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Automatic Sensory Information Processing Abnormalities across the Illness Course of Schizophrenia

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Abstract

Background—Deficits in automatic sensory discrimination, as indexed by a reduction in the mismatch negativity (MMN) and P3a event-related potential amplitudes, are well documented in chronic schizophrenia. However, MMN and P3a have not been sufficiently studied early in the course of psychotic illness. The present study aimed to investigate MMN, P3a, and reorienting negativity (RON) across the course of schizophrenia, from prodrome to the chronic phase of illness.

Methods—MMN, P3a, and RON were assessed in 118 subjects across 4 groups 1) prodromal patients putatively at risk for psychosis (N=26), 2) recent-onset patients (N=31), 3) chronic patients (N=33), and 4) normal controls (N=28) during a duration-deviant auditory oddball paradigm.

Results—Frontocentral deficits in MMN and P3a were present in all patient groups. The at-risk group's MMN and P3a amplitudes were intermediate between those of the control and recent-onset groups. The recent-onset and chronic groups, but not the at-risk group, showed significant RON amplitude reductions, relative to the control group. Associations between MMN, P3a, RON and psychosocial functioning were present in the chronic group only. Impaired P3a and RON correlated with more severe negative symptoms in the at-risk group.

Conclusions—Abnormalities in the automatic processes of sensory discrimination, orienting and reorienting of attention are evident in the early phases of schizophrenia and raise the possibility of progressive worsening across stages of the illness. The finding that MMN and P3a, but not RON, were reduced before psychosis onset supports the continued examination of these components as potential early biomarkers of schizophrenia.

Introduction

It is well documented that cognitive impairment is a hallmark of schizophrenia (Heaton *et al.*, 2001, Palmer *et al.*, 2009) and a better predictor of global functioning than clinical symptomatology (Green, 1996, Green *et al.*, 2000). Disturbances in multiple neurocognitive domains have been reported in the first episode of schizophrenia (Addington *et al.*, 2005, Bilder *et al.*, 2000, Mesholam-Gately *et al.*, 2009) as well as in the prodrome (Eastvold *et al.*, 2007, Jahshan *et al.*, 2010, Lencz *et al.*, 2006, Seidman *et al.*, 2010). The prodrome is the period that precedes illness onset and is characterized by a marked deviation from a person's normal level of functioning (Yung and McGorry, 1996). An emerging view is that

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the commonly observed clinical and cognitive deficits of schizophrenia patients may arise, at least in part by dysfunction in the coordination of neural activity at the earliest stages of sensory and cognitive information processing (Green and Nuechterlein, 1999, Javitt, 2009, Light *et al.*, 2006). Schizophrenia patients exhibit deficits in basic levels of sensory information processing (Leitman *et al.*, 2010, Turetsky *et al.*, 2009). Those general sensory processing abnormalities are present early in the course of the illness and even precede the emergence of psychotic symptoms (Cadenhead *et al.*, 2005, Quednow *et al.*, 2008). Event-related potentials (ERP) allow investigators to interrogate early sensory processes, including sensory discrimination and the orienting and subsequent reorienting of attention, which occur outside of an individual's awareness or conscious control (Callaway and Naghdi, 1982, Ford *et al.*, 2010, Holig and Berti, 2010, Rissling *et al.*, 2010).

In a passive auditory oddball paradigm, a duration-deviant stimulus elicits a mismatch negativity (MMN) response that peaks 100 to 200 ms after the onset of a stimulus deviance (Naatanen *et al.*, 1978). As MMN can be elicited even when participants do not attend to the stimuli, it is assumed to reflect an automatic, sensory-based deviance detection process (Picton *et al.*, 2000), although some studies have shown that MMN and deviance-related negative (DRN) components can be attenuated by strongly focused attention to some other stimulus sequence (Woldorff *et al.*, 1991, 1998).

Deficits in MMN generation using a variety of stimulation parameters (e.g., oddball stimuli that differ in pitch or duration) represent a remarkably robust finding in chronic schizophrenia (Javitt *et al.*, 2000a, Kiang *et al.*, 2009, Light and Braff, 2005a, b, Mathalon *et al.*, 2000, Shelley *et al.*, 1991, Umbricht and Krljes, 2005). Nevertheless, the extant literature on MMN in the early stages of the disease is mixed, with some studies identifying abnormalities (Devrim-Ucok *et al.*, 2008, Hermens *et al.*, 2010, Javitt *et al.*, 2000b) and others failing to detect any significant decrements in either duration or pitch MMN in patients with a psychotic illness duration of less than three years (Salisbury *et al.*, 2002, Umbricht *et al.*, 2006, Valkonen-Korhonen *et al.*, 2003). In a prospective study of first-hospitalized patients with schizophrenia (Salisbury *et al.*, 2007), a strong relationship was found between the progressive reductions of MMN amplitude and left hemisphere Heschl gyrus gray matter volume. To date, only one study has assessed MMN in individuals in the prodromal phase of schizophrenia (Brockhaus-Dumke *et al.*, 2005). Duration MMN amplitudes were slightly lower in at-risk patients compared to normal controls but this difference did not reach statistical significance. The clarification of the extent of MMN deficits in the prodrome contributes to the overall efforts to identify potential markers of vulnerability to schizophrenia and to understand the underlying pathological processes leading to the development of the illness.

Recent studies have also demonstrated that MMN is highly associated with psychosocial functioning in schizophrenia patients (Kawakubo *et al.*, 2007, Light and Braff, 2005b, Rasser *et al.*, 2011) as well as healthy subjects (Light *et al.*, 2007). Yet, only two studies have examined this relationship in first-episode patients; one showed that larger duration MMN is associated with a better score on a quality of life measure (Hermens *et al.*, 2010) while the other did not find a relationship between pitch MMN and social functioning (Salisbury *et al.*, 2007). Given the observation that the at-risk patients who do not convert to psychosis still show substantial impairment in social functioning at outcome (Ballon *et al.*, 2007), it is important to determine whether MMN is associated with the degree of functional disability in the early stage of illness.

In the ERP paradigm, the MMN is often followed by the P3a, a frontocentral positivity peaking between 250–300 ms. The P3a component is assumed to reflect the covert orienting or shift in attention (Friedman *et al.*, 2001). Several studies have found P3a amplitude in

response to infrequent nontarget or distracter stimuli to be decreased in schizophrenia patients (Grillon *et al.*, 1990a, 1990b, Grzella *et al.*, 2001, Mathalon *et al.*, 2000). Nonetheless, only one study has examined P3a in the early stages of the illness, finding impairment in first-episode psychosis patients (Valkonen-Korhonen *et al.*, 2003). To our knowledge, P3a has yet to be examined in subjects at risk for developing psychosis.

Automatic sensory discrimination and covert shifting of attention are important to our understanding schizophrenia, as is the reorienting of attention or the automatic preparation for detecting subsequent stimulus changes (Naatanen *et al.*, 1982). This attentional reorienting or automatic preparation is reflected in an automatically elicited negativity following the P3a, peaking at latencies between 400–600 ms, and centered on frontocentral electrodes (Otten *et al.*, 2000, Schroger *et al.*, 2000). Schröger and Wolff (1998) were the first to refer to this component as the reorienting negativity (RON). RON has been considered an automatically elicited response component during active auditory (Schroger *et al.*, 2000) and visual (Escera *et al.*, 1998, Escera *et al.*, 2001) discrimination tasks (Escera and Corral, 2007). To date, there are no published reports of RON in schizophrenia spectrum populations.

The MMN, P3a and RON complex provides a serial, hierarchical neurophysiological index of the cascade of three main processes involved in involuntary attention control (automatic change detection, orienting of attention, and reorienting of attention) following deviant stimuli (Berti *et al.*, 2004, Horvath *et al.*, 2008). When examined separately, those components may index discrete processes with dissociable underlying neural and genomic substrates as well as relationships to symptoms and functional outcome (Braff and Light, 2004, Light and Braff, 2005a, Light *et al.*, 2010).

The primary aim of the present study was to examine the MMN/P3a/RON response complex across different stages of schizophrenia by assessing the extent of MMN, P3a, and RON amplitude reductions in 1) at-risk, 2) recent-onset, and 3) chronic schizophrenia patients relative to normal controls using a cross-sectional design. We hypothesized that MMN, P3a, and RON amplitudes would be significantly reduced in recent-onset and chronic patients relative to normal controls and that the amplitudes of the at-risk subjects would lie in between those of the normal controls and those of the recent-onset patients. The secondary hypothesis was that MMN, P3a, and RON deficits would be associated with symptoms and social functioning impairment within the patient groups.

Method and Materials

Subjects

At-risk subjects (n=26), recent-onset patients (n=31), chronic patients (n=33), and normal control subjects (n=28) were enrolled in the study. At-risk and recent-onset patients were selected from a pool of individuals who were participating in the Cognitive Assessment and Risk Evaluation (CARE) program at UCSD and referred to the Schizophrenia Program laboratory for EEG testing. They were help-seeking and receiving treatment as usual (pharmacological or psychosocial) according to their presenting symptoms. Chronic patients were recruited from community residential facilities and via physician referral. Normal control subjects were recruited through newspaper advertisements and flyers posted at the UCSD medical center. Subjects over the age of 18 years were asked to give informed consent. Those below the age of 18 (N=12) provided assent, and their guardian was asked to sign a consent form for study participation. All participants were tested on a passive auditory oddball paradigm and scheduled for a short clinical evaluation on the day (if possible), or within a month, of their EEG recording session.

The Structured Interview for Prodromal Symptoms (SIPS; Miller *et al*., 2003) was used to identify subjects at risk for psychosis and measure the severity of prodromal symptoms. The majority of the at-risk subjects met criteria for at least one of the two most common prodromal syndromes (Seeber and Cadenhead, 2005, Yung *et al*., 2005) per the SIPS: "Attenuated Positive Symptom" (new onset of subsyndromal psychotic symptoms) and "Genetic Risk and Deterioration" (family history of schizophrenia in a first-degree relative or criteria for schizotypal personality disorder met in patient, associated with a decline in global functioning over the past year). The recent-onset and chronic patients had a DSM-IV diagnosis of schizophrenia and a mean duration of illness of 1.2 ± 0.82 and 10.7 ± 3.3 years respectively. Normal control subjects were not included if they had a history of mental illness or learning disability, Cluster A personality disorder or prodromal symptoms, a family history of psychotic illness, or a history of taking psychotropic medications.

Axis I and axis II diagnoses were assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders (First *et al*., 1995) and the Structured Interview for DSM-IV Personality Disorders (Pfohl *et al*., 1995) respectively. The Kiddie-Schedule for Affective Disorders and Schizophrenia (Chambers *et al*., 1985) was administered to patients under the age of 16 (N=6). Subjects with a history of head injury, seizures, neurological disorder, or an IQ below 80 were excluded from the study. Those who met DSM-IV criteria for lifetime substance abuse/dependence were included in the sample unless they endorsed having used substances during the month preceding neurophysiological testing or their urine toxicology test results were positive.

Clinical symptoms were evaluated using the Scales for the Assessment of Positive Symptoms (SAPS; Andreasen *et al*., 1977) and Negative Symptoms (SANS; Andreasen, 1984). Current level of functioning was assessed with the Modified Global Assessment of Functioning (Hall and Parks, 1995). Family history of psychiatric illness was assessed, after receiving consent to contact a relative, using the Family History Research Diagnostic Criteria (Andreasen *et al*., 1977). Six at-risk and 3 recent-onset patients had a first-degree relative with psychosis. Seven at-risk, 25 recent-onset, and 31 chronic patients were on at least one atypical antipsychotic with or without other psychotropic medications at the time of testing. These at-risk subjects were prescribed antipsychotics for their attenuated positive symptoms or other mood problems that required treatment. Two of the 26 at-risk subjects transitioned to psychosis; one converted to psychotic mania and one to schizophrenia 25 days and one year after their ERP testing, respectively.

Neurophysiological Testing

Electroencephalographic recordings were acquired with a Neuroscan NuAmp system. EEG was recorded from the scalp using 34 electrodes attached to an electrode cap. The following 34 equidistant electrode positions were used: Fp1, Fp2, Fz, F3, F4, F7, F8, FC1, FC2, FC5, FC6, Cz, C3, C4, CP1, CP2, CP5, CP6, Pz, P3, P4, P7, P8, O1, O2, PO9, PO10, Iz, T1, T2, T7, T8, TP9, and TP10. A reference electrode was placed at the nose tip, in addition to a ground electrode at Fpz. Four additional electrodes were placed above and below the left eye as well as at the outer canthi of both eyes in order to monitor blinks and eye movements. EEG was digitally referenced off-line to linked mastoids (TP9/TP10). All impedances were kept below 4 kΩ. Signals were digitized at a rate of 1 kHz with system acquisition filter settings at 0.5 – 100 Hz. Subjects were presented with binaural tones (1 kHz 85 dB sound pressure level, with 1 ms rise/fall) with a fixed stimulus onset-to-onset asynchrony of 500 ms using a San Diego Instruments ERP-Lab system. Standard (90% probability; 50 ms duration) and deviant (10% probability; 100 ms duration) tones were presented in pseudorandom order using foam insert earphones. During EEG recording, subjects were instructed to watch a silent cartoon video. EEG acquisition was terminated when a minimum of 225 artifact-free deviant trials were collected. Data processing was performed offline

using automated procedures. Continuous recordings were mathematically corrected for eye movement artifact employing standard procedures (Semlitsch *et al*., 1986). Continuous data were divided into epochs relative to the onset of stimuli (−100 to 500 ms) and centered at the mean of the prestimulus baseline. Following blink correction, epochs containing more than ± 50 μV in frontal recording sites were automatically rejected. MMN waveforms were generated by subtracting the ERP waveforms in response to standard tones from the waveforms elicited by the deviant tones. The resultant difference waves were low-pass filtered at 20 Hz (zerophase shift, 24 dB/octave rolloff) to remove any residual high-frequency artifact consistent with established methods (Kiang *et al*., 2009, Light and Braff, 2005a, b, Light *et al*., 2007). ERP component peaks were manually identified using butterfly plots, mean global field power, topographical inspection, and comparison of individual frontocentral and mastoid electrodes. This allowed for the confirmation of polarity inversion at mastoid electrodes for MMN analyses. Search windows for peak MMN, P3a, and RON were 135–205, 250–350, and 350–500 ms, respectively. Mean amplitudes in the 25 ms surrounding the identified peaks were then automatically calculated for each electrode.

Statistical Analyses

In order to investigate group differences in MMN, P3a, and RON amplitudes, a repeated measures analysis of variance (ANOVA) with electrode site as the within-subject variable and diagnostic group as the between-subject variable was performed for each component. Greenhouse-Geisser adjustments were used in the repeated measures ANOVAs that contained more than one degree of freedom. Significant group × electrode interactions were decomposed using a series of oneway ANOVAs to assess group effects at each of the frontocentral electrodes. Cohen's d was also calculated to further characterize group differences and minimize the reliance on p-values for interpreting potential effects. Relationships between MMN, P3a, and RON amplitudes at frontocentral sites and GAF, SAPS, SANS, and SIPS ratings were investigated using Spearman rank correlations. Only significant correlations at contiguous electrodes were reported.

Results

Sample Characteristics

There were significant group differences in age ($F[3,114]=47.75$, $p<.001$) and education ($F[3,113]=3.76$, $p=.01$). As expected, the chronic schizophrenia group was significantly older than all the other groups ($p<.001$) and had significantly fewer years of education than the normal control group ($p=.02$). The at-risk group was also significantly younger than the recent-onset group ($p=.04$). There were no significant group differences in ethnicity ($X^2[12]=15.37$, $p=.22$) and handedness ($X^2[6]=7.03$, $p=.32$) but there were significantly more males than females in the patient groups relative to the normal control group ($X^2[3]=17.34$, $p=.001$). As expected, there were significant differences in SAPS ($F[2,81]=11.38$, $p<.001$), SANS ($F[2,80]=10.53$, $p<.001$), and GAF ($F[2,80]=5.47$, $p=.006$) among the patient groups, with significantly less severe positive symptoms in the at-risk relative to the recent-onset ($p=.006$) and chronic ($p<.001$) groups. Similarly, the chronic group had significantly more severe negative symptoms (SANS) than the recent-onset ($p=.006$) and at-risk ($p<.001$) groups and more impairment in global functioning (GAF) than the at-risk group ($p=.004$) (Table 1).

Given the significant group differences in age and results from our preliminary analyses showing that older age was associated with smaller MMN (r= .36 to .57; Fp1, Fp2, F7, F8, Fz, F3, F4, FC2), P3a (r= −.35 to −.53; Fp2, F8, F4, C4), and RON (r= .38 to .46; Fz, F3, F4, FC1, FC2, Cz) activity in the chronic group ($p<.05$), we included age as a covariate in each of the subsequent analyses. However, age was not a significant covariate for any of the

components (main effect of age: F= .17 to .52, p>.45; electrode × age interaction: F=.70 to 1.99, p>.10) and did not affect the results. Therefore, we decided to exclude it from further analyses. Moreover, in order to control for possible gender confounds, we repeated the analyses below after including gender as another between-subject variable. No significant main effects or interactions with gender were present.

Group Differences in MMN Amplitudes

The repeated measures ANOVA revealed a significant effect of electrode (F[2.56, 291.48]=280.24, p<.001) indicating a frontal maxima in the MMN amplitude distribution, with the expected polarity inversion of responses at temporo-parietal and other posterior electrodes. There was a significant group × electrode interaction (F[7.67,291.48]=3.60, p=.001) indicating the presence of deficits at frontocentral but not temporo-parietal sites. The follow-up ANOVAs revealed significant group differences at p<.01 at all frontocentral electrodes, with the largest effect size differences at FC1. Relative to the normal control group, the chronic (d=−.78 to −1.78) and recent-onset (d=−.52 to −.92) groups had large effect-size MMN decrements at frontocentral recording sites (Fp1, F7, F8, Fz, F3, F4, FC1, FC2, FC5, FC6, C3, Cz, C4, CP1, CP2, CP5, and CP6; p<.01). Similarly, the at-risk group had significant medium effect-size (d= −.49 to −.64) MMN reductions at F3, FC1, FC2, FC5, FC6, CP5, and CP6 (p<.05) relative to the normal control group. There were no significant MMN amplitude differences between the at-risk and recent-onset groups. However, the at-risk group had significantly smaller MMN amplitudes at all frontocentral electrodes (p<.01) relative to the chronic group. There were no significant group differences in peak MMN latency (F[3, 114]=2.29, p=.08, M=182.52, SD=20.0). Mean MMN amplitudes, standard deviations, and effect sizes for each electrode site are presented in Table 2.

Group Differences in P3a Amplitudes

The repeated measures ANOVA revealed a significant effect of electrode (F[3.38, 385.84]=213.20, p<.001) indicating that the P3a response was maximal at frontocentral electrodes, as well as a significant group × electrode interaction (F[10.15, 385.84]=6.33, p<.001) indicating the presence of deficits at frontocentral but not temporo-parietal sites. The follow-up ANOVAs revealed significant group differences at p<.01 at all frontocentral electrodes, with the largest effect size differences at FC1. Both the chronic (d=.71 to 1.46) and recent-onset (d=.66 to 1.19) patients had significant P3a deficits at p<.01 at all frontocentral recording sites. The at-risk group had medium to large effect-size (d=.56 to .96) reductions in P3a amplitudes relative to the normal control group, which were significant at FC1, FC2, FC5, FC6, C3, Cz, CP1, CP2, CP5, and CP6 (p<.01) as well as F7, F8, Fz, F3, F4, and C4 (p<.05). Moreover, there were significant P3a amplitude differences between the at-risk and recent-onset groups at Fp1, F3, Fz, FC1, and FC2 (p<.05), as well as between the at-risk and chronic groups at Fz, FC1, FC2, C3, C4, CP1, CP2 (at p<.01) and F3, F4, FC5 (at p<.05). There were no significant group differences in peak P3a latency (F[3, 114]=.99, p=.40, M=276.53, SD=26.33). Mean P3a amplitudes, standard deviations, and effect sizes for each electrode site are presented in Table 3.

Group Differences in RON Amplitudes

The repeated measures ANOVA revealed a significant effect of electrode (F[3.21, 366.53]=44.17, p<.001) indicating a maximal RON response at frontocentral electrodes, as well as a significant group × electrode interaction (F[9.64, 366.53]=4.49, p<.001) indicating the presence of deficits at frontocentral but not temporo-parietal sites. The follow-up ANOVAs revealed significant group differences at p<.01 only at Fz, F3, F4, FC1, FC2, and Cz. As with MMN and P3a, the largest effect size differences were present at FC1. Both the chronic (d=−.34 to −.89) and recent-onset (d=−.60 to −.96) patients had significant RON

reductions relative to the normal control subjects at Fz, F3, F4, FC1, FC2, and Cz ($p<.05$). However, unlike the recent-onset and chronic patients, the at-risk subjects did not have significant RON deficits at any of the electrodes. The at-risk group had significantly larger RON amplitudes relative to both the recent-onset group (at Fz, F4, FC1, FC2; $p<.01$ and Fp1, F3, FC6, Cz, C4; $p<.05$) and the chronic group (at Fz, FC1, FC2, and Cz; $p<.05$). There were no significant group differences in peak RON latency ($F[3, 114]=.57$, $p=.64$, M=414.50, SD=47.22). Mean RON amplitudes, standard deviations, and effect sizes for each electrode site are presented in Table 4.

Figure 1 shows the grand average waveforms with MMN, P3a, and RON amplitudes at FC1 for each of the groups. The at-risk group's mean MMN and P3a amplitudes were intermediate between those of the normal control group and the recent-onset group. As noted above, two of the at-risk subjects transitioned to psychosis during the study period. These subjects qualitatively appeared to have a more pronounced reduction in MMN and P3a amplitudes relative to the remaining at-risk subjects, although this small N precludes further analyses.

Relationships of MMN, P3a, and RON with Social Functioning and Clinical Symptoms

Spearman rank correlation coefficients were generated in order to assess relationships between MMN, P3a, and RON responses at frontocentral electrodes and social functioning as measured by the GAF scale ratings in the patient groups. There were significant correlations ($p<.05$) between GAF and MMN ($r_s= -.35$ to $-.46$; Fz, F3, F4, F7, F8, Fp1, Fp2, FC2, FC5, Cz, C4) at frontocentral electrodes only in the chronic patients. P3a and RON were not significantly associated with GAF in any of the patient groups.

We found no significant Spearman rank correlations between severity of positive and negative symptoms, as measured by the SAPS and SANS total scores, and MMN, P3a, and RON responses in the recent-onset and chronic patients. However, significant correlations ($p<.05$) between SANS and RON ($r_s = .46$ to $.52$; Fp2, F4, F8), as well as between SIPS Negative and P3a at frontocentral electrodes ($r_s = -.43$ to $-.59$; Fp1, Fp2, F8, Fz, F3, F4, FC6) were present in the at-risk group.

Discussion

To our knowledge, this is the first report of concurrently examining three ERP components (MMN, *P3a*, RON) of automatic, preattentive information processing across different stages of schizophrenia. In a between-groups design, results indicate that individuals identified as being at risk for psychosis have robust deficits in MMN and P3a, whereas patients early in the course of schizophrenia and chronic patients exhibit significant deficits in MMN, P3a, and RON relative to normal controls. Although this is a cross-sectional study, the findings suggest that MMN and P3a abnormalities may precede the onset of psychosis while RON deficits do not emerge until the full manifestation of the illness. Cross-sectionally, it appears as though MMN and P3a deficits progressively increased with illness chronicity. The at-risk group's P3a amplitudes at frontocentral electrodes were significantly different from both the normal control and recent-onset groups' amplitudes. The at-risk group also had MMN amplitudes that were intermediate between those of the normal control and recent-onset groups (although only significantly different from the normal control group's amplitudes). The recent-onset group tended to show less severe MMN, P3a, and RON deficits relative to the chronic group.

Our findings suggest that individuals at risk for developing a psychotic disorder, as well as those with manifest schizophrenia, have deficits in processing auditory input or detecting changes in their acoustic environment, failing to notice stimuli that are salient to most

people (Michie *et al*., 2002). In other words, if someone has difficulty organizing sensory stimulation from their surrounding environment, they may also exhibit difficulty in mounting an appropriate response when necessary. It has been suggested that fundamental sensory processing abnormalities may result in inattentiveness and disorganization, causing significant disruption in everyday functioning (Braff and Light, 2004). Consistent with our previous results (Light and Braff, 2005a), we found significant associations between psychosocial functioning and MMN in the chronic group. P3a and RON, in contrast, were not significantly associated with functional ratings in any of the patient groups.

Previous reports of the association between MMN and symptom severity have yielded inconsistent results, providing more support for an association with negative rather than positive symptoms in both chronic (Umbricht and Krljes, 2005) and first-episode samples (Oades *et al*., 2006, Umbricht *et al*., 2006). We found no associations between MMN and negative symptoms in any the patient groups, which is consistent with previously reported findings in both first-episode (Salisbury *et al*., 2007) and chronic schizophrenia patients (Kasai *et al*., 1999, Light and Braff, 2005b, Shelley *et al*., 1991). Nonetheless, there were significant correlations between both P3a and RON and negative symptoms in the at-risk group, suggesting that further study of the relationships and timing of the emergence of symptoms and neurophysiological abnormalities is warranted.

Certain limitations of our study require appropriate caveats, especially the fact that our samples are relatively modest and unbalanced on key demographic features. We did, however, attempt to control for these potential demographic confounds. Based on our extensive analyses, we believe that the group differences in age and gender did not markedly influence our results. The low conversion rate in our at-risk sample did not yield sufficient statistical power to employ a longitudinal design and assess the potential role of MMN/P3a/RON as predictors of conversion to psychosis. However, the inclusion of newly diagnosed and chronic schizophrenia groups alleviates this problem to some degree. Furthermore, it must be acknowledged that the influence of antipsychotic medications cannot be completely excluded since 27% of the at-risk, 81% of the recent-onset, and 94% of the chronic patients were receiving antipsychotic medications at the time of testing. Independent samples t-tests within the at-risk group revealed no significant differences (all d's < .30) in MMN, P3a, or RON amplitudes between patients who were taking one or more atypical antipsychotics (N=7) and those who were antipsychotic-free (N=19). Although it is hard to make any conclusions regarding treatment effects given our small sample size, there is evidence showing that MMN is uninfluenced by Olanzapine (Korostenskaja et al., 2005), Risperidone (Umbricht et al., 1999), and Clozapine (Umbricht et al., 1998). Also, our patients show substantial deficits despite the possibility that Clozapine may exert some normalization of sensory ERP components (Horton *et al*., 2011, Light *et al*., 2000).

Our results support the utility of examining RON in the context of MMN and P3a in studies of at-risk populations. MMN and P3a appear to be deficient before the onset of full-blown psychosis and RON deficits do not develop until later in the disease process. To date, the literature regarding the utility of the MMN to duration deviants as an endophenotype (Gottesman and Gould, 2003) is inconclusive. Nonetheless, we may be able to argue that MMN and P3a are possible markers of vulnerability to schizophrenia that reflect premorbid neuropathology. Longitudinal designs are needed to determine whether the preattentive auditory processing abnormalities observed in the early course of schizophrenia are trait-related and/or whether they worsen with illness progression, as well as to delineate the rate of change in those risk indicators in subjects who convert to psychosis (Bodatsch et al., 2011). It will be valuable to determine whether the size of the MMN/P3a amplitude can differentiate between subjects at various stages of the prodrome and identify those for whom psychosis is imminent. Additionally, it will be useful to ascertain whether measures derived

from the MMN/P3a/RON complex can be used to predict medication adherence, academic or vocational functioning, and other instrumental activities of daily living in affected subjects (Banati and Hickie, 2009).

It remains an option question as to whether impairment in basic auditory sensory information processing improves the sensitivity and predictive accuracy in conjunction with other known risk factors of psychosis (Cannon *et al.*, 2008), including cannabis abuse (Kristensen and Cadenhead, 2007), severity of subsyndromal symptoms, and decline in social functioning (Haroun *et al.*, 2006), working memory, and processing speed (Jahshan *et al.*, 2010).

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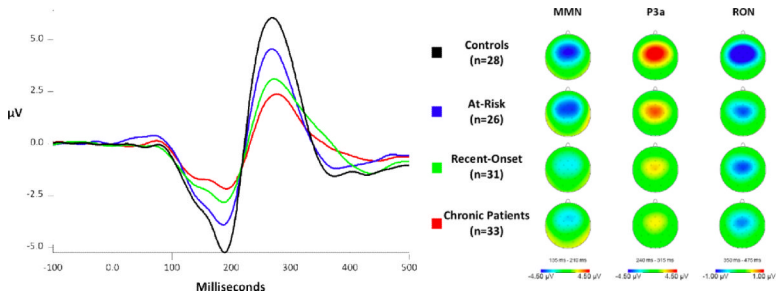

Figure 1.
Grand average difference ERPs, at electrode FC1, and their corresponding scalp distributions, formed by subtracting the ERP elicited by standard tones from the ERP elicited by deviant tones, for each group.

Table 1

Demographic and Clinical Characteristics

	Normal Controls (N=28)	At Risk for Psychosis (N=26)	Recent-Onset Schizophrenia (N=31)	Chronic Schizophrenia (N=33)
Age (Mean/SD)	21.04 (4.43)	19.15 (3.39)	21.90 (3.71)	29.82 (3.56)
Range	12 to 30	13 to 29	14 to 33	24 to 35
Gender (% Male)	39.3%	65.4%	83.9%	81.8%
Ethnicity (% Caucasian)	64.3%	46.2%	54.8%	60.6%
Handedness (% Right)	100%	80.8%	83.9%	84.8%
SIPS Positive (Mean/SD)		6.82 (5.40)		
SIPS Negative (Mean/SD)		11 (7.10)		
SIPS Disorganized (Mean/SD)		4.59 (3.43)		
SIPS General (Mean/SD)		6.50 (5.38)		
SAPS (Mean/SD)		3.81 (3.36)	7.07 (4.27)	8.55 (2.96)
SANS (Mean/SD)		7.20 (5.14)	9.40 (5.88)	13.73 (4.89)
GAF (Mean/SD)		51 (11.76)	46.17 (10.0)	42.45 (6.41)

Table 2

Descriptive Statistics and Effect Sizes of MMN Relative to Normal controls

	Group				Effect Size		
Electrode	**Normal Controls (N=31)**	**At Risk for Psychosis (N=26)**	**Recent-Onset Schizophrenia (N=28)**	**Chronic Schizophrenia (N=33)**	**AR**	**RO**	**SZ**
Fp1	−1.66 (0.99)	−1.26 (1.02)	−0.98 (0.75)	−0.83 (0.82)	−0.42	−0.72	−0.88
Fp2	−1.68 (1.07)	−1.46 (0.99)	−1.18 (0.83)	−0.93 (0.82)	−0.23	−0.52	−0.78
F7	−1.73 (1.05)	−1.35 (1.01)	−1.08 (0.90)	−0.68 (0.81)	−0.38	−0.64	−1.04
F8	−1.81 (1.28)	−1.34 (1.35)	−0.99 (0.96)	−0.65 (0.76)	−0.40	−0.71	−1.00
Fz	−4.47 (2.19)	−3.54 (1.73)	−2.77 (1.72)	−2.04 (1.55)	−0.46	−0.85	−1.78
F3	−3.89 (1.98)	−2.95 (1.42)	−2.28 (1.54)	−1.74 (1.38)	−0.53	−0.91	−1.21
F4	−4.03 (2.02)	−3.19 (1.60)	−2.56 (1.62)	−1.83 (1.28)	−0.46	−0.81	−1.21
FC1	−4.71 (2.50)	−3.64 (1.88)	−2.69 (1.95)	−2.04 (1.48)	−0.49	−0.92	−1.22
FC2	−4.72 (2.48)	−3.64 (1.88)	−2.84 (1.95)	−1.98 (1.32)	−0.50	−0.87	−1.27
FC5	−3.15 (1.68)	−2.26 (1.56)	−1.75 (1.38)	−1.20 (1.16)	−0.56	−0.87	−1.22
FC6	−3.10 (1.95)	−2.19 (1.76)	−1.70 (1.48)	−1.10 (0.84)	−0.54	−0.83	−1.18
C3	−3.76 (2.11)	−2.90 (1.76)	−2.06 (1.77)	−1.40 (1.35)	−0.44	−0.87	−1.21
Cz	−4.46 (2.68)	−3.53 (1.94)	−2.50 (2.10)	−1.64 (1.45)	−0.40	−0.85	−1.22
C4	−3.55 (2.16)	−2.90 (1.77)	−2.02 (1.74)	−1.25 (1.10)	−0.34	−0.80	−1.20
CP1	−3.19 (2.14)	−2.49 (1.66)	−1.63 (1.74)	−1.07 (1.19)	−0.37	−0.83	−1.13
CP2	−3.07 (2.02)	−2.45 (1.63)	−1.55 (1.67)	−0.91 (1.14)	−0.34	−0.84	−1.19
CP5	−1.94 (1.60)	−1.06 (1.35)	−0.65 (1.51)	−0.32 (1.11)	−0.58	−0.85	−1.07
CP6	−1.48 (1.75)	−0.72 (1.47)	−0.27 (1.33)	−.009 (0.88)	−0.52	−0.82	−1.00
P7	0.10 (1.75)	0.83 (1.27)	0.87 (1.19)	1.02 (1.18)	−0.53	−0.56	−0.67
P3	−1.89 (1.89)	−1.15 (1.29)	−0.63 (1.53)	−0.25 (1.09)	−0.47	−0.80	−1.04
Pz	−2.10 (1.82)	−1.53 (1.37)	−0.83 (1.50)	−0.37 (1.07)	−0.36	−0.80	−1.09
P4	−1.44 (1.66)	−0.93 (1.30)	−0.40 (1.36)	−0.05 (1.00)	−0.36	−0.73	−0.98
P8	0.32 (1.95)	1.04 (1.30)	1.27 (1.26)	1.22 (1.13)	−0.49	−0.65	−0.62
T7	−0.93 (.97)	−0.15 (1.35)	−0.09 (1.25)	0.28 (1.03)	−0.64	−0.69	−0.99
T8	−0.63 (1.49)	0.09 (1.66)	0.44 (1.00)	0.44 (0.88)	−0.54	−0.80	−0.80
TP9	1.06 (1.71)	1.47 (1.19)	1.42 (1.10)	1.41 (1.08)	−0.32	−0.28	−0.27
TP10	1.46 (1.55)	2.07 (1.31)	1.86 (1.10)	1.77 (1.15)	−0.48	−0.31	−0.24
T1	0.40 (0.86)	0.81 (0.82)	0.76 (0.78)	0.86 (0.82)	−0.49	−0.43	−0.55

	Group				Effect Size		
Electrode	**Normal Controls (N=31)**	**At Risk for Psychosis (N=26)**	**Recent-Onset Schizophrenia (N=28)**	**Chronic Schizophrenia (N=33)**	**AR**	**RO**	**SZ**
T2	0.78 (0.95)	1.34 (0.94)	1.10 (0.74)	1.19 (0.90)	−0.63	−0.36	−0.46
PO9	0.90 (1.55)	1.29 (1.26)	1.17 (1.00)	1.29 (1.08)	−0.32	−0.22	−0.32
PO10	1.09 (1.44)	1.46 (1.23)	1.51 (1.07)	1.52 (1.13)	−0.30	−0.34	−0.35
O1	0.18 (1.49)	0.60 (1.26)	0.75 (1.13)	0.93 (1.03)	−0.34	−0.57	−0.60
O2	0.16 (1.67)	0.59 (1.18)	0.88 (1.05)	1.05 (1.16)	−0.33	−0.55	−0.68
Iz	0.82 (1.32)	1.21 (1.13)	1.23 (1.01)	1.45 (1.33)	−0.32	−0.34	−0.52

Table 3

Descriptive Statistics and Effect Sizes of P3a Relative to Normal controls

	Group				Effect Size		
Electrode	**Normal Controls (N=31)**	**At Risk for Psychosis (N=26)**	**Recent-Onset Schizophrenia (N=28)**	**Chronic Schizophrenia (N=33)**	**AR**	**RO**	**SZ**
Fp1	1.05 (0.92)	0.75 (0.75)	0.33 (0.53)	0.51 (0.53)	0.39	0.95	0.71
Fp2	1.08 (1.08)	0.76 (0.89)	0.46 (0.73)	0.51 (0.61)	0.37	0.72	0.66
F7	1.60 (0.82)	1.01 (0.94)	0.81 (0.91)	0.62 (0.88)	0.62	0.83	1.03
F8	1.73 (1.24)	1.00 (1.36)	0.85 (1.02)	0.60 (0.79)	0.62	0.75	0.97
Fz	4.60 (1.95)	3.38 (2.15)	2.13 (1.58)	2.02 (1.62)	0.59	1.19	1.24
F3	3.70 (1.53)	2.66 (1.80)	1.76 (1.31)	1.70 (1.30)	0.62	1.15	1.19
F4	3.65 (1.72)	2.60 (1.77)	1.83 (1.40)	1.69 (1.37)	0.61	1.06	1.14
FC1	5.54 (1.84)	4.06 (2.61)	2.81 (1.77)	2.16 (1.82)	0.62	1.15	1.43
FC2	5.38 (1.91)	3.86 (2.53)	2.74 (1.83)	2.24 (1.69)	0.66	1.14	1.36
FC5	3.36 (1.08)	2.14 (1.61)	1.75 (1.24)	1.32 (1.28)	0.81	1.07	1.36
FC6	3.36 (1.74)	1.89 (1.76)	1.74 (1.44)	1.19 (1.13)	0.86	0.95	1.28
C3	4.47 (1.57)	2.91 (2.34)	2.39 (1.52)	1.55 (1.36)	0.78	1.04	1.46
Cz	5.92 (2.10)	4.14 (3.08)	3.13 (2.01)	2.27 (1.71)	0.68	1.07	1.40
C4	4.07 (1.82)	2.91 (2.58)	2.17 (1.59)	1.41 (1.27)	0.56	0.92	1.29
CP1	4.34 (1.78)	2.76 (2.76)	2.34 (1.73)	1.35 (1.25)	0.72	0.92	1.37
CP2	4.13 (1.83)	2.72 (2.74)	2.19 (1.75)	1.30 (1.22)	0.65	0.90	1.31
CP5	2.65 (1.28)	1.07 (2.15)	1.21 (1.26)	0.59 (1.08)	0.96	0.88	1.26
CP6	2.20 (1.51)	0.99 (2.16)	1.11 (1.46)	0.44 (0.91)	0.73	0.66	1.07
P7	0.84 (1.24)	−0.18 (2.17)	0.01 (1.12)	−0.28 (1.16)	0.68	0.55	0.75
P3	2.69 (1.47)	1.26 (2.49)	1.37 (1.55)	0.60 (1.09)	0.78	0.72	1.14
Pz	2.89 (1.68)	1.68 (2.64)	1.60 (1.70)	0.79 (1.06)	0.62	0.66	1.08
P4	2.30 (1.59)	1.06 (2.36)	1.22 (1.52)	0.50 (1.00)	0.71	0.62	1.03
P8	0.92 (1.42)	−0.25 (1.94)	0.16 (1.33)	−0.23 (0.97)	0.79	0.51	0.78
T7	1.71 (1.10)	0.54 (1.71)	0.69 (1.22)	0.20 (1.13)	0.84	0.73	1.11
T8	1.77 (1.64)	0.63 (1.79)	0.67 (1.46)	0.16 (0.92)	0.73	0.70	1.03
TP9	0.06 (1.15)	−0.72 (1.70)	−0.36 (1.10)	−0.66 (1.05)	0.61	0.33	0.56
TP10	0.25 (1.31)	−0.59 (1.40)	−0.21 (1.22)	−0.46 (1.03)	0.67	0.36	0.56
T1	0.19 (0.79)	−0.44 (1.14)	−0.16 (0.85)	−0.43 (1.00)	0.65	0.36	0.64

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	Group				Effect Size		
Electrode	**Normal Controls (N=31)**	**At Risk for Psychosis (N=26)**	**Recent-Onset Schizophrenia (N=28)**	**Chronic Schizophrenia (N=33)**	**AR**	**RO**	**SZ**
T2	0.33 (1.13)	−0.44 (1.06)	−0.18 (0.93)	−0.46 (0.78)	0.76	0.50	0.78
PO9	0.07 (1.16)	−0.70 (1.72)	−0.25 (1.02)	−0.52 (0.94)	0.62	0.26	0.48
PO10	0.08 (1.20)	−0.63 (1.56)	−0.18 (1.20)	−0.42 (0.88)	0.58	0.21	0.41
O1	0.47 (1.34)	−0.37 (2.12)	0.16 (1.27)	−0.21 (1.08)	0.56	0.21	0.46
O2	0.49 (1.32)	−0.40 (1.90)	0.11 (1.35)	−0.19 (0.96)	0.63	0.27	0.48
Iz	0.23 (1.46)	−0.72 (1.56)	−0.11 (1.13)	−0.51 (1.12)	0.71	0.25	0.55

Table 4

Descriptive Statistics and Effect Sizes of RON Relative to Normal controls

	Group				Effect Size		
Electrode	**Normal Controls (N=31)**	**At Risk for Psychosis (N=26)**	**Recent-Onset Schizophrenia (N=28)**	**Chronic Schizophrenia (N=33)**	**AR**	**RO**	**SZ**
Fp1	−0.20 (0.45)	−0.06 (0.40)	0.24 (0.62)	0.02 (0.59)	−0.25	−0.80	−0.40
Fp2	−0.20 (0.54)	0.04 (0.55)	0.28 (0.57)	0.04 (0.61)	−0.41	−0.81	−0.41
F7	0.01 (0.51)	0.09 (0.55)	0.29 (0.70)	0.10 (0.40)	−0.14	−0.51	−0.16
F8	0.14 (0.55)	0.23 (0.59)	0.51 (0.60)	0.16 (0.52)	−0.15	−0.64	−0.34
Fz	−1.22 (1.40)	−0.86 (0.94)	0.08 (1.57)	−0.16 (1.05)	−0.26	−0.96	−0.78
F3	−0.78 (1.07)	−0.49 (0.75)	0.17 (1.24)	−0.10 (0.81)	−0.28	−0.90	−0.65
F4	−0.68 (1.07)	−0.48 (0.89)	0.23 (1.04)	−0.08 (0.77)	−0.20	−0.91	−0.60
FC1	−1.43 (1.39)	−1.08 (0.96)	−0.20 (1.44)	−0.29 (0.89)	−0.27	−0.95	−0.88
FC2	−1.28 (1.36)	−1.03 (0.98)	−0.17 (1.33)	−0.25 (0.83)	−0.20	−0.90	−0.84
FC5	−0.46 (0.81)	−0.21 (0.66)	0.18 (0.98)	0.01 (0.58)	−0.31	−0.80	−0.59
FC6	−0.22 (0.83)	−0.04 (0.82)	−0.40 (0.81)	0.09 (0.61)	−0.23	0.23	−0.39
C3	−0.75 (1.08)	−0.48 (0.84)	−0.05 (1.04)	−0.12 (0.67)	−0.28	−0.74	−0.66
Cz	−1.43 (1.43)	−1.09 (1.04)	−0.36 (1.30)	−0.33 (0.80)	−0.27	−0.86	−0.89
C4	−0.41 (1.05)	−0.44 (1.05)	0.17 (0.99)	−0.04 (0.70)	0.03	−0.60	−0.38
CP1	−0.67 (1.17)	−0.46 (0.92)	−0.13 (1.05)	−0.13 (0.69)	−0.21	−0.55	−0.55
CP2	−0.48 (1.19)	−0.42 (1.09)	0 (1.07)	−0.03 (0.68)	−0.06	−0.47	−0.44
CP5	0.01 (0.94)	0.22 (0.87)	0.24 (0.95)	0.16 (0.67)	−0.25	−0.27	−0.18
CP6	0.39 (0.90)	0.33 (1.03)	0.51 (0.86)	0.27 (0.72)	0.07	−0.14	0.14
P7	0.38 (0.87)	0.46 (0.83)	0.32 (0.81)	0.29 (0.71)	−0.10	0.08	0.11
P3	0.04 (1.05)	0.14 (0.88)	0.10 (0.93)	0.10 (0.68)	−0.11	−0.07	−0.07
Pz	−0.05 (1.17)	−0.05 (0.93)	0.02 (1.00)	0.03 (0.67)	0	−0.07	−0.08
P4	0.29 (1.09)	0.18 (0.97)	0.27 (0.96)	0.11 (0.66)	0.12	0.02	0.20
P8	0.54 (0.83)	0.51 (0.88)	0.49 (0.70)	0.31 (0.58)	0.04	0.07	0.31
T7	0.13 (0.73)	0.29 (0.77)	0.30 (0.97)	0.27 (0.65)	−0.20	−0.22	−0.18
T8	0.30 (0.67)	0.46 (0.81)	0.63 (0.74)	0.34 (0.70)	−0.22	−0.45	−0.05
TP9	0.24 (0.67)	0.36 (0.64)	0.23 (0.67)	0.27 (0.64)	−0.18	0.15	−0.05
TP10	0.42 (0.74)	0.42 (0.69)	0.38 (0.53)	0.29 (0.55)	0	0.06	0.21
T1	0.15 (0.53)	0.23 (0.51)	0.20 (0.64)	0.22 (0.50)	−0.15	−0.09	−0.13

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	Group				Effect Size		
Electrode	**Normal Controls (N=31)**	**At Risk for Psychosis (N=26)**	**Recent-Onset Schizophrenia (N=28)**	**Chronic Schizophrenia (N=33)**	**AR**	**RO**	**SZ**
T2	0.21 (0.51)	0.39 (0.45)	0.36 (0.46)	0.29 (0.60)	−0.35	−0.29	−0.16
PO9	0.27 (0.70)	0.36 (0.61)	0.12 (0.58)	0.15 (0.58)	−0.14	0.24	0.19
PO10	0.36 (0.78)	0.36 (0.70)	0.18 (0.55)	0.20 (0.50)	0	0.29	0.25
O1	0.28 (0.94)	0.39 (0.71)	0.17 (0.77)	0.15 (0.67)	−0.14	0.14	0.17
O2	0.35 (0.91)	0.37 (0.75)	0.26 (0.77)	0.24 (0.55)	−0.03	0.12	0.15
Iz	0.22 (0.73)	0.31 (0.60)	0.08 (0.60)	0.19 (0.66)	−0.14	0.21	0.05

Tables 2, 3, 4. Data are given as Mean (SD) amplitude of ERP response. Effect sizes are calculated as Cohen's d.

AR = At-Risk; RO = Recent-Onset Schizophrenia; SZ = Chronic Schizophrenia.