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Heritability of acoustic startle magnitude, prepulse inhibition, and startle latency in schizophrenia and control families

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ABSTRACT

Prepulse inhibition (PPI) is an acoustic startle paradigm that has been used as an operational measure of sensorimotor gating. Many patients with schizophrenia have impaired PPI, and several lines of evidence suggest that PPI may represent a heritable endophenotype in this disease. We examined startle magnitude and latencies in 40 schizophrenia patients, 58 first-degree relatives of these patients, and 100 healthy controls. After removing low-startlers, we investigated PPI and startle habituation in 34 schizophrenia patients, 43 relatives, and 86 control subjects. Heritability analyses were conducted using a variance-component approach. We found significant heritability of 45% for PPI at the 60-ms interval and 67% for startle magnitude. Onset latency heritability estimates ranged between 39% and 90% across trial types, and those for peak latency ranged from 29% to 68%. Heritability of startle habituation trended toward significance at 31%. We did not detect differences between controls and either schizophrenia patients or their family members for PPI, startle magnitude, or habituation. Startle latencies were generally longer in schizophrenia patients than controls. The heritability findings give impetus to applying genetic analyses to PPI variables, and suggest that startle latency may also be a useful measure in the study of potential endophenotypes for schizophrenia.

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1. Introduction

Within genetic studies of schizophrenia, both phenotypic heterogeneity and genetic heterogeneity complicate the ability to map genetic variants that increase the risk of the disease. To increase the potential for identifying such disease variants, researchers have begun to analyze schizophrenia-related *endophenotypes*, which are measurable traits discoverable by a biological test (Gottesman and Gould, 2003). Initial requirements for a given trait to be considered a viable endophenotype for schizophrenia include 1) association with schizophrenia, 2) stability of the trait, even when patient is in partial or complete remission, and 3) evidence that the trait originates in part from a significant genetic component and is therefore heritable. Additional requirements concerning family members of schizophrenia patients (SCZ) include 4) that the potential endophenotype is found in unaffected family members at a higher rate than in the general population, and 5) that within families, the endophenotype and illness co-segregate (Gershon and Goldin, 1986; Gottesman and Gould, 2003; Berrettini, 2005).

In this study, we examined on prepulse inhibition (PPI), a potential endophenotype for schizophrenia research. Patients with schizophrenia have difficulty automatically screening out or "gating" irrelevant thoughts and sensory information from conscious awareness (Venables, 1960; Braff and Geyer, 1990; Braff, 1993). These gating deficits are hypothesized to contribute to sensory overload, interceptive stimuli, and cognitive fragmentation, resulting in psychotic symptoms and cognitive deficits (McGhie and Chapman, 1961; Braff and Geyer, 1990; Braff, 1993). The acoustic startle response is a reflex contraction of the skeletal muscles in response to a sudden acoustic stimulus (Landis and Hunt, 1939). The inhibition of the acoustic startle response by a preliminary nonstartling acoustic stimulus, termed PPI, is used as an operational measure of sensorimotor gating (Hoffman and Searle, 1968; Graham, 1975). From a conceptual standpoint, sensorimotor gating is thought to "protect" the information contained in the prepulse stimulus by inhibiting the organism's response to additional incoming stimuli.

It has been suggested that PPI may be an endophenotype in schizophrenia based on several lines of evidence (Braff and Freedman, 2002; Gottesman and Gould, 2003). Many studies have found that SCZ

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subjects exhibit reduced PPI (Braff et al., 1978, 2001; Braff, 1992; Grillon et al., 1992; Dawson et al., 1993; Cadenhead et al., 2000; Parwani et al., 2000; Leumann et al., 2002; Ludewig et al., 2002; Duncan et al., 2003a; Kunugi et al., 2007). Some studies have shown these PPI deficits to be stable regardless of medication status (Braff et al., 1978; Braff, 1992; Grillon et al., 1992; Dawson et al., 1993; Cadenhead et al., 2000; Parwani et al., 2000; Hamm et al., 2001; Ludewig et al., 2002; Mackeprang et al., 2002; Perry et al., 2002; Duncan et al., 2003a,b). However, there have also been numerous studies indicating that medication can increase or normalize PPI deficits in SCZ subjects (Kumari et al., 1999, 2000, 2002, 2007; Weike et al., 2000; Kumari and Sharma, 2002; Leumann et al., 2002; Oranje et al., 2002; Quednow et al., 2006; Swerdlow et al., 2006; Wynn et al., 2007).

Within human populations, there is growing evidence that PPI is partially influenced by genetic factors. One typically quantifies this genetic contribution by a measure called heritability, which is equivalent to the proportion of variation in a measure of interest explained by genetic factors. Heritability can be estimated from the correlation in trait outcomes among different relative pairs. For PPI, a study in healthy twins reported a heritability estimate of 38–58% for PPI at 120 ms (Anokhin et al., 2003). In addition, a study designed to evaluate genetic contribution to potential endophenotypes in SCZ subjects and their siblings reported a heritability estimate of 32% for PPI at 60 ms (Greenwood et al., 2007). More recently, a study in a Dutch population found that PPI at 25 ms had a significant heritability estimate of 38%, and reported that this phenotype fits a pattern similar to that for dominant gene transmission (Aukes et al., 2008). With regard to individual genes, new reports have implicated specific polymorphisms in several genes as influencing PPI levels in humans, including catechol O-methyltransferase (COMT), dopamine receptor 3, serotonin receptor 2A, and neuregulin 1 (Hong et al., 2008; Quednow et al., 2008b, 2010; Quednow et al., 2009; Roussos et al., 2008a, b); however, one study found no influence of dopamine receptor 2 or COMT polymorphisms on PPI (Montag et al., 2008).

Researchers have reasoned that if PPI is partially determined by genetic factors, then intermediate levels of PPI may be present in family members of SCZ subjects (falling between those seen in probands and controls), based on the assumption that some family members will carry the genes contributing to reduced PPI, while others will not. To this end, several studies have investigated PPI levels in unaffected relatives of SCZ subjects. The first study found reduced PPI in both SCZ subjects and their non-schizophrenia relatives compared to healthy controls (CON; Cadenhead et al., 2000). Similarly, another study found that unaffected siblings of SCZ subjects had reduced PPI compared to CON subjects (Kumari et al., 2005). However, a third study found no PPI impairments in either SCZ subjects or their unaffected siblings compared to controls (Wynn et al., 2004). Thus, there is some evidence for abnormal PPI in family members of SCZ subjects, but the nature of these impairments likely depends on the specifics of the subject sample and paradigm employed.

To date, no study has simultaneously investigated PPI heritability in both schizophrenia and control families, thereby enabling a comparison of PPI levels in SCZ subjects and their family members to controls, while also estimating the contribution of genetic factors to the PPI phenotype. The present study was an attempt to extend our knowledge of whether PPI is 1) heritable, and 2) compromised in SCZ subjects and their family members. To this end, we analyzed PPI in SCZ subjects and their first-degree relatives (SCZ-FAM), as well as in CON families. In addition, we assessed levels of startle magnitude, habituation and latency in these subjects. For all of these variables, we estimated heritability using variance-component procedures adjusting for potentially influential covariates (i.e., age, gender, race, and smoking status). We also used variance-component procedures to test whether these outcomes differed in the SCZ subjects and their relatives compared to controls, after adjusting for the same covariates used in the heritability analyses.

2. Methods

2.1. Subjects

Forty adult SCZ subjects and 58 of their SCZ-FAM subjects, along with 100 CON subjects from 45 families, met study inclusion criteria and signed a consent form approved by the Institutional Review Board at Emory University and the Atlanta VA Research and Development Committee as an indication of informed consent. The diagnosis of schizophrenia was established on the basis of chart review (when possible) and the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), Axis-I (SCID-I; First et al., 2001), and symptoms were rated using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). The SCID-I was also administered to SCZ-FAM and CON subjects in order to identify Axis I disorders. Exclusion criteria included current substance dependence, positive urine toxicology, history of sustained loss of consciousness, major neurological or medical illness, known hearing impairment, or history of major mental illness (for CON subjects only; four SCZ-FAM subjects were affected by psychotic disorders such as bipolar disorder). All subjects were initially screened for normal hearing acuity using a Grason-Stadler audiometer (Model GS1710). To be included, subjects had to be able to detect tones bilaterally at a threshold of 40 dB[A] at 250, 500, 1000, 2000, 4000 and 8000 Hz. All female participants were tested during the first 2 weeks of their menstrual cycle (follicular phase), as studies have shown that women express reduced PPI during the luteal phase (Swerdlow et al., 1997; Jovanovic et al., 2004).

Demographic information for all subjects as well as medication status and symptom ratings for the SCZ subjects are shown in Table 1. To compare the distribution of these outcomes among SCZ, SCZ-FAM, and CON subjects, we implemented appropriate linear and non-linear mixed-effect models (SAS PROC NLMIXED) that incorporated random effects allowing for within-family correlation.

All subjects were included for analyses of startle magnitude and latency; values were calculated on trials on which measurable responses occurred. However, the inclusion of subjects with very low startle amplitudes can skew the calculated values of variables such as PPI and habituation. Thus, for analyses of these two variables, subjects were excluded for low startle response if their startle response was zero (i.e., below the level of detection) on more than 2/3 of pulse alone trials during the PPI-BLOCK portion of the session (see below). Thirty-five subjects were excluded from this analysis for low startle (SCZ, $n=6$; SCZ-FAM, $n=14$; CON, $n=15$; distribution of subjects excluded for low startle between groups: $P=0.11$). Thus, the final sample for PPI and habituation analyses included 34 SCZ, 43 SCZ-FAM, and 86 CON subjects from 36 families. The

Table 1
Demographic and clinical information by group.

	SCZ ($n=40$)	SCZ-FAM ($n=58$)	CON ($n=100$)
Age (years, mean ± S.D.)[a]	41.8 ± 12.2	48.8 ± 16.5	35.4 ± 15.5
Gender (percentage)[b]			
Male	75	41	30
Female	25	59	70
Race (percentage)[c]			
African American (AA)	30	34	35
Caucasian (Cauc)	62.5	57	50
Other	7.5	9	15
Smoker (percentage)[d]			
Yes	47.5	22	7
No	52.5	78	93
Handedness (percentage)[e]			
Right	92.5	90	93
Left	7.5	10	7
Low startle (percentage)[f]			
Yes	15	26	14
No	85	74	86
Medication (frequency)			
Atypicals	32	1	–
Typicals	1	–	–
Atypical + typical 4	–	–	–
No antipsychotic	3	–	–
PANSS rating (mean ± S.D.)			
Positive symptoms	17.7 ± 6.7	–	–
Negative symptoms	15.0 ± 5.1	–	–
General psychopathology	30.1 ± 9.5	–	–
Total	62.4 ± 18.3	–	–

P-values were obtained from likelihood-ratio tests derived from appropriate linear and non-linear mixed models that accounted for relatedness among subjects.

[a] Age between groups: $P<0.001$.
[b] Gender between groups: $P<0.001$.
[c] Race between groups: $P=0.79$.
[d] Smoking between groups: $P<0.001$.
[e] Handedness between groups: $P=0.95$.
[f] Low startle between groups: $P=0.11$.

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