Event-Related Potentials in Adolescents with Schizophrenia and Their Siblings: A Comparison with Attention-Deficit/Hyperactivity Disorder

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Background: Identifying trait markers specific to schizophrenia might uncover mechanisms underlying illness susceptibility. Previous research shows the N2 and P3 event-related potentials are abnormal in schizophrenia; specificity of these potential trait markers has not been well established.

Methods: Electroencephalogram data were recorded from four adolescent groups: early-onset schizophrenia patients (SZ; $n = 30$); non-psychotic siblings of schizophrenia patients (SZ-SIB; $n = 36$); healthy control subjects (HC; $n = 36$); a neurodevelopmental attention-deficit/hyperactivity disorder (ADHD) comparison group ($n = 27$), during auditory oddball and visual go/no-go tasks. The P3 was measured to targets in the oddball task. The N2 and P3 were measured to go and no-go stimuli in the go/no-go task.

Results: Compared with the HC group, the SZ and SZ-SIB groups showed significantly reduced auditory oddball P3 amplitude. Visual P3 amplitude was significantly reduced in the SZ group for no-go stimuli and the SZ-SIB group for go and no-go stimuli. The P3 amplitude in the ADHD group was not significantly reduced for either paradigm. The SZ and ADHD groups showed significantly reduced N2 amplitude in the go/no-go task; the SZ-SIB group was not significantly different from the HC group.

Conclusions: Results revealed reduced P3 amplitude in schizophrenia patients and adolescent non-psychotic siblings in an auditory oddball and a visual go/no-go task. The SZ-SIB and ADHD groups showed a different ERP profile when each was compared with the HC group: siblings showed reduced P3 amplitude in both tasks and normal N2 in the go/no-go task; the opposite pattern was observed in the ADHD group.

Key Words: ADHD, electrophysiology, high-risk, schizophrenia, trait markers

First-degree relatives of patients with schizophrenia have a 7%–10% increased risk of developing a schizophrenia-spectrum disorder compared with 1% in the general population (1). The aim of research studying these genetic high-risk groups is to identify which cognitive and neuro-physiological abnormalities found in schizophrenia patients are related to increased liability for illness in first-degree relatives. It is hoped that in the long term, such trait markers will prove more effective in identifying genes contributing to susceptibility for schizophrenia than has so far been possible with the diagnostic phenotype. This might enable the development of targeted early detection and intervention programs for vulnerable individuals.

An additional concern is the identification of markers that discriminate between schizophrenia and other psychiatric disorders. When considering the potential for using trait markers in early detection and intervention programs, a useful approach is to compare schizophrenia and another neurodevelopmental disorder such as attention-deficit/hyperactivity disorder (ADHD). The merit of this comparison is supported by extensive evidence of early neurodevelopmental impairments in schizophrenia (2). These include features commonly found in ADHD such as conduct disorder, attention difficulties, and social problems (3,4). Furthermore, diagnosis of ADHD is greater among those with family history of schizophrenia (5), and rates of psychosis are greater in those with childhood diagnosis of ADHD (6–8) than in the general population. Although comorbidity rates for psychosis and ADHD are generally low in these studies, the evidence suggests some phenotypic overlap between ADHD and the childhood premorbid course of schizophrenia. Identification of trait markers specific to schizophrenia would allow vulnerable individuals to be differentiated from those with disorders such as ADHD. Clinically, this might be important, because young people vulnerable to schizophrenia presenting with symptoms of ADHD might respond adversely to psychostimulant medication.

Event-related potentials (ERPs) provide sensitive, non-invasive measures of covert brain activity that represent voltage fluctuations in electroencephalogram data time-locked to an event of interest. They provide millisecond resolution about the timing of neural processes and are useful indexes of cognitive processing. In the present study three ERPs were investigated as potential trait markers for schizophrenia: the P3 to targets in an auditory oddball task, and the N2 and P3 to visual stimuli in a response inhibition paradigm.

The oddball P3 is a positive voltage deflection distributed over parietal electrode sites, occurring roughly 300 msec after the rare target stimulus in an auditory oddball paradigm. The functional significance of the P3 has not been fully elucidated, but one theory advances it as a marker of attention and working memory processes during stimulus categorization (9). Amplitude reduction and prolonged latency of the auditory P3 have been identified in first episode (10–12) and medication-naïve (13,14) schizophrenia patients and in first-degree relatives (15–19), supporting them as trait markers for the disorder.

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In response inhibition paradigms such as the go/no-go task in which a prepotent response to a frequent stimulus must be inhibited, a negative voltage deflection occurs approximately 200 msec after the target stimulus, the N2. This has most commonly been interpreted as an index of response inhibition (20) or response conflict (21), although others regard it as a measure of stimulus categorization (22). The N2 is followed by a P3 that, on response inhibition trials, has a more centralized topography than the traditional oddball P3, referred to as "No-go anteriorization" (23). Although studies with stimulus classification paradigms have shown reduced amplitude and increased latency of visual N2 and P3 in schizophrenia (24–27), visual P3 is less reliably reduced in schizophrenia than auditory P3 (28,29) and few studies have investigated these ERPs with the go/no-go paradigm in schizophrenia. To date, two studies report normal N2 amplitude with reduced P3 (30,31), one reports reduced N2 and P3 (32), and two report reduced no-go anteriorization of the P3 (33,34). There are no results published in high-risk groups. The status of inhibition-related N2 and P3 abnormalities as trait markers for schizophrenia is therefore uncertain.

To date no studies have been published that directly compare these ERPs in schizophrenia and ADHD. Previous research has shown abnormalities in both the P3 (35) and N2 (36–39) in children with ADHD and a lack of no-go anteriorization of the P3 (37), suggesting these abnormalities might not be specific to schizophrenia. However, given the possibility of age-related changes, it is necessary to compare psychiatric disorders and high-risk groups at different points during development. The present study measured the auditory oddball P3 and visual go/no-go N2 and P3 in the following groups in adolescence: early-onset schizophrenia patients, non-psychotic siblings of schizophrenia patients, healthy individuals, and ADHD patients. We predicted reduced amplitude and increased latency in the schizophrenia patients and unaffected siblings compared with the healthy group indicating sensitivity of the markers to risk for schizophrenia. We also predicted a different profile of abnormalities in the schizophrenia patients and siblings compared with the ADHD group; the direction of group differences was not predicted.

Methods and Materials

Participants

Ethical approval was granted by the Trent Multi-centre Research Ethics Committee (MREC) and by the Research and Development department of the Nottinghamshire Healthcare NHS Trust. Participants were 30 adolescent-onset schizophrenia patients (SZ; 20 male, mean age = 19.21 ± 1.7 years), 36 siblings of adolescent-onset schizophrenia patients (SZ-SIB; 15 male, mean age = 17.50 ± 2.18 years), 27 adolescents with ADHD (ADHD; 25 male, mean age = 15.69 ± 1.47 years), and 36 healthy control subjects (HC; 15 male, mean age = 17.19 ± 2.03 years). All were aged 14–21 years. Participants gave informed consent if 16 years of age or older; parental consent (with participant assent) was obtained for those < 16 years. There were significant group differences for age [$F(3,74) = 6.260$, $p = .001$] and gender [$\chi^2(3) = 29.749$, $p < .001$]. Participants in the SZ group were significantly older than participants in the HC, SZ-SIB ($p < .05$), and ADHD ($p < .001$) groups. The SZ and ADHD groups had a significantly higher male/female ratio than the HC and SZ-SIB groups [$\chi^2(3) = 30.525$, $p < .001$]. There were no significant differences between groups on parental socioeconomic status, measured with the National Statistics for Socio-Economic Classification (40). All participants were free from current significant substance abuse and neurological disorder and had an IQ of 70 or greater on the Wechsler Abbreviated Scale of Intelligence (WASI) (41). The hyperactivity-inattention subscale of the Strengths and Difficulties Questionnaire (SDQ) (42) completed by parents and self-rated was used to assess levels of inattention or hyperactivity in all participants. Scores of 6 or more in the HC, SZ, and SZ-SIB groups resulted in exclusion.

SZ. One hundred and forty-nine young people aged 14–21 diagnosed with any functional psychosis were referred for inclusion in the study; 85 were willing to take part. The Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (43) was conducted and Consensus DSM-IV diagnosis was made by three psychiatrists. Of 85 cases assessed for inclusion in the study, 33 did not have a diagnosis of schizophrenia spectrum disorder (DSM-IV code 295) and 2 had IQ < 70. The remaining 50 satisfied the inclusion criteria and gave permission for a sibling to be approached for inclusion in the study. Twenty patients withdrew from the study after clinical assessment, leaving 30 patients for ERP assessment. There were no significant differences in age, gender, socioeconomic status, age of illness onset, or diagnosis between those who took part and those who withdrew from the study. Of those who took part, 29 were diagnosed with paranoid schizophrenia (DSM-IV 295.3), 1 with schizoaffective disorder (DSM-IV 295.7). The mean age of illness-onset was 16.5 (SD = 2.01) years. All patients were within 5 years of illness onset. Twenty-six patients were medicated with atypical anti-psychotic drugs, 2 of whom were receiving additional antidepressant medication. One patient was medicated with antidepressant medication only and 1 with depot injections of a typical antipsychotic drug. Patients were assessed for current levels of symptomatology on the day of ERP assessment, with the Signs and Symptoms of Psychotic Illness (SSPI) scale (44). The group had a median score of 17, indicating partial remission.

SZ-SIB. Of 50 schizophrenia patients satisfying the study inclusion criteria, 41 had a sibling eligible for inclusion. Thirty-six siblings were willing to take part; 1 sibling was recruited / patient. All were shown to be free from psychotic and prodromal symptoms with the Structured Interview for Prodromal Symptoms (SIPS) (45) and Psychosis Screening Questionnaire (PSQ) (46). Of 36 siblings, 26 were related to a patient in the SZ group; thus 26 sibling pairs took part in ERP assessment.

ADHD. Forty-six young people diagnosed with ADHD were approached for inclusion in the study; 34 were willing to take part, and thorough psychiatric assessment was conducted with the Parental Account of Childhood Symptoms (PACS) (47). All were diagnosed with DSM-IV ADHD combined type (314.01) after a consensus conference of three psychiatrists. Three were excluded, owing to IQ < 70, and three were excluded after scoring > 22 on the Social Communication Questionnaire (48), a threshold indicating pervasive developmental disorder. Contact was lost with 1 participant, leaving 27 available for ERP assessment. All were receiving stimulant medication from which they were withdrawn 24 hours before testing.

HC. Of 72 healthy control subjects recruited from local schools, further education colleges, and the University of Nottingham, 36 subjects were selected for pairwise matching to a member of the SZ-SIB group on the following demographic characteristics: age, gender, and parental socioeconomic status. All participants were free from psychosis or schizophrenia prodrome (assessed with the PSQ and the SIPS), as were their immediate family members. One participant completed the auditory oddball paradigm but withdrew from further testing.