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Sensory gating disturbances in the spectrum: Similarities and differences in schizotypal personality disorder and schizophrenia

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ABSTRACT

Background: DSM-5 places schizophrenia on a continuum from severe, chronic schizophrenia to the attenuated schizophrenia-like traits of schizotypal personality disorder (SPD), the prototypic schizophrenia-related personality disorder. SPD shares common genetic and neurobiological substrates with schizophrenia, including information processing abnormalities, although they are less marked. This is the first study to directly compare the P50 evoked electroencephalographic response—a measure of sensory gating and a neurophysiological endophenotype—between schizophrenia-spectrum groups. Two hypotheses were tested: (1) Compared with healthy controls (HCs), schizophrenia patients show reduced P50 suppression and SPD patients resemble schizophrenia but exhibit less marked deficits; and (2) Deficient P50 suppression in SPD is associated with *greater* clinical symptom severity.

Methods: P50 was assessed in 32 schizophrenia-spectrum disorder patients (12 SPD, 20 schizophrenia patients) and 25 demographically-matched HCs. The standard conditioning (C)-testing (T) paradigm was used and P50 suppression was quantified using the T–C difference and the T/C ratio.

Results: All P50 measures showed a linear, stepwise pattern with the SPD group intermediate between the HC and schizophrenia groups. Compared with HCs, both patient groups had lower conditioning and T–C difference values. Among the SPD group, *greater* clinical symptom severity was associated with greater conditioning-response amplitude deficits.

Conclusion: These findings: (1) are novel in showing that P50 deficits in SPD resemble those observed in schizophrenia, albeit less marked; (2) support the concept that the phenomenological link between SPD and schizophrenia lies in shared neurocognitive/neurophysiological pathologies; and (3) provide evidence that P50 is a neurophysiological endophenotype for schizophrenia-spectrum disorders.

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1. Introduction

Schizotypal personality disorder (SPD) is phenomenologically and genetically linked to schizophrenia (Siever et al., 1993) and in the DSM-5, it is categorized as a schizophrenia-spectrum disorder (American Psychiatric Association, 2013). Individuals with SPD are free of overt psychotic symptoms, but exhibit many of the same cognitive and information-processing deficits as patients with schizophrenia, albeit less severe (Braff, 1999; Siever and Davis, 2004; McClure et al., 2013; Hazlett et al., 2014). Studying individuals with SPD offers advantages in terms of eliminating potential confounds because they are typically never medicated, have not been hospitalized for chronic mental illness, and rarely present with acute psychotic symptoms (Cadenhead et al., 2000a; Turetsky et al., 2007).

A core feature observed in schizophrenia-spectrum disorders, which are conceptualized as disorders of attention and information processing, is the inability to appropriately filter sensory stimuli. It is challenging for these individuals to attend to what is salient and ignore what is extraneous (Cadenhead et al., 2000a; Hazlett et al., 2003, 2014; Turetsky et al., 2007). These inhibitory-processing deficits permeate many areas of daily perception and functioning. An ideal approach for objectively studying and quantifying cognitive/information-processing disturbances in the schizophrenia spectrum is to employ psychophysiological measures such as the P50-evoked electroencephalographic (EEG) response to repeated auditory stimuli as a measure of sensory-gating dysfunction (Adler et al., 1982). This standardized paired-stimulus paradigm measures the amplitude of the P50 component of the cerebral EEG evoked response to each of two consecutive auditory clicks (called conditioning and test, respectively). In healthy individuals, the second

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P50 response is suppressed, or "gated", because of the inhibitory effects of the first click (Adler et al., 1982, 1998; Miller and Freedman, 1995; Olincy et al., 2010). The first stimulus is hypothesized to excite target neurons, as well as relevant inhibitory neurons. The second, tests the effect of the inhibitory circuits on the response of the target neurons, which is why it is referred to as the conditioning-test paradigm (Olincy et al., 2010). Impaired suppression of the P50 wave has been identified as a vulnerability marker or endophenotype for the sensory-gating deficits observed in schizophrenia patients and their relatives (Siegel et al., 1984; Waldo et al., 1991; Clementz et al., 1998; Olincy et al., 2010).

P50 integrity is measured in terms of how well an individual suppresses their response to the second stimulus. It can be calculated either by taking the ratio of the amplitude of the test response to that of the conditioning response (T/C ratio), or by taking the difference between the test and conditioning amplitude (T–C). Schizophrenia patients and their clinically unaffected first-degree relatives exhibit impaired P50 suppression, indicated by both a higher T/C ratio and a smaller T–C difference between responses compared with healthy controls (HCs) (Clementz et al., 1998; Olincy et al., 2010). Two of the largest P50 studies conducted to date, reported that compared with HCs, schizophrenia patients exhibited the poorest P50 suppression, while their unaffected relatives showed significant but less marked impairment (Clementz et al., 1998; Olincy et al., 2010). This stepwise, linear pattern of results supports the concept that deficient cerebral inhibition measured with P50 suppression is a genetically-based endophenotype and the genetic basis of schizophrenia-spectrum disorders lies in shared neurocognitive pathologies (Cadenhead et al., 2000a). Prior work examining the relationship between P50 suppression and measures of cognitive function in schizophrenia is mixed with some studies reporting no evidence of an association (e.g., Sánchez-Morla et al., 2013) and others showing greater P50-suppression deficits are associated with greater attentional deficits as measured with a neuropsychological battery (e.g., Cullum et al., 1993; Erwin et al., 1998).

P50 sensory gating deficits have also been reported in adolescents genetically at high-risk for developing schizophrenia (i.e. either the offspring of a schizophrenia patient or the offspring of unaffected parents with at least two affected siblings), as well as adolescents with low-genetic liability but identified as potentially prodromal for schizophrenia (Myles-Worsley et al., 2004). Others have shown deficits in healthy individuals with high scores on scales measuring schizotypy psychometrically (Croft et al., 2001, 2004; Wan et al., 2006, 2007). Further, Croft et al. (2001) examined individual differences and reported that greater abnormal perceptual experiences and magical ideation were associated with poorer P50 suppression. Limited research has examined P50 in SPD. To date, two studies (Cadenhead et al., 2000a, 2002) reported that compared with HCs, SPD patients showed significantly reduced P50 suppression. While these findings are the first to demonstrate deficient P50 suppression in SPD, some of the patients were receiving antipsychotic medication which potentially confounded the results. Prior work indicates that atypical (second-generation) antipsychotics have been shown to partially ameliorate P50-suppression deficits in schizophrenia (e.g., Light et al., 2000; Adler et al., 2004; Becker et al., 2004). Additionally, Cadenhead et al. (2000a, 2002) did not examine whether P50-suppression deficits in SPD are associated with clinical symptom severity and a schizophrenia comparison group was not included as a contrast. The current study aimed to address these issues.

We examined P50 across the schizophrenia spectrum by directly comparing three groups: HCs, antipsychotic-naïve individuals with SPD, and schizophrenia patients. Consistent with prior P50 studies examining samples of SPD and schizophrenia patients, separately, and work examining neurocognition across the spectrum (e.g., Cadenhead et al., 1999; Weiser et al., 2003; Siever and Davis, 2004; Harvey et al., 2006; McClure et al., 2013), we tested the hypothesis that a stepwise, linear pattern for P50 suppression would be observed reflecting that compared with HCs, schizophrenia patients exhibit the poorest P50 suppression, while SPD patients show significant but less marked impairment. We also conducted an exploratory analysis to determine whether *more deficient* P50 suppression is associated with *greater* clinical symptom severity in SPD.

2. Methods

2.1. Participants

The sample comprised three demographically-matched groups: 25 HCs, 12 SPD patients, and 20 schizophrenia patients (Table 1). The HC and SPD participants were recruited from the community surrounding Mount Sinai Hospital using local newspaper advertisements and social media as in our prior research, e.g., Mitropoulou et al. (2005) and Hazlett et al. (2014). The schizophrenia patients were referred for study participation from Mount Sinai outpatient psychiatry clinics and outreach to other psychiatric treatment and group-home facilities. The Mount Sinai recruited HC and schizophrenia patients were a subset of those who participated in the COGS study (Calkins et al., 2007) and their P50 data were previously published as part of a larger study (Olincy et al., 2010). However, it is important to note that neither the SPD data, nor the HC vs. SPD vs. schizophrenia statistical comparison presented in this paper has previously been published. The SPD participants were interviewed with the Structured Clinical Interview for DSM-IV (First et al., 1995) for Axis-I disorders and the Revised Schedule for DSM-IV Personality Disorders (Pfohl et al., 1997). The schizophrenia patients and HCs received the Diagnostic Interview for Genetics Studies (DIGS), and related instruments, as described in previous publications from the Consortium (Calkins et al., 2007). The HCs had no personal or family history of psychosis or Cluster A personality disorder. SPD patients met the DSM-IV criteria based upon the structured diagnostic interview and were excluded if they had any history of a psychotic disorder (including schizophrenia, bipolar-I disorder), or met the criteria for current major depressive disorder (i.e. an episode within $\leq$3 months of study enrollment). All participants were screened by a physician for neurological and severe medical illness (e.g., head trauma, stroke, HIV, diabetes, history of IV drug use). Participants were excluded if they met lifetime criteria for substance dependence or abuse during the 6-month period prior to study enrollment, or had a positive urine toxicology screen for drugs-of-abuse. None of the SPD patients had ever received psychotropic medication. One of the schizophrenia patients was unmedicated and the remaining 19 were taking psychoactive medication at the time of their P50 testing (Table 1). Schizophrenia patients were excluded if taking clozapine, known to improve P50 suppression (Nagamoto et al., 1999). Participants were not allowed to smoke or use nicotine within 30 min of P50 testing.

2.2. Electrophysiological recording and scoring

The P50 paradigm was administered under procedures identical to the COGS study (Olincy et al., 2010). A 0.04 ms square wave was amplified from 20 Hz to 12 kHz and delivered through earphones. The participant's threshold for this stimulus was determined in each ear, and the stimulus for each ear was set to 50 dB above this threshold. The stimuli were paired with intra-pair interval of 0.5 s and inter-pair interval of 10 s. EEG recordings were made from the vertex referenced to the left ear lobe. Electro-oculographic activity was recorded between the lateral canthus and the superior orbit of the right eye.

Participants sat semi-recumbent in a relaxation chair. They were instructed to remain awake and to fix their eyes on the wall 2 m across from the chair. Stimuli were delivered as 5 blocks of 20 stimulus pairs with 2-min rest periods between blocks. The tester remained in the room in order to reinforce the instructions and ensure that the participant remained awake and alert, as judged by their appearance. The tester could observe if the electrical activity deviated by more than 50 μV from baseline, a sign of likely startle or movement artifact, and then stop recording. Stimuli were reduced by 2 dB if such artifacts