P50 Suppression in Individuals at Risk for Schizophrenia: The Convergence of Clinical, Familial, and Vulnerability Marker Risk Assessment

Kristin S. Cadenhead, Gregory A. Light, Kathleen M. Shafer, and David L. Braff

Background: *Identification of individuals at risk for the development of schizophrenia is important because it can lead to a greater understanding of the early stages of the illness. The aim of the present study was to determine whether individuals "at risk" for schizophrenia have deficits in P50 suppression, a preattentive measure of sensory gating.*

Methods: *Thirty-one at-risk and 21 normal comparison subjects were referred to the CARE (Cognitive Assessment and Risk Evaluation) Program at University of California San Diego. The primary aim of the CARE Program is to identify individuals who are at the greatest risk for conversion to psychosis, with a combination of clinical, familial, and vulnerability markers, including P50 suppression.*

Results: *As a group, the at-risk subjects had modestly lower levels (effect size = .43) of P50 suppression (55.1%, SD = 39.8) relative to comparison subjects (71.5%, SD = 34.7). At-risk subjects with a first-degree relative with schizophrenia had profoundly deficient P50 suppression (16.4%, SD = 33.8) compared with other at-risk ($p < .05$) and comparison subjects ($p < .005$).*

Conclusions: *Ongoing longitudinal follow-up studies will determine whether it is possible to improve the predictive validity of the clinical and familial variables by using P50 suppression alone or in combination with other measures in determining which individuals are at greatest risk for schizophrenia.*

Key Words: Prodromal, schizophrenia, endophenotype, P50 suppression, sensory gating

Schizophrenia is a devastating illness that typically emerges during adolescence or young adulthood, a time of rapid brain development in neural substrates (e.g., the dorsolateral prefrontal cortex) that are implicated in the pathogenesis of schizophrenia (Thompson et al 2001). Although some recent studies have demonstrated that early intervention might improve the prognosis and outcome of schizophrenia (Harrigan et al 2003; Keshavan et al 2003; Malla et al 2002), many individuals do not receive treatment for their illness for more than 1 year from the onset of symptoms. Identification of individuals who are at risk for developing schizophrenia, in the prodromal stages of the illness, could lead to earlier treatment and potentially prevent the onset or decrease the severity of psychosis and associated hospitalizations, psychosocial decline, and disease progression (McGorry 2001).

Individuals with a new onset of subsyndromal psychotic symptoms and/or a familial (and putatively a genetic) predisposition for schizophrenia who have a recent decline in functioning are at increased risk for developing the disorder (Yung and McGorry 1996). Because the term "prodromal schizophrenia" can only truly be used retrospectively, the term "at-risk" is used throughout this article to refer to a sample of individuals who are clinically and/or genetically at risk for schizophrenia per the criteria outlined by Yung and McGorry. Among these at-risk individuals, previous studies have reported that 25%–40% go on to develop psychosis within 1 to 2 years (Cornblatt et al 2003; Miller et al 2002; Yung et al 2003). The use of vulnerability markers for schizophrenia in conjunction with the clinical and familial risk factors might further increase our ability to predict the level of risk for transition to psychosis (Cadenhead 2002). Additionally, by using biological vulnerability markers in a population at risk for psychosis, it might be possible to identify specific pathologic processes that are active during the early course of schizophrenia.

A number of different neurocognitive, neurophysiologic, neuroanatomic, and information processing measures have been identified as vulnerability or endophenotypic markers in genetic studies of schizophrenia (Braff and Freedman 2002; Cadenhead 2002; Cadenhead et al 2002; Cannon et al 2001; Cornblatt and Malhotra 2001; Gottesman and Gould 2003). Strong candidate endophenotypes for schizophrenia should be heritable, stable, state-independent traits that index intermediate phenotypic expressions of an underlying genetic susceptibility for the disease (Gottesman and Gould 2003). In addition, the vulnerability markers should differentiate individuals with schizophrenia, unaffected relatives of schizophrenia patients, and individuals with schizotypal personality disorder (SPD) from normal comparison subjects.

The CARE (Cognitive Assessment and Risk Evaluation) Program at the University of California San Diego (UCSD) is a National Institute of Mental Health–funded longitudinal study that uses vulnerability markers in individuals at risk for schizophrenia to determine whether it is possible to improve the predictive validity of the clinical and familial criteria. Participants in the program are assessed on a comprehensive clinical and neurophysiologic battery every 6 months, with several measures that are likely to detect a vulnerability to psychosis, including the P50 event-related potential (ERP) suppression paradigm.

The P50 ERP suppression paradigm has become an important tool for understanding the pathophysiology and genetic basis of schizophrenia (Freedman et al 1999). Schizophrenia patients, their relatives, and SPD subjects all show reduced P50 suppression relative to normal comparison subjects (Cadenhead et al 2000; Clementz et al 1998a; Siegel et al 1984; Waldo et al 1987; Yee et al 1998). Taken together, the current schizophrenia spectrum literature supports the notion that P50 suppression might be a heritable trait. In a recent study, Myles-Worsley et al (2004) found P50 suppression deficits in at-risk adolescents from

From the Department of Psychiatry, University of California San Diego, La Jolla, California.

Address reprint requests to Kristin S. Cadenhead, M.D., University of California San Diego, Department of Psychiatry, 0810, 9500 Gilman Drive, La Jolla, CA 92093-0810; E-mail: kcadenhead@ucsd.edu.

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a South Pacific isolate population that has a high rate of schizophrenia. Additionally, twin studies (Myles-Worsley et al 1996; Young et al 1996) have shown that P50 suppression is a heritable trait that has now been linked to chromosome 22 (Myles-Worsley et al 1999a) and a polymorphism in the promoter region of the α-7 nicotinic receptor on chromosome 15 (Freedman et al 1997; Leonard et al 2002).

The aim of the present study was to determine whether individuals at risk for schizophrenia have P50 suppression deficits. Because not all subjects classified as being "at-risk" for schizophrenia will go on to develop the disorder, we anticipated that as a group, the at-risk subjects would have lower mean levels of P50 suppression. On the basis of our previous work (Cadenhead et al 2000), we hypothesized that individuals with greater familial risk (history of schizophrenia in a first-degree family member) and/or who met the criteria for SPD would have more prominent P50 suppression deficits.

Methods and Materials

Participants

Thirty-one individuals (aged 12–30 years) at risk for schizophrenia were recruited throughout the community of San Diego. The at-risk subjects were compared with 21 age-matched normal comparison subjects. All subjects provided written informed consent after the procedures were fully explained (UCSD IRB# 030829).

Recruitment and Assessment

Individuals classified as "at risk" for schizophrenia were identified through a broad community outreach program. Educational lectures regarding schizophrenia and the prodromal symptoms were provided to the public schools, community colleges, university student health offices, primary care settings, the National Alliance for the Mentally Ill, and mental health professionals in the San Diego community. Individuals recommended for referral to the CARE Program included 1) those with subsyndromal psychotic symptoms characterized as "troubling changes in thoughts, behavior, or emotions"; or 2) first-degree relatives of individuals with schizophrenia who had had a decline in functioning or new onset of symptoms. Subjects with a history of neurologic disorders, serious head injury, or hearing impairment were excluded. Any subject with a history of substance abuse or dependence in the last month or a positive urine toxicology screen for illicit substances was excluded.

All at-risk subjects were assessed with the Structured Interview for Prodromal Syndromes (SIPS) (Miller et al 1999) by trained (Miller et al 2003) doctoral-level clinicians. Participants met criteria for at least one of three at-risk states (brief psychosis, subsyndromal symptoms, or genetic risk and deterioration), as defined by the criteria in Table 1. These CARE at-risk criteria were derived from the Criteria of Prodromal Syndromes (COPS 3.0) (Miller et al 1999) and the Comprehensive Assessment of At-Risk Mental States (CAARMS) Intake Criteria Checklist (Yung et al 2002). The CARE at-risk criteria differ from the COPS in that we also include disorganized symptom items, which parallel disorganized symptoms of schizophrenia, for inclusion as an at-risk subject. Additionally, we have used the frequency criteria from the CAARMS and simplified the deterioration in functioning criteria used in the COPS. Individuals in the genetic risk and deterioration group can have any deterioration in functioning per global assessment of functioning (GAF) score and/or a new onset of symptoms of any kind. Additional clinical assessments included the Structured Clinical Interview for DSM-IV Axis I Disorders-Patient version (SCIDI/P), patient version (First et al 1995) for individuals aged >16 years and the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Epidemiologic Version (KSADS-E; Orvaschel and Puig-Antich 1987) for teenagers aged 12–16 years. Subjects were also assessed on the Structured Interview for DSM-IV Personality (SIDP-IV; Pfohl et al 1995), the Schedules for the Assessment of Negative and Positive Symptoms (SANS/SAPS; Andreasen 1984a, 1984b), and the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962). Family history of mental illness was assessed according to the Family History Research Diagnostic Criteria (FH-RDC; Andreasen et al 1977). At-risk subjects were included who did not have an Axis I disorder that accounted for the presenting symptoms (i.e., schizophrenia, schizoaffective disorder, major depression with psychotic features, bipolar I disorder, obsessive compulsive disorder, pervasive developmental disorder, or drug-induced psychosis).

Table 1. At-Risk Groups

Brief Psychosis Group
Severity Scale Score of 6 on one item P1–P5 or D1–D4 from SIPS
Frequency <1 hour and <3–6×/week *or* >1 hour and ≤2×/week
Each episode of symptoms is present for <1 week and symptoms spontaneously remit on every occasion
Symptoms began or worsened in the last year
Subsyndromal Group
Severity Scale Score of 3–5 on one item P1–P5 or D1–D4 from SIPS
Frequency at least 1× in the past month
Symptoms began or worsened in the last year
Genetic Risk and Deterioration Group
Family history of psychosis in first degree relative *or* schizotypal personality disorder in identified patient
Deterioration in functioning and/or mood, anxiety, or deficit symptoms
Symptoms began or worsened in the last year
Psychotic Syndrome
Severity Scale Score of 6 on one item from P1–P5 or D1–D4 from SIPS
Frequency daily or >1 hour 3–6×/week
Symptoms present for >1 week
Severity and frequency met within last 12 months

P1–P5, psychosis items 1 through 5 from the Structured Interview for Prodromal Syndromes (SIPS); D1–D5, disorganized items 1 through 5 from the SIPS.

The majority of the at-risk subjects met criteria for more than one subgroup (see Figure 1). Seventeen met criteria for the genetic risk and deterioration group because they had a first-degree relative with schizophrenia ($n = 4$), met criteria for SPD ($n = 12$), or both ($n = 1$) and had a deterioration in functioning or new onset of symptoms. Nine at-risk subjects had a family history of schizophrenia or psychosis in a second-degree relative or greater. The at-risk subjects had a mean (SD) SIPS subscale total positive symptoms rating of 8.9 (3.9), total negative symptoms rating of 9.6 (7.1), total disorganized symptoms rating of 6.6 (4.2), and total general symptoms rating of 5.7 (3.8). The at-risk group had a Global SANS score of 6.9 (2.9), Global SAPS score of 5.7 (4.4), BPRS total score of 16.0 (5.7), and a GAF rating of 52.8 (10.9). The at-risk sample was clinically heterogeneous. Seventeen at-risk subjects presented with a history of depressive symptoms (major depression in partial or full remission, dysthymia, subsyndromal depressive symptoms, adjustment disorder with depressed mood, or depression not otherwise specified), six had a history of anxiety symptoms (social phobia, panic disorder, anxiety disorder not otherwise specified, or obsessive-compul-