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Neural substrates of normal and impaired preattentive sensory discrimination in large cohorts of nonpsychiatric subjects and schizophrenia patients as indexed by MMN and P3a change detection responses☆

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ABSTRACT

Objective: Schizophrenia (SZ) patients have information processing deficits, spanning from low level sensory processing to higher-order cognitive functions. Mismatch negativity (MMN) and P3a are event-related potential (ERP) components that are automatically elicited in response to unattended changes in ongoing, repetitive stimuli that provide a window into abnormal information processing in SZ. MMN and P3a are among the most robust and consistently identified deficits in SZ, yet the neural substrates of these responses and their associated deficits in SZ are not fully understood. This study examined the neural sources of MMN and P3a components in a large cohort of SZ and nonpsychiatric control subjects (NCS) using Exact Low Resolution Electromagnetic Tomography Analyses (eLORETA) in order to identify the neural sources of MMN and P3a as well as the brain regions associated with deficits commonly observed among SZ patients.

Methods: 410 SZ and 247 NCS underwent EEG testing using a duration-deviant auditory oddball paradigm (1-kHz tones, 500 ms SOA; standard $p = 0.90$, 50-ms duration; deviant tones $P = 0.10$, 100-ms duration) while passively watching a silent video. Voxel-by-voxel within- (MMN vs. P3a) and between-group (SZ vs. NCS) comparisons were performed using eLORETA.

Results: SZ had robust deficits in MMN and P3a responses measured at scalp electrodes consistent with other studies. These components mapped onto neural sources broadly distributed across temporal, frontal, and parietal regions. MMN deficits in SZ were associated with reduced activations in discrete medial frontal brain regions, including the anterior–posterior cingulate and medial frontal gyri. These early sensory discriminatory MMN impairments were followed by P3a deficits associated with widespread reductions in the activation of attentional networks (frontal, temporal, parietal regions), reflecting impaired orienting or shifts of attention to the infrequent stimuli.

Conclusions: MMN and P3a are dissociable responses associated with broadly distributed patterns of neural activation. MMN deficits among SZ patients appear to be primarily accounted for by reductions in medial prefrontal brain regions that are followed by widespread dysfunction across cortical networks associated with P3a in a manner that is consistent with hierarchical information processing models of cognitive deficits in SZ patients. Impairments in automatic stimulus discrimination may contribute to higher-order cognitive and psychosocial deficits in SZ.

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Introduction

Schizophrenia patients exhibit neurocognitive deficits across multiple domains, from the earliest levels of sensory information processing (Braff, 1989; Grillon et al., 1990; Light and Braff, 2005a,b; Shelley et al., 1991) through progressively higher-order cognitive domains including attention, memory, language, and social functioning (e.g. Heaton et al., 2001; Light and Braff, 2005a,b; Rissling et al., 2012). Some neurophysiological measures probe the earliest stages of cognition, are automatically

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elicited, and require little or no effort, attention, engagement, or even awareness on the part of the subject (Braff and Light, 2004; Callaway and Naghdi, 1982; Näätänen, 1992). Deficits in these early stages of sensory information processing may underlie some clinical symptoms in schizophrenia (Fisher et al., 2008; Ford et al., 2007; Mathalon and Ford, 2008), and may govern deficits in more complex cognitive operations and real-world psychosocial functioning of schizophrenia patients (Braff and Light, 2004; Rissling et al., in press; Tiitinen et al., 1994). The purpose of the current study was to employ novel computational imaging analyses in order to identify the neural substrates of normal and impaired preattentive sensory discrimination in a large cohort of nonpsychiatric control subjects and schizophrenia patients.

Scalp-recorded event-related potential (ERP) measures are often used to reliably quantify the neural processing associated with sensory and cognitive events with millisecond (ms) resolution. Although the spatial resolution of EEG measures has traditionally been less precise than functional magnetic resonance imaging, novel analytic techniques can now be used to elucidate the contribution of distributed neuroanatomic sources to scalp-recorded ERP components (Makeig et al., 1997, 2004; Pascual-Marqui, 2002, 2007; Pascual-Marqui et al., 1994, 2011; Rissling et al., 2010).

The auditory mismatch negativity (MMN) is a negative-going deflection in the ERP that is evoked when a sequence of repetitive "standard" stimuli is occasionally interrupted by infrequent oddball or "deviant" stimuli that differ in some stimulus characteristic such as duration or pitch. The onset of the MMN response occurs within 50 ms of stimulus deviance, and peaks after an additional 100–150 ms. Since MMN requires no overt behavioral response and can be elicited even in the absence of directed attention (Näätänen, 1992; Rinne et al., 2001; Sussman et al., 2003), it is presumed to reflect a predominantly automatic, pre-conscious process of detecting a "mismatch" between the deviant stimulus and a sensory–memory trace (Näätänen et al., 1989).

The MMN response is followed by a positive-going ERP deflection peaking at 250–300 ms after stimulus onset (Alho et al., 1997; Paavilainen et al., 1989). This "P3a" component is thought to reflect a reorienting or covert shifting of attention (Friedman et al., 2001; Polich, 2007; Squires et al., 1975). Since both MMN and P3a are elicited even in the absence of directed attention, these measures are often used to assess impairments in the initial stages of cognitive information processing and are presumed to be relatively immune to interference from inattentiveness, incomplete effort or engagement (Light et al., 2010). These aspects of the MMN and P3a are thought to be strengths given that inattentiveness and incomplete effort can confound the assessment of some higher cognitive operations among SZ patients.

Many studies have demonstrated that MMN and P3a are reduced in SZ patients (Michie, 2001; Turetsky et al., 2007; Umbricht and Krljes, 2005) with distinct relationships to important demographic, clinical, and functional characteristics which suggests that these measures index discrete processes with dissociable underlying neural substrates (Rissling et al., 2012).

MMN fulfills criteria for use as an endophenotypic marker (Gottesman and Gould, 2003) of the disease since it is: (a) associated with SZ (Umbricht and Krljes, 2005); (b) heritable (Hall et al., 2006; Price et al., 2006); (c) independent of fluctuations of clinical state and symptoms (Light et al., 2012; Shinozaki et al., 2002); and (d) present in individuals at genetic risk for developing schizophrenia (Atkinson et al., 2012; Baker et al., 2005; Jahshan et al., 2012; Jessen et al., 2001; Michie et al., 2002; Schreiber et al., 1992). Furthermore, MMN may also serve as a biomarker of treatment response in clinical trials, because it is: (e) extremely reliable in both normal individuals and schizophrenia patients tested over a 1-year interval (Light et al., 2012); (f) insensitive to order or practice effects (Kathmann et al., 1999; Pekkonen et al., 1995); (g) robustly related to level of everyday functioning in schizophrenia patients (Friedman et al., 2012; Kawakubo et al., 2007; Kiang et al., 2007; Light and Braff, 2005a,b; Rasser et al., 2011; Wynn et al., 2010) (h) responsive to pharmacologic models of schizophrenia (Javitt et al., 1996; Lavoie et al., 2008; Umbricht et al., 2000, 2002); and (i) easily assessed in patients with a broad range of function given the low effort associated with task demands. On the basis of these features, Belger and colleagues (Belger et al., 2012) argued that MMN may be the biomarker "we've been waiting for" since it represents a unique window into disturbed central auditory processing in schizophrenia and related conditions as reviewed by Näätänen et al. (2012). Though the P3a has not been studied as extensively as MMN, studies have shown robust and reliable amplitude deficits in schizophrenia patients comparable in magnitude to MMN (A.J. Rissling et al., in press; Grillon et al., 1990; Jahshan et al., 2012; Kiang et al., 2009; Mathalon et al., 2000; Rissling et al., 2012; Turetsky et al., 1998). Thus, P3a may also serve as a useful biomarker in clinical research studies of schizophrenia (Javitt et al., 2008; Light et al., 2012).

While many studies have demonstrated the substantial utility of MMN and P3a in SZ research, typically only the latency and amplitude at selected electrodes (e.g., Fz) and singular time points are used to characterize these neural responses. The measurement of ERP peak voltage may not fully capture the complexity of neural processing that underlies these sensory-based cognitive processes. Multi-sensor EEG data allows for the spatio-temporal quantification of these responses (Hamm et al., in press) as well as the identification of the neural architecture that underlies normal and abnormal scalp-recorded ERPs. Unfortunately, a significant gap exists in the MMN/P3a literature: relatively few studies have examined the neural sources of MMN and P3a in normal subjects or the regions that prominently contribute to the deficits observed in schizophrenia. Previous MEG, fMRI, and intracranial animal studies of MMN sources have consistently identified generators in the primary and secondary auditory cortices resulting in the common assumption that schizophrenia-related deficits in these measures arise from impaired activation in temporal structures (e.g., see Figure 1 in Umbricht and Krljes, 2005). In contrast, surface and intracranial EEG, PET, and fMRI studies (reviewed by Schönwiesner et al., 2007) suggest additional contributions from frontal regions such as the inferior frontal gyrus (Marco-Pallares et al., 2005; Park et al., 2002; Rinne et al., 2000; Schönwiesner et al., 2007), medial frontal gyrus (Marco-Pallares et al., 2005; Restuccia et al., 2005), and anterior cingulate cortex (Jemel et al., 2002; Oknina et al., 2005; Waberski et al., 2001; Wild-Wall et al., 2005). Notably, the contribution of parietal cortices to MMN has also been observed (Kasai et al., 1999; Lavikainen et al., 1995; Levänen et al., 1996; Molholm et al., 2005; Schall et al., 2003), although it is possible that the observed parietal involvement may have been related to the subsequent generation of the P3a rather than MMN. Thus, clarification of the neural sources of MMN and P3a generation is an important step in the elucidation of SZ-related deficits in sensory discriminatory processes.

Since the brain activity of MMN and P3a is spatially distributed and not confined to single point sources, a distributed EEG/MEG tomography may offer some advantages over some traditional methods of dipole fitting. To address this limitation, Low Resolution Electromagnetic Tomography (LORETA; publicly available free academic software at http://www.uzh.ch/keyinst/loreta.htm) algorithms based on discrete, three-dimensional (3D) distributed, linear, minimum norm inverse solutions have been developed for the examination of neural activity. Recently, the LORETA methods have been refined via standardized (i.e., sLORETA) and exact (i.e., eLORETA) procedures that can correctly localize deep structures such as the anterior cingulate cortex (Pizzagalli et al., 2001), and mesial temporal lobes (Zumsteg et al., 2006a), which may be under-recognized using other localization procedures.

Previous LORETA-based studies of healthy normal subjects support the role of temporal (Laufer and Pratt, 2005; Marco-Pallares et al., 2005; Maurer et al., 2003; Zaehle et al., 2009), frontal (Marco-Pallares