Neural Anomalies During Sustained Attention in First-Degree Biological Relatives of Schizophrenia Patients

Scott R. Sponheim, Kathryn A. McGuire, and John J. Stanwyck

Background: *A deficit in sustained attention might serve as an endophenotype for schizophrenia and therefore be a useful tool in understanding the genetic underpinnings of the disorder. We sought to detail functional brain abnormalities associated with sustained attention (i.e., vigilance) in individuals with genetic liability for schizophrenia.*

Methods: *We gathered electrophysiological data from 23 schizophrenia patients, 28 first-degree biological relatives of schizophrenia patients, and 23 nonpsychiatric control subjects while they performed a degraded-stimulus continuous performance task. Inclusion of sensory control trials allowed separation of target detection and vigilance effects on brain potentials.*

Results: *Schizophrenia patients, but not relatives, showed a behavioral deficit in sustained attention. During target detection, relatives exhibited diminished late positive amplitudes (P3b, i.e., P300) over parietal brain regions and augmented early posterior (P1) and right frontal (anterior N1) potentials. Electrophysiological anomalies were still evident after the exclusion of three relatives with histories of psychosis.*

Conclusions: *Genetic liability for schizophrenia is associated with augmented early and diminished late brain potentials during sustained attention. Electrophysiological anomalies suggestive of right frontal–posterior parietal dysfunction might represent neural expression of genetic liability for schizophrenia. Electrophysiological indices also seem to be more sensitive than behavioral measures in assessing genetic liability for schizophrenia.*

Key Words: Schizophrenia, sustained attention, vigilance, electrophysiology, genetic liability, evoked potential

Evidence suggests that a deficit in visual sustained attention might serve as an alternative phenotype (i.e., endophenotype [Gottesman and Gould 2003]) for studying genetic vulnerability for schizophrenia. Remitted schizophrenia patients and biological relatives of individuals with schizophrenia exhibit impaired detection of behaviorally relevant "targets" during sustained attention, whereas individuals with other mental disorders generally fail to exhibit a similar trait-based dysfunction (Cornblatt and Keilp 1994; Liu et al 2002). Researchers have described poor target detection during sustained attention as a "vigilance deficit," with vigilance defined as "a state of readiness to detect and respond to certain small changes occurring at random time intervals in the environment" (Mackworth 1957). Although simpler and more specific than the clinical phenotype of schizophrenia, poor performance on a vigilance task is less likely to directly map onto effects of gene expression than a biological index of brain function. Therefore, it might be advantageous to delineate specific neural processes that contribute to vigilance deficits, to detail how genes predisposing for schizophrenia affect brain function. To determine neural phenomena associated with vigilance deficits in schizophrenia and genetic liability for the disorder, we studied electrophysiological characteristics of schizophrenia patients and first-degree biological relatives of schizophrenia patients during a continuous performance task.

From the Veterans Affairs Medical Center (SRS, KAM, JJS); and the Departments of Psychiatry and Psychology (SRS), University of Minnesota, Minneapolis, Minnesota.

Address reprint requests to Scott R. Sponheim, Ph.D., Veterans Affairs Medical Center (116B), One Veterans Drive, Minneapolis, MN 55417; E-mail: sponh001@umn.edu.

Received June 13, 2005; revised September 9, 2005; accepted November 18, 2005.

Among the variety of continuous performance tasks used to study schizophrenia, a desirable test for revealing the neural underpinnings of impaired vigilance is one that specifically assesses attention and visual perception (Chen and Faraone 2000). The degraded-stimulus continuous performance task (DS-CPT) places sizable demands on the visual perception system (Nuechterlein et al 1983). The task reveals poor vigilance in schizophrenia if stimuli are brief (<70 msec), substantially degraded, and occur at high event rates (Maier et al 1992). Given these characteristics, CPTs with degraded stimuli have reliably revealed schizophrenia patients to exhibit vigilance deficits that are not the result of medications (Liu et al 2000; Nuechterlein 1991). Seven studies in which the DS-CPT was used have demonstrated vigilance deficits in adult first-degree relatives of schizophrenia patients (Asarnow et al 2002; Chen et al 1998; Condray and Steinhauer 1992; Grove et al 1991; Laurent et al 2000; Maier et al 1992; Saoud et al 2000), and one study yielded low d′ scores (i.e., poor target detection during vigilance) in children of mothers with schizophrenia (Nuechterlein 1983). Consequently, investigators have viewed vigilance deficits as potentially valuable in characterizing genetic vulnerability for schizophrenia (Chen and Faraone 2000; Nuechterlein 1991). The two published studies that failed to show diminished DS-CPT performance in schizophrenia patients or their relatives enrolled control subjects who were older than the relatives studied, thus failing to consider age effects on vigilance (Jones et al 2001), or strictly examined adolescents with schizophrenia, suggesting that variation in brain maturation during adolescence might make vigilance deficits more difficult to detect (Rund et al 1998). A stable impairment in vigilance might be specific to schizophrenia (Liu et al 2002). Schizophrenia patients in symptom remission produce low d′ scores on the DS-CPT (Nuechterlein 1991; Nuechterlein et al 1994), whereas unipolar (Liu et al 2002; Suslow and Arolt 1997) and obsessive-compulsive (Milliery et al 2000) patients fail to exhibit stable deficits. Studies using DS-CPTs have shown bipolar patients to have improved vigilance with symptom reduction (Liu et al 2002; Sax et al 1998), and stable bipolar outpatients fail to show persistent vigilance deficits that are

0006-3223/06/$32.00
doi:10.1016/j.biopsych.2005.11.017

Table 1. Characteristics of Participants (Schizophrenia Patients, First-Degree Relatives of Schizophrenia Patients, and Nonpsychiatric Control Subjects)

Variable	Patients ($n = 23$)	Relatives ($n = 28$)	Control Subjects ($n = 23$)	Statistic	p (ANOVA)
Age (y)	45.0 (9.6)	47.5 (8.7)	46.0 (9.1)	$F(2,71) = .50$	ns
% Female	13[a,b]	57	48	$\chi^2(2) = 10.92$	.004[c]
Education (y)	14.2 (2.2)	14.9 (2.5)	15.4 (1.8)	$F(2,71) = 1.72$	ns
Estimated IQ	99.6 (11.9)[a,b]	108.7 (10.3)	110.7 (10.6)	$F(2,71) = 6.87$	<.002
BPRS Total Score	42.6 (10.8)	NA	NA	NA	ns
SPQ Total Score	NA	12.9 (6.8)	9.7 (6.4)	$t(46) = 1.6$	ns

Data are presented as mean (SD). Estimated IQ was derived from the formula of Brooker and Cyr (1986) with Vocabulary and Block Design subtests. ANOVA, analysis of variance; IQ, intelligence quotient; BPRS, Brief Psychiatric Rating Scale (Lukoff et al 1986); NA, not applicable; SPQ, Schizotypal Personality Questionnaire (Raine 1991).

[a]Different from control group mean ($p < .05$).

[b]Different from relatives of schizophrenia group mean ($p < .05$).

[c]Significance level for χ^2 test.

significantly worse than in normal control subjects (Liu et al 2002; Wilder-Willis et al 2001). Recent findings of euthymic bipolar subjects exhibiting sustained attention deficits on nondegraded CPTs that involve working memory (Clark et al 2005) highlight how degraded and perceptually challenging stimuli reveal vigilance deficits specific to schizophrenia.

Evidence suggests that aberrant frontal and temporal lobe processes underlie vigilance dysfunction in schizophrenia. A set of positron emission tomography studies carried out more than a decade ago revealed hypometabolism in frontal and medial temporal cortices in individuals with schizophrenia performing the DS-CPT (Buchsbaum et al 1992; Siegel et al 1993). Both of these studies failed to include a condition controlling for aspects of the task unrelated to vigilance (e.g., visual processing), thereby leaving open the possibility that findings are not specific to target detection in the DS-CPT. Although no magnetic resonance imaging studies of brain function in schizophrenia during the DS-CPT appear in the literature, a more recent positron emission tomography study points to temporal and dorsolateral prefrontal metabolic anomalies during the task (Potkin et al 2002). Abnormal frontal activation during sustained attention is consistent with anterior anomalies in a lateral prefrontal–posterior parietal system subserving sustained attention (Pardo et al 1991; Posner and Petersen 1990). Only a single published report describes electrophysiological abnormalities associated with DS-CPT performance in schizophrenia (Knott et al 1999). In 14 chronic medicated schizophrenia outpatients, Knott et al found diminished positive potentials (P3b) over parietal brain regions at 400 msec after stimulus onset, perhaps suggesting poor updating of the posterior aspect of the frontal–parietal sustained attention system (Pardo et al 1991). To our knowledge, no published studies have implemented the DS-CPT to characterize neural anomalies during sustained attention in relatives of schizophrenia patients presumed to carry genes predisposing the disorder.

To examine neural correlates of impaired vigilance and genetic liability for schizophrenia, we used the DS-CPT to study electrophysiological characteristics of first-degree biological relatives of schizophrenia patients and chronic schizophrenia outpatients. The work was specifically designed to address whether 1) relatives of schizophrenia patients exhibit diminished P3b (i.e., P300) amplitudes in response to target stimuli during the DS-CPT; 2) schizophrenia patients exhibit diminished P3b amplitudes during a single-stimulus DS-CPT; 3) schizophrenia patients and relatives exhibit early processing abnormalities evident in early evoked potentials; and 4) electrophysiological anomalies in relatives are dependent on the presence of schizophrenia spectrum symptomatology. With inclusion of sensory control trials, we sought to determine separate effects of target identification and vigilance on early and late event-related brain activity during sustained attention.

Methods and Materials

Participants

Table 1 presents the characteristics of participants. We recruited stable outpatient schizophrenia participants from the clinics of the Minneapolis Veterans Affairs (VA) Medical Center, community support programs for the mentally ill, and a county mental health clinic. First-degree biological relatives were identified through interviews with schizophrenia participants and were invited by letter and telephone to participate. We identified potential nonpsychiatric control subjects through posting announcements at community libraries, fitness centers, the Minneapolis VA Medical Center, and in newsletters for veterans and fraternal organizations. Staff excluded potential control subjects for personal or family histories of psychotic symptoms or affective disorder as defined by the DSM-IV (American Psychiatric Association 1994). Patients and control subjects were excluded for histories of substance dependence but were not excluded for past alcohol dependence, as long as they had not abused alcohol in the past month. Because we sought to maximally describe electrophysiological characteristics of families from which the schizophrenia probands came, we did not exclude family members with histories of substance dependence. All participants completed an informed consent process, and the Minneapolis VA Medical Center and University of Minnesota Institutional Review Boards approved the study protocol and performed annual reviews of the study consent procedures.

To obtain diagnostic information, a trained doctoral-level clinical psychologist completed the Diagnostic Interview for Genetic Studies (DIGS; Nurnberger et al 1994) with each patient. From the DIGS and supplemental questions, the interviewer made symptom ratings of patients, using the Scale for the Assessment of Negative Symptoms (Andreasen 1983), the Scale for the Assessment of Positive Symptoms (Andreasen 1984), and the 24-item version of the Brief Psychiatric Rating Scale (Lukoff et al 1986). Relatives and control subjects completed the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First et al 1996), the Structured Interview for Schizotypy (SIS; Kendler et al