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Demand and Modality of Directed Attention Modulate “Pre-attentive” Sensory Processes in Schizophrenia Patients and Nonpsychiatric Controls

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Abstract

Background—Mismatch negativity (MMN) and P3a are event related potential (ERP) measures of early sensory information processing. These components are usually conceptualized as being “pre-attentive” and therefore immune to changes with variations in attentional functioning. This study aimed to determine whether manipulations of attention influence the amplitudes and latencies of MMN and P3a and, if so, the extent to which these early sensory processes govern concurrent behavioral vigilance performance in schizophrenia patients and normal subjects.

Methods—Schizophrenia patients (SZ; n=20) and Nonpsychiatric Control Subjects (NCS; n=20) underwent auditory ERP testing to assess MMN and P3a across 4 EEG recording sessions in

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Contributors

Authors Gregory Light and Sung-Hyouk Park designed the study. Authors Joyce Sprock, Marlena Pela and Daniel Mathias recruited and assessed patient participants. Author Sung-Hyouk Park collected electrophysiological data. Author Anthony Rissling, managed the literature searches. Author Catherine Sugar and Anthony Rissling undertook the statistical analysis. Authors Anthony Rissling, Sung-Hyouk Park, Catherine Sugar and Gregory Light wrote the manuscript. Author David Braff offered supplemental support and revisions of the manuscript. Author Richard Sharp provided technical support including programming and equipment manufacture. All authors have approved the final manuscript.

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which attentional demand (low vs. high) and sensory modality of directed attention (visual vs. auditory) were experimentally varied.

Results—Across conditions, SZ patients exhibited deficits in MMN and P3a amplitudes. Significant amplitude and latency modulation were observed in both SZ and NCS but there were no group-by-condition interactions. The amount of MMN amplitude attenuation from low- to high-demand tasks was significantly associated with increased vigilance performance in both SZ and NCS groups ($r=-0.67$ and $r=-0.60$).

Conclusions—Attentional demand and modality of directed attention significantly influence the amplitude and latencies of “pre-attentive” ERP components in both SZ and NCS. Deficits in MMN and P3a were not “normalized” when attention was directed to the auditory stimuli in schizophrenia patients. The adaptive modulation of early sensory information processing appears to govern concurrent attentional task performance. MMN and P3a may serve as a gateway to some higher order cognitive operations necessary for psychosocial functioning.

Introduction

Navigation through stimulus-laden environments requires the adaptive processing of a variety of sensory inputs. When attention is focused on a task, the efficient processing of background stimuli must occur in order for a person to attend to important changes in the environment while gating out task irrelevant stimuli. Successful real-world functioning requires efficiency at the earliest stages of information processing in order to automatically allocate finite processing resources to salient stimuli and, reciprocally, to prevent irrelevant stimuli from flooding **attention** (Braff and Light, 2004; Callaway and Naghdi, 1982; Javitt, 2009). Schizophrenia patients exhibit a spectrum of deficits ranging from abnormalities in basic sensory processing to impairments in complex cognitive tasks. Cascade models suggest that at least some of the cognitive deficits observed in schizophrenia patients arise from dysfunction in the coordination of neural activity in the early stages of sensory information processing (Green and Nuechterlein, 1999; Javitt et al., 1995; Leitman et al., 2010; Martínez et al., 2011; Tiitinen et al., 1994). Event-related potential (ERP) measures allow investigators to quantify the neural processing associated with sensory-perceptual and cognitive events with millisecond precision, including the routine processing of sensory stimuli and the subsequent transitions to higher-order cognitive functions (Luck, 2005; Näätänen, 1992; Rissling et al., 2010).

Mismatch negativity (MMN) and P3a are ERP components which are automatically evoked in the context of an auditory oddball paradigm. In such a paradigm, a sequence of frequently (e.g., 80%) presented “standard” stimuli is occasionally (e.g., 20%) interrupted by non-target, task-irrelevant “oddball” stimuli that differ in some physical characteristic such as duration or pitch. The MMN response begins as early as 50 ms after the onset of oddball stimuli, peaks after an additional 100-150 ms and is usually followed by the positive-going “P3a” component in the 225–300 ms range at frontocentral electrodes (Friedman et al., 2001; Näätänen, 1992; Polich, 2007; Squires et al., 1975). These two ERP measures are widely considered indices of “pre-attentive” operations since they can be elicited in the absence of directed attention and require no overt behavioral responses. Whereas MMN is believed to reflect automatic sensory discrimination, P3a is thought to index the rapid involuntary redirection of attention (Frank et al., 2012; Polich, 2007).

MMN can be assessed in fetuses, newborn babies (Alho et al., 1990; Draganova et al., 2005; Huotilainen et al., 2003; Nashida et al., 2000) and even individuals who are comatose or in a persistent vegetative state prior to regaining consciousness (Kane et al., 1996; Morlet et al., 2000; Wijnen et al., 2007). Both MMN and P3a are important measures in neuropsychiatric research since they show significant deficits in schizophrenia patients (Kiang et al., 2009a;

Mathalon et al., 2000b; Michie, 2001; Rissling et al., 2012; Turetsky et al., 2007; Turetsky et al., 1998; Umbricht and Krljes, 2005) and are associated with important clinical features of the illness, including social cognition (Wynn et al., 2010), functional status and outcome (Friedman et al., 2012; Kawakubo and Kasai, 2006; Light and Braff, 2005a, b; Rasser et al., 2011). These measures have been used as endophenotypes in genetic association studies (Hall et al., 2007; Hall et al., 2006), as biomarkers for tracking the emergence and progression of deficits across the course of illness (Atkinson et al., 2011; Jahshan et al., 2012; Kaur et al., 2012; Salisbury et al., 2002; Shaikh et al., 2011; Umbricht et al., 2006) and as responses to pharmacologic and psychosocial interventions (Kawakubo et al., 2007; Lavoie et al., 2007; Umbricht et al., 2003).

While many studies have examined different stimulus characteristics and recording parameters for eliciting deficits (e.g., Umbricht et al., 2003), a debate continues concerning the susceptibility of MMN to attentional manipulation under highly focused attention in nonpsychiatric individuals (see Haroush et al., 2010 for review). Further, little is known about the potential effects of attentional demands and modality of directed attention on either MMN or P3a in schizophrenia patients. These ERP components have been studied in schizophrenia using a variety of background tasks which vary in attentional demand and modality (auditory/visual) of directed attention, including silent video (Light and Braff, 2005a), low-volume video (Michie et al., 2002), reading a book (Muller-Gass et al., 2005), performing a difficult visual continuous performance task (CPT) (Paavilainen et al., 1993; Umbricht et al., 2006) or while actively attending to target tones (Lavoie et al., 2007). Meta-analyses of MMN in schizophrenia (Umbricht and Krljes, 2005) confirm that deficits are robust, with a mean effect size $d=0.99$, although effect sizes in individual studies have ranged from $d=-0.47$ to $d=4.37$. It is possible that variations in the background task demands account for some of the discrepancies observed across studies (Niznikiewicz et al., 2005).

MMN is usually elicited in the absence of directed attention while subjects engage in a visual distracter task (Light and Braff, 2005a, b; Light et al., 2007; Michie et al., 2002; Paavilainen et al., 1993). A few studies of nonpsychiatric subjects engaging in difficult dichotic listening tasks have shown larger MMN amplitudes in response to auditory stimuli presented in the attended ear (Alain and Woods, 1997; Trejo et al., 1995; Woldorff et al., 1991), which suggests possible attentional influences on MMN. The measurement of responses to attended stimuli does not, however, readily allow for the differentiation of MMN from N2b, a large-amplitude ERP component which occurs in the same latency range as MMN in response to **target** stimuli in the attended channel (Kasai et al., 1999; Naatanen, 1991; Näätänen et al., 1982; Sussman, 2007).

Most MMN studies have shown that auditory MMN is unaffected when attention is directed to the visual modality (Alho et al., 1992; Dittmann-Balcar et al., 1999; Kathmann et al., 1999; Otten et al., 2000; Paavilainen et al., 1993) or by the visual processing load (Alho et al., 1992; Dittmann-Balcar et al., 1999; Muller-Gass et al., 2006; Otten et al., 2000). In the case of the subsequent P3a component, some studies of normal subjects have shown amplitude attenuation with competing visual task demands (Harmony et al., 2000; Kathmann et al., 1999) whereas other studies have observed no effects (Muller-Gass et al., 2007; Munka and Berti, 2006; Paavilainen et al., 1993; **Yucel et al., 2005**) or even amplitude increases (Zhang et al., 2006).

The extent to which MMN and P3a are influenced by attentional manipulations is therefore unresolved in the extant literature and has not, to our knowledge, been systematically investigated in schizophrenia patients. In addition, no previous studies have examined the relationship of MMN and P3a modulation to concurrently assessed attentional functioning. Given the importance of identifying biomarkers that are sensitive to the activity of

remediable cognitive systems in schizophrenia (Swerdlow, 2011), we examined the malleability of MMN and P3a under different task demands in schizophrenia patients and normal control subjects (NCS). This experiment was designed to quantify potential attentional influences on MMN and P3a and to address longstanding questions in the neuropsychiatric literature such as: Can directed attention improve preattentive/involuntary functions in schizophrenia patients, even if deficient at baseline? If MMN and P3a are sensitive to attentional modulation, is the amount of MMN or P3a change correlated with concurrent attentional task performance as would be suggested by information processing cascade models? Such findings would substantiate the oft-hypothesized links between antecedent sensory processes and subsequent downstream cognitive functions.

To our knowledge, no previous studies have examined the attentional modulation of preattentive sensory processes (MMN, P3a) as it relates to shifts of attentional demand or cognitive capacity. The aims of this study were to: 1) assess the extent to which variations in attentional load and modality of directed attention influence the amplitude and latencies of MMN and P3a responses to non-target stimuli; 2) determine whether there are differential modulatory effects of attention in schizophrenia patients and NCS (i.e., do patients exhibit a greater benefit of directed attention to the auditory stimuli or normalized performance?); and 3) examine whether any observed neurophysiological attentional effects are associated with concurrently measured indices of attentional functioning or the clinical characteristics of the patient cohort. Based on the literature, we hypothesized that: 1) schizophrenia patients would exhibit MMN and P3a amplitude deficits across conditions; 2) MMN and P3a would show significant modulation when attention was directed to the auditory modality compared to the commonly used passive visual condition; 3) deficits in schizophrenia patients would not be ameliorated with attention directed to the auditory stimuli; and 4) MMN and P3a would be associated with indices of attentional functioning in the control and schizophrenia patient groups.

Methods and Materials

Subjects

Forty subjects including 20 schizophrenia (SZ) patients (10 male, 10 female) and 20 age-matched **nonpsychiatric** comparison subjects (NCS; 10 male, 10 female) participated in the study. All subjects were assessed for their capacity to provide informed consent and provided written informed consent per UCSD IRB-approved forms (protocol #:080199). Urine toxicology screens were used to rule out recent drug use. Participants were diagnostically assessed using the Structured Clinical Interview for DSM-IV (First et al., 1995). No SZ patient had an Axis I diagnosis other than SZ, and the NCS did not have any Axis I diagnoses or history of psychosis in a first-degree relative. Participants in both groups denied a history of significant neurologic insults such as major head trauma and/or loss of consciousness. Clinical symptoms in the SZ patients were evaluated with the Scales for the Assessment of Negative Symptoms (SANS; Andreasen, 1984a) and Positive Symptoms (SAPS; Andreasen, 1984b). Functional status was evaluated with the Modified Global Assessment of Functioning (GAF; Hall, 1995) and the Scale of Functioning (SOF; Rapaport, 1996). Table 1 shows the demographic characteristics of both groups and the clinical characteristics of the SZ group. The SZ patients were all medicated with 2nd generation antipsychotics and were recruited from community residential facilities. NCS were recruited through newspaper and internet advertisements per our established methods (Kiang et al., 2009b; Kirihaara et al., 2012; Rissling et al., 2012). Audiometer testing was used to ensure that all participants had normal hearing and could detect 1000 Hz tones in both ears at 40-dB sound pressure level.

Auditory Oddball Paradigm

EEG acquisition and data processing procedures are described in the Supplemental Methods. Briefly, subjects were presented with binaural tones (1-kHz 85-dB sound pressure level, with 1-millisecond increase/decrease) with a fixed stimulus onset asynchrony (SOA) of 500 ms using a San Diego Instruments stimulus generator. Auditory stimuli consisted of standard (84%, 50-ms), duration deviant (DD; 8%, 100-ms) and white noise deviant (WND; 8%, 50-ms) tones presented to subjects using foam insert earphones.

Experimental Procedures

Auditory stimuli were presented using a fixed order across 4 identical recordings that varied only in attentional demand and modality of directed attention (Figure 1). All ERPs were assessed in response to non-target stimuli while subjects: 1) passively watched a silent video (low demand, visual modality); 2) performed the identical-pairs CPT (high demand, visual modality); or were instructed to press a button when they detected the 3) WND (low-demand “easy”, auditory modality) or 4) DD (high-demand “difficult”, auditory modality).

During the low visual demand condition, subjects watched a silent cartoon video and were instructed that they might be asked questions about the video at the end of testing and that they should ignore the auditory stimuli. During the high visual demand condition, subjects were required to perform a visual Continuous Performance Test-Identical Pairs version (CPT-IP; Comblatt et al., 1988) and told to ignore the auditory stimuli. The CPT-IP is considered a gold standard neurocognitive measure of vigilance functioning as determined by an expert consensus panel convened for the Measurement and Treatment Research to Improve Cognition in Schizophrenia initiative (Green and Nuechterlein, 2004). Prior to testing and EEG recording, standardized instructions and a block of practice CPT-IP trials were administered to ensure that participants understood the instructions and would perform the CPT-IP task appropriately. The CPT-IP consisted of 2-, 3-, and 4-digit subtests. During the CPT-IP task, participants were required to respond with a button press when the same number occurred twice in a row. The CPT-IP stimuli were flashed for 50 ms once every 1,000 ms. The subtests each consisted of 150 trials and continued for 2.5 minutes. In each subtest, 30 trials (20%) were target trials and required a response. Participants were given a short break after completing each subtest (7.5 min).

During the auditory target detection recording sessions, subjects were instructed to press a button in response to target stimuli (WND, low-demand auditory; DD, high-demand auditory) in 2 separate recordings with target order counterbalanced. Standardized instructions were followed by a practice block to ensure that participants understood the task. To avoid learning or carryover effects across conditions (Naatanen et al., 1993), the auditory discrimination tasks were always administered following the low and high demand visual directed attention tasks. Participants were given a break every 7.5 minutes during each task as well as between tasks. Data from one control subject was lost due to equipment malfunction. Four schizophrenia patients were unable to detect the DD and could therefore not complete the high auditory demand condition.

Behavioral Performance and EEG Data Processing

Performance data were collected while subjects completed the CPT-IP (i.e., high visual demand) and when attention was directed to the auditory stimuli to detect either WND or DD stimuli (i.e., low and high auditory demand). In the CPT-IP task, a response occurring between 150 and 1500 ms of target presentation was scored as correct. Behavioral dependent measures included: reaction time to correct trials and d' as an index of sensitivity (Young et al., 2009a).

MMN and P3a waveforms were generated by subtracting ERPs in response to standard tones from the ERPs generated in response to the DD or WND tones. ERP measurements were recorded on DD trials for the low-auditory demand and on WND trials for the high auditory demand conditions respectively. This ensured that ERP components across all conditions were measured in response to non-target stimuli even when attention was directed to the auditory stimuli (Figure 1). In addition, only trials with correct rejections (i.e., no button press response) to non-target stimuli were used for generating ERPs in order to minimize the impact of potentially confounding N2b and P3b components. The order of the target stimuli was counterbalanced across 2 recordings in order to compare non-target ERP waveforms to DD and WND stimuli while subjects were attending to auditory stimuli.

ERP waveforms were low-pass filtered at 20 Hz (zero-phase shift, 24-dB/octave roll-off). For both MMN and P3a, the largest responses were present at electrode Fz (Figure 2). MMN and P3a peaks were initially inspected following automated peak scanning procedures in the 135-220, and 225-350 ms windows respectively from Fz, which served as the basis of subsequent analyses. Peaks were then manually corrected if necessary. Separate time windows for the automated processing script were not used for different trial or stimulus types. Determination of a single fixed peak latency for each component also involved examination of: 1) butterfly plots with topographic voltage distribution maps; 2) mean global field power to confirm acceptable signal to noise ratio by requiring that post-stimulus mean global activity was at least twice pre-stimulus activity; and 3) individual frontocentral and mastoid electrodes to confirm polarity inversion at mastoid electrodes for MMN analyses. Once the single peak latency was established for the ERP components, the amplitudes were measured as the mean voltage in the 25 ms surrounding this peak.

Statistical Analyses

To determine how key dependent variables differed as a function of Group (SZ, NCS), Target Stimulus Type (DD, WND), and Task Paradigm (Video, CPT-IP, Auditory), we used general linear mixed models (GLMMs). GLMMs allow for flexible covariance structures to account for within-subject correlations, easily accommodate covariates of all types and automatically handle missing data, producing unbiased estimates as long as the pattern of missing data is ignorable (i.e. depends only on observed factors). Specifically, we fit models with MMN and P3a ERP components of amplitude and peak latency, as well as behavioral measures (reaction time, d') as the outcomes. We included group as a between-subjects variable, Stimulus Type and Task Paradigm as within-subjects factors, and their two- and three-way interactions to obtain fully parameterized primary models. Age and gender were included as covariates. We were also interested in effects of sensory modality (Visual vs. Auditory) and Attentional Demand (High vs. Low) which correspond to specific contrasts (or equivalently reparameterizations) within the primary model framework. Similarly, comparisons between groups for a specific task paradigm or within group between task paradigms could then be performed using appropriate contrasts (equivalent to two-sample or paired t-tests respectively) to further characterize the patterns of observed results. All models were fit in SAS PROC Mixed with restricted maximum likelihood estimation (REML) and used an unstructured covariance matrix to provide maximum flexibility. All post hoc comparisons were two-tailed with α -level=0.05. To assess the relationships between MMN and P3a with behavioral performance and clinical symptoms, Spearman's non-parametric correlation coefficients (r_s) were examined.

Results

Event-Related Potentials

Table 2 provides a summary of main effects and interactions for MMN and P3a variables as well as visual and auditory vigilance performance. Significant main effects of group were found for both MMN and P3a amplitudes across task paradigms, with SZ exhibiting significantly reduced amplitudes compared to NCS. The difference waves to DD and WND across task paradigms for each group are presented in Figures 1-2 while the amplitudes and latencies are presented in Figure 3.

MMN Amplitude—Main effects were observed for Group ($F_{1, 34.1} 6.73, p.0139$), Stimulus Type ($F_{1, 35.8} 90.26, p<.0001$) and Task Paradigm ($F_{2, 34.3} 7.81, p.0016$) but there were no significant interaction effects (Figures 2-3). The main effect of task paradigm (video, CPT-IP, audio) implies the presence of attentional effects for MMN. Importantly, no differential attentional modulation was observed between SZ and NCP groups (group-by-task paradigm interaction). We also examined specific contrasts for sensory modality auditory (2 measurements) vs. visual (4 measurements) and attentional demand high (CPT-IP and auditory-DD target) vs. low (video and auditory-WN target). We found significant effects of both sensory modality ($F_{1, 33.9} 5.97, p <.05$; Auditory MMN responses were more negative) and attentional demand ($F_{1, 34.8} 45.35, p<.0001$; High demand MMN scores were less negative; Figure 4).

P3a Amplitude—Main effects were observed for Group ($F_{1, 33} 12.03, p.01$) and Task Paradigm ($F_{2, 33.8} 17.31, p.0001$). Attentional effects were present for P3a amplitude with a significant stimulus type-by-task paradigm interaction ($F_{2, 33.6} 28.02, p<0.0001$) (Figures 2-3) with reduced DD P3a amplitudes present in the CPT relative to the other tasks following a similar pattern to MMN findings. For WN stimuli, however, the effect of task paradigm was much more pronounced ($F_{2, 30} 31.46, p<0.001$) with amplitudes linearly increasing across the 3 tasks consistent with (Combs and Polich, 2006). Follow-up tests indicated that P3a amplitude was significantly attenuated in the high- (i.e., CPT-IP) vs. low visual-demand (i.e., video) ($F_{1, 34.2} 13.21, p.001$) and auditory target detection ($F_{1, 31.3} 15.36, p.001$) conditions. Importantly, no differential attentional modulation was observed between SZ and NCP groups (group-by-task paradigm interaction). We also examined specific contrasts for sensory modality auditory (2 measurements) vs. visual (4 measurements) and attentional demand high (CPT-IP and auditory-DD target) vs. low (video and auditory-WN target). We found significant effects of both sensory modality ($F_{1, 32.9} 27.90, p.0001$; Auditory P3a responses were more positive) and attentional demand ($F_{1, 30.8} 26.18, p<.0001$; High demand p3a scores were less positive).

MMN Latency—Main effects were observed for Stimulus Type ($F_{1, 35.5} 259.98, p.0001$) with significantly shorter MMN latency to the WND than to the DD stimuli and Task Paradigm ($F_{2, 31.7} 16.77, p.0001$); and significantly longer MMN latency to the ATD vs. CPT and Video tasks. No significant stimulus or task paradigm interactions with group were present (Figures 2-3). Specific contrasts revealed significant effects of both sensory modality ($F_{1, 30.3} 32.40, p.0001$, with MMN peaking later in auditory than visual tasks) and attentional demand ($F_{1, 28.1} 50.42, p<.0001$ with MMN peaking later in High than low demand.)

Amplitude and latency modulation indices were not calculated for auditory target detection tasks since MMN may have been influenced by carryover N2b effects. Nevertheless, there were no significant group differences in latency in this or any other task and, as noted above, only EEG trials with correct non-responses (i.e., button presses) were included in averaging.

P3a Latency—Main effects were observed for Stimulus Type ($F_{1, 34.3}490.12$, $p<.0001$ with significantly shorter P3a latency to the WND than to the DD stimuli and Task Paradigm ($F_{2, 35.5}11.50$, $p<.0001$ with significantly shorter P3a latency to the CPT and Video than ATD tasks.) No significant stimulus or task paradigm interactions with group were present (Figures 2-3). Specific contrasts revealed significant effects of both sensory modality ($F_{1, 34.1}21.54$, $p<.0001$; P3a peaking later in auditory than visual tasks) and attentional demand ($F_{1, 35}30.19$, $p<.0001$; MMN peaking later in High vs. low demand.)

Vigilance Performance (d')

Main effects were observed for Group ($F_{1, 31.8}22.85$, $p<.0001$) and Task Paradigm ($F_{2, 36}131.32$, $p<.0001$). For the CPT-IP, the patients performed significantly worse than NCS in sensitivity (d') ($F_{1, 34.2}41.89$, $p<.0001$), with an expected pattern of performance decrements with increasing task difficulty observed across groups (Figure 5). In the auditory target detection tasks, the discriminability to the WND (i.e., “easy-to-detect”) targets was better than to the more difficult-to-detect DD targets ($F_{1, 36}38.50$, $p<.0001$) across groups. Patients exhibited significantly reduced performance (d') to both the DD ($F_{1, 33.8}10.90$, $p<.01$) and WND ($F_{1, 34.5}6.42$, $p<.05$) (Figure 5).

Reaction Time

Main effects were observed for Group ($F_{1, 33.5}9.59$, $p<.01$) and Task Paradigm ($F_{2, 35}55.92$, $p<.0001$), with both groups slower to respond overall in the CPT-IP than the ATD tasks ($F_{1, 35}41.12$, $p<.0001$) and to the DD than to the WN ($F_{1, 35}21.32$, $p<.0001$).

Neurophysiological Associations with Clinical and Behavioral Measures

In schizophrenia patients, sensitivity (d') to the DD during the high-demand, auditory directed attention task was correlated with clinical ratings of positive (SAPS; $r_s=-0.70$, $p<.01$) and negative (SANS; $r_s=-0.35$, $p<.01$) symptoms and psychosocial functioning (GAF; $r_s=0.71$, $p<.001$; SOF $r_s=0.66$, $p<.001$). P3a amplitude to the DD during the low-demand visual task was also correlated with positive (SAPS; $r_s=-0.75$, $p<.001$) and negative (SANS; $r_s=-0.40$, $p<.01$) symptom ratings and psychosocial functioning (SOF; $r_s=0.69$, $p<.001$).

MMN amplitude elicited in response to WND stimuli during auditory target detection was correlated with overall visual CPT performance ($r_s=-0.53$, $p<.001$). MMN amplitude *modulation* to the WND stimuli was also highly correlated with overall CPT-IP performance in both the SZ ($r_s=-0.67$, $p<.001$) and NCS ($r_s=-0.60$, $p<.01$; Figure 6) with decreases in responses relating to increased performance. For P3a, CPT-IP performance was correlated with DD amplitude during the high-demand visual ($r_s=-0.46$, $p<.01$) and low-demand auditory ($r_s=0.44$, $p<.01$) tasks and the P3a latency modulation to DD stimuli ($r_s=-0.45$, $p<.01$). CPT-IP performance was also significantly associated with WND P3a amplitude during the high-demand visual ($r_s=0.53$, $p<.001$) and high-demand auditory ($r_s=0.45$, $p<.01$) tasks. No other significant associations were observed.

Discussion

This experiment was designed to assess the extent to which early “pre-attentive” event-related potential measures of sensory information processing (i.e., mismatch negativity and P3a) are influenced by variations in attentional demand and modality of directed attention. Given the importance of identifying biomarkers that are sensitive to the activity of remediable cognitive systems in schizophrenia (Swerdlow, 2011), we examined the malleability of MMN and/or P3a under different experimental task paradigms in both schizophrenia patients and **nonpsychiatric** comparison subjects. This study answers

longstanding questions in the neuropsychiatric literature such as: can directed attention improve preattentive functions in schizophrenia patients, even if deficient at baseline?

In this study, participants underwent 4 EEG recordings where attentional demand (low vs. high) and modality (visual, auditory) of directed attention were experimentally manipulated (Figure 1). We found that: 1) schizophrenia patients have robust deficits in MMN and P3a amplitudes across tasks (Figures 2-3) as well as pronounced cognitive impairments in visual and auditory attentional functioning (Figure 5); 2) MMN and P3a amplitudes and latencies are significantly modulated by variations in attentional demand and modality of directed attention (Figure 4); 3) schizophrenia patients exhibit normal modulation of MMN and P3a amplitudes across tasks (Figures 2-3), although deficits are not ameliorated with attention directed to the auditory stimuli; and 4) the amount of MMN modulation with variations in attentional load is highly associated with concurrent vigilance performance in both schizophrenia patients and normal control subjects (Figure 6).

Results of this study demonstrate that the processing of task-irrelevant auditory stimuli can be modulated at an early sensory level under conditions of highly focused selective attention in both schizophrenia patients and **nonpsychiatric** subjects. As noted above, directed attention to the auditory stimuli did not normalize either MMN or P3a deficits in schizophrenia patients or significantly increase ERP amplitudes in either group (cf, Alain and Woods, 1994; Arnott and Alain, 2002). When attention was directed to the auditory stimuli, MMN and P3a latencies were prolonged suggesting that top-down target vs. non-target decision-related processes interfered with the routine processing of the non-target stimuli (Figure 2). In contrast, directed attention away from the auditory stimuli to a demanding visual attention task resulted in significant diminution of MMN amplitudes comparably in both groups. Thus, the attentional modulation of MMN and P3a amplitudes and latencies under varying visual or auditory attentional loads appears to be intact in schizophrenia patients.

Several important associations among neurophysiological, clinical, and cognitive measures were observed. Importantly, the amount of MMN amplitude modulation from the low- to high-demand visual background processing tasks was highly associated with concurrent vigilance performance on the CPT-IP in both schizophrenia patients and **nonpsychiatric** subjects. As shown in Figure 6, participants with the greatest reduction of MMN amplitude from the low- to high-demand visual directed attention tasks exhibited the best overall vigilance performance, suggesting the ability to filter out task-irrelevant auditory stimuli is associated with better concurrent attentional task performance. This reduction in MMN amplitude with increased visual attentional demand may be a neurophysiologic correlate of the experience of the “tuning out” of irrelevant background stimuli when completing a demanding foreground task (in this case, the CPT-IP). In contrast, some participants exhibited a significant increase in their MMN amplitudes to task-irrelevant auditory stimuli when completing the foreground behavioral task. Those subjects displayed significantly worse attentional functioning and may therefore be characterized as being relatively more prone to distraction by task irrelevant stimuli. This pattern of results substantiates the oft hypothesized links between early sensory processes and concurrent behavioral/cognitive functioning and raises the question of whether modulation of MMN is a neurophysiological representation of selective attention. The results also suggest that the adaptive modulation of early sensory information processing partially governs the efficient performance of some cognitive operations necessary for psychosocial functioning.

Many other expected patterns of results were confirmed in this study which increased our confidence in the fidelity of the novel findings. For example, behavioral indices of attentional performance (reaction time) and sensitivity (d') were deficient in schizophrenia

patients in both the visual and auditory modalities. The CPT-IP yielded the expected performance decrement with increasing difficulty across tasks. A similar pattern was demonstrated in the auditory target detection task: behavioral discriminability was greater for the easier-to-detect white noise (WN) stimuli compared to stimuli that differed in duration (DD). The ERP results also followed the expected patterns of longer latencies and larger MMN to DD vs. WN stimuli. In addition, P3a amplitude was highly correlated with both positive symptoms and psychosocial functioning in the schizophrenia group, consistent with previous studies (Hermens et al., 2010; Light et al., 2012; Mathalon et al., 2000a).

An important limitation of this study is that the medications in the schizophrenia patients were not experimentally controlled. In a previous cross-sectional study of a large cohort (n=429) of schizophrenia patients, we reported that medication status does not appear to significantly impact MMN and P3a responses (Rissling et al., 2012) consistent with other studies (Schall et al., 1998; Umbricht et al., 1998, 1999). We cannot exclude the possibility of medications exerting some influence, however, on the pattern of results--although medicated patients exhibited normal modulation of ERP components across tasks and robust correlations with vigilance functioning similar in magnitude to those observed in **nonpsychiatric** subjects (Figure 6).

Another limitation of this study is that the within-subjects design does not readily allow for the assessment of carryover effects in the auditory target detection tasks. Although these tasks always followed the visual tasks with counterbalancing the auditory target/non-target stimulus order, (i.e., once a stimulus is a target, it maintains salience even after it is no longer a target in a separate recording session; Naatanen et al., 1993). It is therefore possible that MMN amplitudes in the auditory target detection tasks may have been confounded with N2b, a later ERP component related to processing target stimuli. Future studies using distinct subject groups without prior exposure to targets would be needed to disentangle MMN from N2b responses.

In addition to the relevance of this work to understanding the cognitive deficits of schizophrenia (Braff and Light, 2004; Callaway and Naghdi, 1982; Javitt, 2009), the current findings also contribute to long-standing debates about the relationships of sensory-based neurophysiological measures to various constructs of attention (Näätänen et al., 1978; Sussman et al., 2005; Sussman et al., 2002; Sussman, 2007; Woldorff et al., 1991). For example, since MMN and P3a demonstrate attentional modulation, should they still be considered "preattentive?" The extant literature suggests that these measures are functionally preattentive since they can be automatically elicited in the absence of directed attention, conscious control or even awareness on the part of the subject (Näätänen, 1992). That MMN and P3a are malleable under specific experimental manipulations--the amount of which is highly associated with cognitive capacity--does not undermine the substantial literature supporting their preattentive nature or utility in schizophrenia research as probes of early sensory processing deficits. Under basal conditions (i.e., the low-demand video task of this study) MMN and P3a are extremely stable over 1 year (ICCs in the 0.90 range) in both schizophrenia patients and controls (Light and Braff, 2005a; Light et al., 2012), predictive of conversion to psychosis in high-risk individuals (Brockhaus-Dumke et al., 2005; Jahshan et al., 2012; Michie et al., 2002), and are highly correlated with psychosocial functioning in schizophrenia patients and even healthy controls (Friedman et al., 2012; Kawakubo et al., 2007; Light and Braff, 2005a; Light et al., 2007; Wynn et al., 2010). In addition, MMN and P3a are now being used as endophenotypes in genomic studies (Hall et al., 2007; Hall et al., 2006) and as biomarkers of treatment response (Kawakubo et al., 2007; Lavoie et al., 2007). Furthermore, well-validated cross-species tests of both attentional functioning and MMN are currently available (Ehrlichman et al., 2008; Young et al., 2009a; Young et al., 2009b) and may be amenable to concurrent assessment for preclinical drug development contexts. These

(and other) characteristics have resulted in the view of MMN and P3a as “mature” neurophysiological measures (Green et al., 2009), perhaps even being the biomarkers “we’ve been waiting for” (Belger et al., 2012) in neuropsychiatric research. In conclusion, results from this experiment suggest changes in early automatic sensory processes are strongly associated with selective attention and may therefore serve as a gateway to higher cognitive and psychosocial functioning (Friedman et al., 2012; Kawakubo et al., 2007; Kawakubo and Kasai, 2006; Light and Braff, 2005a, b; Light et al., 2007; Rasser et al., 2011; Wynn et al., 2010).

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Figure 1. Experimental Design

Figure depicts the visual and auditory stimuli across tasks and stimulus types. The arrows denote modality of directed attention with number of arrows indicating attentional demand (low- vs. high-demand). Auditory stimuli included standard (S), duration deviant (D), and white noise (WN) stimuli. Average MMN and P3a ERP responses to nontarget stimuli from the Fz electrode site are shown for Schizophrenia Patients (red) and Healthy Controls C (blue) subjects. Scalp topography maps for MMN and P3a at each group is also provided.

Figure 2. MMN and P3a event-related potentials across tasks

Schizophrenia patients exhibited robust deficits across tasks. Main effects of task paradigm were present, demonstrating significant amplitude and latency modulation across tasks. For example, significant MMN amplitude reductions were present when subjects completed the high-demand visual CPT task (shaded region). In contrast, MMN amplitudes in the passive video and auditory target detection task were not significantly different. When attention was directed to the auditory stimuli, MMN and P3a latencies were significantly prolonged relative to the other task paradigms (shown by brackets). No group-by-task paradigm interactions were present, indicating that schizophrenia patients exhibited normal amplitude and latency modulation across tasks.

Figure 3. MMN and P3a amplitude and latency modulation at electrode Fz across task paradigms

Significant main effects of group were present, indicating amplitude deficits in schizophrenia patients. Main effects of task paradigm were present, demonstrating significant amplitude and latency modulation. Significant latency main effects were present with increased latencies to non-target stimuli when attention was directed to the auditory stimuli. Latencies were prolonged by 13-16 msec for MMN and 29-32 msec for P3a. No group-by-task paradigm interactions were present, indicating that schizophrenia patients exhibited normal amplitude and latency modulation across tasks. Note: * indicates a significant group difference.

Figure 4.

Across groups, MMN responses were larger under conditions with low vs. high task demand with no group by demand interaction. In contrast, P3a responses were larger in the high attentional demand conditions with no group by demand interaction. For both MMN and P3a, amplitudes were larger when attention was directed to the auditory vs. visual modality with no group by modality interaction. Note: * indicates a significant effect of modality and significant effect of task demand.

Figure 5.

Schizophrenia patients exhibited deficits in reaction time and sensitivity (d') in both the visual and auditory modalities. Expected patterns of performance decrement were observed with increasing task difficulty in both modalities of attention and both groups. Behavioral discriminability was greater for the easier-to-detect WN vs. DD stimuli across both groups.

Figure 6. Attentional modulation of MMN is associated with behavioral attentional performance
 Amount of MMN modulation (low- minus high-demand visual directed attention tasks) in response to WN stimuli is significantly correlated with CPT-IP behavioral performance in both schizophrenia patients and controls. Both groups exhibit shifts of processing resources from pre- to post-attentive levels of processing with increasing attentional demands. This pre-attentive ERP amplitude tradeoff (i.e., attenuation) was present in both groups. Subjects with a greater reduction in MMN amplitude with increased visual task demands had better CPT-IP attentional functioning.

Table 1

Demographic and clinical characteristics of the schizophrenia patient and nonpsychiatric comparison groups (means $\pm$ SD given where applicable).

Demographic and Clinical Characteristics	Schizophrenia Patients (n=20)		Nonpsychiatric Comparison Subjects (n=20)	
	Mean	SD	Mean	SD
Gender (% male)	50.00	---	50.00	----
Age (years)	50.00	7.80	48.00	6.49
Years of Education	13.00	2.70	15.00	1.96
Age of Illness Onset	22.00	6.00		
Duration of Illness	28.15	9.60		
Number of Hospitalizations	8.00	7.00		
SANS Total Score	13.15	6.00		
SAPS Total Score	8.75	4.60		
GAF	48.47	6.05		
SOF	43.42	5.30		

Abbreviations: SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; GAF, Global Assessment of Functioning; SOF, Scale of Functioning.

Table 2

Summary of General Linear Mixed Model Results (F Values) for ERP and Attentional Parameters.

MMN	Amplitude Effects	Latency Effects
Group (deficits in patients)	6.73 **	1.77
Stimulus Type (DD vs. WND)	90.26 ****	259.98 ****
Attentional Demand (High vs. Low)	45.35 ***	50.42 ****
Modality (Audio vs. Visual)	5.97 *	32.40 ****
Task Paradigm (Video, CPT, ATD)	7.81 **	16.77 ****
Stimulus Type-by-Task Paradigm	0.70	.63
Group-by-Stimulus Type	0.24	1.90
Group-by- Task Paradigm	1.93	3.23
P3a		
Group (deficits in patients)	12.03 ****	0.27
Stimulus Type (DD vs. WND)	1.52	490.12 ****
Attentional Demand (High vs. Low)	26.18 ****	30.19 ****
Modality (Audio vs. Visual)	27.90 ****	21.54 ****
Task Paradigm (Video, CPT, ATD)	17.31 ****	11.50 ****
Stimulus Type-by-Task Paradigm	28.02 ****	0.46
Group-by-Stimulus Type	0.15	0.56
Group-by- Attentional Condition	0.24	0.96
Attentional Performance	Sensitivity, d'	Reaction Time
Group (deficits in patients)	22.85 ****	9.59 **
Attentional Demand (High vs. Low)	38.50 ****	21.32 ***
Modality (Audio vs. Visual)	153.07 ****	41.12 ****
Group-by-Condition	2.31	2.27

*
p<0.05**
p<0.01***
p<0.001****
p<0.0001