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Disentangling Early Sensory Information Processing Deficits in Schizophrenia

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Abstract

Objective—The disentangling of early sensory information processing deficits and examination of their relationships to demographic and clinical factors are important steps for the validation of potential biomarkers and/or endophenotypes of schizophrenia. The aims of the present study were to characterize commonly used sensory event-related potential deficits, to determine whether they are 1) distinct from one another and 2) independently associated with important clinical characteristics.

Methods—MMN, P3a and RON event-related potentials (ERP) were recorded from schizophrenia patients (SZ; n=429) and nonpsychiatric comparison subjects (NCS; n=286). Subgroup analyses on demographic and clinical variables were performed.

Results—Schizophrenia patients exhibited robust ERP deficits at frontocentral electrodes (MMN: $d=1.10$; P3a: $d=0.87$; RON: $d=0.77$), consistent with previous studies. Each ERP component uniquely accounted for variance in amplitude and schizophrenia deficits. Amplitude reductions occurred with increasing age in both NCS and SZ patients. A small subset of patients prescribed combinations of 1st and 2nd generation antipsychotics exhibited significantly reduced MMN amplitude relative to other medication-defined subgroups.

Conclusions—MMN, P3a, and RON are dissociable deficits with distinct relationships to age and medication status in schizophrenia patients, potentially reflecting divergent pathophysiological processes. Reduced MMN in patients taking multiple antipsychotic

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medications appear to be attributable to greater severity of symptoms and functional impairments, rather than a medication effect.

Significance—Independent information processing deficits in schizophrenia patients may differentially contribute to the commonly observed deficits in neurocognitive and psychosocial functioning.

Keywords

Mismatch Negativity; P300; Reorienting Negativity; Attention; Event Related Potentials

Introduction

Navigation through the stimulus-laden and complex psychosocial environments of humans requires the adaptive and integrative processing of a host of sensory inputs (Braff, 1993; Leitman, et al., 2010). Successful information processing requires efficiency at preattentive, automatic levels to allocate finite processing resources to novel and/or salient stimuli and, reciprocally, to inhibit responses to redundant or irrelevant stimuli (Grillon, Courchesne, Ameli, Geyer, & Braff, 1990).

Event related potentials (ERPs) allow for the quantitative examination of discrete stages of information processing with millisecond precision. ERP studies have revealed robust deficits in neuropsychiatric patient populations including schizophrenia ranging from impairments in sensory registration to impairments in integrative cognitive functions (Force, Venables, & Sponheim, 2008; Kiang, Braff, Sprock, & Light, 2009; Kiang, et al., 2007; Leitman, et al., 2010; Mathalon, Ford, Rosenbloom, & Pfefferbaum, 2000; Rissling & Light, 2010). Sequential components of sensory ERP waveforms are often thought to reflect important hierarchical information processing cascades across automatic change detection, orienting or covert shifting of attention, and the reorienting of attention following salient and or distracting stimuli (Horváth, Winkler, & Bendixen, 2008).

These predominantly automatic processes can be assessed via a passive auditory oddball paradigm where repetitive standard stimuli are occasionally interrupted by stimuli that differ in physical characteristics (e.g., a longer duration). Mismatch negativity (MMN) is an ERP component that is automatically elicited in response to unattended and, in some cases, preconscious discrimination of oddball stimuli. As MMN can be automatically elicited even when participants do not attend to the stimuli, it is assumed to reflect a predominantly pre-attentive and automatic deviance detection process (Näätänen, 1990).

MMN is typically followed by the P3a component that peaks 250-300 ms. The P3a is thought to reflect the covert shifting of or “automatic” orienting of attention towards deviant stimuli (Escera, Alho, Schröger, & Winkler, 2000; Ford, et al., 2010). Several studies have found that both MMN and P3a amplitude are decreased in schizophrenia patients in response to infrequent nontarget or distracter stimuli at frontocentral electrodes (Hölig & Berti, 2010; Light & Braff, 2005a, 2005b; Michie, et al., 2000; Turetsky, et al., 2007), reflecting “two-factor” deficits of sensory discrimination and orienting of attention (Grillon, et al., 1990).

A relatively less explored, but potentially informative third component in the automatic change detection sequence involves the re-orienting of attention or preparation for detecting subsequent stimulus changes (Näätänen, Simpson, & Loveless, 1982). This process is thought to be reflected in the negative going wave that follows the P3a, peaking at latencies between 400-500 ms, and also centered on frontocentral electrodes. This late negative wave has been referred to as the “reorienting negativity” (RON; Schröger & Wolff, 1998), although this component has been primarily studied in the context of *active* rather than

passive auditory (Schröger & Wolff, 1998) or visual discrimination tasks (cf Escera & Corral, 2007).

Taken together, MMN, P3a and RON provide a serial, hierarchical neurophysiological index of the cascade of three fundamental processes involved in involuntary attention control (automatic change detection, orienting of attention, and the reorienting of attention) following unattended oddball stimuli (Escera, et al., 2000). These processes appear to occur at the transitions from sensory-perceptual change detection to higher-order cognitive operations (Ford, et al., 2010; Hölig & Berti, 2010; Rissling, Makeig, Braff, & Light, 2010). Whether MMN, P3a, and RON components reflect a tightly coupled evoked response complex (e.g. Horváth, et al., 2008; Sussman, Winkler, & Schröger, 2003), vs. dissociable components of relevance to neuropsychiatric disorders remains an open question. For example, do deficits in earlier processes account for the abnormalities in later ERP components and other “downstream” cognitive operations? Are these ERP measures suitable for use as biomarkers of drug response and/or as endophenotypes in genomic studies, either via the characterization of the singular response complex or via the separate examination of individual components? A previous study (János Horváth, et al., 2008) of 12 nonpsychiatric subjects tested in the context of an active target detection paradigm suggested that MMN, P3a, and RON are not strongly coupled in normal subjects. To our knowledge no previous studies have conducted similar analyses in either schizophrenia patients or in the context of a passive auditory oddball paradigm as is typically utilized in MMN and, to some extent, P3a studies.

When examined separately, the MMN, P3a and RON components may index discrete processes with dissociable underlying neural and genomic substrates as well as relationships to important demographic and clinical features of schizophrenia (Braff & Light, 2004; Light & Braff, 2005a; Rissling, et al., 2010). Increasingly, neurophysiological biomarkers of these processes are utilized in a variety of neuroscience research applications including as endophenotypes in genetic association studies (Force, et al., 2008; Greenwood, et al., 2007), as targets for assessing drug response (Ehrlichman, et al., 2009), for predicting response to pharmacologic and/or psychosocial treatments, and for tracking the emergence and progression of deficits across the course of illness (Jahshan, et al., 2011).

As reviewed by Luck and colleagues, (Luck, et al., 2011), several challenges in the development and validation of neurophysiological biomarkers must be overcome before ERPs become widely used as biomarkers of schizophrenia, including the identification of subject-level factors that account for variability of responses, including age. Likewise, deficits in MMN, P3a and RON may be associated with (or perhaps influenced by) clinical variables including antipsychotic medications, duration of illness, or illness severity. The aims of the present study were to: 1) characterize the magnitude of MMN, P3a and RON profile of auditory information processing deficits in schizophrenia; 2) determine whether the MMN, P3a and RON represent a unitary response complex vs. dissociable independent processes; and 3) to assess their associations to key demographic and clinical variables including age, age of illness onset, gender, duration of illness, positive and negative symptoms, and medication subgroups.

Methods and Materials

Participants

Schizophrenia patients (n=428) and nonpsychiatric comparison subjects (NCS) (n=285) were recruited and tested in accordance with our established methods^{12, 13, 25, 26}. All participants were assessed on their capacity to provide informed consent. After receiving a detailed description of the study procedures, written informed consent was obtained per

University of California, San Diego (UCSD) IRB-approved procedures (UCSD IRB protocols #071128 and #071831). All participants received a urine toxicology screen to rule out recent drug use and were assessed diagnostically using the Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon, & Williams, 1995). Patients did not have an Axis I diagnosis other than schizophrenia; nonpsychiatric comparison subjects did not have any Axis I diagnosis. Participants in both groups had not experienced a neurologic insult such as significant head trauma and/or loss of consciousness. Audiometric testing was used to ensure that all participants could detect 40-dB tones at 1000 Hz. Nonpsychiatric comparison subjects were recruited through newspaper advertisements, postings on the Internet, and fliers posted at the UCSD Medical Center. Schizophrenia patients were recruited from community residential facilities and via physician referral. Table 1 shows demographic characteristics of the sample and clinical characteristics of the patient group. The majority of patients were prescribed 2nd generation antipsychotics (n=301), while 60 were prescribed both 1st and 2nd generation, 30 were prescribed 1st generation and 38 patients were unmedicated (see Table 2)

Stimuli

Subjects were presented with binaural tones (1-kHz 85-dB, with 1-ms increase/decrease) with stimulus onset-to-onset asynchrony of 500 ms. Standard ($p=.90$, 50-ms duration) and deviant ($p=.10$, 100-ms duration) tones were presented in pseudorandom order with a minimum of 6 standard stimuli were presented between each duration deviant. Stimuli were presented to subjects using foam insert earphones (model 3A; Aearo Company Auditory Systems, Indianapolis, IN). During the approximately 20-min session, participants watched a silent, benign, cartoon video to divert attention from the tones. The participants were instructed that they should ignore the tones and pay attention to the video as they may be asked to answer questions regarding the video at the end of the session.

Electroencephalographic (EEG) recording

EEG recordings were acquired with a NuAmps system (Neuroscan Labs) using sintered Ag/AgCl electrodes embedded in a cap (EasyCap, Falk Minow Services) at the following 32 positions: Fp1, Fp2, Fz, F3, F4, F7, F8, FC1, FC2, FC5, FC6, Cz, C3, C4, CP1, CP2, CP5, CP6, Pz, P3, P4, P7, P8, PO9, PO10, T1, T2, T7, T8, TP9, TP10. Electrodes placed at the nose tip and at Fpz served as reference and ground respectively. Four additional electrodes placed above and below the left eye and at the outer canthi of both eyes were used for monitoring blinks and eye movements. All impedances were below 4 k Ω . Signals were digitized at 1 kHz with system acquisition filter settings at 0.5–100 Hz.

The EEG and stimulus markers were recorded continuously. During testing, online ERP averages to standard and deviant tones were monitored to ensure signal quality and to track the number of trials free of gross artifact ($\pm 100 \mu V$ from -100 to 500 ms relative to stimulus onset). EEG acquisition was terminated when a minimum of 225 artifact-free deviant trials were collected. No participant required presentation of more than 300 deviant tones in order to achieve 225 artifact-free trials (mean NCS=272; schizophrenia patients=265). Data processing was performed offline and blind to group membership using automated procedures. First, the continuous EEG recordings were mathematically corrected for eye movement artifact using established regression based procedures. Continuous data were epoched relative to the onset of stimuli (-100–500 ms), with mean voltage of the prestimulus interval used as baseline. Following blink correction, epochs containing $> \pm 50$ microvolts in frontal recording sites (F7, F8, Fp1, Fp2, F3, F4, Fz) were rejected. ERP waveforms were generated by averaging responses to standard and deviant tones, respectively. MMN, P3a and RON waveforms were generated by subtracting ERPs elicited by standard tones from ERPs elicited by deviant tones (Figure 1). The resultant difference waves were low-pass

filtered at 20 Hz (FIR, zero-phase shift, 24 dB/octave rolloff) to remove any residual high-frequency artifact consistent with established methods.

For both MMN and P3a, the largest responses were evident at electrode Fz; while for RON the largest responses were at Cz (see Table 3, Figure 1). MMN and P3a peaks were initially inspected following automated peak scanning procedures in the 135 to 205 and 250 to 350 windows from Fz. The RON component was identified in the 350-500 ms window from electrode Cz. Selection of a single fixed peak latency for each component also involved examination of: 1) butterfly plots of all electrodes and mean global field power to confirm acceptable signal to noise ratio by requiring that post-stimulus mean global activity was at least 2x pre-stimulus activity; and 2) 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 fixed latency for each electrode. Well-defined MMN, P3a and RON responses were present in all subjects and verified by inspection of butterfly plots.

Statistical analyses

To determine whether ERP amplitudes differed between the two groups, a mixed model analysis was conducted separately for the MMN, P3a and RON amplitudes. The mixed model allows for the full utilization of the hierarchical nature of the data with 32 electrode locations per participant and participants nested within the diagnostic groups, while taking into account the spatial autocorrelation of measurements on different electrodes on the same subject. Additionally it allows for controlling for participant level covariates like age and gender. In addition to the overall main effects, the differences between patients and the nonpsychiatric comparison subjects based on the specific contrasts within these mixed models are reported. Cohen's *d* was also calculated to further characterize group differences and minimize the reliance on *p* values for interpreting potential effects.

To determine the strength of the association among the ERP components, we conducted three separate mixed models, one for each of the associations of interest (MMN/P3a, P3a/RON and MMN/RON). We parameterized the association between the ERPs of interest using one as the dependent variable measured within each participant and the other as a spatially varying covariate with age and gender included as participant level covariates.

In order to further evaluate whether the three ERP components represent independent deficits or a unitary phenomenon, structural equation modeling (SEM) using EQS Structural Equation Package (Bentler, 1996) was also employed using frontal and central electrodes since these are electrodes with similarly largest responses observed in both groups and where significant differences between patients and comparison subjects were observed. Temporoparietal, occipital, and other electrodes were not included in the SEM analyses since overall activation of the MMN, P3a and RON and the schizophrenia patient and NCP effect sizes were low (see Figure 1, Table 3). Twenty one subjects (5%) had data missing for 1 or more electrode, which was handled using the list wise deletion approach (Jamshidian & Bentler, 1999). The models were estimated using maximum likelihood solution. Two nested models (single-factor solution, 3-factor model) were compared using a chi-square difference test.

To determine if specific patient characteristics beyond diagnosis were associated with ERP amplitude of the MMN, P3a and RON components, separate mixed models were conducted controlling for age and gender in the patient sample. The variables of interest included positive and negative symptoms, age of illness onset, number of hospitalizations and antipsychotic medication type (unmedicated, 1st generation, 2nd generation, or combined 1st

and 2nd generation, Figure 1, Table 2). To extend our previous findings of diminution of MMN and P3a with increasing age (Kiang, et al., 2009) and to include RON and effect size deficits in patients, age-defined subgroup analyses were performed (18-30 years vs. 31-40 vs. 41-50 vs. 51-60 vs. 60-above as between-subjects factors; Table 4).

Results

Group differences in MMN/P3a/RON amplitude

Robust MMN, P3a, and RON components were elicited in both schizophrenia patients and comparison subjects (means significantly different from 0; all F -values > 946, all $p < 0.0001$ all Cohen's $d > 2.3$). Figure 1 presents the grand average MMN, P3a, and RON waveforms at electrode (Fz) from the schizophrenia patients and nonpsychiatric comparison subjects, scalp distributions of all three components as well as t -test maps computed from the EEG waveforms. Table 3 presents the ERP amplitudes, standard deviations and between group effect sizes (Cohen, 1988) across electrodes for the MMN, P3a and RON components. As can be seen from Figure 1 and Table 3, largest amplitudes and group differences were present at frontal and central electrodes for MMN ($d=1.10$), P3a ($d=0.87$) and RON ($d=0.77$).

Association of MMN, P3a, and RON

Significant electrode-specific differences as parameterized by the group by electrode interaction were present for MMN ($F_{32, 21557}=32.5$, $p < 0.0001$), P3a ($F_{32, 21554}=19.7$, $p < 0.0001$), and RON ($F_{32, 21560}=2.96$, $p < 0.0001$), suggesting that each component reveals unique deficits above-and-beyond the other two components. For example, MMN deficits remained significant after controlling for P3a and RON deficits. Moreover, the association between MMN and P3a was significant even after controlling for gender, age, group and electrode effects (standardized regression coefficient = -0.28, $F_{1, 22002}=1710.6$, $p < 0.001$), as were the relationships between P3a and RON (standardized regression coefficient = -0.34, $F_{1, 22588}=3079.6$, $p < 0.001$) and MMN and RON (standardized regression coefficient = 0.36, $F_{1, 22874}=2958$, $p < 0.001$). Follow up analyses show that in each case there was a significant three way interaction (MMN with P3a: $F_{32, 21525}=4.5$, $p < 0.001$; P3a with RON: $F_{32, 22040}=1.7$, $p=.007$; and MMN with RON: $F_{32, 22349}=3.57$, $p < 0.001$), suggesting that the relationship among components is dependent on both the electrode and the group membership, with deficits in patients primarily evident at frontocentral electrodes (Figure 1).

The large sample size of both groups allowed us to corroborate and extend the mixed model analyses to structural equation modeling (SEM) in order to determine whether the three ERP components represent independent deficits or a unitary phenomenon. Two nested models (single-factor solution, 3-factor model) were compared using a chi-square difference test (Bentler, 1996; Jamshidian & Bentler, 1999; Ullman, 2001). Due to the consistent significant amplitude deficits at frontal and central electrode sites across the three components in the patient group (Figure 1), each ERP component (MMN, P3a, and RON) was indexed with the following frontal (Fp1, Fp2, Fz, F3, F4, F7, F8, FC1, FC2, FC5, FC6) and central electrodes (Cz, C3, C4, CP1, CP2, CP5, CP6). Figure 2 presents the factor loadings and standardized path coefficients per group. In the single-factor model, all six indices (frontocentral electrodes for the three ERP components) were loaded on one factor. The independence model, testing whether or not the observed data fit the expected data, was rejected¹ for the schizophrenia patients ($\chi^2_{(15, N=408)}=2297.3$, $p < 0.01$), and the NCS group ($\chi^2_{(15, N=273)}=976.0$, $p < 0.01$). All indicators had moderate-to-high loadings on their respective latent variables, and all were significant at the 0.05 level. However, the single-

¹The χ^2 for the independence model should always be significant, indicating that there is a relationship among the variables

factor solution provided a poor fit for the data for both the schizophrenia patients ($\chi^2_{(9, N=408)}=1155.0, p<0.01, CFI=0.50$), as well as for the NCS group ($\chi^2_{(9, N=273)}=323.3, p<0.01, CFI=0.67$).

We then compared this single-factor model to a 3-factor model, in which the frontocentral electrodes were loaded on three different factors representing the separate ERP components. The independence model for the 3-factor solution was again readily rejected for the schizophrenia patients ($\chi^2_{(15, N=408)}=2297.3, p<0.01$), and the nonpsychiatric comparison sample ($\chi^2_{(15, N=273)}=976.0, p<0.01$). All indicators had moderate-to-high loadings on their respective latent variables, and all were significant at the 0.05 level (Figure 2). The 3-factor model provided a very good fit for the data for both the schizophrenia patients ($\chi^2_{(6, N=408)}=78.6, p<0.01, CFI=0.97$) and for the nonpsychiatric comparison sample ($\chi^2_{(6, N=273)}=39.8, p<0.01, CFI=0.96$). Importantly, despite the moderate and statistically significant covariance among the latent variables, the 3-factor model provided a significant improvement over the single-factor model for both the schizophrenia patients ($\chi^2_{\text{diff}}(3, N=408)=1076.4, p<0.01$) as well as for the nonpsychiatric comparison sample ($\chi^2_{\text{diff}}(3, N=273)=283.5, p<0.01$) suggesting that the three ERP components appear to be indexing unique neural processes and are therefore not redundant for either group. In the nonpsychiatric comparison sample the frontal electrodes accounted for most of the variance, although it should be noted that these standardized coefficients are affected by all the other relationships in the model. The key covariances between the factors were overall very similar between the two groups.

Relationships of MMN, P3a and RON with clinical characteristics

Medication Type—Within the schizophrenia patients, medication type was an electrode specific predictor for both MMN ($F_{96,13013}=2.2, p<0.001$) and P3a ($F_{96,13042}=1.32, p=.02$), but not for RON ($F_{128,13628}=0.8, p=.89$). One degree of freedom post-hoc tests show that this electrode specific effect is primarily attributable to the unmedicated patients having larger MMN and P3a amplitudes compared to the patients treated with a combination of 1st and 2nd generation antipsychotics at frontal electrodes (MMN: FC2, F3, F4, FZ) (P3a: F3, F7, F8, FC6) Figure 1, Table 2).

Post hoc analyses also revealed that the unmedicated patients had slightly higher ratings of positive symptoms ($t_{93}=2.17, p<0.05, d=0.45$), but performed better on tests of real-world functional capacity as measured using the University of California San Diego Performance-Based Skills Assessment (UPSA) ($t_{93}=2.50, p<0.05, d=0.51$) and had higher ratings of functional status using the Scale of Functioning (SOF; Rapaport, Bazetta, McAdams, Patterson, & Jeste, 1996) ($t_{93}=2.50, p<0.05, d=0.41$) compared to the mixed 1st and 2nd generation antipsychotic medication group. No significant differences were observed between unmedicated vs. medicated patients for MMN, P3a, or RON (all $t<1.0$, all $p>0.30$; see Table 2).

The sample of schizophrenia patients on second generation antipsychotics, allowed for the finer parsing of medication defined subgroups (Table 2), similar to (Adler, et al., 2004) where significant P50 gating ratio differences were observed according to specific primary antipsychotic medication. In the present study, however, no significant MMN, P3a, or RON differences were observed between patients treated with risperidone ($N=79$), olanzapine ($N=46$), quetiapine ($N=44$), aripiprazole ($N=27$), clozapine ($N=19$), or ziprasidone ($N=11$) (Main effect MMN: $F_{5, 225}=1.616, p=0.16$; P3a: $F_{5, 225}=1.34, p=0.25$; RON: $F_{5, 225}=1.04, p=0.40$).

Age of Onset and Number of Hospitalizations—The mixed model revealed that age of onset was not a significant predictor overall for MMN, P3a, or RON (all $F<0.6$, all

$p > 0.40$) nor was it an electrode specific predictor (all $F < 1.1$, all $p > 0.30$). Similarly, number of previous hospitalizations was not significant overall for MMN ($F_{1,350} = 0.4$, $p = 0.51$), P3a ($F_{1,346} = 0.1$, $p = 0.71$) or RON ($F_{1,362} = 3.3$, $p = .07$) nor was it an electrode specific predictor (all $F < 0.8$, all $p > 0.80$).

Discussion

As reviewed by Luck and colleagues, (Luck, et al., 2011), several challenges in the development and validation of neurophysiological biomarkers must be overcome before ERPs become widely used as biomarkers of schizophrenia, including determining the sensitivity and selectivity of the measures and the identification of subject-level factors that account for variability of responses. In the present study MMN, P3a and the reorienting negativity (RON) were assessed in a large cohort of schizophrenia patients and nonpsychiatric comparison subjects. Results indicate that MMN, P3a and RON amplitudes were significantly reduced in schizophrenia patients with large effect sizes (MMN: $d = 1.10$; P3a: $d = 0.87$; RON: $d = 0.77$), consistent with previous studies (Jahshan, et al., 2011; Light & Braff, 2005a; Wynn et al., 2010). Importantly, these ERP components appear to represent dissociable processes, accounting for unique information processing deficits in schizophrenia patients. Therefore, MMN does not determine P3a or RON amplitude nor does it fully account for the P3a and RON deficits observed in schizophrenia patients. As with many traditional neuropsychological tests that show a performance decrement with aging, MMN, P3a, and RON amplitudes are also reduced with increasing age, although robust and significant deficits were present in schizophrenia at all age groups. Likewise, all antipsychotic medication-defined patient subgroups exhibited deficits on these ERP components relative to nonpsychiatric comparison subjects, although a subset of patients receiving combinations of 1st and 2nd generation antipsychotic medications had significant MMN reductions relative to the unmedicated patient subgroup.

There are questions in the extant literature as to whether MMN, P3a, and RON components in healthy controls reflect a tightly coupled evoked response complex e.g. (János Horváth, et al., 2008; Sussman, Winkler, & Wang, 2003). Establishing the specificity of these indices will aid in their validation as biomarkers of schizophrenia (Luck, et al., 2011) and corroborate evidence of their differing sensitivity to clinical and demographic variables (Jahshan, et al., 2011). In the present study, we extended this line of investigation to determine whether deficits in these ERP components in schizophrenia are distinct or simply a consequence of the overlap among responses. The scalp topography of the three components and their distribution of deficits in schizophrenia are remarkably similar with maximal responses in both groups and schizophrenia-related deficits present at frontocentral electrodes (Figure 1, Table 3). Further mixed model and SEM analyses revealed that MMN, P3a, and RON, however, appear to be separable with significant deficits in each component persisting even after controlling for the overlap among ERP measures. Deficits in MMN, P3a and RON may therefore result from divergent underlying functional, anatomical or genomic sources. We hypothesize the divergent ERPs have varying underlying neural generators that may be clarified with advances in EEG processing analyses that facilitate identification and spatial resolution of the neural sources of these responses (Anemüller, Sejnowski, & Makeig, 2003; Onton, et al., 2006; Makeig, Debener, Onton, & Delorme 2004).

Basic demographic and clinical characteristics of the patients including estimated age of illness onset and number of previous hospitalizations were not associated with MMN, P3a or RON components. Significant amplitude reductions in these responses were associated, however, with increasing age in both schizophrenia patients and nonpsychiatric comparison

subjects, extending our previous results in the sample size as well as the examination of RON and group deficits in RON (Kiang, et al., 2009).

The present study identified some cross-sectional medication effects. Most notably, patients taking combinations of 1st and 2nd generation antipsychotic medications exhibited significantly reduced MMN compared to unmedicated patients. In contrast to other ERP measures (e.g. P50 gating; Adler, et al., 2004), no significant differences were observed between subgroups of patients taking 1st generation antipsychotics or risperidone, olanzapine, quetiapine, aripiprazole, clozapine, or ziprasidone (Table 2).

Previous studies of antipsychotic medication effects on MMN measures have yielded mixed results. For example, most previous studies have failed to detect changes in MMN amplitude associated with a switching from a 1st generation compound to clozapine (Schall, et al., 1998; Umbricht, et al., 1998) or risperidone (Umbricht, et al., 1999). Moreover, no changes were detected in MMN amplitude with changes in clinical symptoms or states (Umbricht & Krljes, 2005). Devrim-Üçok et al (2008), however, reported normal MMN amplitude in neuroleptic naïve, acute first episode patients (cf Jahshan, et al., 2011; Salisbury, Shenton, Griggs, Bonner-Jackson, & McCarley, 2002) followed by a subsequent attenuation of their MMN, perhaps attributable to the initiation of antipsychotic treatments. In the present study, the unmedicated patients' robust ERP deficits were comparable in magnitude to patients treated with 1st generation or 2nd generation antipsychotic medication groups. The observational design of the present study cannot exclude the possibility that antipsychotic medications may exert some influences on MMN and P3a since no pre-morbid baseline recordings are available in this chronic cohort of patients. Thus, any observed MMN and P3a amplitude differences in medication-defined subgroups should therefore be interpreted with caution as several factors can influence medication status and adherence (e.g., efficacy, side-effect profile, insurance coverage) that cannot be fully addressed in the context of a cross-sectional study. Future prospective controlled studies with randomization are needed to clarify the potential impact of antipsychotic medications on neurophysiological measures and to disentangle potentially important confounding patient characteristics.

To our knowledge, this study is the largest investigation of auditory sensory processing published to date in schizophrenia (N=428, including 38 unmedicated patients), and nonpsychiatric comparison subjects (N=285). Indeed, a meta-analysis of MMN deficits in schizophrenia (Umbricht & Krljes, 2005) revealed that the average sample size for MMN studies in schizophrenia patients was 17.5 (SD=5.3; range N=11-30). Thus, we believe that this report will serve as a definitive characterization of sensory processing abnormalities associated with automatic and passively elicited sensory discrimination in schizophrenia.

In summary, the results of the present study indicate that the MMN, P3a, and RON represent sequential multi-component characterization of automatic sensory discrimination following subtle, unattended, and task-irrelevant changes in stimulus duration. The current study is only the second to report RON deficits in schizophrenia during a passive oddball paradigm (cf. Jahshan, et al., 2011). These components are thought to precede and perhaps index the transitions from sensory discrimination through higher-order decision-related processes. Cascade models suggest that abnormalities in early information processing underlie the “downstream” clinical and cognitive impairments that ultimately contribute to the psychosocial disability observed in many patients with schizophrenia. In this context, several previous studies have suggested that MMN generation may extend to other higher order cognitive deficits (e.g., Kiang, et al., 2007; Light, Swerdlow, Braff, 2007; Tiitinen, May, Reinikainen, Näätänen, 1994). The current results suggest that these ERP components, though correlated, represent unique independent information processing deficits in the schizophrenia patients and therefore may differentially contribute to neurocognitive deficits

and psychosocial disability. Future studies are needed to experimentally assess the influence of potential modulatory effects on these ERP components to further differentiate their contribution to the commonly observed neurocognitive deficits of schizophrenia patients, and to further characterize the neural and genomic architecture of these core schizophrenia related deficits.

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Highlights

- MMN, P3a and RON ERP components each uniquely accounted for variance in amplitude and schizophrenia deficits.
- This study is the largest investigation of auditory MMN, P3a, and RON published to date in schizophrenia and therefore may serve as a definitive characterization of sensory processing abnormalities in schizophrenia.
- Deficits in MMN, P3a and RON may be associated with (or perhaps influenced by) clinical and demographic variables including antipsychotic medication type or status and age and therefore may result from divergent underlying functional, anatomical and genomic sources.

Figure 1.

Grand average difference waves formed by subtracting average ERPs to standard tones from average ERPs to deviant tones, for nonpsychiatric comparison sample and the schizophrenia patient medication subgroups (unmedicated, 1st generation antipsychotics, 2nd generation, and mixed 1st and 2nd generation antipsychotics at electrode site CZ. To the right are two-dimensional scalp topography of grand average MMN, P3a and RON responses and t-tests comparing group amplitude differences. Note: the medication subgroups did not significantly differ in age.

Figure 2.

A 3-factor SEM model of the MMN, P3a, and RON responses. Final model. Circles represent latent variables, and rectangles represent measured variables. Values are standardized path coefficients. The 3-factor SEM model provided a significant improvement over a single-factor model in both groups, suggesting that the three ERP components may be tapping unique neural processes and are not redundant

Table 1

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

Demographic and Clinical Characteristics	Schizophrenia Patients (n=429)		Nonpsychiatric Comparison Subjects (n=286)	
	Mean	SD	Mean	SD
*Gender (% male)	70.63	---	47.90	----
Age (years)	45.80	9.70	45.70	12.18
Years of Education Completed	11.97	2.07	14.92	2.27
Age of Illness Onset	18.67	8.30		
Duration of Illness	24.12	10.47		
Number of Hospitalizations	9.01	12.77		
SANS Total Score	8.96	4.10		
SAPS Total Score	14.55	4.30		
UPSA Total Score	78.89	14.24		

Abbreviations: SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; UPSA, UCSD Performance Based Skills Assessment.

Table 2

ERP amplitude at electrode Fz (MMN and P3a) and Cz (RON) across antipsychotic medication subgroups. Data are given as mean and standard deviation marginal means of age-adjusted event related potential amplitudes.

	MMN	P3a	RON
Group	Mean (SD)	Mean (SD)	Mean (SD)
<u>Nonpsychiatric Comparison Subjects (N=286)</u>	-2.56 (1.65)	2.88 (1.93)	-1.90 (1.04)
<u>Schizophrenia Patients (all; N=429)</u>	-1.26 (1.18)	1.63 (1.39)	-1.24 (0.87)
• Unmedicated (No Antipsychotic; n=38)	-1.48 (1.35)	1.70 (1.27)	-1.14 (0.59)
• 1 st Generation Antipsychotic (n=30)	-1.48 (1.12)	1.64 (1.04)	-1.26 (0.66)
• 2 nd Generation Antipsychotic (n=226)	-1.30 (1.21)	1.65 (1.52)	-1.29 (0.95)
Risperidone (n=79)	-1.34 (1.14)	1.44 (1.27)	-1.09 (0.92)
Olanzapine (n=46)	-1.36 (1.25)	2.21 (1.61)	-1.45 (0.89)
Quetiapine (n=44)	-1.29 (1.05)	1.59 (1.25)	-1.12 (0.80)
Aripiprazole (n=27)	-1.58 (0.91)	1.65 (1.38)	-1.42 (0.85)
Clozapine (n=19)	-0.88 (1.14)	1.46 (1.32)	-1.41 (0.69)
Ziprasidone (n=11)	-0.73 (0.82)	2.80 (2.93)	-1.53 (1.13)
• Multiple 2 nd Generation (n=75)	-1.33 (1.41)	1.43 (1.51)	-1.36 (1.14)
• Mixed 1 st and 2 nd Generation (n=60)	-0.87 (0.91)	1.50 (0.87)	-1.08 (0.69)

Descriptive statistics and effect sizes of MMN, P3a and RON amplitude of event related potential response across scalp electrodes between schizophrenia patients and nonpsychiatric comparison group. Standard Deviation (*SD*) and effect size calculated as Cohen's *d*.

Table 3

Elect	Schizophrenia Patients (N=429)			Nonpsychiatric Comparison Subjects (N=286)			Effect Size (<i>d</i>)		
	MMN	P3a	RON	MMN	P3a	RON	MMN	P3a	RON
Fz	-1.26 (1.18)	1.62 (1.39)	-1.14 (0.84)	-2.57 (1.65)	2.88 (1.93)	-1.68 (0.90)	1.05	0.87	0.60
F3	-1.12 (1.06)	1.66 (1.49)	-0.96 (0.70)	-2.31 (1.40)	2.84 (1.75)	-1.42 (0.75)	1.08	0.80	0.62
F4	1.17 (1.10)	1.66 (1.51)	-0.99 (0.69)	-2.41 (1.44)	2.87 (1.75)	-1.47 (0.75)	1.09	0.81	0.66
F7	-0.51 (0.63)	1.20 (1.22)	-0.47 (0.49)	-1.08 (0.74)	1.99 (1.37)	-0.67 (0.49)	0.90	0.67	0.40
F8	-0.50 (0.72)	1.10 (1.10)	-0.50 (0.50)	-1.27 (0.96)	1.95 (1.19)	-0.80 (0.59)	1.02	0.79	0.59
Fp1	-0.62 (0.65)	0.76 (0.87)	-0.48 (0.44)	-1.22 (0.76)	1.11 (0.92)	-0.65 (0.48)	0.91	0.38	0.37
Fp2	-0.63 (0.69)	0.82 (0.93)	-0.49 (0.57)	-1.23 (0.87)	1.30 (1.00)	-0.71 (0.53)	0.85	0.54	0.42
FC1	-1.20 (1.22)	1.48 (1.45)	-1.21 (0.87)	-2.59 (1.68)	2.80 (2.27)	-1.85 (0.99)	1.08	0.82	0.74
FC2	-1.21 (1.22)	1.49 (1.47)	-1.23 (0.90)	-2.61 (1.68)	2.81 (2.13)	-1.85 (0.95)	1.09	0.85	0.65
FC5	-0.78 (0.90)	1.23 (1.29)	-0.76 (0.60)	-1.79 (1.14)	2.22 (1.64)	-1.18 (0.68)	1.10	0.76	0.70
FC6	-0.80 (0.94)	1.39 (1.51)	-0.79 (0.61)	-1.93 (1.27)	2.55 (1.70)	-1.24 (0.71)	1.16	0.79	0.73
C3	-0.86 (1.16)	1.28 (1.36)	-0.97 (0.73)	-2.05 (1.38)	2.43 (1.90)	-1.50 (0.85)	1.02	0.81	0.74
Cz	-0.99 (1.20)	1.40 (1.56)	-1.24 (0.87)	-2.32 (1.65)	2.63 (2.49)	-1.91 (1.04)	1.06	0.71	0.77
C4	-0.83 (1.05)	1.14 (1.38)	-0.98 (0.70)	-1.96 (1.60)	2.10 (1.94)	-1.45 (0.99)	0.98	0.66	0.63
CP1	-0.59 (1.06)	0.80 (1.23)	-0.97 (0.73)	-1.60 (1.38)	1.63 (2.18)	-1.44 (0.91)	0.93	0.57	0.63
CP2	-0.55 (1.03)	0.77 (1.19)	-0.96 (0.73)	-1.54 (1.40)	1.53 (1.96)	-1.41 (0.87)	0.92	0.57	0.60
CP5	-0.13 (0.93)	0.20 (1.05)	-0.59 (0.61)	-0.76 (1.18)	0.56 (1.78)	-0.90 (0.78)	0.66	0.30	0.48
CP6	-0.02 (0.86)	0.45 (1.05)	-0.58 (0.57)	-0.70 (1.14)	0.94 (1.57)	-0.87 (0.74)	0.76	0.43	0.48

Elect	Schizophrenia Patients (N=429)			Nonpsychiatric Comparison Subjects (N=286)			Effect Size (d)		
	MMN	P3a	RON	MMN	P3a	RON	MMN	P3a	RON
P7	0.72 (1.07)	0.20 (1.12)	-0.22 (0.49)	0.69 (1.02)	0.36 (1.31)	-0.32 (0.63)	0.02	0.14	0.23
P3	-0.03 (0.98)	0.45 (1.07)	-0.65 (0.64)	-0.83 (3.17)	0.89 (1.62)	-1.68 (0.55)	0.46	0.37	0.16
Pz	-0.12 (1.10)	0.23 (1.06)	-0.74 (0.68)	-0.82 (1.20)	0.54 (1.75)	-1.04 (0.79)	0.69	0.26	0.44
P4	0.04 (0.95)	0.28 (1.18)	-0.63 (0.60)	-0.56 (1.16)	0.81 (1.36)	-0.89 (0.77)	0.64	0.45	0.42
P8	0.76 (1.06)	0.10 (0.85)	-0.22 (0.49)	-0.65 (1.09)	0.41 (1.01)	-0.32 (0.63)	0.10	0.37	0.20
T7	0.10 (0.81)	-0.05 (0.96)	-0.31 (0.92)	-0.23 (0.80)	0.13 (1.48)	-0.57 (0.67)	0.41	0.18	0.30
T8	0.11 (0.79)	0.03 (0.93)	-0.38 (0.57)	-0.47 (0.99)	0.34 (1.48)	-0.65 (0.72)	0.72	0.31	0.45
TP9	0.98 (1.07)	-0.34 (0.61)	-0.03 (0.47)	1.26 (0.98)	-0.38 (0.70)	-0.02 (0.55)	0.26	0.07	0.01
TP10	1.00 (1.05)	-0.23 (0.62)	-0.01 (0.46)	1.11 (1.03)	-0.14 (0.76)	-0.06 (0.55)	0.10	0.15	0.15
T1	0.48 (0.78)	-0.28 (0.80)	-0.03 (0.42)	0.63 (0.73)	-0.43 (1.13)	-0.07 (0.47)	0.18	0.17	0.08
T2	0.56 (0.78)	-0.25 (0.70)	-0.04 (0.42)	0.55 (0.79)	-0.35 (1.04)	-0.13 (0.50)	0.01	0.13	0.19
PO9	0.94 (1.09)	-0.30 (0.82)	-0.03 (0.48)	1.17 (1.03)	-0.55 (0.97)	-0.04 (1.30)	0.21	0.30	0.01
PO10	0.99 (1.10)	-0.27 (0.81)	0.00 (0.45)	1.16 (1.02)	-0.57 (0.93)	0.00 (0.53)	0.15	0.34	0.01
O1	0.72 (1.11)	-0.28 (0.81)	-0.19 (0.55)	0.74 (1.02)	-0.56 (1.07)	-0.22 (0.65)	0.01	0.33	0.06
O2	0.73 (1.09)	-0.05 (0.63)	-0.21 (0.51)	0.68 (1.07)	-0.09 (0.62)	-0.23 (0.62)	0.04	0.07	0.05

ERP amplitude at electrode Fz (MMN and P3a) and Cz (RON) across participant groups, and Cohen's effect size d of the difference in amplitude between groups, by age category. Data are given as mean and standard deviation amplitude of event related potential response.

Table 4

Age	N=	Schizophrenia Patients (N=429)				Nonpsychiatric Comparison Subjects (N=286)				Effect Size (d)			
		MMN	P3a	RON	N=	MMN	P3a	RON	N=	MMN	P3a	RON	N=
18-30	34	-2.33 (1.70)	2.16 (1.75)	-1.70 (1.61)	38	-3.44 (1.89)	4.24 (2.42)	-1.92 (1.90)		.62	1.03	0.41	
31-40	83	-1.41 (1.20)	1.79 (1.26)	-1.22 (0.79)	48	-2.81 (1.93)	3.08 (1.47)	-1.69 (0.89)		1.10	1.12	0.64	
41-50	177	-1.24 (1.04)	1.66 (1.46)	-1.13 (0.72)	103	-2.48 (1.58)	2.58 (1.88)	-1.72 (0.81)		1.13	0.65	0.87	
51-60	110	-0.91 (.96)	1.40 (1.22)	-0.96 (0.62)	72	-2.10 (1.28)	2.52 (1.68)	-1.44 (0.76)		1.20	0.88	0.77	
>60	25	-0.85 (1.10)	1.10 (1.21)	-1.06 (0.93)	25	-2.48 (1.49)	2.76 (2.00)	-1.81 (1.05)		1.30	1.13	0.77	