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Auditory steady state response in the schizophrenia, first-degree relatives, and schizotypal personality disorder

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ABSTRACT

The power and phase synchronization of the auditory steady state response (ASSR) at 40 Hz stimulation is usually reduced in schizophrenia (SZ). The sensitivity of the 40 Hz ASSR to schizophrenia spectrum phenotypes, such as schizotypal personality disorder (SPD), or to familial risk has been less well characterized. We compared the ASSR of patients with SZ, persons with schizotypal personality disorder, first degree relatives of patients with SZ, and healthy control participants. ASSRs were obtained to 20, 30, 40 and 50 Hz click trains, and assessed using measures of power (mean trial power or MTP) and phase consistency (phase locking factor or PLF). The MTP to 40 Hz stimulation was reduced in relatives, and there was a trend for MTP reduction in SZ. The 40 Hz ASSR was not reduced in SPD participants. PLF did not differ among groups. These data suggest the 40 Hz ASSR is sensitive to familial risk factors associated with schizophrenia.
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1. Introduction

The electroencephalogram (EEG) and magnetoencephalogram (MEG) entrain in frequency and phase to periodic stimuli across a wide range of frequencies. The EEG response entrained to auditory stimuli is referred to as the auditory steady state response (ASSR), and is primarily generated by synchronous activity of neurons in the auditory cortex (Pastor et al., 2002; Simpson et al., 2005; Brenner et al., 2009). In humans, the largest amplitude ASSR is elicited by stimuli modulated in the 35–40 Hz range (Pastor et al., 2002). ASSRs are usually characterized using time–frequency analysis, such as using the Fast Fourier Transform (FFT) to isolate power at the driving frequency and harmonics in a power spectrum. More recently, time frequency measures have been used to differentiate the magnitude of the change in power from baseline at a given frequency and the reliability of phase across trials. Change in power has been referred to as mean trial power (MTP; Krishnan et al., 2009) or event-related spectral perturbation (Delorme and Makeig, 2004), while phase reliability or synchrony has been termed phase locking factor (PLF; Tallon-Baudry et al., 1996) or inter-trial coherence (Delorme and Makeig, 2004).

ASSR measures of overall power, MTP, and PLF have been reported to be reduced in schizophrenia (SZ), most consistently at 40 Hz stimulation (Kwon et al., 1999; Light et al., 2006; Spencer et al., 2008; Teale et al., 2008; Vierling-Claassen et al., 2008). Two studies using amplitude modulated tones rather than click trains have demonstrated reductions at lower frequencies of stimulation as well (Brenner et al., 2003; Krishnan et al., 2009). The neural mechanisms that produce ASSR abnormalities in schizophrenia are not well characterized, but both anatomic and neurophysiological disturbances in the auditory cortex have been implicated. Schizophrenia is associated with volumetric reductions in the posterior superior temporal gyrus (McCarley et al., 1999) as well as reductions of pyramidal neuron volume in deep layer 3 of primary and secondary auditory cortices (Sweet et al., 2003). Dysfunctional γ-aminobutyric acid (GABA) and glutamate signaling may contribute to auditory EEG abnormalities in schizophrenia due to their role in the generation, synchronization, range, and maintenance of oscillations (Uhlhaas and Singer, 2006). Medication may impact the 40 Hz ASSR. Hong et al. (2004) did not find a deficit in 40 Hz power in SZ, but reported that patients receiving conventional antipsychotic agents had reduced ASSR power compared to patients receiving novel antipsychotic agents.

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Investigating individuals who share phenotypic similarities or familial risk with schizophrenia may provide insight into whether ASSR deficits occur in the absence of psychosis and associated confounds. Individuals with schizotypal personality disorder (SPD) exhibit clinical symptoms, cognitive deficits, and neurobiological abnormalities which are often similar to SZ, though usually of lesser severity (Cadenhead et al., 1999). Brenner et al. (2003) reported that ASSR power to amplitude modulated tones was unaffected across a wide range of stimulus frequencies in a small sample of persons with SPD ($n=11$). However, abnormalities in auditory EEG and event-related potential (ERP) response (Niznikiewicz et al., 2009; Shin et al., 2010) and reduced volume of the superior temporal gyrus (Dickey et al., 2002; Goldstein et al., 2009; Takahashi et al., 2010) in SPD suggest potential impairment in the auditory pathways. First-degree relatives of schizophrenia patients share genetic and environmental risk factors with SZ patients in the absence of psychosis and are not typically prescribed antipsychotic medications. Hong et al. (2004) found that ASSR power to 40 Hz click stimulation was reduced in a sample of first degree relatives of patients with SZ, suggesting that ASSR may be an indicator of familial risk. Notably, the relatives in Hong et al. had elevated schizotypal personality traits. Other studies indicate that relatives show disturbances in auditory pathways, evidenced by abnormalities in auditory EEG or ERP measures in discordant siblings (Karoumi et al., 2000; Winterer et al., 2003), twin pairs (Weisbrod et al., 1999), and first-degree relatives (Bramon et al., 2005; Turetsky et al., 2008; Leicht et al., 2011). Additionally, reductions in superior temporal gyrus volume have been reported in relatives (Rajarethinam et al., 2004).

We recorded ASSRs in SZ, first degree relatives, SPD, and healthy control participants to four frequencies of stimulation (20, 30, 40 and 50 Hz), and measured MTP and PLF to evaluate entrainment at each frequency. MTP reflects the change in power relative to background activity in the baseline EEG, capturing both phase-locked and non-phase-locked activity across trials, whereas PLF measures EEG phase synchronization across trials (45). We expected to observe a pattern of deficits corresponding to symptom severity in the power and phase locking of ASSR at 40 Hz stimulation, ranging from a robust response in control participants, an intermediate deficit in SPD participants and relatives, and the most severe deficit in SZ patients. In contrast, we expected all groups to show comparable ASSRs to 20 and 30 Hz stimulation.

2. Materials and methods

2.1. Participants

Schizophrenia and schizoaffective disorder patients ($N=42$), first-degree relatives of schizophrenia patients ($N=35$), SPD participants ($N=34$), and non-psychiatric comparison participants ($N=56$) volunteered for the present study (see Table 1 for characteristics). The patient sample was recruited through outpatient and inpatient units at community and state hospitals. Relatives were recruited through probands with SZ. Thirteen schizophrenia patients were related to one ($n=6$), two ($n=3$), three ($n=3$), or four ($n=1$) relatives in the study. An additional eight relatives were related to SZ patients who were disqualified ($n=4$) or did not have ASSR recorded ($n=4$). The relative status of two individuals was based on self-report; their exclusion did not change the outcome of the ASSR measures. SPD and control participants were recruited through newspaper and internet advertisements. All participants received detailed oral and written information about the study protocol and gave written and oral informed consent. The protocol was approved by the Indiana University–Purdue University Indianapolis Human Subjects Review Committee. Participants were paid ten dollars per hour for participation. Participants did not differ on age ($F(3,163)<1$) or gender ($\chi^2=3.987$, $p=.263$); however, control and SPD participants ($F(3,163)=18.421$, $p<.001$) and their mothers ($F(3,156)=3.137$, $p=.027$) completed more education than SZ patients and relatives ($F(3,163)=18.421$, $p<.001$) (Table 1). Paternal education did not differ among groups ($F(3,140)=2.145$, $p=.097$).

Table 1
Characteristics and performance on neuropsychological measures.

	Control ($N=56$)	SPD ($N=34$)	SZ ($N=42$)	Relatives ($N=35$)	N	Sig<.05
Age	38.75 (10.4)	37.35 (9.2)	36.86 (12.8)	36.03 (12.5)	167	n.s.
Gender (M:F)	26:30	20:14	23:19	13:22	167	n.s.
Education level						
Participant	4.07 (0.81)	3.85 (1.02)	3.10 (0.88)	2.89 (1.01)	167	C, SPD > SZ, Rel
Mother	3.62 (1.18)	3.73 (1.31)	3.13 (0.94)	3.12 (1.13)	160	C, SPD > SZ, Rel
Father	3.63 (1.41)	3.59 (1.46)	3.21 (1.48)	2.89 (1.01)	144	n.s.
Schizotypal Personality Questionnaire						
Cognitive perceptual	4.55	16.59	18.89	11.71	161	C<Rel<SZ, SPD
Interpersonal	6.44	15.12	19.68	14.53	161	C<Rel, SPD<SZ
Disorganized	2.78	8.44	8.34	5.56	152	C<Rel<SZ, SPD
Wechsler Adult Intelligence Scale						
Picture Completion	10.78	10.42	7.31	8.35	158	C, SPD > SZ, Rel
Digit Symbol	11.16	9.47	6.93	8.03	162	C > SPD > SZ, Rel
Similarities	9.96	10.48	8.21	8.25	159	C, SPD > SZ, Rel
Digit Span	9.95	10.61	8.26	9.00	158	C, SPD > SZ; SPD > Rel

Note. C = control, SPD = schizotypal personality disorder; SZ = schizophrenia; Rel = relatives. Education level included self-report data on completion of grade school (1), junior high school (2), high school (3), some college (4), bachelor's degree (5), master's degree (6), and doctoral degree (7).

SZ patients were evaluated using the Structured Clinical Interview for Axis I disorders (SCID-I; First et al., 2001b), supplemented by clinical observation and medical chart review. Participants in the SPD and relative groups were diagnosed using the SCID-II for Axis II disorders (SCID-II; First et al., 1997) and the SCID-I. Control participants were interviewed using the non-patient version of SCID-I (First et al., 2001a) and the schizoid, paranoid and schizotypal personality disorder modules of the SCID II to exclude psychiatric disorders. The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) assessed positive symptoms ($M=15.4$, $SD=5.7$), negative symptoms ($M=14.7$, $SD=6.8$), and general function ($M=30.4$, $SD=8.3$) for 37 patients interviewed within three months of completing the study.

The Family Interview for Genetic Studies (FIGS) was used to obtain probable diagnoses of schizophrenia in first degree relatives of all participants (Maxwell, 1992). Exclusion criteria for all participants included a history of neurological or cardiovascular disease, clinically documented hearing loss, head injury that resulted in loss of consciousness for more than 5 min, electroconvulsive therapy, and IQ below 70. SZ, SPD, and control participants were excluded if they had a positive drug urine screen or a current diagnosis of substance abuse or dependence. SPD participants were excluded if they had a diagnosis of bipolar disorder. Control participants were excluded if they or a diagnosis of Axis I psychiatric illness. Family members were not excluded for a diagnosis of SPD ($n=5$), bipolar disorder ($n=4$), dysthymia ($n=1$), current substance use ($n=3$ by positive drug screen) or past substance abuse or dependence ($n=8$), because these disorders may reflect expression of risk factors also associated with schizophrenia. Eight SZ patients and two SPD participants met criteria for past substance abuse or dependence. Table 2 describes the prescribed medication types among study participants.

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