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

Wendy Hasenkamp[a,*], **Michael P. Epstein**[b], **Amanda Green**[a], **Lisette Wilcox**[a], **William Boshoven**[a], **Barbara Lewison**[a], and **Erica Duncan**[a,c]

[a]Mental Health Service, Atlanta Veterans Affairs Medical Center, Decatur, GA, USA

[b]Department of Human Genetics, Emory University School of Medicine, Atlanta, GA, USA

[c]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA

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.

Keywords

startle; prepulse inhibition; latency; heritability; genetics; schizophrenia

1. Introduction

Within genetic studies of schizophrenia, both phenotypic heterogeneity and genetic heterogeneity complicate the ability to map genetic variants that increase 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 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 focused attention 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 prepulse inhibition (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 schizophrenia patients exhibit reduced PPI (Braff et al., 1978; Braff, 1992a; Grillon et al., 1992; Dawson et al., 1993; Cadenhead et al., 2000; Parwani et al., 2000; Braff et al., 2001; 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, 1992a; 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; Duncan et al., 2003b). However, there have also been numerous studies indicating that medication can increase or normalize PPI deficits in schizophrenia patients (Kumari et al., 1999; Kumari et al., 2000; Weike et al., 2000; Kumari and Sharma, 2002; Kumari et al., 2002; Leumann et al., 2002; Oranje et al., 2002; Quednow et al., 2006; Swerdlow et al., 2006; Kumari et al., 2007; 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 schizophrenia patients 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; Quednow et al., 2008c; Roussos et al., 2008a; Roussos et al., 2008b); 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 schizophrenia patients (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 schizophrenia patients. The first study found reduced PPI in both schizophrenia patients and their non-schizophrenic relatives compared to healthy controls (Cadenhead et al., 2000). Similarly, another study found that unaffected siblings of schizophrenia patients had reduced PPI compared to healthy controls (Kumari et al., 2005). However, another study found no PPI impairments in either schizophrenia patients or their unaffected siblings compared to controls (Wynn et al., 2004). Thus, there is some evidence for abnormal PPI in family members of schizophrenia patients, 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 schizophrenia patients 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 schizophrenia patients and their family members. To this end, we analyzed PPI in schizophrenia patients and their first-degree relatives, as well as in healthy control 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 schizophrenia patients and their relatives compared to controls, after adjusting for the same covariates used in the heritability analyses.

2. Methods

2.1 Subjects

Forty adult schizophrenia patients (SCZ) and 58 of their first-degree relatives (SCZ-FAM), along with 100 healthy controls (CON) 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 DSM-IV, Axis-I (SCID-I; First, 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 were: 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 two 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, 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 exclusion of these subjects did not change any of the group differences on demographic variables compared to the entire sample.

2.2 Acoustic Startle Measurement

Methodology for measuring the acoustic startle reflex was similar to that of Braff and colleagues (Braff, 1992a), and to that used previously in our laboratory (Parwani et al., 2000; Duncan et al., 2003a; Duncan et al., 2003b; Jovanovic, 2004; Hasenkamp et al., 2008). Further description of methodology can be found in Supplementary Methods. Briefly, subjects were seated in a chair in an audiology booth and asked to look straight ahead at a neutral picture and keep their eyes open during the test session. All acoustic stimuli were delivered binaurally through headphones (Maico, TDH-39-P). The startle session began with a 60-second acclimation period consisting of 70 dB white noise, which continued as the background noise throughout the session. The pulse alone stimulus was a 116 dB, 40-ms burst of white noise; the prepulse stimuli were 85 dB, 20-ms bursts of white noise presented 30, 60, and 120 ms prior to the startle stimulus. The session began with a habituation block of six pulse alone stimuli (HAB1). The main part of the session consisted of nine pulse alone trials and nine prepulse trials (prepulse plus pulse) at each of the three designated prepulse intervals (30-, 60- and 120-ms), for a total of 36 startle stimuli (PPI-BLOCK) presented in a pseudorandom order. Finally, a second habituation block of six pulse alone stimuli was presented at the end (HAB2) of the session. Inter-trial intervals were 10–25 sec (average 15 sec).

2.3 Definition of Variables

PPI (100 - [100 × mean magnitude on prepulse trials / mean magnitude on PPI-BLOCK pulse alone trials]) was calculated for each of the three prepulse intervals. Mean startle magnitude was calculated for the 9 pulse alone trials during the PPI-BLOCK portion of the session, and also during the first 6 habituation trials as a measure of initial startle reactivity. Percent habituation was calculated using the first and last six pulse alone trials (100 × [(mean HAB1-mean HAB2)/mean HAB1]). Onset and peak latencies (as defined above) were determined for pulse alone and the three prepulse intervals by averaging the latencies acquired during the appropriate trials during the PPI-BLOCK portion of the session.

2.4 Heritability Analysis

To assess whether these variables possessed a significant genetic component, we conducted a heritability analysis using a variance-components model (Amos, 1994; Almasy and Blangero, 1998) that partitioned the trait covariance of a family into components due either

to shared additive genetic effects (polygenic component) or independent unmeasured environmental factors (environmental component) while simultaneously adjusting for covariates consisting of age, gender, race, and smoking status. Assuming the trait outcome follows a multivariate normal distribution within a family, we applied maximum-likelihood procedures to estimate both the variance components and the fixed covariate effects in this model. We evaluated the heritability of a trait outcome as the estimated polygenic variance in the sample divided by the total estimated variance (polygenic and environmental components). We examined whether the heritability was significantly greater than zero (implying that the trait has a significant genetic component) using a likelihood-ratio test based on the variance-component model. Under the null hypothesis, the likelihood-ratio test follows a 50:50 mixture of a chi-squared distribution with 1 degree of freedom and a point mass of zero (Self, 1987). As variance-component analyses are sensitive to non-normality and skewness in the trait data (Allison et al., 1999; Blangero et al., 2001), we normalized the data prior to analysis using an inverse-normal transformation. In addition, we conditioned our variance-component analyses on the trait outcomes of schizophrenic probands to accommodate their non-random ascertainment into the study. We conducted all heritability analyses using the MENDEL 8.0.1 software package (Lange, 2001).

2.5 Acoustic Startle Data Analysis

We also used a variance-component model in MENDEL 8.0.1 to investigate whether SCZ and SCZ-FAM subjects differed from CON subjects on PPI, startle magnitude, initial startle reactivity, habituation, and onset and peak latency. Prior to analysis, we transformed each outcome to achieve approximate normality using an inverse-normal transformation. We analyzed the transformed data while simultaneously adjusting for covariates consisting of age, gender, race, and smoking status. Furthermore, because our subject groups consisted of related (and hence dependent) individuals, we could not apply standard regression or ANOVA procedures to analyze the data. Thus, we incorporated a random effect in our between group analyses to accommodate within-family correlation – an important control that has not been implemented in previous studies (Cadenhead et al., 2000; Wynn et al., 2004). To further examine the effects of gender and smoking on PPI levels in our sample (Duncan et al., 2001a; Kumari et al., 2004; Swerdlow et al., 2006), we performed secondary analyses that examined between-group differences stratified by these factors. The nominal significance level alpha was set at 0.05 for all analyses. (For ease of interpretability of results, Figure 1 presents raw data; analyzing raw data did not change the significance of any of the results.)

3. Results

3.1 Subject Demographics

Demographic information for all subjects in this study is listed in Table 1. Age was differentially distributed across groups; the SCZ-FAM group was older than the CON group. Gender distribution was also different between groups, with the SCZ group having a greater percentage of men than the other groups. Racial background was not differentially distributed across groups. There was a higher percentage of smokers in the SCZ and SCZ-FAM groups than the CON group. Finally, no differences existed between groups in the distribution of handedness, with at least 90% of subjects in all groups being right-handed.

3.2 Heritability Analysis

Table 2 summarizes the results of the heritability analyses for PPI, startle magnitude, initial startle reactivity, habituation, and onset and peak latencies.

We found a significant heritability estimate of 45% in this subject population for PPI at 60-ms, while the heritability for PPI at 120-ms trended toward significance at 33%. The heritability estimate of PPI at 30-ms was not significant. We found no significant effect of age, gender, race or smoking status on PPI at any interval.

Heritability analysis of startle magnitude revealed the outcome to be 67% heritable. In examining the effects of covariates, we found that race was strongly associated with startle magnitude with Caucasian subjects having higher startle magnitudes than African-American subjects, in support of previous studies (Brown et al., 2006; Hasenkamp et al., 2008). We also found a significant relationship between age and startle magnitude, as shown previously (Ellwanger et al., 2003), although the magnitude of the effect size was small, accounting for less than 2% of the variance. Gender and smoking status were not significant covariates in this analysis. Similar results were found for initial startle reactivity, with heritability estimated at 54% (see Table 2). We found that onset latency demonstrated a significant genetic component with the largest heritability estimate of 90% for pulse alone trials. We further estimated the heritability for onset latency to be 70% for the 30-ms prepulse, 39% for the 60-ms prepulse, and 63% for the 120-ms prepulse. Similarly, peak latency was significantly heritable, with estimates of 68% for pulse alone trials, 42% for the 60-ms prepulse, and 68% for the 120-ms prepulse. Age significantly influenced most of the latency analyses (see Table 2), but again, the magnitude of the effect was small. Race was also a significant factor for onset and peak latency, with Caucasians having consistently shorter latencies than African-Americans. Gender and smoking status were not significant covariates in this analysis. Lastly, we found trend-level evidence of a 31% genetic component for the habituation of the startle response.

3.3 Between-Group Analysis: Prepulse Inhibition

Results from between-group comparisons are presented in Table 3 and Figure 1.

Figure 1a shows levels of PPI for all groups at the three prepulse intervals. We did not detect any significant differences in PPI at any prepulse interval between CON and SCZ or SCZ-FAM subjects, using models that controlled for age, sex, race and smoking status.

As gender was differentially distributed across groups, and has been shown to influence PPI levels (Swerdlow et al., 1997; Jovanovic, 2004; Kumari et al., 2004), we directly investigated the effects of gender on PPI in this sample. Within each gender, however, patterns of PPI distribution between groups were similar to that seen in the entire sample, with no significant group differences detected (Suppl. Figure 1 and Suppl. Table 1). Similar analyses were performed to investigate the effect of smoking status on PPI levels (Duncan et al., 2001a; Swerdlow et al., 2006), also with negative results (Suppl. Table 2). In addition, we examined our PPI dataset for outliers, and removed 5 subjects (1 SCZ, 1 SCZ-FAM and 3 CON) whose data were greater than 3 standard deviations from the mean. Removal of these subjects did not change the relative pattern of PPI between groups, nor did it result in any significant differences between groups on PPI.

3.4 Between-Group Analysis: Other Startle Measures

There were no differences between groups for startle magnitude (Figure 1b), initial startle reactivity (Figure 1c) or habituation of startle (Figure 1d). Onset latencies were significantly longer in the SCZ subjects compared to CON subjects for pulse alone, 30-ms and 60-ms trial types, with a trend toward significance at the 120-ms trial type (Figure 1e). SCZ-FAM subjects had longer onset latencies than CON subjects at the 60-ms trial type (Figure 1e). Similarly, peak latencies were longer in the SCZ group than the CON group for pulse alone,

30-ms and 120-ms trial types (Figure 1f). SCZ-FAM subjects had longer peak latencies than CON subjects at the 30-ms trial type (Figure 1f).

4. Discussion

This study sought to determine whether PPI is 1) a heritable trait, and 2) impaired in schizophrenia patients and their relatives compared to healthy controls. These are two conditions that are required for PPI to be considered a valid endophenotype for schizophrenia (Gottesman and Gould, 2003). We also evaluated startle magnitude, habituation and latency in this sample. The findings for each of these variables as they relate to heritability, as well as distribution between groups, are discussed below.

4.1 Prepulse Inhibition

We found significant evidence that PPI contains a genetic component, as we estimated the heritability of the outcome to be 45% at 60-ms. The heritability estimate for PPI at the 120-ms interval trended towards significance at 33%. This is the first published report of PPI heritability in a sample of both schizophrenia and healthy control subjects and their first-degree relatives. These heritability estimates are in agreement with previous studies. Anokhin and colleagues (Anokhin et al., 2003) evaluated the heritability of PPI at 120-ms in healthy twins with two strategies, either using the entire session or only the first half of the trials, to reduce habituation effects. When analyzing the full session, as was done in the present study, they reported a heritability estimate of 38%. Similarly, Greenwood et al. evaluated heritability in schizophrenia patients and their siblings (Greenwood et al., 2007), and calculated a heritability estimate of 32% for PPI at 60-ms. The general consistency of these estimates across studies, populations, disease state and prepulse intervals provides strong evidence that PPI contains a significant genetic component. An important caveat to the heritability of PPI reported here concerns the possible effect of antipsychotic medication in SCZ subjects. If medication has influenced PPI in these subjects (see discussion below), this effect will lead to an underestimation of the true heritability of PPI, as SCZ-FAM subjects were not on medication. Indeed, when heritability estimates were investigated in this sample without medicated subjects, heritability was higher for all three intervals, and PPI at 30-ms became significant (30-ms: 49%, P=0.03; 60-ms: 74%, P=0.005; 120-ms: 35%, P=0.14). Thus, medication effects on PPI in this sample may obscure the full genetic contribution to this variable. The ideal way to disentangle medication effects is to study these processes in first-episode, medication-naïve patients; future studies will need to confirm the present findings in such a population.

We did not detect any group differences in PPI across trial types between CON and SCZ or SCZ-FAM subjects (Figure 1a). It should be noted that nearly all of the schizophrenia subjects tested here were stabilized on medication, with 90% taking atypical antipsychotics (Table 1). While some studies have found that PPI impairment in schizophrenia does not normalize with treatment (Braff et al., 1978; Braff, 1992a; 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; Duncan et al., 2003b), a growing body of literature suggests that atypical antipsychotics can increase or normalize PPI deficits in schizophrenia patients (Kumari et al., 1999; Kumari et al., 2000; Weike et al., 2000; Kumari and Sharma, 2002; Kumari et al., 2002; Leumann et al., 2002; Oranje et al., 2002; Quednow et al., 2006; Swerdlow et al., 2006; Kumari et al., 2007; Wynn et al., 2007) and healthy subjects (Vollenweider et al., 2006). Our results are consistent with the latter hypothesis, although this study was not powered to directly investigate the effects of medication status. It should be noted that, for the present study, while medication status may have played a role in PPI levels in schizophrenia patients, it should not have influenced our findings in family members, as 93% of these subjects were psychologically healthy and

only one was on an atypical antipsychotic medication. It is also possible that ascertainment bias resulted in the recruitment of higher-functioning patients who were able and willing to participate, and likewise, higher-functioning family members (Calkins et al., 2007). This idea is supported by the relatively low PANSS ratings for the SCZ subjects presented in Table 1.

It should also be mentioned that the PPI values for our CON subjects were lower than our group has found previously, particularly for the 30-ms and 120-ms trial types (Parwani et al., 2000; Duncan et al., 2001a; Duncan et al., 2001b; Jovanovic, 2004). Thus, we cannot rule out the possibility that the lack of significant group differences may be due not to increased or normalized SCZ PPI levels, but lower-than-expected CON PPI levels. To investigate potential reasons underlying this effect, we employed several additional data analysis strategies. However, stratification by gender showed no group differences (Suppl. Figure 1, Suppl. Table 1), and similar non-significant results were obtained when PPI was stratified by smoking status (Suppl. Table 2). Further, removal of outliers did not change the relative distribution of PPI values between groups. Thus, while the reasons for lower-than-expected CON PPI values remain unclear at this time, these findings suggest that this outcome was not due to differences in gender and smoking status or the present of outliers in the sample. While recruitment strategies for this study were similar to those in our previous work in New York, this is the first cohort that has been studied in the Atlanta area, and there may be unexamined demographic differences that could account for lower PPI levels in the current control cohort compared to other published studies.

4.2 Startle Magnitude

We also found significant evidence of a genetic component for startle magnitude, and estimated the heritability to be 67%. This heritability estimate is in strong agreement with a previous study, which also estimated the heritability of the outcome to be 67% across the full session in healthy twins (Anokhin et al., 2003). Furthermore, racial background was a significant covariate in the present analysis, with Caucasian subjects having higher startle magnitudes than African-American subjects, a finding that supports earlier studies on this topic (Brown et al., 2006; Hasenkamp et al., 2008). No differences between CON and SCZ or SCZ-FAM were detected in this study for startle magnitude (Figure 1b), in line with previous findings (Braff et al., 1992; Cadenhead et al., 2000; Parwani et al., 2000; Ludewig et al., 2002; Perry et al., 2002; Wynn et al., 2004; Braff et al., 2005; Swerdlow et al., 2006; Takahashi et al., 2008), but see (Quednow et al., 2006; Minassian et al., 2007). In general, comparable results were found for initial startle reactivity, with heritability at 54%, and no differences between groups. The slightly lower heritability is likely due to variable effects of habituation within the first six trials from which this variable was calculated.

4.3 Habituation of Startle

This is the first report, to the authors' knowledge, of an assessment of heritability for startle habituation. Our results suggest a possible genetic component for percent habituation, with a heritability estimate of 31%, but significance was only trend-level. This suggests that startle habituation may be influenced by genetics, but a large portion of this phenotype is determined by environmental factors. Furthermore, no differences were found between CON and SCZ or SCZ-FAM for habituation (Figure 1d). This finding is in agreement with many (Ludewig et al., 2002; Perry et al., 2002; Wynn et al., 2004; Braff et al., 2005; Quednow et al., 2006; Kunugi et al., 2007; Minassian et al., 2007; Quednow et al., 2008a), but not all (Parwani et al., 2000; Ludewig et al., 2003; Meincke et al., 2004; Takahashi et al., 2008) previous reports in schizophrenia populations.

4.4 Startle Latency

This is also the first study to assess heritability for startle onset and peak latency. We found a robust and significant heritability for onset latency, with estimates ranging from 39–90%, indicating that this startle parameter has a substantial genetic basis. Similarly, peak latency was also significantly heritable, with estimates ranging from 29–68%. In general, startle latency heritability tended to be highest at the pulse alone and 120-ms trial types, and lowest at the 60-ms trial type. In addition, Caucasians had consistently shorter onset and peak latencies than African-Americans, complementing previous findings of racial differences in acoustic startle latency (Swerdlow et al., 2005) and supporting a strong role for genetics in this phenotype. Indeed, a recent study found that dopamine receptor 3 genotype significantly predicted startle latency in human subjects (Roussos et al., 2008a).

We also identified an alteration in onset and peak latencies in SCZ patients compared to controls; this longer latency was most robust at the pulse alone trial type, but was also seen at the prepulse trial types (Figure 1e, 1f). In addition, compared to CON subjects, longer onset latency was found in SCZ-FAM subjects at the 60-ms trial type, and peak latency was longer among SCZ-FAM subjects at the 30-ms trial type. Startle response latencies have not been as thoroughly studied in schizophrenia as PPI, but differences have been reported previously [(Braff et al., 1978; Geyer and Braff, 1982; Braff et al., 1999; Swerdlow et al., 2006), but see (Braff, 1992b; Parwani et al., 2000)]. Previous work has implicated the dopaminergic system in regulating startle latency (Naudin et al., 1990; Svensson, 1990; Roussos et al., 2008a). This raises an interesting possibility, as dysregulation of dopamine systems has long been thought to underlie the pathology of schizophrenia (Carlsson and Carlsson, 2006; Toda and Abi-Dargham, 2007; Murray et al., 2008). However, it should be emphasized that the majority of these SCZ subjects were on antipsychotic medications, most of which have significant dopaminergic activity. Thus, longer startle latencies in the SCZ group may be due either to an effect of disease state or medication. However, because these measures show high heritability, and the SCZ-FAM group showed deficits that were less severe than the SCZ probands, it is possible that startle latency may be genetically associated with schizophrenia. From a cognitive perspective, longer latency to the startle response may indicate that schizophrenia is associated with slower processing speed, although future studies will need to address the nature of this deficit, and whether it is subserved by central or peripheral mechanisms.

In the recent search for endophenotypes in schizophrenia, several groups have sought to determine whether PPI is impaired in family members of schizophrenia patients, with mixed results (Cadenhead et al., 2000; Wynn et al., 2004; Kumari et al., 2005). This approach is based on the assumption that if PPI is heritable, family members will show some intermediate level of impairment on this measure due to shared genetic influences (Gottesman and Gould, 2003). However, the results of the present study reveal significant levels of heritability in the absence of any group differences on PPI in the same subjects. This suggests that comparing family members of schizophrenia patients to controls may not be sufficient to indicate heritability of putative endophenotypes.

This study adds to a growing literature in support of genetic influences on PPI in schizophrenia and control families. The lack of significant group differences in PPI is in line with many recent studies of SCZ patients treated with atypical antipsychotic medication. The robustness of our heritability findings give impetus to applying genetic analyses to startle and PPI variables, and suggest that startle latency may also be a useful measure in the study of potential endophenotypes for schizophrenia. Further work is needed to delineate the precise nature and stability of the proposed impairment in PPI to inform its use as an endophenotype for genetic studies of schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

Allison DB, Neale MC, Zannolli R, Schork NJ, Amos CI, Blangero J. Testing the robustness of the likelihood-ratio test in a variance-component quantitative-trait loci-mapping procedure. American Journal of Human Genetics. 1999; 65:531–544. [PubMed: 10417295]

Almasy L, Blangero J. Multipoint quantitative-trait linkage analysis in general pedigrees. American Journal of Human Genetics. 1998; 62:1198–1211. [PubMed: 9545414]

Amos CI. Robust variance-components approach for assessing genetic linkage in pedigrees. American Journal of Human Genetics. 1994; 54:535–543. [PubMed: 8116623]

Anokhin AP, Heath AC, Myers E, Ralano A, Wood S. Genetic influences on prepulse inhibition of startle reflex in humans. Neuroscience Letters. 2003; 353:45–48. [PubMed: 14642434]

Aukes MF, Alizadeh BZ, Sitskoorn MM, Selten JP, Sinke RJ, Kemner C, Ophoff RA, Kahn RS. Finding suitable phenotypes for genetic studies of schizophrenia: heritability and segregation analysis. Biological Psychiatry. 2008; 64:128–136. [PubMed: 18295748]

Berrettini WH. Genetic bases for endophenotypes in psychiatric disorders. Dialogues in Clinical Neuroscience. 2005; 7:95–101. [PubMed: 16262206]

Blangero J, Williams JT, Almasy L. Variance component methods for detecting complex trait loci. Advances in Genetics. 2001; 42:151–181. [PubMed: 11037320]

Braff D, Grillon C, Geyer MA. Gating and habituation of the startle reflex in schizophrenic patients. Archives of General Psychiatry. 1992a; 49:206–215. [PubMed: 1567275]

Braff D, Stone C, Callaway E, Geyer M, Glick I, Bali L. Prestimulus effects on human startle reflex in normals and schizophrenics. Psychophysiology. 1978; 14:339–343. [PubMed: 693742]

Braff D, Swerdlow N, Geyer M. Symptom correlates of prepulse inhibition deficits in male schizophrenic patients. American Journal of Psychiatry. 1999; 156:596–602. [PubMed: 10200740]

Braff DL. Information processing and attention dysfunctions in schizophrenia. Schizophrenia Bulletin. 1993; 19:233–259. [PubMed: 8322034]

Braff, DL.; Freedman, R. Endophenotypes in studies of the genetics of schizophrenia. In: Davis, KL.; Charney, D.; Coyle, JT.; Nemeroff, C., editors. Neuropsychopharmacology: The Fifth Generation of Progress. New York: Lippincott Williams & Wilkins; 2002.

Braff DL, Geyer MA. Sensorimotor gating and schizophrenia: human and animal model studies. Archives of General Psychiatry. 1990; 47:181–188. [PubMed: 2405807]

Braff DL, Geyer MA, Swerdlow NR. Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies. Psychopharmacology. 2001; 156:234–258. [PubMed: 11549226]

Braff DL, Grillon C, Geyer MA. Gating and habituation of the startle reflex in schizophrenic patients. Archives of General Psychiatry. 1992; 49:206–215. [PubMed: 1567275]

Braff DL, Grillon C, Geyer MA. Gating and habituation of the startle reflex in schizophrenic patients. Archives of General Psychiatry. 1992b; 49:206–215. [PubMed: 1567275]

Braff DL, Light GA, Ellwanger J, Sprock J, Swerdlow NR. Female schizophrenia patients have prepulse inhibition deficits. Biological Psychiatry. 2005; 57:817–820. [PubMed: 15820241]

Brown LM, Bradley MM, Lang PJ. Affective reactions to pictures of ingroup and outgroup members. Biological Psychology. 2006; 71:303–311. [PubMed: 16054283]

Cadenhead KS, Swerdlow NR, Shafer KM, Diaz M, Braff DL. Modulation of the startle response and startle laterality in relatives of schizophrenic patients and in subjects with schizotypal personality disorder: evidence of inhibitory deficits. American Journal of Psychiatry. 2000; 157:1660–1668. [PubMed: 11007721]

Calkins ME, Dobie DJ, Cadenhead KS, Olincy A, Freedman R, Green MF, Greenwood TA, Gur RE, Gur RC, Light GA, Mintz J, Nuechterlein KH, Radant AD, Schork NJ, Seidman LJ, Siever LJ, Silverman JM, Stone WS, Swerdlow NR, Tsuang DW, Tsuang MT, Turetsky BI, Braff DL. The Consortium on the Genetics of Endophenotypes in Schizophrenia: model recruitment, assessment, and endophenotyping methods for a multisite collaboration. Schizophrenia Bulletin. 2007; 33:33–48. [PubMed: 17035358]

Carlsson A, Carlsson ML. A dopaminergic deficit hypothesis of schizophrenia: the path to discovery. Dialogues in Clinical Neuroscience. 2006; 8:137–142. [PubMed: 16640125]

Dawson ME, Hazlett EA, Filion DL, Nuechterlein KN, Schell AM. Attention and schizophrenia: Impaired modulation of the startle reflex. Journal of Abnormal Psychology. 1993; 102:633–641. [PubMed: 8282934]

Duncan E, Madonick S, Chakravorty S, Parwani A, Szilagyi S, Efferen T, Gonzenbach S, Angrist B, Rotrosen J. Effects of smoking on acoustic startle and prepulse inhibition in humans. Psychopharmacology. 2001a; 156:266–272. [PubMed: 11549228]

Duncan E, Madonick S, Parwani A, Angrist B, Rajan R, Chakravorty S, Efferen T, Szilagyi S, Stephanides M, Chappell P, Gonzenbach S, Ko G, Rotrosen J. Clinical and sensorimotor gating effects of ketamine in normals. Neuropsychopharmacology. 2001b; 25:72–83. [PubMed: 11377920]

Duncan E, Szilagyi S, Schwartz M, Kunzova A, Negi S, Efferen T, Peselow E, Chakravorty S, Stephanides M, Harmon J, Bugarski-Kirola D, Gonzenbach S, Rotrosen J. Prepulse inhibition of acoustic startle in subjects with schizophrenia treated with olanzapine or haloperidol. Psychiatry Research. 2003a; 120:1–12. [PubMed: 14500109]

Duncan EJ, Szilagyi S, Efferen TR, Schwartz MP, Parwani A, Chakravorty S, Madonick SH, Kunzova A, Harmon JW, Angrist B, Gonzenbach S, Rotrosen JP. Effect of treatment status on prepulse inhibition of acoustic startle in schizophrenia. Psychopharmacology. 2003b; 167:63–71. [PubMed: 12632245]

Ellwanger J, Geyer MA, Braff DL. The relationship of age to prepulse inhibition and habituation of the acoustic startle response. Biological Psychology. 2003; 62:175–195. [PubMed: 12633977]

First M, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV-TR Axis I Disorders. New York State Psychiatric Institute, Biometrics Research Department. 2001

Gershon ES, Goldin LR. Clinical methods in psychiatric genetics. I. Robustness of genetic marker investigative strategies. Acta Psychiatrica Scandinavica. 1986; 74:113–118. [PubMed: 3465198]

Geyer MA, Braff DL. Habituation of the Blink reflex in normals and schizophrenic patients. Psychophysiology. 1982; 19:1–6. [PubMed: 7058230]

Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. American Journal of Psychiatry. 2003; 160:636–645. [PubMed: 12668349]

Graham F. The more or less startling effects of weak prestimulus. Psychophysiology. 1975; 12:238–248. [PubMed: 1153628]

Greenwood TA, Braff DL, Light GA, Cadenhead KS, Calkins ME, Dobie DJ, Freedman R, Green MF, Gur RE, Gur RC, Mintz J, Nuechterlein KH, Olincy A, Radant AD, Seidman LJ, Siever LJ, Silverman JM, Stone WS, Swerdlow NR, Tsuang DW, Tsuang MT, Turetsky BI, Schork NJ. Initial heritability analyses of endophenotypic measures for schizophrenia: the consortium on the genetics of schizophrenia. Archives of General Psychiatry. 2007; 64:1242–1250. [PubMed: 17984393]

Grillon C, Ameli R, Charney D, Krystal J, Braff D. Startle gating deficits occur across prepulse intensities in schizophrenic patients. Biological Psychiatry. 1992; 32:939–943. [PubMed: 1467378]

Hamm A, Weike A, Schupp H. The effect of neuroleptic medication on prepulse inhibition in schizophrenia patients: current status and future issues. Psychopharmacology. 2001; 156:259–265. [PubMed: 11549227]

Hasenkamp W, Norrholm SD, Green A, Lewison B, Boshoven W, Keyes M, Duncan E. Differences in startle reflex and prepulse inhibition in European-Americans and African-Americans. Psychophysiology. 2008; 45:876–882. [PubMed: 18665868]

Hoffman HS, Searle JL. Acoustic and temporal factors in the evocation of startle. Journal of the Acoustical Society of America. 1968; 43:269–282. [PubMed: 5636789]

Hong LE, Wonodi I, Stine OC, Mitchell BD, Thaker GK. Evidence of missense mutations on the neuregulin 1 gene affecting function of prepulse inhibition. Biological Psychiatry. 2008; 63:17–23. [PubMed: 17631867]

Jovanovic T, Szilagyi S, Chakravorty S, Fiallos AM, Lewison BJ, Parwani A, Schwartz MP, Gonzenbach S, Rotrosen JP, Duncan EJ. Menstrual cycle phase effects on prepulse inhibition of acoustic startle. Psychophysiology. 2004; 41:401–406. [PubMed: 15102125]

Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia Bulletin. 1987; 13:261–276. [PubMed: 3616518]

Kumari V, Aasen I, Sharma T. Sex differences in prepulse inhibition deficits in chronic schizophrenia. Schizophrenia Research. 2004; 69:219–235. [PubMed: 15469195]

Kumari V, Antonova E, Geyer MA, Ffytche D, Williams SC, Sharma T. A fMRI investigation of startle gating deficits in schizophrenia patients treated with typical or atypical antipsychotics. International Journal of Neuropsychopharmacology. 2007; 10:463–477. [PubMed: 16923324]

Kumari V, Das M, Zachariah E, Ettinger U, Sharma T. Reduced prepulse inhibition in unaffected siblings of schizophrenia patients. Psychophysiology. 2005; 42:588–594. [PubMed: 16176381]

Kumari V, Sharma T. Effects of typical and atypical antipsychotics on prepulse inhibition in schizophrenia: a critical evaluation of current evidence and directions for future research. Psychopharmacology. 2002; 162:97–101. [PubMed: 12110987]

Kumari V, Soni W, Mathew VM, Sharma T. Prepulse inhibition of the startle response in men with schizophrenia: effects of age of onset of illness, symptoms, and medication. Archives of General Psychiatry. 2000; 57:609–614. [PubMed: 10839340]

Kumari V, Soni W, Sharma T. Normalization of information processing deficits in schizophrenia with clozapine. American Journal of Psychiatry. 1999; 156:1046–1051. [PubMed: 10401450]

Kumari V, Soni W, Sharma T. Prepulse inhibition of the startle response in risperidone-treated patients: comparison with typical antipsychotics. Schizophrenia Research. 2002; 55:139–146. [PubMed: 11955973]

Kunugi H, Tanaka M, Hori H, Hashimoto R, Saitoh O, Hironaka N. Prepulse inhibition of acoustic startle in Japanese patients with chronic schizophrenia. Neuroscience Research. 2007; 59:23–28. [PubMed: 17692982]

Landis, C.; Hunt, W. The Startle Paradigm. New York: Farrar and Rinehart; 1939.

Lange K, Cantor R, Horvath S, Perola M, Sabatti C, Sinsheimer J, Sobel E. Mendel Version 4.0: A complete package for the exact genetic analysis of discrete traits in pedigree and population data sets. American Journal of Human Genetics. 2001; 69 (Suppl) A1886.

Leumann L, Feldon J, Vollenweider FX, Ludewig K. Effects of typical and atypical antipsychotics on prepulse inhibition and latent inhibition in chronic schizophrenia. Biological Psychiatry. 2002; 52:729–739. [PubMed: 12372664]

Ludewig K, Geyer MA, Etzensberger M, Vollenweider FX. Stability of the acoustic startle reflex, prepulse inhibition, and habituation in schizophrenia. Schizophrenia Research. 2002; 55:129–137. [PubMed: 11955972]

Ludewig K, Geyer MA, Vollenweider FX. Deficits in prepulse inhibition and habituation in never-medicated, first-episode schizophrenia. Biological Psychiatry. 2003; 54:121–128. [PubMed: 12873801]

Mackeprang T, Kristiansen KT, Glenthoj BY. Effects of antipsychotics on prepulse inhibition of the startle response in drug-naive schizophrenic patients. Biological Psychiatry. 2002; 52:863–873. [PubMed: 12399139]

McGhie A, Chapman J. Disorders of attention and perception in early schizophrenia. Brit Journal of Medical Psychology. 1961; 34:102–116.

Meincke U, Light GA, Geyer MA, Braff DL, Gouzoulis-Mayfrank E. Sensitization and habituation of the acoustic startle reflex in patients with schizophrenia. Psychiatry Research. 2004; 126:51–61. [PubMed: 15081627]

Minassian A, Feifel D, Perry W. The relationship between sensorimotor gating and clinical improvement in acutely ill schizophrenia patients. Schizophrenia Research. 2007; 89:225–231. [PubMed: 17005374]

Montag C, Hartmann P, Merz M, Burk C, Reuter M. D2 receptor density and prepulse inhibition in humans: negative findings from a molecular genetic approach. Behav Brain Res. 2008; 187:428–432. [PubMed: 18037170]

Murray RM, Lappin J, Di Forti M. Schizophrenia: from developmental deviance to dopamine dysregulation. European Neuropsychopharmacology. 2008; 18 Suppl 3:S129–S134. [PubMed: 18499406]

Naudin B, Canu S, Costentin J. Effects of various direct or indirect dopamine agonists on the latency of the acoustic startle response in rats. Journal of Neural Transmission. 1990; 82:43–53. [PubMed: 1976319]

Oranje B, Van Oel CJ, Gispen-De Wied CC, Verbaten MN, Kahn RS. Effects of typical and atypical antipsychotics on the prepulse inhibition of the startle reflex in patients with schizophrenia. Journal of Clinical Psychopharmacology. 2002; 22:359–365. [PubMed: 12172334]

Parwani A, Duncan E, Bartlett E, Madonick S, Efferen T, Rajan R, Sanfilipo M, Chappell P, Chakravorty S, Gonzenbach S, Ko G, Rotrosen J. Impaired prepulse inhibition of acoustic startle in schizophrenics. Biological Psychiatry. 2000; 47:662–669. [PubMed: 10745060]

Perry W, Feifel D, Minassian A, Bhattacharjie I, Braff DL. Information processing deficits in acutely psychotic schizophrenia patients medicated and unmedicated at the time of admission. American Journal of Psychiatry. 2002; 159:1375–1381. [PubMed: 12153831]

Quednow BB, Frommann I, Berning J, Kuhn KU, Maier W, Wagner M. Impaired sensorimotor gating of the acoustic startle response in the prodrome of schizophrenia. Biological Psychiatry. 2008a; 64:766–773. [PubMed: 18514166]

Quednow BB, Kuhn KU, Mossner R, Schwab SG, Schuhmacher A, Maier W, Wagner M. Sensorimotor Gating of Schizophrenia Patients Is Influenced by 5-HT(2A) Receptor Polymorphisms. Biological Psychiatry. 2008b; 64:434–437. [PubMed: 18420180]

Quednow BB, Wagner M, Mossner R, Maier W, Kuhn KU. Sensorimotor Gating of Schizophrenia Patients Depends on Catechol O-Methyltransferase Val158Met Polymorphism. Schizophrenia Bulletin. 2008c Jul 17. (adv).

Quednow BB, Wagner M, Westheide J, Beckmann K, Bliesener N, Maier W, Kuhn KU. Sensorimotor gating and habituation of the startle response in schizophrenic patients randomly treated with amisulpride or olanzapine. Biological Psychiatry. 2006; 59:536–545. [PubMed: 16139819]

Roussos P, Giakoumaki SG, Bitsios P. The Dopamine D(3) Receptor Ser9Gly Polymorphism Modulates Prepulse Inhibition of the Acoustic Startle Reflex. Biological Psychiatry. 2008a; 64:235–240. [PubMed: 18325483]

Roussos P, Giakoumaki SG, Rogdaki M, Pavlakis S, Frangou S, Bitsios P. Prepulse inhibition of the startle reflex depends on the catechol O-methyltransferase Val158Met gene polymorphism. Psychological Medicine. 2008b; 38:1651–1658. [PubMed: 18261249]

Self S, Liang K-Y. Asymptotic properties of maximum likelihood estimators and likelihood ratio tests under nonstandard conditions. Journal of the American Statistical Association. 1987; 82:605–610.

Svensson L. The role of the dopaminergic system in the modulation of the acoustic startle response in the rat. European Journal of Pharmacology. 1990; 175:107–111. [PubMed: 1969797]

Swerdlow NR, Hartman PL, Auerbach PP. Changes in sensorimotor inhibition across the menstrual cycle: implications for neuropsychiatric disorders. Biological Psychiatry. 1997; 41:452–460. [PubMed: 9034539]

Swerdlow NR, Light GA, Cadenhead KS, Sprock J, Hsieh MH, Braff DL. Startle gating deficits in a large cohort of patients with schizophrenia: relationship to medications, symptoms, neurocognition, and level of function. Archives of General Psychiatry. 2006; 63:1325–1335. [PubMed: 17146007]

Swerdlow NR, Talledo JA, Braff DL. Startle modulation in Caucasian-Americans and Asian-Americans: a prelude to genetic/endophenotypic studies across the 'Pacific Rim'. Psychiatric Genetics. 2005; 15:61–65. [PubMed: 15722959]

Takahashi H, Iwase M, Ishii R, Ohi K, Fukumoto M, Azechi M, Ikezawa K, Kurimoto R, Canuet L, Nakahachi T, Iike N, Tagami S, Morihara T, Okochi M, Tanaka T, Kazui H, Yoshida T, Tanimukai H, Yasuda Y, Kudo T, Hashimoto R, Takeda M. Impaired prepulse inhibition and habituation of acoustic startle response in Japanese patients with schizophrenia. Neuroscience Research. 2008; 62:187–194. [PubMed: 18789980]

Toda M, Abi-Dargham A. Dopamine hypothesis of schizophrenia: making sense of it all. Current Psychiatry Reports. 2007; 9:329–336. [PubMed: 17880866]

Venables PH. The effect of auditory and visual stimulation on the skin potential responses of schizophrenics. Brain. 1960; 83:77–92. [PubMed: 13841650]

Vollenweider FX, Barro M, Csomor PA, Feldon J. Clozapine enhances prepulse inhibition in healthy humans with low but not with high prepulse inhibition levels. Biological Psychiatry. 2006; 60:597–603. [PubMed: 16997001]

Weike AI, Bauer U, Hamm AO. Effective neuroleptic medication removes prepulse inhibition deficits in schizophrenia patients. Biological Psychiatry. 2000; 47:61–70. [PubMed: 10650450]

Wynn JK, Dawson ME, Schell AM, McGee M, Salveson D, Green MF. Prepulse facilitation and prepulse inhibition in schizophrenia patients and their unaffected siblings. Biological Psychiatry. 2004; 55:518–523. [PubMed: 15023580]

Wynn JK, Green MF, Sprock J, Light GA, Widmark C, Reist C, Erhart S, Marder SR, Mintz J, Braff DL. Effects of olanzapine, risperidone and haloperidol on prepulse inhibition in schizophrenia patients: a double-blind, randomized controlled trial. Schizophrenia Research. 2007; 95:134–142. [PubMed: 17662577]
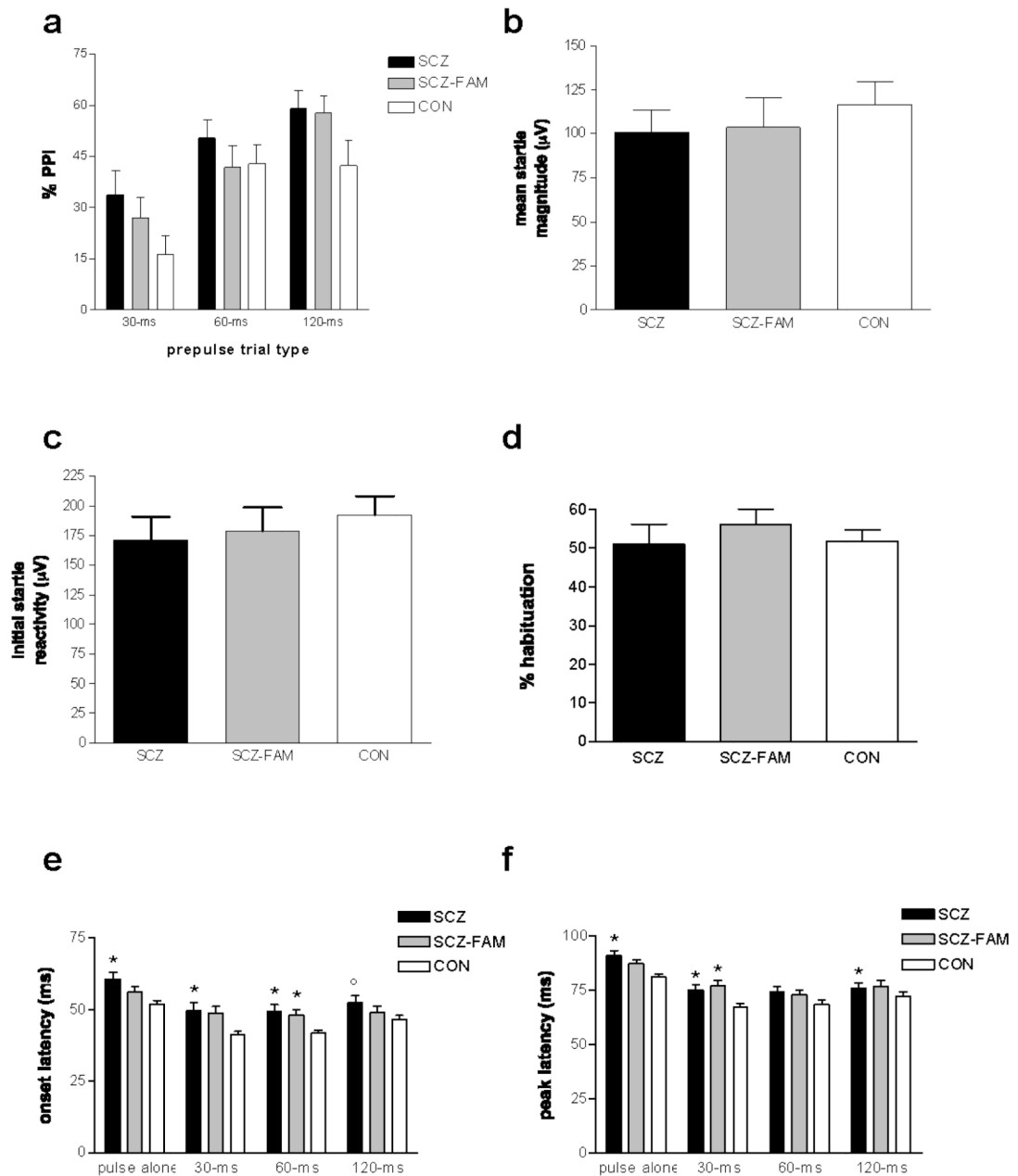
Figure 1.
Levels of PPI and basic startle parameters (Mean + SE). (a) Percent PPI for 30-ms, 60-ms and 120-ms trial types. Subjects with low startle response were excluded from this analysis. Neither SCZ nor SCZ-FAM groups differed from CON. (b) Startle magnitude in the SCZ, SCZ-FAM and CON groups. Neither SCZ nor SCZ-FAM groups differed from CON. (c) Initial startle reactivity (mean startle magnitude during the first six habituation trials) in the SCZ, SCZ-FAM and CON groups. Neither SCZ nor SCZ-FAM groups differed from CON. (d) Percent habituation in the SCZ, SCZ-FAM and CON groups. Subjects with low startle response were excluded from this analysis. Neither SCZ nor SCZ-FAM groups differed from CON. (e) Onset latency values for pulse alone, 30-ms, 60-ms and 120-ms trial types.

(f) Peak latency values for pulse alone, 30-ms, 60-ms and 120-ms trial types. * $P<0.05$, different from CON, ° $P=0.06$ different from CON.

Table 1

Demographic and clinical information by group

	SCZ (*n*=40)	SCZ-FAM (*n*=58)	CON (*n*=100)
Age (years, mean ± SD)[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 ± SD)			
Positive Symptoms	17.7 ± 6.7	-	-
Negative Symptoms	15.0 ± 5.1	-	-
General Psychopathology	30.1 ± 9.5	-	-
Total	62.4 ± 18.3	-	-

[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

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

Table 2

Heritability Estimates for Startle Measures

	% PPI			Startle Magnitude	Initial Startle Reactivity	% Habituation	Onset Latency				Peak Latency			
	30-ms	60-ms	120-ms				pulse alone	30-ms	60-ms	120-ms	pulse alone	30-ms	60-ms	120-ms
n	163	163	163	198	198	163	186	183	182	168	186	183	182	168
Heritability														
Genetic														
Component	0.19	0.45	0.33	0.67	0.54	0.31	0.90	0.70	0.39	0.63	0.68	0.29	0.42	0.68
SD	2.18	1.92	2.43	1.55	1.69	2.15	1.36	1.62	1.76	1.43	1.36	2.43	2.16	1.69
LR Statistic	0.91	5.41	1.80	12.22	20.25	1.96	24.81	11.90	4.22	12.41	13.60	1.50	3.54	12.53
P-value	*0.17*	*0.01*	*0.09*	*<0.001*	*<0.001*	*0.08*	*<0.001*	*<0.001*	*0.02*	*<0.001*	*<0.001*	*0.11*	*0.03*	*0.002*
Covariates														
Age														
Beta	0.01	-0.01	0.003	-0.02	-0.02	0.001	0.01	0.02	0.01	0.01	0.01	0.03	0.01	0.001
SD	0.06	0.06	0.08	0.07	0.06	0.07	0.05	0.05	0.07	0.07	0.07	0.07	0.07	0.07
Wald Statistic	2.42	1.79	0.22	11.02	11.95	0.037	7.88	23.2	5.42	2.54	6.63	10.2	4.71	0.41
P-value	*0.12*	*0.18*	*0.64*	*<0.001*	*<0.001*	*0.97*	*0.005*	*<0.001*	*0.02*	*0.11*	*0.01*	*<0.001*	*0.03*	*0.84*
Gender														
Beta	-0.02	0.04	0.02	0.07	0.06	-0.01	-0.01	-0.06	0.01	-0.10	-0.06	-0.08	0.01	0.03
SD	1.28	1.15	1.15	1.13	1.13	1.15	0.95	0.95	1.08	1.04	1.09	1.08	1.08	1.17
Wald Statistic	0.06	0.17	0.05	0.77	0.57	0.03	0.01	0.77	0.01	1.38	0.57	1.03	0.03	0.11
P-value	*0.80*	*0.68*	*0.82*	*0.38*	*0.45*	*0.87*	*0.93*	*0.38*	*0.91*	*0.24*	*0.45*	*0.31*	*0.86*	*0.74*
Smoking														
Beta	-0.22	0.05	-0.05	-0.10	-0.15	-0.24	0.10	0.10	0.15	0.10	-0.26	-0.05	0.09	-0.36
SD	3.46	3.46	3.58	3.10	3.19	3.31	2.44	2.57	3.24	2.99	2.72	3.11	3.24	3.51
Wald Statistic	0.65	0.03	0.03	0.18	0.41	0.86	0.31	0.25	0.39	0.19	1.72	0.05	0.14	1.8
P-value	*0.42*	*0.86*	*0.86*	*0.67*	*0.52*	*0.35*	*0.58*	*0.62*	*0.53*	*0.66*	*0.19*	*0.83*	*0.71*	*0.18*
Race														
Cauc vs. AA														
Beta	0.17	-0.06	-0.41	0.63	0.52	-0.44	-0.89	-0.81	-0.55	-0.61	-0.62	-0.50	-0.57	-0.43
SD	2.55	2.94	2.94	3.10	2.91	2.71	3.00	2.57	2.70	2.85	2.73	2.43	2.70	3.24

	% PPI			Startle Magnitude	Initial Startle Reactivity	% Habituation	Onset Latency				Peak Latency			
	30-ms	60-ms	120-ms				pulse alone	30-ms	60-ms	120-ms	pulse alone	30-ms	60-ms	120-ms
Wald Statistic	0.71	0.07	3.28	8.28	6.30	4.30	16.32	18.14	7.55	7.67	9.55	7.88	8.28	2.97
P-value	0.40	0.79	0.07	0.004	0.01	0.04	<0.001	<0.001	0.006	0.006	0.002	0.005	0.004	0.085
Other vs. AA														
Beta	−0.14	−0.21	−0.40	0.29	0.24	−0.44	−0.61	−0.53	−0.29	−0.40	−0.78	−0.09	−0.55	−0.14
SD	3.83	4.21	4.21	4.50	4.24	3.90	4.09	3.79	3.91	4.15	3.96	3.79	4.05	4.67
Wald Statistic	0.22	0.39	1.50	0.84	0.64	2.07	4.22	3.55	0.99	1.57	7.23	0.1	3.3	0.15
P-value	0.64	0.53	0.22	0.36	0.42	0.15	0.04	0.06	0.32	0.21	0.01	0.75	0.07	0.70

Table 3

Between Group Differences for Startle Measures

	% PPI			Startle Magnitude	Initial Startle Reactivity	% Habituation	Onset Latency				Peak Latency			
	30-ms	60-ms	120-ms				pulse alone	30-ms	60-ms	120-ms	pulse alone	30-ms	60-ms	120-ms
n	163	163	163	198	198	163	186	183	182	168	186	183	182	168
SCZ vs. CON														
Beta	0.30	0.12	0.42	0.16	0.10	0.05	0.44	0.40	0.49	0.44	0.54	0.41	0.30	0.53
SD	3.06	3.19	3.06	2.95	2.95	3.10	2.73	2.57	2.83	2.98	2.73	2.57	2.83	2.98
LR Statistic	1.56	0.23	3.06	0.58	0.23	0.04	4.84	4.43	5.44	3.66	7.29	4.66	2.04	5.31
P-value	*0.21*	*0.63*	*0.08*	*0.45*	*0.63*	*0.84*	*0.03*	*0.04*	*0.02*	*0.06*	*0.01*	*0.03*	*0.15*	*0.02*
SCZ-FAM vs. CON														
Beta	0.01	−0.01	0.33	−0.06	0.05	0.16	0.11	0.25	0.35	0.14	0.19	0.34	0.16	0.33
SD	2.55	2.68	2.55	2.53	2.53	2.66	2.45	2.30	2.43	2.72	2.32	2.30	2.56	2.72
LR Statistic	0.002	0.002	2.72	0.11	0.08	0.62	0.37	2.16	3.78	0.44	1.25	4.00	0.71	2.47
P-value	*0.96*	*0.96*	*0.10*	*0.74*	*0.78*	*0.43*	*0.54*	*0.14*	*0.05*	*0.51*	*0.26*	*0.05*	*0.40*	*0.12*
Covariates														
Age														
Beta	0.01	−0.01	0.003	−0.02	−0.02	0.001	0.02	0.02	0.01	0.01	0.02	0.03	0.01	0.003
SD	0.06	0.06	0.06	0.06	0.06	0.06	0.05	0.05	0.07	0.06	0.07	0.05	0.07	0.06
Wald Statistic	3.95	4.14	0.64	24.30	15.10	0.00	25.2	26.3	3.95	4.14	17.4	49.3	3.93	0.36
P-value	*0.05*	*0.04*	*0.42*	*<0.001*	*<0.001*	*0.99*	*<0.001*	*<0.001*	*0.05*	*0.04*	*<0.001*	*<0.001*	*0.05*	*0.55*
Gender														
Beta	−0.02	−0.01	0.03	0.07	0.05	−0.01	−0.05	−0.06	−0.00	−0.06	−0.08	−0.03	−0.01	0.05
SD	1.05	1.06	1.05	0.98	1.00	1.08	0.95	0.81	0.94	1.04	0.95	0.95	0.94	1.04
Wald Statistic	0.06	0.02	0.13	1.00	0.55	0.01	0.51	1.00	0.00	0.56	1.31	0.18	0.04	0.39
P-value	*0.81*	*0.90*	*0.71*	*0.32*	*0.46*	*0.92*	*0.48*	*0.32*	*0.95*	*0.45*	*0.25*	*0.67*	*0.84*	*0.53*
Smoking														
Beta	−0.03	0.02	−0.12	−0.08	−0.16	0.07	0.16	0.14	0.15	−0.12	−0.05	−0.02	0.18	−0.28
SD	2.68	2.68	2.68	2.39	2.51	2.75	2.18	2.16	2.56	2.46	2.18	2.30	2.56	2.59
Wald Statistic	0.02	0.01	0.33	0.22	0.78	0.11	1.00	0.76	0.62	0.39	0.10	0.01	0.90	1.96
P-value	*0.88*	*0.92*	*0.57*	*0.64*	*0.38*	*0.74*	*0.32*	*0.38*	*0.43*	*0.53*	*0.76*	*0.91*	*0.34*	*0.16*

	% PPI			Startle Magnitude	Initial Startle Reactivity	% Habituation	Onset Latency				Peak Latency			
	30-ms	60-ms	120-ms				pulse alone	30-ms	60-ms	120-ms	pulse alone	30-ms	60-ms	120-ms
Race														
Cauc vs. AA														
Beta	0.07	0.03	−0.36	0.53	0.45	−0.27	−0.70	−0.69	−0.48	−0.43	−0.57	−0.44	−0.47	−0.27
SD	2.30	2.55	2.43	2.53	2.40	2.46	2.45	2.16	2.29	2.46	2.18	2.03	2.29	2.46
Wald Statistic	0.15	0.02	3.60	7.88	6.88	1.96	15.1	18.6	7.88	5.09	12.7	8.58	7.64	2.02
P-value	0.70	0.88	0.06	0.01	0.01	0.16	<0.001	<0.001	0.01	0.02	<0.001	0.003	0.01	0.16
Other vs. AA														
Beta	−0.20	−0.10	−0.28	0.22	0.21	−0.30	−0.41	−0.37	−0.22	−0.23	−0.60	−0.09	−0.49	0.01
SD	3.45	3.70	3.57	3.66	3.63	3.62	3.55	3.38	3.37	3.76	3.27	3.11	3.51	3.76
Wald Statistic	0.55	0.12	1.00	0.72	0.63	1.12	2.48	2.19	0.77	0.63	6.31	0.15	3.57	0.00
P-value	0.46	0.73	0.32	0.40	0.43	0.29	0.12	0.14	0.38	0.43	0.01	0.70	0.06	0.97