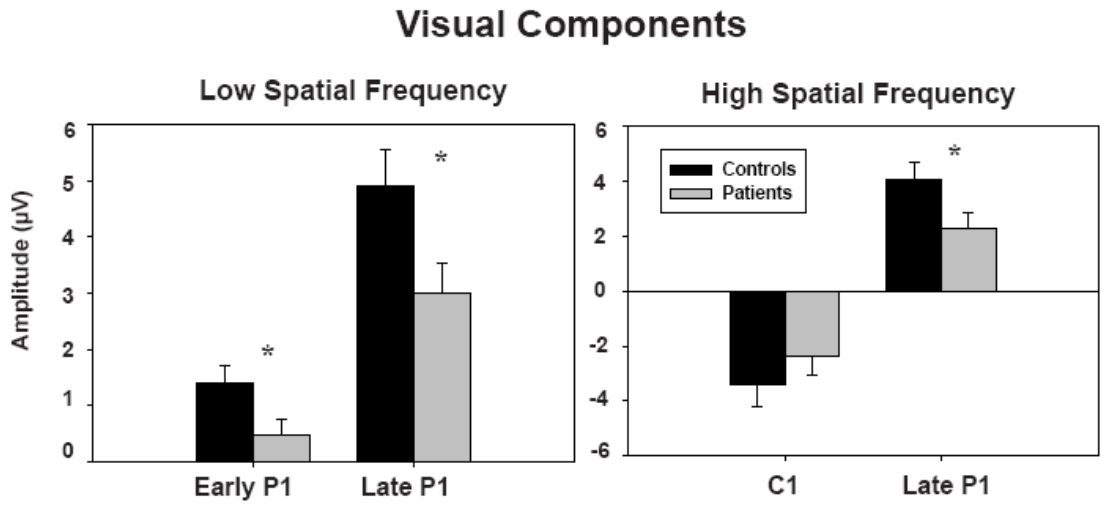


Figure 4. Patients' v. controls' amplitudes in response to low spatial frequency and high spatial frequency stimuli. Error bars represent the standard error of the mean for patients and controls.

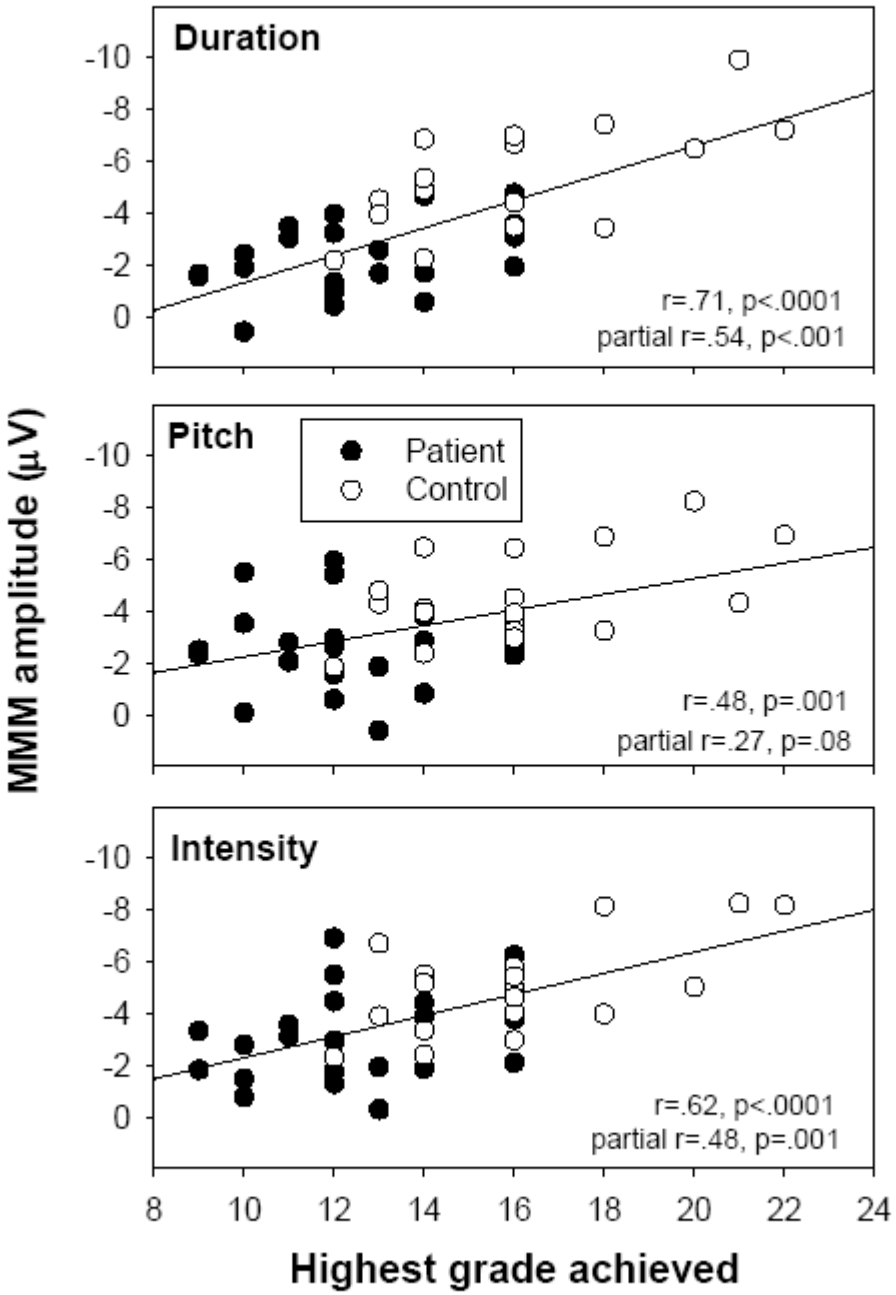


Figure 5. Correlations between MMN amplitudes to each deviant type and premorbid educational status in patients and controls.

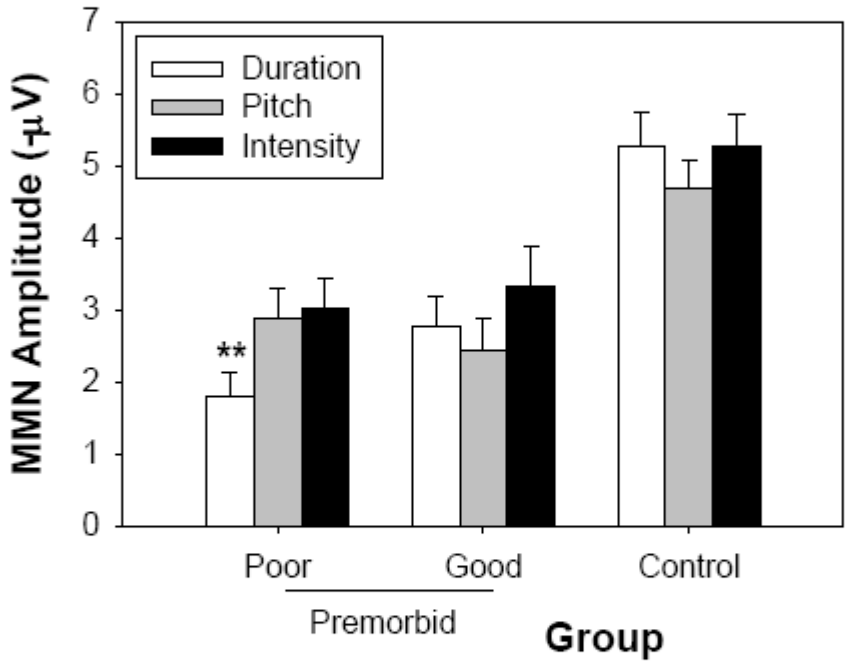


Figure 6. MMN amplitudes in response to deviant types in patients with good and poor premorbid functioning and in controls. ** p<.002

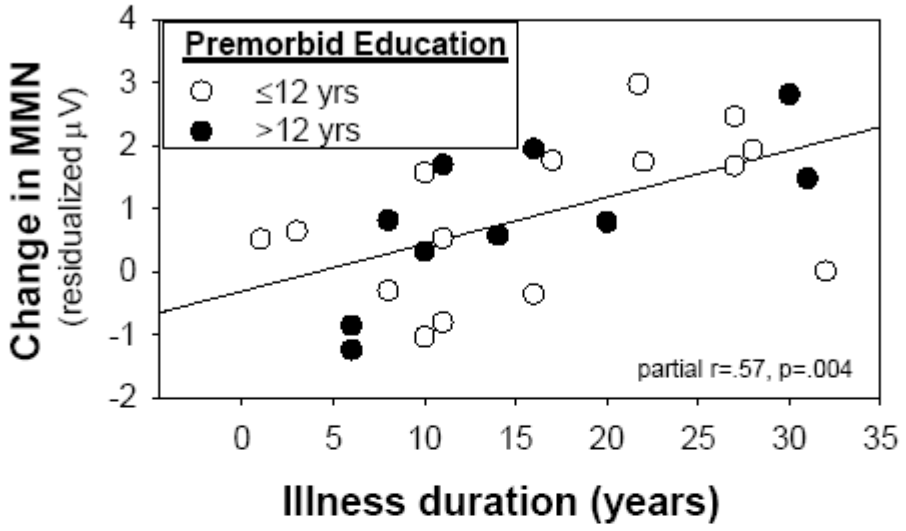
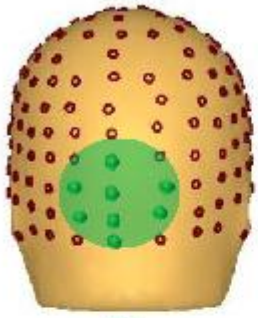


Figure 7. Correlations between change in MMN amplitudes and years of illness duration for patients with good v. poor premorbid function. MMN values are residualized relative to contributions of good vs. poor premorbid function.

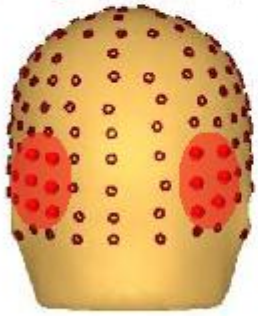
APPENDIX

Electrode Placement

Visual



C1
(High density: A14, A15, A22, A23, A24, A25, A27, A28
Corresponding 10/20: O1, P0Z, OZ, O2)



P1
(High density: E31, E30, E29, A11, A10, A9 (R) B8, B7, B6, B13, B12, B11
Corresponding 10/20: (L) P03, P07, P5, P09 (R) P04, P08, P6, P010)

Auditory

MMN
(High Density: C1, D1, D2, D3
Corresponding10/20: Fz, FCz, and Cz)

Data were collected from a high density montage, as described in Methods. Because of the custom montage, the electrodes do not have standard 10/20 designations. The electrodes highlighted above reflect the high density montage.

Amplitudes of Patients and Controls

Mismatch Negativity

Deviant Type	**Controls (n=19) Mean ± SD**	**Patients (n=26) Mean ± SD**
Duration	-5.3 ± 2.1	-2.3 ± 1.3 ***
Frequency	-4.7 ± 1.7	-2.1 ± 3.2 **
Intensity	-5.3 ± 1.9	-2.0 ± 6.0 *

Visual Measures

Spatial Frequency	**Component**		
High	**C1**	-3.4 ± 4.0	-2.4 ± 3.0
	Late P1	4.1 ± 3.3	2.3 ± 2.1 *
Low	**Early P1**	1.4 ± 1.4	.5 ± 1.3 *
	Late P1	4.9 ± 3.6	2.9 ± 1.9 *

* p <.05, ** p <.005, *** p<.0001

Supplementary Table 2. Latency Intervals

Component		Selected for Study (ms)	Significantly different as determined by t-tests (ms)
Auditory (MMN)	Duration	200-250	118.7-128.5, 161-275 (p=.05) 165-271 (p=.01)
	Frequency	100-190	69-249 (p=.05) 129-187 (p=.01)
	Intensity	140-200	150-214 (p=.05) 171-187 (p=.01)
Visual (HSF)	C1	90-125	
	Late P1	125-160	(L) 138-157, 220-257 (p=.05) (R) 138-157, 218-286 (p=.05)
(LSF)	Early P1	90-125	(L) 136-159, 208-273 (R) 72-156, 210-282 (p=.05)
	Late P1	125-160	

Regression with Cohort, ERPs, and Education

Component	R^2 Change	F value	P value
Mismatch Negativity	.21	6.02	.002
HSF Visual (C1, Late P1)	.04	1.18	.32
LSF Visual (Early P1, Late P1)	.04	1.16	.33

BIBLIOGRAPHY

Adler, L. E., Pachtman, E., Franks, R. D., Pecevich, M., Waldo, M. C., & Freedman, R. (1982). Neurophysiological evidence for a defect in neuronal mechanisms involved in sensory gating in schizophrenia. *Biol Psychiatry, 17*(6), 639-654.

Alain, C., Hargrave, R., & Woods, D. L. (1998). Processing of auditory stimuli during visual attention in patients with schizophrenia. *Biol Psychiatry, 44*(11), 1151-1159.

Albus, M., Hubmann, W., Scherer, J., Dreikorn, B., Hecht, S., Sobizack, N., et al. (2002). A prospective 2-year follow-up study of neurocognitive functioning in patients with first-episode schizophrenia. *Eur Arch Psychiatry Clin Neurosci, 252*(6), 262-267.

Alho, K., Sainio, K., Sajaniemi, N., Reinikainen, K., & Naatanen, R. (1990). Event-related brain potential of human newborns to pitch change of an acoustic stimulus. *Electroencephalogr Clin Neurophysiol, 77*(2), 151-155.

Alho, K., Woods, D. L., & Algazi, A. (1994). Processing of auditory stimuli during auditory and visual attention as revealed by event-related potentials. *Psychophysiology, 31*(5), 469-479.

Alho, K., Woods, D. L., Algazi, A., Knight, R. T., & Naatanen, R. (1994). Lesions of frontal cortex diminish the auditory mismatch negativity. *Electroencephalogr Clin Neurophysiol, 91*(5), 353-362.

Ardekani, B. A., Nierenberg, J., Hoptman, M. J., Javitt, D. C., & Lim, K. O. (2003). MRI study of white matter diffusion anisotropy in schizophrenia. *Neuroreport, 14*(16), 2025-2029.

Association, A. (2000). *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision ed.). Washington: American Psychiatric Press Inc.

Association, A. P. (2000). *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision ed.): Washington: American Psychiatric Press Inc.

Atanasova, B., Graux, J., El Hage, W., Hommet, C., Camus, V., & Belzung, C. (2008). Olfaction: a potential cognitive marker of psychiatric disorders. *Neurosci Biobehav Rev, 32*(7), 1315-1325.

Bendixen, A., Prinz, W., Horvath, J., Trujillo-Barreto, N. J., & Schroger, E. (2008). Rapid extraction of auditory feature contingencies. *Neuroimage, 41*(3), 1111-1119.

Bleuler, E. (1920). *Lehrbuch der Psychiatrie*. Berlin, Germany: Springer Verlag.

Bodatsch, M., Ruhrmann, S., Wagner, M., Muller, R., Schultze-Lutter, F., Frommann, I., et al. (2010). Prediction of Psychosis by Mismatch Negativity. *Biol Psychiatry*.

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.

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.

Bruder, G., Kayser, J., Tenke, C., Rabinowicz, E., Friedman, M., Amador, X., et al. (1998). The time course of visuospatial processing deficits in schizophrenia: an event-related brain potential study. *J Abnorm Psychol, 107*(3), 399-411.

Buchsbaum, M. S. (1977). The middle evoked response components and schizophrenia. *Schizophr Bull, 3*(1), 93-104.

Butler, P. D., Abeles, I. Y., Weiskopf, N. G., Tambini, A., Jalbrzikowski, M., Legatt, M. E., et al. (2009). Sensory contributions to impaired emotion processing in schizophrenia. *Schizophr Bull, 35*(6), 1095-1107.

Butler, P. D., Hoptman, M. J., Nierenberg, J., Foxe, J. J., Javitt, D. C., & Lim, K. O. (2006). Visual white matter integrity in schizophrenia. *Am J Psychiatry, 163*(11), 2011-2013.

Butler, P. D., & Javitt, D. C. (2005). Early-stage visual processing deficits in schizophrenia. *Curr Opin Psychiatry, 18*(2), 151-157.

Butler, P. D., Martinez, A., Foxe, J. J., Kim, D., Zemon, V., Silipo, G., et al. (2007). Subcortical visual dysfunction in schizophrenia drives secondary cortical impairments. *Brain, 130*(Pt 2), 417-430.

Butler, P. D., Schechter, I., Zemon, V., Schwartz, S. G., Greenstein, V. C., Gordon, J., et al. (2001). Dysfunction of early-stage visual processing in schizophrenia. *Am J Psychiatry, 158*(7), 1126-1133.

Butler, P. D., Zemon, V., Schechter, I., Saperstein, A. M., Hoptman, M. J., Lim, K. O., et al. (2005). Early-stage visual processing and cortical amplification deficits in schizophrenia. *Arch Gen Psychiatry, 62*(5), 495-504.

Byun, M. S., Kim, J. S., Jung, W. H., Jang, J. H., Choi, J. S., Kim, S. N., et al. (2012). Regional cortical thinning in subjects with high genetic loading for schizophrenia. *Schizophr Res, 141*(2-3), 197-203.

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.

Censits, D. M., Ragland, J. D., Gur, R. C., & Gur, R. E. (1997). Neuropsychological evidence supporting a neurodevelopmental model of schizophrenia: a longitudinal study. *Schizophr Res, 24*(3), 289-298.

Chen, Y., Bidwell, L. C., & Norton, D. (2006). Trait vs. State Markers for Schizophrenia: Identification and Characterization through Visual Processes. *Curr Psychiatry Rev, 2*(4), 431-438.

Cheour-Luhtanen, M., Alho, K., Sainio, K., Rinne, T., Reinikainen, K., Pohjavuori, M., et al. (1996). The ontogenetically earliest discriminative response of the human brain. *Psychophysiology, 33*(4), 478-481.

Clark, K. A., Nuechterlein, K. H., Asarnow, R. F., Hamilton, L. S., Phillips, O. R., Hageman, N. S., et al. (2011). Mean diffusivity and fractional anisotropy as indicators of disease and genetic liability to schizophrenia. *J Psychiatr Res, 45*(7), 980-988.

Clark, V. P., & Hillyard, S. A. (1996). Spatial selective attention affects early extrastriate but not striate components of the visual evoked potential. *J Cogn Neurosci, 8*, 387-402.

Cowan, N., Winkler, I., Teder, W., & Naatanen, R. (1993). Memory prerequisites of mismatch negativity in the auditory event-related potential (ERP). *J Exp Psychol Learn Mem Cogn, 19*(4), 909-921.

Derrington, A. M., & Lennie, P. (1984). Spatial and temporal contrast sensitivities of neurones in lateral geniculate nucleus of macaque. *J Physiol, 357*, 219-240.

Di Russo, F., Martinez, A., Sereno, M. I., Pitzalis, S., & Hillyard, S. A. (2002). Cortical sources of the early components of the visual evoked potential. *Hum Brain Mapp, 15*(2), 95-111.

Dickinson, D., & Harvey, P. D. (2009). Systemic hypotheses for generalized cognitive deficits in schizophrenia: a new take on an old problem. *Schizophr Bull, 35*(2), 403-414.

Dickinson, D., Ramsey, M. E., & Gold, J. M. (2007). Overlooking the obvious: a meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. *Arch Gen Psychiatry, 64*(5), 532-542.

Doniger, G. M., Foxe, J. J., Murray, M. M., Higgins, B. A., & Javitt, D. C. (2002). Impaired visual object recognition and dorsal/ventral stream interaction in schizophrenia. *Arch Gen Psychiatry, 59*(11), 1011-1020.

Donohoe, G., Frodl, T., Morris, D., Spoletini, I., Cannon, D. M., Cherubini, A., et al. (2010). Reduced occipital and prefrontal brain volumes in dysbindin-associated schizophrenia. *Neuropsychopharmacology, 35*(2), 368-373.

Donohoe, G., Morris, D. W., De Sanctis, P., Magno, E., Montesi, J. L., Garavan, H. P., et al. (2008). Early visual processing deficits in dysbindin-associated schizophrenia. *Biol Psychiatry, 63*(5), 484-489.

Dorph-Petersen, K. A., Pierri, J. N., Wu, Q., Sampson, A. R., & Lewis, D. A. (2007). Primary visual cortex volume and total neuron number are reduced in schizophrenia. *J Comp Neurol, 501*(2), 290-301.

Draganova, R., Eswaran, H., Murphy, P., Huotilainen, M., Lowery, C., & Preissl, H. (2005). Sound frequency change detection in fetuses and newborns, a magnetoencephalographic study. *Neuroimage, 28*(2), 354-361.

Fischer, C., Morlet, D., Bouchet, P., Luaute, J., Jourdan, C., & Salord, F. (1999). Mismatch negativity and late auditory evoked potentials in comatose patients. *Clin Neurophysiol, 110*(9), 1601-1610.

Ford, J. M., & Hillyard, S. A. (1981). Event-related potentials (ERPs) to interruptions of a steady rhythm. *Psychophysiology, 18*(3), 322-330.

Ford, J. M., Roth, W. T., & Kopell, B. S. (1976). Auditory evoked potentials to unpredictable shifts in pitch. *Psychophysiology, 13*(1), 32-39.

Foxe, J. J., Doniger, G. M., & Javitt, D. C. (2001). Early visual processing deficits in schizophrenia: impaired P1 generation revealed by high-density electrical mapping. *Neuroreport, 12*(17), 3815-3820.

Funke, B., Finn, C. T., Plocik, A. M., Lake, S., DeRosse, P., Kane, J. M., et al. (2004). Association of the DTNBP1 locus with schizophrenia in a U.S. population. *Am J Hum Genet, 75*(5), 891-898.

Green, M. F., Kern, R. S., & Heaton, R. K. (2004). Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. *Schizophr Res, 72*(1), 41-51.

Green, M. F., Schooler, N. R., Kern, R. S., Frese, F. J., Granberry, W., Harvey, P. D., et al. (2011). Evaluation of functionally meaningful measures for clinical trials of cognition enhancement in schizophrenia. *Am J Psychiatry, 168*(4), 400-407.

Hari, R., Hamalainen, M., Kaukoranta, E., Makela, J., Joutsiniemi, S. L., & Tiihonen, J. (1989). Selective listening modifies activity of the human auditory cortex. *Exp Brain Res, 74*(3), 463-470.

Hazlett, E. A., Buchsbaum, M. S., Haznedar, M. M., Newmark, R., Goldstein, K. E., Zelmanova, Y., et al. (2008). Cortical gray and white matter volume in unmedicated schizotypal and schizophrenia patients. *Schizophr Res, 101*(1-3), 111-123.

Heaton, R. K., Gladsjo, J. A., Palmer, B. W., Kuck, J., Marcotte, T. D., & Jeste, D. V. (2001). Stability and course of neuropsychological deficits in schizophrenia. *Arch Gen Psychiatry, 58*(1), 24-32.

Heinrichs, R. W., & Zakzanis, K. K. (1998). Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology, 12*(3), 426-445.

Hirayasu, Y., McCarley, R. W., Salisbury, D. F., Tanaka, S., Kwon, J. S., Frumin, M., et al. (2000). Planum temporale and Heschl gyrus volume reduction in schizophrenia: a magnetic resonance imaging study of first-episode patients. *Arch Gen Psychiatry, 57*(7), 692-699.

Holcomb, H. H., Ritzl, E. K., Medoff, D. R., Nevitt, J., Gordon, B., & Tamminga, C. A. (1995). Tone discrimination performance in schizophrenic patients and normal volunteers: impact of stimulus presentation levels and frequency differences. *Psychiatry Res, 57*(1), 75-82.

Holzman, P. S. (1972). Assessment of perceptual functioning in schizophrenia. *Psychopharmacologia, 24*(1), 29-41.

Howard, R., Rabins, P. V., Seeman, M. V., & Jeste, D. V. (2000). Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: an international consensus. The International Late-Onset Schizophrenia Group. *Am J Psychiatry, 157*(2), 172-178.

Hughes, C., Kumari, V., Soni, W., Das, M., Binneman, B., Drozd, S., et al. (2003). Longitudinal study of symptoms and cognitive function in chronic schizophrenia. *Schizophr Res, 59*(2-3), 137-146.

Huotilainen, M., Kujala, A., Hotakainen, M., Parkkonen, L., Taulu, S., Simola, J., et al. (2005). Short-term memory functions of the human fetus recorded with magnetoencephalography. *Neuroreport, 16*(1), 81-84.

Jaaskelainen, I. P., Pekkonen, E., Alho, K., Sinclair, J. D., Sillanaukee, P., & Naatanen, R. (1995). Dose-related effect of alcohol on mismatch negativity and reaction time performance. *Alcohol, 12*(6), 491-495.

Jablensky, A. (2010). The diagnostic concept of schizophrenia: its history, evolution, and future prospects. *Dialogues Clin Neurosci, 12*(3), 271-287.

Javitt, D. C. (1987). Negative schizophrenic symptomatology and the PCP (phencyclidine) model of schizophrenia. *Hillside J Clin Psychiatry, 9*(1), 12-35.

Javitt, D. C. (2000). Intracortical mechanisms of mismatch negativity dysfunction in schizophrenia. *Audiol Neurootol, 5*(3-4), 207-215.

Javitt, D. C. (2007). Glutamate and schizophrenia: phencyclidine, N-methyl-D-aspartate receptors, and dopamine-glutamate interactions. *Int Rev Neurobiol, 78*, 69-108.

Javitt, D. C. (2009a). Sensory processing in schizophrenia: neither simple nor intact. *Schizophr Bull, 35*(6), 1059-1064.

Javitt, D. C. (2009b). When doors of perception close: bottom-up models of disrupted cognition in schizophrenia. *Annu Rev Clin Psychol, 5*, 249-275.

Javitt, D. C., Doneshka, P., Zylberman, I., Ritter, W., & Vaughan, H. G., Jr. (1993). Impairment of early cortical processing in schizophrenia: an event-related potential confirmation study. *Biol Psychiatry, 33*(7), 513-519.

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., Liederman, E., Cienfuegos, A., & Shelley, A. M. (1999). Panmodal processing imprecision as a basis for dysfunction of transient memory storage systems in schizophrenia. *Schizophr Bull, 25*(4), 763-775.

Javitt, D. C., Shelley, A., & Ritter, W. (2000). Associated deficits in mismatch negativity generation and tone matching in schizophrenia. *Clin Neurophysiol, 111*(10), 1733-1737.

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., Spencer, K. M., Thaker, G. K., Winterer, G., & Hajos, M. (2008). Neurophysiological biomarkers for drug development in schizophrenia. *Nat Rev Drug Discov, 7*(1), 68-83.

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.

Javitt, D. C., Strous, R. D., Grochowski, S., Ritter, W., & Cowan, N. (1997). Impaired precision, but normal retention, of auditory sensory ("echoic") memory information in schizophrenia. *J Abnorm Psychol, 106*(2), 315-324.

Javitt, D. C., & Zukin, S. R. (1991). Recent advances in the phencyclidine model of schizophrenia. *Am J Psychiatry, 148*(10), 1301-1308.

Jeffreys, D. A., & Axford, J. G. (1972). Source locations of pattern-specific components of human visual evoked potentials. II. Component of extrastriate cortical origin. *Exp Brain Res, 16*(1), 22-40.

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.

Kane, N. M., Curry, S. H., Butler, S. R., & Cummins, B. H. (1993). Electrophysiological indicator of awakening from coma. *Lancet, 341*(8846), 688.

Kantrowitz, J. T., & Javitt, D. C. (2010). N-methyl-d-aspartate (NMDA) receptor dysfunction or dysregulation: the final common pathway on the road to schizophrenia? *Brain Res Bull, 83*(3-4), 108-121.

Kaplan, E. (1991). The receptive field structure of retinal ganglion cells in cat and monkey. In A. G. Leventhal (Ed.), *Vision and visual dysfunction* (pp. 10-40
). Boston, MA: CRC Press.

Kasai, K., Shenton, M. E., Salisbury, D. F., Hirayasu, Y., Onitsuka, T., Spencer, M. H., et al. (2003). Progressive decrease of left Heschl gyrus and planum temporale gray matter volume in first-episode schizophrenia: a longitudinal magnetic resonance imaging study. *Arch Gen Psychiatry, 60*(8), 766-775.

Kaukoranta, E., Sams, M., Hari, R., Hamalainen, M., & Naatanen, R. (1989). Reactions of human auditory cortex to a change in tone duration. *Hear Res, 41*(1), 15-21.

Kay, S. R. (1990). Positive-negative symptom assessment in schizophrenia: psychometric issues and scale comparison. *Psychiatr Q, 61*(3), 163-178.

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull, 13*(2), 261-276.

Kiang, M., Light, G. A., Prugh, J., Coulson, S., Braff, D. L., & Kutas, M. (2007). Cognitive, neurophysiological, and functional correlates of proverb interpretation abnormalities in schizophrenia. *J Int Neuropsychol Soc, 13*(4), 653-663.

Kraepelin, E. (1899). *Psychiatrie. Ein Lehrbuch für Studierende und Aerzte.* (6th Edition ed.). Austria: Barth.

Lee, K., Yoshida, T., Kubicki, M., Bouix, S., Westin, C. F., Kindlmann, G., et al. (2009). Increased diffusivity in superior temporal gyrus in patients with schizophrenia: a Diffusion Tensor Imaging study. *Schizophr Res, 108*(1-3), 33-40.

Leitman, D. I., Laukka, P., Juslin, P. N., Saccente, E., Butler, P., & Javitt, D. C. (2010). Getting the cue: sensory contributions to auditory emotion recognition impairments in schizophrenia. *Schizophr Bull, 36*(3), 545-556.

Leitman, D. I., Sehatpour, P., Higgins, B. A., Foxe, J. J., Silipo, G., & Javitt, D. C. (2010). Sensory deficits and distributed hierarchical dysfunction in schizophrenia. *Am J Psychiatry, 167*(7), 818-827.

Leung, A., & Chue, P. (2000). Sex differences in schizophrenia, a review of the literature. *Acta Psychiatr Scand Suppl, 401*, 3-38.

Liberman, R. P., Wallace, C. J., Blackwell, G., Kopelowicz, A., Vaccaro, J. V., & Mintz, J. (1998). Skills training versus psychosocial occupational therapy for persons with persistent schizophrenia. *Am J Psychiatry, 155*(8), 1087-1091.

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

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.

Light, G. A., Williams, L. E., Minow, F., Sprock, J., Rissling, A., Sharp, R., et al. (2010). Electroencephalography (EEG) and event-related potentials (ERPs) with human participants. *Curr Protoc Neurosci, Chapter 6*, Unit 6 25 21-24.

Loeb, P. (1996). *Independent Living Scales Manual*. San Antonio, TX: Psychological Corporation, Hartcourt Brace Jovanovich.

Lund, J. S. (1973). Organization of neurons in the visual cortex, area 17, of the monkey (Macaca mulatta). *J Comp Neurol, 147*(4), 455-496.

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.

Martinez, A., Anllo-Vento, L., Sereno, M. I., Frank, L. R., Buxton, R. B., Dubowitz, D. J., et al. (1999). Involvement of striate and extrastriate visual cortical areas in spatial attention. *Nat Neurosci, 2*(4), 364-369.

Mausbach, B. T., Moore, R., Bowie, C., Cardenas, V., & Patterson, T. L. (2009). A review of instruments for measuring functional recovery in those diagnosed with psychosis. *Schizophr Bull, 35*(2), 307-318.

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

Merigan, W. H., & Maunsell, J. H. (1993). How parallel are the primate visual pathways? *Annu Rev Neurosci, 16*, 369-402.

Michie, P. T., Budd, T. W., Todd, J., Rock, D., Wichmann, H., Box, J., et al. (2000). Duration and frequency mismatch negativity in schizophrenia. *Clin Neurophysiol, 111*(6), 1054-1065.

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.

Moberg, P. J., Agrin, R., Gur, R. E., Gur, R. C., Turetsky, B. I., & Doty, R. L. (1999). Olfactory dysfunction in schizophrenia: a qualitative and quantitative review. *Neuropsychopharmacology, 21*(3), 325-340.

Mohamed, S., Paulsen, J. S., O'Leary, D., Arndt, S., & Andreasen, N. (1999). Generalized cognitive deficits in schizophrenia: a study of first-episode patients. *Arch Gen Psychiatry, 56*(8), 749-754.

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.

Molholm, S., Ritter, W., Murray, M. M., Javitt, D. C., Schroeder, C. E., & Foxe, J. J. (2002). Multisensory auditory-visual interactions during early sensory processing in humans: a high-density electrical mapping study. *Brain Res Cogn Brain Res, 14*(1), 115-128.

Mukundan, C. R. (1986). Middle latency components of evoked potential responses in schizophrenics. *Biol Psychiatry, 21*(11), 1097-1100.

Murray, M. M., Foxe, J. J., Higgins, B. A., Javitt, D. C., & Schroeder, C. E. (2001). Visuo-spatial neural response interactions in early cortical processing during a simple reaction time task: a high-density electrical mapping study. *Neuropsychologia, 39*(8), 828-844.

Naatanen, R. (1979). Orienting and Evoked Potentials. In H. Kimmel, E. van Olst & J. Orlebeke (Eds.), *The orienting reflex in humans* (pp. 61-75). New Jersey: Erlbaum.

Naatanen, R. (1995). The mismatch negativity: a powerful tool for cognitive neuroscience. *Ear Hear, 16*(1), 6-18.

Naatanen, R., & Gaillard, A. (1983). The N2 deflection of the ERP and the orienting reflex. In A. Gaillard & W. Ritter (Eds.), *Tutorials in event-related potential research: endogenous components* (pp. 119-141). Amsterdam: North Holland.

Naatanen, R., Gaillard, A. W., & Mantysalo, S. (1978). Early selective-attention effect on evoked potential reinterpreted. *Acta Psychol (Amst), 42*(4), 313-329.

Naatanen, R., Jacobsen, T., & Winkler, I. (2005). Memory-based or afferent processes in mismatch negativity (MMN): a review of the evidence. *Psychophysiology, 42*(1), 25-32.

Naatanen, R., Jiang, D., Lavikainen, J., Reinikainen, K., & Paavilainen, P. (1993). Event-related potentials reveal a memory trace for temporal features. *Neuroreport, 5*(3), 310-312.

Naatanen, R., & Kahkonen, S. (2009). Central auditory dysfunction in schizophrenia as revealed by the mismatch negativity (MMN) and its magnetic equivalent MMNm: a review. *Int J Neuropsychopharmacol, 12*(1), 125-135.

Naatanen, R., & Michie, P. T. (1979). Early selective attention effects on the evoked potential. A critical review and reinterpretation. *Biol Psychiatry, 8*, 81-136.

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.

Neeltje, E., van Haren, M., Schnack, H., Cahn, W., van den Heuvel, M., Lepage, C., et al. (2011). Changes in cortical thickness during the course of illness in schizophrenia. *Arch Gen Psychiatry, 68*(9), 871-880.

Nieuwenhuys, R. (1994). The neocortex. An overview of its evolutionary development, structural organization and synaptology. *Anat Embryol (Berl), 190*(4), 307-337.

Nordby, H., Roth, W. T., & Pfefferbaum, A. (1988). Event-related potentials to breaks in sequences of alternating pitches or interstimulus intervals. *Psychophysiology, 25*(3), 262-268.

Norman, J. (2002). Two visual systems and two theories of perception: An attempt to reconcile the constructivist and ecological approaches. *Behav Brain Sci, 25*(1), 73-96; discussion 96-144.

Paavilainen, P., Alho, K., Reinikainen, K., Sams, M., & Naatanen, R. (1991). Right hemisphere dominance of different mismatch negativities. *Electroencephalogr Clin Neurophysiol, 78*(6), 466-479.

Paavilainen, P., Simola, J., Jaramillo, M., Naatanen, R., & Winkler, I. (2001). Preattentive extraction of abstract feature conjunctions from auditory stimulation as reflected by the mismatch negativity (MMN). *Psychophysiology, 38*(2), 359-365.

Pekkonen, E., Jousmaki, V., Kononen, M., Reinikainen, K., & Partanen, J. (1994). Auditory sensory memory impairment in Alzheimer's disease: an event-related potential study. *Neuroreport, 5*(18), 2537-2540.

Peralta, V., & Cuesta, M. J. (2001). How many and which are the psychopathological dimensions in schizophrenia? Issues influencing their ascertainment. *Schizophr Res, 49*(3), 269-285.

Phillips, O. R., Nuechterlein, K. H., Asarnow, R. F., Clark, K. A., Cabeen, R., Yang, Y., et al. (2011). Mapping corticocortical structural integrity in schizophrenia and effects of genetic liability. *Biol Psychiatry, 70*(7), 680-689.

Pulvermuller, F., & Shtyrov, Y. (2006). Language outside the focus of attention: the mismatch negativity as a tool for studying higher cognitive processes. *Prog Neurobiol, 79*(1), 49-71.

Rasser, P. E., Schall, U., Todd, J., Michie, P. T., Ward, P. B., Johnston, P., et al. (2009a). Gray matter deficits, mismatch negativity, and outcomes in schizophrenia. *Schizophr Bull, 37*(1), 131-140.

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

Rasser, P. E., Schall, U., Todd, J., Michie, P. T., Ward, P. B., Johnston, P., et al. (2011). Gray matter deficits, mismatch negativity, and outcomes in schizophrenia. *Schizophr Bull, 37*(1), 131-140.

Revheim, N., Butler, P. D., Schechter, I., Jalbrzikowski, M., Silipo, G., & Javitt, D. C. (2006). Reading impairment and visual processing deficits in schizophrenia. *Schizophr Res, 87*(1-3), 238-245.

Revheim, N., & Medalia, A. (2004). The independent living scales as a measure of functional outcome for schizophrenia. *Psychiatr Serv, 55*(9), 1052-1054.

Revheim, N., Schechter, I., Kim, D., Silipo, G., Allingham, B., Butler, P., et al. (2006). Neurocognitive and symptom correlates of daily problem-solving skills in schizophrenia. *Schizophr Res, 83*(2-3), 237-245.

Riley, B., & Kendler, K. S. (2006). Molecular genetic studies of schizophrenia. *Eur J Hum Genet, 14*(6), 669-680.

Riley, E. M., McGovern, D., Mockler, D., Doku, V. C., S, O. C., Fannon, D. G., et al. (2000). Neuropsychological functioning in first-episode psychosis--evidence of specific deficits. *Schizophr Res, 43*(1), 47-55.

Russeler, J., Altenmuller, E., Nager, W., Kohlmetz, C., & Munte, T. F. (2001). Event-related brain potentials to sound omissions differ in musicians and non-musicians. *Neurosci Lett, 308*(1), 33-36.

Saccuzzo, D. P., & Braff, D. L. (1981). Early information processing deficit in schizophrenia. New findings using schizophrenic subgroups and manic control subjects. *Arch Gen Psychiatry, 38*(2), 175-179.

Saha, S., Chant, D., Welham, J., & McGrath, J. (2005). A systematic review of the prevalence of schizophrenia. *PLoS Med, 2*(5), e141.

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.

Sams, M., Hamalainen, M., Antervo, A., Kaukoranta, E., Reinikainen, K., & Hari, R. (1985). Cerebral neuromagnetic responses evoked by short auditory stimuli. *Electroencephalogr Clin Neurophysiol, 61*(4), 254-266.

Sams, M., Kaukoranta, E., Hamalainen, M., & Naatanen, R. (1991). Cortical activity elicited by changes in auditory stimuli: different sources for the magnetic N100m and mismatch responses. *Psychophysiology, 28*(1), 21-29.

Sams, M., Paavilainen, P., Alho, K., & Naatanen, R. (1985). Auditory frequency discrimination and event-related potentials. *Electroencephalogr Clin Neurophysiol, 62*(6), 437-448.

Santor, D. A., Ascher-Svanum, H., Lindenmayer, J. P., & Obenchain, R. L. (2007). Item response analysis of the Positive and Negative Syndrome Scale. *BMC Psychiatry, 7*, 66.

Sayed, Y., & Garrison, J. M. (1983). The dopamine hypothesis of schizophrenia and the antagonistic action of neuroleptic drugs--a review. *Psychopharmacol Bull, 19*(2), 283-288.

Saykin, A. J., Shtasel, D. L., Gur, R. E., Kester, D. B., Mozley, L. H., Stafiniak, P., et al. (1994). Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia. *Arch Gen Psychiatry, 51*(2), 124-131.

Schechter, I., Butler, P. D., Zemon, V. M., Revheim, N., Saperstein, A. M., Jalbrzikowski, M., et al. (2005). Impairments in generation of early-stage transient visual evoked potentials to magno- and parvocellular-selective stimuli in schizophrenia. *Clin Neurophysiol, 116*(9), 2204-2215.

Scherg, M., & Berg, P. (1991). Use of prior knowledge in brain electromagnetic source analysis. *Brain Topogr, 4*(2), 143-150.

Scherg, M., Vajsar, J., & Picton, T. (1989). A source analysis of the late human auditory evoked potentials. *Journal of Cognitive Neuroscience, 5*, 825-828.

Schlaepfer, T. E., Harris, G. J., Tien, A. Y., Peng, L. W., Lee, S., Federman, E. B., et al. (1994). Decreased regional cortical gray matter volume in schizophrenia. *Am J Psychiatry, 151*(6), 842-848.

Schroeder, C. E., Mehta, A. D., & Givre, S. J. (1998). A spatiotemporal profile of visual system activation revealed by current source density analysis in the awake macaque. *Cereb Cortex, 8*(7), 575-592.

Schroger, E. (1998). Application of ERP measures in psychological research: measurement and interpretation of mismatch negativity. *Behavior Research Methods, Instruments, and Computers, 30*(1), 131-145.

Schroger, E., & Wolff, C. (1996). Mismatch response of the human brain to changes in sound location. *Neuroreport, 7*(18), 3005-3008.

Schuepbach, D., Keshavan, M. S., Kmiec, J. A., & Sweeney, J. A. (2002). Negative symptom resolution and improvements in specific cognitive deficits after acute treatment in first-episode schizophrenia. *Schizophr Res, 53*(3), 249-261.

Selemon, L. D., & Begovic, A. (2007). Stereologic analysis of the lateral geniculate nucleus of the thalamus in normal and schizophrenic subjects. *Psychiatry Res, 151*(1-2), 1-10.

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.

Shenton, M. E., Kikinis, R., Jolesz, F. A., Pollak, S. D., LeMay, M., Wible, C. G., et al. (1992). Abnormalities of the left temporal lobe and thought disorder in schizophrenia. A quantitative magnetic resonance imaging study. *N Engl J Med, 327*(9), 604-612.

Shin, K. S., Kim, J. S., Kang, D. H., Koh, Y., Choi, J. S., O'Donnell, B. F., et al. (2009). Pre-attentive auditory processing in ultra-high-risk for schizophrenia with magnetoencephalography. *Biol Psychiatry, 65*(12), 1071-1078.

Smiley, J. F., Rosoklija, G., Mancevski, B., Mann, J. J., Dwork, A. J., & Javitt, D. C. (2009). Altered volume and hemispheric asymmetry of the superficial cortical layers in the schizophrenia planum temporale. *Eur J Neurosci, 30*(3), 449-463.

Sokolov, E. N., Spinks, J. A., Naatanen, R., & Lyytinen, H. (2002). *The orienting response in information processing*. Mahwah, NJ: Erlbaum.

Startup, M., Jackson, M. C., & Bendix, S. (2002). The concurrent validity of the Global Assessment of Functioning (GAF). *Br J Clin Psychol, 41*(Pt 4), 417-422.

Strous, R. D., Cowan, N., Ritter, W., & Javitt, D. C. (1995). Auditory sensory ("echoic") memory dysfunction in schizophrenia. *Am J Psychiatry, 152*(10), 1517-1519.

Sun, J., Kuo, P. H., Riley, B. P., Kendler, K. S., & Zhao, Z. (2008). Candidate genes for schizophrenia: a survey of association studies and gene ranking. *Am J Med Genet B Neuropsychiatr Genet, 147B*(7), 1173-1181.

Sweet, R. A., Pierri, J. N., Auh, S., Sampson, A. R., & Lewis, D. A. (2003). Reduced pyramidal cell somal volume in auditory association cortex of subjects with schizophrenia. *Neuropsychopharmacology, 28*(3), 599-609.

Todd, J., Michie, P. T., & Jablensky, A. V. (2003). Association between reduced duration mismatch negativity (MMN) and raised temporal discrimination thresholds in schizophrenia. *Clin Neurophysiol, 114*(11), 2061-2070.

Todd, J., Michie, P. T., Schall, U., Karayanidis, F., Yabe, H., & Naatanen, R. (2008). Deviant matters: duration, frequency, and intensity deviants reveal different patterns of mismatch negativity reduction in early and late schizophrenia. *Biol Psychiatry, 63*(1), 58-64.

Tootell, R. B., Silverman, M. S., Hamilton, S. L., Switkes, E., & De Valois, R. L. (1988). Functional anatomy of macaque striate cortex. V. Spatial frequency. *J Neurosci, 8*(5), 1610-1624.

Townsend, L. A., Malla, A. K., & Norman, R. M. (2001). Cognitive functioning in stabilized first-episode psychosis patients. *Psychiatry Res, 104*(2), 119-131.

Turetsky, B. I., Bilker, W. B., Siegel, S. J., Kohler, C. G., & Gur, R. E. (2009). Profile of auditory information-processing deficits in schizophrenia. *Psychiatry Res, 165*(1-2), 27-37.

Umbricht, D., Bates, J., Lieberman, J., Kane, J., & Javitt, D. (2006). Electrophysiological Indices of Automatic and Controlled Auditory Information Processing in First-Episode, Recent-Onset and Chronic Schizophrenia. *Biological Psychiatry, 59*(8), 762-772.

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. S., 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.

Ungerleider, L., & Mishkin, M. (1982). Two cortical visual systems. In D. Ingle, R. Mansfield & M. Goodale (Eds.), *The analysis of visual behavior* (pp. 549-586). Cambridge, MA: MIT Press.

Van den Oord, E. J., Rujescu, D., Robles, J. R., Giegling, I., Birrell, C., Bukszar, J., et al. (2006). Factor structure and external validity of the PANSS revisited. *Schizophr Res, 82*(2-3), 213-223.

Vidyasagar, T. R. (1999). A neuronal model of attentional spotlight: parietal guiding the temporal. *Brain Res Brain Res Rev, 30*(1), 66-76.

Whitford, T. J., Grieve, S. M., Farrow, T. F., Gomes, L., Brennan, J., Harris, A. W., et al. (2006). Progressive grey matter atrophy over the first 2-3 years of illness in first-episode schizophrenia: a tensor-based morphometry study. *Neuroimage, 32*(2), 511-519.

Williams, N. M., Preece, A., Morris, D. W., Spurlock, G., Bray, N. J., Stephens, M., et al. (2004). Identification in 2 independent samples of a novel schizophrenia risk haplotype of the dystrobrevin binding protein gene (DTNBP1). *Arch Gen Psychiatry, 61*(4), 336-344.

Woldorff, M. G., Hillyard, S. A., Gallen, C. C., Hampson, S. R., & Bloom, F. E. (1998). Magnetoencephalographic recordings demonstrate attentional modulation of mismatch-related neural activity in human auditory cortex. *Psychophysiology, 35*(3), 283-292.

Wynn, J. K., Sugar, C., Horan, W. P., Kern, R., & Green, M. F. (2010). Mismatch negativity, social cognition, and functioning in schizophrenia patients. *Biol Psychiatry, 67*(10), 940-947.

Yeap, S., Kelly, S. P., Sehatpour, P., Magno, E., Garavan, H., Thakore, J. H., et al. (2008). Visual sensory processing deficits in Schizophrenia and their relationship to disease state. *Eur Arch Psychiatry Clin Neurosci, 258*(5), 305-316.

Yeap, S., Kelly, S. P., Sehatpour, P., Magno, E., Javitt, D. C., Garavan, H., et al. (2006). Early visual sensory deficits as endophenotypes for schizophrenia: high-density electrical mapping in clinically unaffected first-degree relatives. *Arch Gen Psychiatry, 63*(11), 1180-1188.

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.

Zion-Golumbic, E., Deouell, L. Y., Whalen, D. H., & Bentin, S. (2007). Representation of harmonic frequencies in auditory memory: a mismatch negativity study. *Psychophysiology, 44*(5), 671-679.