



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 ≤ 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 μ V from baseline, a sign of likely startle or movement artifact, and then stop recording. Stimuli were reduced by 2 dB if such artifacts

Table 1
Sample demographic and clinical characteristics.

Characteristic	Healthy controls (n = 25)			SPD patients (n = 12)			Schizophrenia patients (n = 20)			Statistical analysis t, df, p-value
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	
Age (years):	39.9	11.9	22–63	38.2	11.4	21–53	37.5	10.5	24–60	HC v. SPD: 0.42, 35, 0.67; HC v. SZ: 0.73, 43, 0.47; SPD v. SZ: 0.18, 30, 0.86
Education (years):	15.4	2.4	11–19	14.5	1.7	12–16	13.5	2.5	10–18	HC v. SPD: 1.21, 35, 0.23; HC v. SZ: 2.69, 43, < 0.05; SPD v. SZ: 1.26, 30, 0.22
Parental education (years):							15.2	3.5	10.5–24.5	HC v. SZ: 0.32, 42, 0.75
	n	%		n	%		n	%		χ^2 df, p-value
Gender:										HC v. SPD: 0.18, 1, 0.89; HC v. SZ: 0.93, 1, 0.34; SPD v. SZ: – – 0.70
Men	14	56		7	58		14	70		
Women	11	44		5	42		6	30		
Number of Smokers:	2	8		4	33		11	55		HC v. SPD: – – 0.07; HC v. SZ: 11.9, 1, < 0.01; SPD v. SZ: 1.41, 1, 0.23
Medication status ^a :										
Atypical antipsychotic				0	0		15	75		
Typical antipsychotic				0	0		3	15		
Other medications				0	0		1	5		
Unmedicated							1	5		
				Mean	SD	Range	Mean	SD	Range	
Chlorpromazine equivalent: SPD symptom severity ^b :				7.2	1.0	6–9	352.8	295.8	0–1200	
Schizophrenia symptom severity ^c :										
SAPS							5.5	4.0	0–12	
SANS							6.6	5.0	0–18	
Duration of illness (years):							15.5	10.4	3–35	

^a 75% of the schizophrenia patients were taking atypical antipsychotic medications, thus group size was too small for statistical comparison between medication subgroups.

^b In order to assess clinical symptom severity in the SPD patients, each of the nine DSM-IV SPD criteria was rated during the SIDP structured diagnostic interview on a 4-point scale (0 = absent, 0.5 = somewhat present, 1.0 = definitely present; prototypical, 2.0 = severe; pervasive). Based on our prior work (e.g., Hazlett et al., 2011, 2014), overall clinical symptom severity for SPD patients was calculated as the sum of these nine scores (with a possible range of 5 to 18).

^c Two scales were used to assess clinical symptom severity in the schizophrenia patients. The Scale for the Assessment of Positive Symptoms (SAPS) was used to assess the severity of positive symptoms. It was calculated based on their SAPS global summary score, which collapses the four subscales (hallucinations, delusions, bizarre behavior, and thought disorder). The Scale for the Assessment of Negative Symptoms (SANS) was used to assess severity of negative symptoms. It was calculated based on the global summary score which collapses the five subscales (flat affect, avolition, anhedonia, and attention).

^c Chi-Square analyses were performed for gender and number of smokers. When cell counts satisfied the minimum expected values, the Pearson Chi-Square values were reported. When cell counts were below the minimum expected values, only the Fisher's Exact Test (two-tailed) level of significance was reported.

occurred. Stimuli were also decreased by 2 dB if a prominent P30, indicative of myogenic artifact, was observed. Stimuli were increased by 4 dB if P50 was less than 1.5 μ V and 4 dB if P50 was less than 0.9 μ V during recording. The final P50 amplitude was determined after offline blinded re-analysis; rejection of tracings with electro-oculographic or myogenic artifacts could result in lower wave amplitudes than those observed during recording. The five blocks were averaged separately by an investigator blind to subject identity.

Digital filtering isolated activity between 10 and 100 Hz. The lower frequency limit was initially adopted because it was shown to isolate the P50 wave from the temporally overlapping, but lower frequency N100 wave, which can also begin as early as 50 ms after the stimulus (Jerger et al., 1992). Jansen et al. (2004) reported abnormalities in the EEG in schizophrenia in phase synchronization for frequencies below 12 Hz at the expected latency of P50, but they also noted that exclusion of these lower frequencies did not significantly alter P50 amplitude. Averages which contained deflections greater than 50 μ V were excluded to prevent inclusion of movement artifacts and then a grand average was constructed.

Application of the P50 detection algorithm to the prestimulus EEG was used to estimate the probability that a signal could be differentiated from background EEG activity. The mean and standard deviation for prestimulus activity with the filters used in the present study is 6.3 μ V (SD 2.3) (Freedman et al., 1996). Therefore waves of up to 10.9 μ V (mean plus two SD) could be expected to occur unrelated to the auditory stimuli. If 100 trials are averaged, the upper 95% confidence limit for background peak amplitude is thus 1 μ V, because averaging reduces amplitude unrelated temporally to the stimulus by the square root of the number of sweeps.

Therefore, averages with conditioning wave amplitudes less than 1 μ V were not accepted for data analysis. Averages with electro-oculographic potentials at 50 ms that were greater than the vertex EEG potential were also excluded (Griffith et al., 1995).

The P50 wave was identified in a window 40 to 75 ms post conditioning stimulus and its amplitude measured relative to the first preceding negativity using the previously described computerized algorithm (Nagamoto et al., 1989). The test wave had to be within ± 10 ms of the latency from the test stimulus as the conditioning wave. Its amplitude was measured relative to its preceding negativity. This criterion reflects the 95% confidence limit for the latency variance between test and conditioning waves (Nagamoto et al., 1989). All recordings were reviewed by an investigator blind to participant identity for fidelity to this protocol.

2.3. Statistical analysis

To examine between-group differences in P50, mixed-model analysis of variance (ANOVA) was conducted (StatSoft, 2013) with the conditioning and test amplitudes (as repeated measures), T–C difference score, and T/C ratio as the dependent variables, in three separate analyses. In all ANOVAs, Diagnostic group (HC-vs.-SPD-vs.-Schizophrenia) was the between-subjects factor. For all significant interactions involving Diagnostic group, Fisher's LSD tests were used to determine the direction of the significant interaction effect. Exploratory Pearson's correlation coefficients were calculated between significant P50 variables and clinical symptom severity scores.

To determine whether years of education should be a covariate, we conducted a correlation between years of education (both self and

parental) and the P50 variables. All of the r values were nonsignificant (r -values < 0.26 and p -values > 0.36). Given this lack of correlation, it is not statistically appropriate to use education as a covariate. Additionally, to determine whether smoking status should be used as a covariate, we conducted a correlation between smoking status (0 = no, 1 = yes) and the P50 variables. Across all three groups, smoking was significantly correlated with smaller T–C difference scores ($r = -0.30$, $p < 0.03$) and larger T/C ratios ($r = 0.29$, $p < 0.03$) but not with the conditioning or test amplitudes (r -values < 0.15 , p -values > 0.28). Based on these findings, we conducted ANCOVAs with smoking status as a covariate for the T–C difference score and T/C ratio analyses (reported in the Results section).

Lastly, to determine whether medication dosage was a factor affecting P50 in the schizophrenia group, a correlation was conducted between medication dosage (chlorpromazine equivalent) and the P50 variables. All of the r values were nonsignificant (r -values < 0.31 and p -values > 0.21).

3. Results

3.1. Group differences in P50

The HC group showed significantly larger amplitude of the P50 wave in response to the conditioning stimulus compared with both the SPD and schizophrenia groups (post-hoc p -values < 0.03), and there were no group differences for the test stimulus, Diagnostic group \times Stimulus type interaction, $F[2,54] = 15.57$, $p < 0.00001$ (Fig. 1). While intermediate between the HC and schizophrenia groups for amplitude of the conditioning stimulus, the SPD group did not significantly differ from the schizophrenia group.

A stepwise, linear schizophrenia-spectrum pattern was also observed for the T–C difference scores: schizophrenia patients showed significantly smaller values compared with both the HC and SPD groups, and the SPD group was intermediate between the HC and schizophrenia groups, $F[2,54] = 15.57$, $p < 0.00001$ (Fig. 2). Additionally, the SPD group showed a significantly smaller T–C difference score compared with the HCs (all between-group post hoc p -values < 0.03 ; Fig. 2). Smoking status was not significant when used as a covariate ($F[1,53] = 0.31$, $p = 0.58$) and the between-group effect for T–C difference scores remained significant ($F[2,53] = 7.47$, $p < 0.01$).

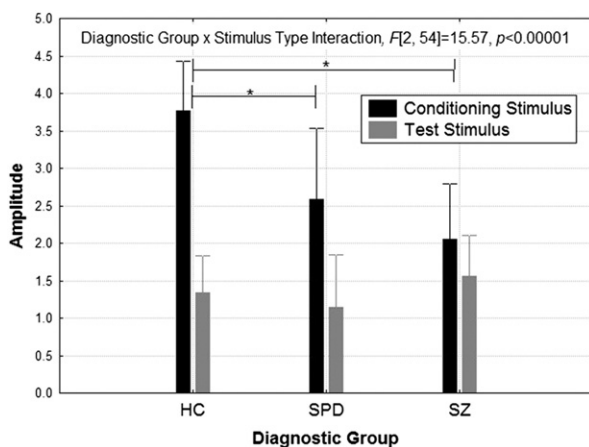


Fig. 1. P50 amplitude for each of the three diagnostic groups is shown for both the conditioning and test stimuli. Compared with the healthy control (HC) group, P50 amplitude for the conditioning stimulus was significantly smaller in both the schizophrenia and the schizotypal personality disorder (SPD) groups. The P50 conditioning stimulus amplitude for the SPD group was intermediate between the HC and schizophrenia groups and while it was significantly smaller compared with the HC group, it did not differ from the schizophrenia group. There were no group differences for P50 amplitude to the test stimulus. * $p < 0.03$, Fisher's LSD test. Error bars are standard error of the mean.

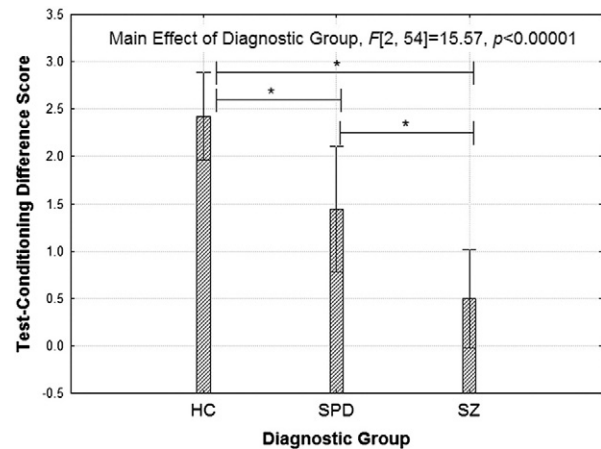


Fig. 2. P50 Test-Conditioning difference scores are shown for the three groups. Schizophrenia patients showed significantly smaller T–C difference scores compared with both the healthy control (HC) and schizotypal personality disorder (SPD) groups. The SPD group was intermediate between the HC and schizophrenia groups and significantly differed from both. * $p < 0.03$, Fisher's LSD test. Error bars are standard error of the mean.

Lastly, Fig. 3 shows a similar linear, stepwise schizophrenia-spectrum pattern for the T/C ratios. Schizophrenia patients exhibited significantly larger T/C ratios compared with both the HC and SPD groups, and the SPD patients were intermediate between the HC and schizophrenia groups, $F[2,54] = 10.65$, $p < 0.0002$. Post-hoc analyses confirmed that the schizophrenia patients showed significantly larger T/C ratios compared with both HC and SPD groups (p -values < 0.02) but despite the SPD group having larger ratios than the HC group, this difference was nonsignificant ($p = 0.26$). Smoking status was not significant when used as a covariate ($F[1,53] = 0.04$, $p = 0.83$) and the between-group effect for T–C difference scores remained significant ($F[2,53] = 15.76$, $p < 0.0001$).

3.2. Clinical correlates of P50

Among the SPD patients, greater conditioning amplitude was associated with less severity of SPD symptoms, $r(10) = -0.60$, $p < 0.053$ (approached significance for two-tailed correlation). The correlations with T/C ratio and T–C difference were nonsignificant (both $p > 0.43$). There were no significant correlations between the SANS and SAPS scores and the P50 variables in the schizophrenia group.

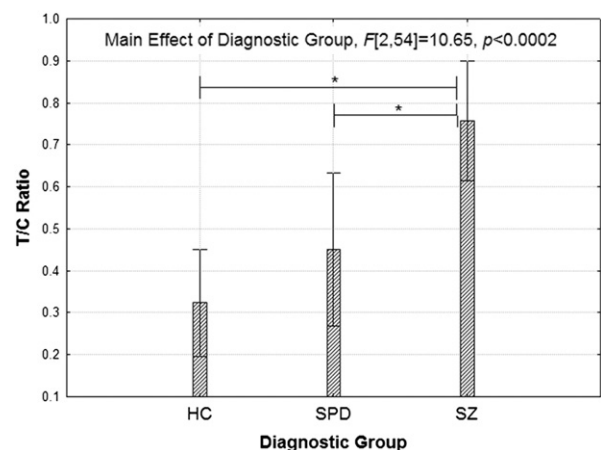


Fig. 3. P50 T/C ratio scores are shown for the three groups. Schizophrenia patients showed significantly greater T/C ratio scores compared with both the HC and SPD groups. The SPD group was intermediate between the HC and schizophrenia groups but only differed significantly from the schizophrenia group. * $p < 0.02$, Fisher's LSD test. Error bars are standard error of the mean.

4. Discussion

The novel finding of this study is that compared with HCs, SPD patients show significant P50 sensory-gating abnormalities closely resembling schizophrenia patients, although they are less marked. Specifically, both schizophrenia and SPD patients showed poor gating because the initial response (conditioning amplitude) is abnormally small in the presence of an otherwise normal second (test amplitude) response. One explanation for this pattern is that poor gating is due to a failure of the nervous system to register and/or attend to important information, including the initial conditioning stimulus (Brenner et al., 2009). Smaller P50 amplitude to the conditioning stimulus has been reported in schizophrenia (e.g., Jin and Potkin, 1996; Clementz and Blumenfeld, 2001). Event-related potentials elicited during the paired conditioning-test paradigm are thought to reflect the abilities of the nervous system to both (a) “gate in” novel, or salient information as measured by P50 amplitude to the initial conditioning stimulus (Boutros et al., 2004) and (b) filter or “gate out” extraneous information as measured by amplitude suppression to the second, or test stimulus. The present findings suggest that aberrant salience detection of the conditioning stimulus in SPD and schizophrenia is the primary mechanism underlying impaired P50 suppression. These findings extend prior work indicating that P50 suppression is abnormal in schizophrenia patients and their first-degree relatives (Clementz et al., 1998; Olincy et al., 2010), as well as individuals with SPD (Cadenhead et al., 2000a) suggesting this measure may be a useful intermediate phenotype marker for sensory-gating deficits in the schizophrenia spectrum.

The stepwise, linear pattern of T/C ratio and T–C difference scores reported in this study reflect an early information processing impairment in SPD that is similar, yet attenuated compared with schizophrenia and resembles prior neurocognitive work in the spectrum (Cadenhead et al., 1999; Barch et al., 2004; Siever and Davis, 2004; Seeber and Cadenhead, 2005; Harvey et al., 2006; McClure et al., 2013). SPD patients perform significantly worse than HCs on a variety of working memory, spatial memory, and attentional tasks (e.g., Cadenhead et al., 1999; Barch et al., 2004; Siever and Davis, 2004; McClure et al., 2013). Across varied neurocognitive tasks, impairments in SPD are less severe than those observed in schizophrenia (Cadenhead et al., 1999; Seeber and Cadenhead, 2005; McClure et al., 2013). Given that P50 suppression involves memory, attention, and information filtering processes, it is not surprising that the present P50 findings show a similar dimensional pattern with schizophrenia showing greater impairment relative to SPD (Cadenhead et al., 2000a; Olincy et al., 2010).

The finding of a smaller conditioning response across schizophrenia-spectrum disorders is consistent with previous schizophrenia research, e.g., Olincy et al. (2010) but is the first such finding in SPD. Taken together, the conditioning response and P50-suppression deficits in schizophrenia-spectrum patients provide further support for the concept that SPD and schizophrenia share neurocognitive dysfunction, although deficits in SPD are less marked than schizophrenia likely due to protective factors, including frontal-lobe sparing (Siever and Davis, 2004; Hazlett et al., 2008).

P50 impairments have also been observed in bipolar disorder patients with psychotic features and their non-affected relatives, suggesting that gating deficits are heritable—similar to those observed in schizophrenia (Olincy and Martin, 2005; Schulze et al., 2007; Sánchez-Morla et al., 2008). These findings lend further support to the hypothesis that sensory-gating deficits exist across the psychosis spectrum and may be linked to shared neurophysiological and cognitive deficits in these disorders (Olincy and Martin, 2005; Burdick et al., 2006; Schulze et al., 2007; Martinez-Aran et al., 2008; Sánchez-Morla et al., 2008).

The present findings are also consistent with schizophrenia-spectrum studies that demonstrate deficits in sensorimotor gating and the early stages of information processing assessed with other psychophysiological measures such as passive (Braff et al., 1978; Cadenhead

et al., 2000b) and active-attentional (Hazlett et al., 2003, 2007) modulation of the startle-eyeblink response. Prior work suggests that P50 suppression and prepulse inhibition (PPI) of startle-eyeblink are both psychophysiological measures of sensory-inhibition function (Cadenhead et al., 1993; Lamberti et al., 1993; Schwarzkopf et al., 1993). Abnormalities in P50 and PPI are thought to reflect impaired gating of sensory input (Braff, 1993; Swerdlow et al., 2006) which leads to sensory overload and cognitive fragmentation (Braff et al., 1978; Swerdlow et al., 2006). Our findings support the concept that P50-suppression deficits may be an indicator of a schizophrenia-spectrum disorder, particularly if the individual has a family history of schizophrenia or SPD (Olincy et al., 2000, 2010; Cadenhead et al., 2005; Seeber and Cadenhead, 2005).

fMRI and EEG source analysis studies have implicated multiple neural generators of the P50 response, including the hippocampus, thalamus, dorsolateral prefrontal cortex (DLPFC), and superior temporal gyrus (STG) (Adler et al., 1998; Thoma et al., 2003, 2008; Tregellas et al., 2007; Williams et al., 2011). Schizophrenia patients have reduced volume in all of these regions (e.g., Suddath et al., 1990; Siever and Davis, 2004; Hazlett et al., 2008; Thoma et al., 2008; Byne et al., 2009). It has been hypothesized that “sparing” of gray matter volume in the DLPFC of SPD patients protects against psychosis and possibly attenuates the severity of both positive and negative (e.g., cognitive dysfunction) symptoms of schizophrenia (Siever and Davis, 2004; McClure et al., 2008; Hazlett et al., 2014). In schizophrenia and SPD, a stepwise pattern for severity of reduced gray matter volume has been reported for the STG (HC > SPD > Schizophrenia)—an area of the brain associated with auditory processing and thought to play an important role in sensory gating (Buchsbaum et al., 1997; Dickey et al., 1999; Kawasaki et al., 2004; Takahashi et al., 2006; Tregellas et al., 2007; Hazlett et al., 2008; Goldstein et al., 2009; Williams et al., 2011). Future multi-modality research across the spectrum that includes P50 and MRI measures is needed to determine whether the stepwise linear pattern for STG volume and P50 gating are associated.

The present study is consistent with the two other studies in terms of reporting a SPD-related deficiency in P50 suppression (measured as percent change in P50 suppression in Cadenhead et al., 2000a, 2002, as compared to T–C difference and T/C ratio in the current study) and the first to report a SPD-related reduction in conditioning stimulus amplitude which was not found by Cadenhead et al. One possibility for this discrepancy is that some of the SPD participants in the Cadenhead et al. studies were receiving antipsychotic medications at the time of testing and this may have helped to normalize their conditioning amplitude values. Schizophrenia research has demonstrated that atypical antipsychotic medications partially ameliorate the P50 inhibitory deficit (Adler et al., 2004; Becker et al., 2004). Additionally, it is unclear how many of the SPD participants in the Cadenhead et al. studies were cigarette smokers and whether nicotine was allowed just prior to testing which also helps to normalize P50 disturbances (Adler et al., 1993, 1998; Leonard et al., 1998; Olincy et al., 2010).

This study is the first to examine clinical symptom correlates of P50 in SPD and report that *smaller conditioning amplitude is associated with greater symptom severity*. This finding is consistent with prior work in schizophrenia demonstrating that greater P50-suppression deficits are associated with greater negative symptom severity (Ringel et al., 2004; Arnfred, 2006). However, a prior review paper on clinical correlates concluded that P50 measures do not reflect specific clinical symptom severity features of schizophrenia, although they are related to attentional deficits (Potter et al., 2006). The schizophrenia patients in the current study are a subset of those examined in the larger COGS study (n = 181 patients; Olincy et al., 2010) which reported no relationship between P50 suppression and clinical symptom severity. Thus, we did not expect to see a significant clinical correlation in schizophrenia. Our findings do suggest that studying medication-naïve SPD patients, as in the current study is advantageous for assessing clinical symptom correlates.

Study limitations include the small sample size of SPD patients, although despite this, we report significant P50 group differences for HC-SPD and SPD-schizophrenia comparisons. Additional investigation with a larger spectrum sample is needed for replication and to examine how P50 deficiencies relate to family history, medication status, clinical outcome, and genetics. The present findings support the concept of a schizophrenia spectrum (Siever and Davis, 2004) and the dimensional approach of the NIH Research Domain Criteria (Insel et al., 2010). Despite various discrepancies in schizophrenia-related P50 research, e.g., effects of second-generation antipsychotics, relationship to clinical status, and some questions regarding P50 specificity and stability (Patterson et al., 2008), P50 event-related potential suppression is one of the most robust endophenotypic measures in schizophrenia research.

5. Conclusion

In summary, these novel findings indicate: (a) a shared P50-suppression deficit in schizophrenia and SPD patients, largely determined by a smaller-than-normal P50 event-related potential to the initial conditioning stimulus and (b) among the unmedicated SPD sample, those exhibiting a greater underlying neurobiological abnormality in information processing—characterized by smaller P50 amplitude to the conditioning stimulus—have greater symptom severity. This conditioning amplitude deficit indicates that abnormal stimulus registration/salience detection may be the primary mechanism underlying P50-suppression deficits in schizophrenia-spectrum disorders. A shared P50 deficit is consistent with the notion that observed attention and cognitive impairments in schizophrenia-spectrum patients are secondary to deficits in inhibitory functioning that cause sensory overload by external and internal stimuli (Venables, 1960; McGhie and Chapman, 1961; Bleuler, 2010). The present findings support the concept of P50 deficits as a vulnerability marker for schizophrenia-spectrum disorders but future studies are needed to incorporate neuroimaging, genetics, and a common measure of symptom severity together with P50 measures, including both amplitude and frequency domain analyses, across the spectrum.

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Contributors

Dr. Hazlett wrote this manuscript together with Mr. Rothstein, whom she mentored on this project, conducted all of the statistical analyses, made all of the figures, and revised the manuscript. Dr. Olincy helped with writing the paper and contributed to the protocol for evoked potential recording and scoring of the data. Mr. Ferreira participated in the collection of the data. Drs. Silverman and Siever participated in the design of the overall protocol and discussions about its significance. All coauthors were involved in recruitment, diagnostic assessment, and/or testing of the participants, and provided feedback on the paper. All authors have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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