Psychiatry Research 178 (2010) 236–243

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

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], 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

ARTICLE INFO

Article history:
Received 13 March 2009
Received in revised form 29 October 2009
Accepted 9 November 2009

Keywords:
Startle
Prepulse inhibition
Latency
Heritability
Genetics
Schizophrenia

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.

Published by Elsevier Ireland Ltd.

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

* Corresponding author. Atlanta Department of Veterans Affairs Medical Center, 1670 Clairmont Road, MHSL 116A, Decatur, GA 30033, USA. Tel.: +1 404 321 6111x7154; fax: +1 404 417 2911.
E-mail address: wendy.hasenkamp@va.gov (W. Hasenkamp).

0165-1781/$ – see front matter. Published by Elsevier Ireland Ltd.
doi:10.1016/j.psychres.2009.11.012

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: $P=0.11$.

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, 1992), and to that used previously in our laboratory (Parwani et al., 2000; Duncan et al., 2003a,b; Jovanovic et al., 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-s 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 s (average 15 s).

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 nine pulse-alone trials during the PPI-BLOCK portion of the session, and also during the first six 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 to either 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 and Liang, 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 schizophrenia probands to accommodate their non-random ascertainment into the study. We conducted all heritability analyses using the MENDEL 8.0.1 software package (Lange et al., 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 analysis of variance (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, Fig. 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: PPI

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

Fig. 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 et al., 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. Fig. 1 and Suppl. Table 1). Similar analyses were performed to investigate the

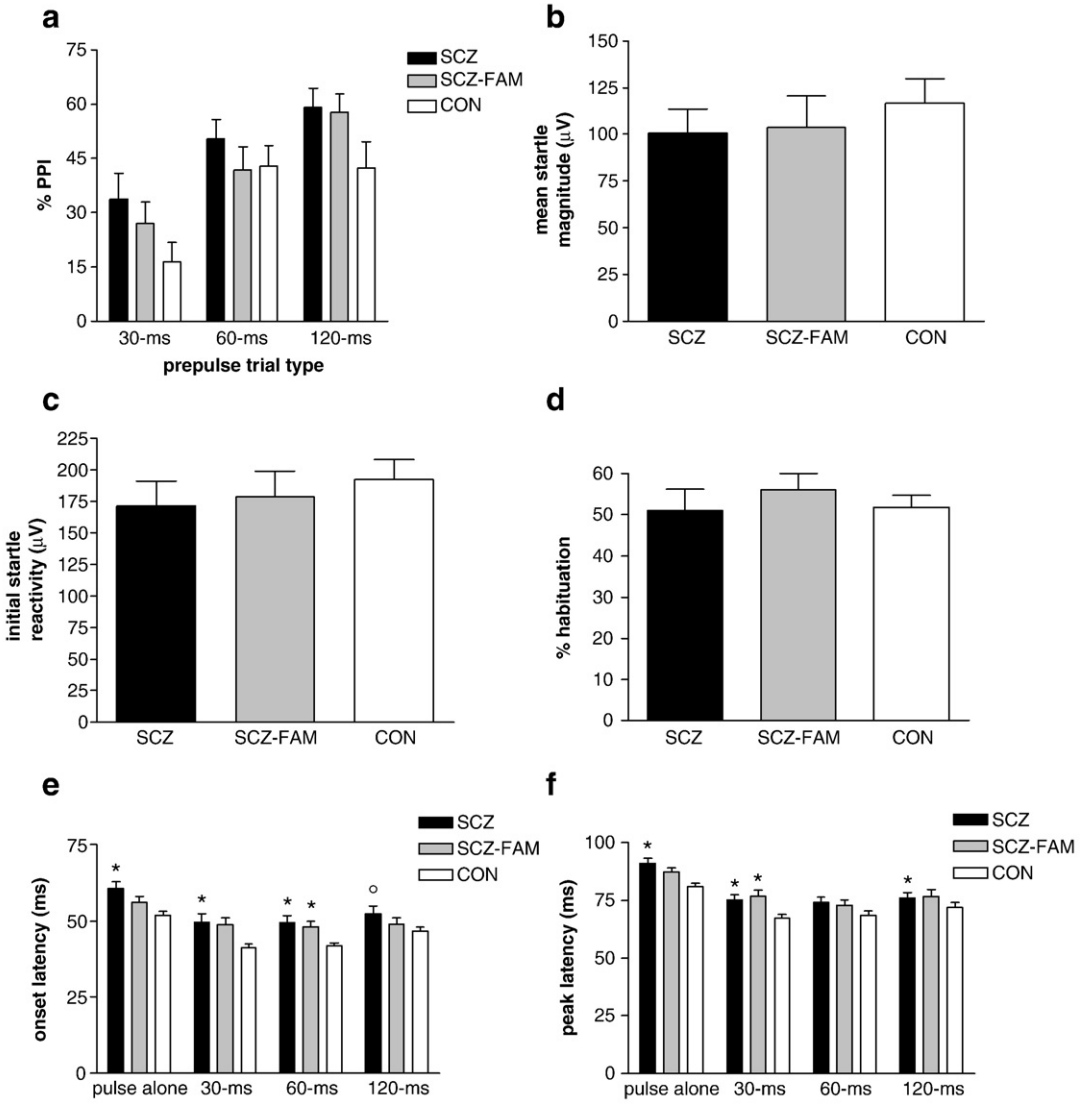

Fig. 1. Levels of PPI and basic startle parameters (mean + SE). (a) Percent PPI for 30-ms, 60-ms, and 120-ms trial types. Subjects with low startle response were excluded from this analysis. Neither SCZ nor SCZ-FAM groups differed from CON. (b) Startle magnitude in the SCZ, SCZ-FAM, and CON groups. Neither 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.

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 data set for outliers, and removed five 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 (Fig. 1b), initial startle reactivity (Fig. 1c), or habituation of startle (Fig. 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 (Fig. 1e). SCZ-FAM subjects had longer onset latencies than CON subjects at the 60-ms trial type (Fig. 1e). Similarly, peak latencies were longer in the SCZ group than the CON group for pulse-alone, 30-ms, and 120-ms trial types (Fig. 1f). SCZ-FAM subjects had longer peak latencies than CON subjects at the 30-ms trial type (Fig. 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

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
S.D.	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
S.D.	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	23.20	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
S.D.	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
S.D.	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	1.80
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
S.D.	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
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
S.D.	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	0.10	3.30	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

trended toward significance at 33%. This is the first published report of PPI heritability in a sample of both SCZ and CON subjects and their SCZ-FAM subjects. These heritability estimates are in agreement with previous studies. 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. (2007) evaluated heritability in schizophrenia patients and their siblings, 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 (Fig. 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, 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), a growing body of literature suggests that atypical antipsychotics can increase or normalize PPI deficits in schizophrenia patients (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) 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,b; Jovanovic et al., 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

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
S.D.	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
S.D.	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
S.D.	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	25.20	26.30	3.95	4.14	17.40	49.30	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
S.D.	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
S.D.	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
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
S.D.	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	15.10	18.60	7.88	5.09	12.70	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
S.D.	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

this effect, we employed several additional data analysis strategies. However, stratification by gender showed no group differences (Suppl. Fig. 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 presence 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 (Fig. 1b), in line with previous findings (Braff et al., 1992, 2005; Cadenhead et al., 2000; Parwani et al., 2000; Ludewig et al., 2002; Perry et al., 2002; Wynn et al., 2004; Swerdlow et al., 2006; Takahashi et al., 2008), but see Quednow et al. (2006) and 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 (Fig. 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, 2008a; Kunugi et al., 2007; Minassian et al., 2007), 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% to 90%, indicating that this startle parameter has a substantial genetic basis. Similarly, peak latency was also significantly heritable, with estimates ranging from 29% to 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 not only was most robust at the pulse-alone trial type, but was also seen at the prepulse trial types (Fig. 1e and f). 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, 1999; Geyer and Braff, 1982; Swerdlow et al., 2006), but see (Braff, 1992; 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 to either 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.

4.5. Conclusions

In the recent search for endophenotypes in schizophrenia, several groups have sought to determine whether PPI is impaired in family members of SCZ 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 SCZ patients to CON subjects 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.

Acknowledgements

This work was supported by the Department of Veterans Affairs Merit Review Program (E.D.), the Mental Health Service of the Atlanta Department of Veterans Affairs Medical Center, the National Institute of Drug Abuse (R01DA018294, E.D.), and the Department of Psychiatry and Behavioral Sciences of Emory University School of Medicine.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2009.11.012.

References

Allison, D.B., Neale, M.C., Zannolli, R., Schork, N.J., Amos, C.I., Blangero, J., 1999. Testing the robustness of the likelihood-ratio test in a variance-component quantitative-trait loci-mapping procedure. American Journal of Human Genetics 65, 531–544.
Almasy, L., Blangero, J., 1998. Multipoint quantitative-trait linkage analysis in general pedigrees. American Journal of Human Genetics 62, 1198–1211.
Amos, C.I., 1994. Robust variance-components approach for assessing genetic linkage in pedigrees. American Journal of Human Genetics 54, 535–543.
Anokhin, A.P., Heath, A.C., Myers, E., Ralano, A., Wood, S., 2003. Genetic influences on prepulse inhibition of startle reflex in humans. Neuroscience Letters 353, 45–48.
Aukes, M.F., Alizadeh, B.Z., Sitskoorn, M.M., Selten, J.P., Sinke, R.J., Kemner, C., Ophoff, R.A., Kahn, R.S., 2008. Finding suitable phenotypes for genetic studies of schizophrenia: heritability and segregation analysis. Biological Psychiatry 64, 128–136.
Berrettini, W.H., 2005. Genetic bases for endophenotypes in psychiatric disorders. Dialogues in Clinical Neuroscience 7, 95–101.
Blangero, J., Williams, J.T., Almasy, L., 2001. Variance component methods for detecting complex trait loci. Advances in Genetics 42, 151–181.
Braff, D.L., 1993. Information processing and attention dysfunctions in schizophrenia. Schizophrenia Bulletin 19, 233–259.
Braff, D.L., Freedman, R., 2002. Endophenotypes in studies of the genetics of schizophrenia. In: Davis, K.L., Charney, D., Coyle, J.T., Nemeroff, C. (Eds.), Neuropsychopharmacology: The Fifth Generation of Progress. Lippincott Williams & Wilkins, New York.
Braff, D.L., Geyer, M.A., 1990. Sensorimotor gating and schizophrenia: human and animal model studies. Archives of General Psychiatry 47, 181–188.
Braff, D., Stone, C., Callaway, E., Geyer, M., Glick, I., Bali, L., 1978. Prestimulus effects on human startle reflex in normals and schizophrenics. Psychophysiology 14, 339–343.
Braff, D., Grillon, C., Geyer, M.A., 1992. Gating and habituation of the startle reflex in schizophrenic patients. Archives of General Psychiatry 49, 206–215.
Braff, D., Swerdlow, N., Geyer, M., 1999. Symptom correlates of prepulse inhibition deficits in male schizophrenic patients. American Journal of Psychiatry 156, 596–602.
Braff, D.L., Geyer, M.A., Swerdlow, N.R., 2001. Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies. Psychopharmacology 156, 234–258.
Braff, D.L., Light, G.A., Ellwanger, J., Sprock, J., Swerdlow, N.R., 2005. Female schizophrenia patients have prepulse inhibition deficits. Biological Psychiatry 57, 817–820.
Brown, L.M., Bradley, M.M., Lang, P.J., 2006. Affective reactions to pictures of ingroup and outgroup members. Biological Psychology 71, 303–311.
Cadenhead, K.S., Swerdlow, N.R., Shafer, K.M., Diaz, M., Braff, D.L., 2000. 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 157, 1660–1668.
Calkins, M.E., Dobie, D.J., Cadenhead, K.S., Olincy, A., Freedman, R., Green, M.F., Greenwood, T.A., Gur, R.E., Gur, R.C., Light, G.A., Mintz, J., Nuechterlein, K.H., Radant, A.D., Schork, N.J., Seidman, L.J., Siever, L.J., Silverman, J.M., Stone, W.S., Swerdlow, N.R., Tsuang, D.W., Tsuang, M.T., Turetsky, B.I., Braff, D.L., 2007. The Consortium on the Genetics of Endophenotypes in Schizophrenia: model recruitment, assessment, and endophenotyping methods for a multisite collaboration. Schizophrenia Bulletin 33, 33–48.
Carlsson, A., Carlsson, M.L., 2006. A dopaminergic deficit hypothesis of schizophrenia: the path to discovery. Dialogues in Clinical Neuroscience 8, 137–142.
Dawson, M.E., Hazlett, E.A., Filion, D.L., Nuechterlein, K.N., Schell, A.M., 1993. Attention and schizophrenia: impaired modulation of the startle reflex. Journal of Abnormal Psychology 102, 633–641.
Duncan, E., Madonick, S., Chakravorty, S., Parwani, A., Szilagyi, S., Efferen, T., Gonzenbach, S., Angrist, B., Rotrosen, J., 2001a. Effects of smoking on acoustic startle and prepulse inhibition in humans. Psychopharmacology 156, 266–272.
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., 2001b. Clinical and sensorimotor gating effects of ketamine in normals. Neuropsychopharmacology 25, 72–83.

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., 2003a. Prepulse inhibition of acoustic startle in subjects with schizophrenia treated with olanzapine or haloperidol. Psychiatry Research 120, 1–12.

Duncan, E.J., Szilagyi, S., Efferen, T.R., Schwartz, M.P., Parwani, A., Chakravorty, S., Madonick, S.H., Kunzova, A., Harmon, J.W., Angrist, B., Gonzenbach, S., Rotrosen, J.P., 2003b. Effect of treatment status on prepulse inhibition of acoustic startle in schizophrenia. Psychopharmacology 167, 63–71.

Ellwanger, J., Geyer, M.A., Braff, D.L., 2003. The relationship of age to prepulse inhibition and habituation of the acoustic startle response. Biological Psychology 62, 175–195.

First, M., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 2001. Structured Clinical Interview for DSM-IV-TR Axis I Disorders. New York State Psychiatric Institute, Biometrics Research Department.

Gershon, E.S., Goldin, L.R., 1986. Clinical methods in psychiatric genetics. I. Robustness of genetic marker investigative strategies. Acta Psychiatrica Scandinavica 74, 113–118.

Geyer, M.A., Braff, D.L., 1982. Habituation of the Blink reflex in normals and schizophrenic patients. Psychophysiology 19, 1–6.

Gottesman, I.I., Gould, T.D., 2003. The endophenotype concept in psychiatry: etymology and strategic intentions. American Journal of Psychiatry 160, 636–645.

Graham, F., 1975. The more or less startling effects of weak prestimulus. Psychophysiology 12, 238–248.

Greenwood, T.A., Braff, D.L., Light, G.A., Cadenhead, K.S., Calkins, M.E., Dobie, D.J., Freedman, R., Green, M.F., Gur, R.E., Gur, R.C., Mintz, J., Nuechterlein, K.H., Olincy, A., Radant, A.D., Seidman, L.J., Siever, L.J., Silverman, J.M., Stone, W.S., Swerdlow, N.R., Tsuang, D.W., Tsuang, M.T., Turetsky, B.I., Schork, N.J., 2007. Initial heritability analyses of endophenotypic measures for schizophrenia: the consortium on the genetics of schizophrenia. Archives of General Psychiatry 64, 1242–1250.

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

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

Hasenkamp, W., Norrholm, S.D., Green, A., Lewison, B., Boshoven, W., Keyes, M., Duncan, E., 2008. Differences in startle reflex and prepulse inhibition in European-Americans and African-Americans. Psychophysiology 45, 876–882.

Hoffman, H.S., Searle, J.L., 1968. Acoustic and temporal factors in the evocation of startle. Journal of the Acoustical Society of America 43, 269–282.

Hong, L.E., Wonodi, I., Stine, O.C., Mitchell, B.D., Thaker, G.K., 2008. Evidence of missense mutations on the neuregulin 1 gene affecting function of prepulse inhibition. Biological Psychiatry 63, 17–23.

Jovanovic, T., Szilagyi, S., Chakravorty, S., Fiallos, A.M., Lewison, B.J., Parwani, A., Schwartz, M.P., Gonzenbach, S., Rotrosen, J.P., Duncan, E.J., 2004. Menstrual cycle phase effects on prepulse inhibition of acoustic startle. Psychophysiology 41, 401–406.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia Bulletin 13, 261–276.

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

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

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

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

Kumari, V., Aasen, I., Sharma, T., 2004. Sex differences in prepulse inhibition deficits in chronic schizophrenia. Schizophrenia Research 69, 219–235.

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

Kumari, V., Antonova, E., Geyer, M.A., Ffytche, D., Williams, S.C., Sharma, T., 2007. A fMRI investigation of startle gating deficits in schizophrenia patients treated with typical or atypical antipsychotics. International Journal of Neuropsychopharmacology 10, 463–477.

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

Landis, C., Hunt, W., 1939. The startle paradigm. Farrar and Rinehart, New York.

Lange, K., Cantor, R., Horvath, S., Perola, M., Sabatti, C., Sinsheimer, J., Sobel, E., 2001. 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 69 (Suppl), A1886.

Leumann, L., Feldon, J., Vollenweider, F.X., Ludewig, K., 2002. Effects of typical and atypical antipsychotics on prepulse inhibition and latent inhibition in chronic schizophrenia. Biological Psychiatry 52, 729–739.

Ludewig, K., Geyer, M.A., Etzensberger, M., Vollenweider, F.X., 2002. Stability of the acoustic startle reflex, prepulse inhibition, and habituation in schizophrenia. Schizophrenia Research 55, 129–137.

Ludewig, K., Geyer, M.A., Vollenweider, F.X., 2003. Deficits in prepulse inhibition and habituation in never-medicated, first-episode schizophrenia. Biological Psychiatry 54, 121–128.

Mackeprang, T., Kristiansen, K.T., Glenthoj, B.Y., 2002. Effects of antipsychotics on prepulse inhibition of the startle response in drug-naive schizophrenic patients. Biological Psychiatry 52, 863–873.

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

Meincke, U., Light, G.A., Geyer, M.A., Braff, D.L., Gouzoulis-Mayfrank, E., 2004. Sensitization and habituation of the acoustic startle reflex in patients with schizophrenia. Psychiatry Research 126, 51–61.

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

Montag, C., Hartmann, P., Merz, M., Burk, C., Reuter, M., 2008. D2 receptor density and prepulse inhibition in humans: negative findings from a molecular genetic approach. Behavioural Brain Research 187, 428–432.

Murray, R.M., Lappin, J., Di Forti, M., 2008. Schizophrenia: from developmental deviance to dopamine dysregulation. European Neuropsychopharmacology 18 (Suppl 3), S129–S134.

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

Oranje, B., Van Oel, C.J., Gispen-De Wied, C.C., Verbaten, M.N., Kahn, R.S., 2002. Effects of typical and atypical antipsychotics on the prepulse inhibition of the startle reflex in patients with schizophrenia. Journal of Clinical Psychopharmacology 22, 359–365.

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

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

Quednow, B.B., Wagner, M., Westheide, J., Beckmann, K., Bliesener, N., Maier, W., Kuhn, K.U., 2006. Sensorimotor gating and habituation of the startle response in schizophrenic patients randomly treated with amisulpride or olanzapine. Biological Psychiatry 59, 536–545.

Quednow, B.B., Frommann, I., Berning, J., Kuhn, K.U., Maier, W., Wagner, M., 2008a. Impaired sensorimotor gating of the acoustic startle response in the prodrome of schizophrenia. Biological Psychiatry 64, 766–773.

Quednow, B.B., Kuhn, K.U., Mossner, R., Schwab, S.G., Schuhmacher, A., Maier, W., Wagner, M., 2008b. Sensorimotor gating of schizophrenia patients is influenced by 5-HT(2A) receptor polymorphisms. Biological Psychiatry 64, 434–437.

Quednow, B.B., Wagner, M., Mossner, R., Maier, W., Kuhn, K.U., 2010. Sensorimotor gating of schizophrenia patients depends on catechol o-methyltransferase Val158Met polymorphism. Schizophrenia Bulletin 36, 341–348.

Quednow, B.B., Schmechtig, A., Ettinger, U., Petrovsky, N., Collier, D.A., Vollenweider, F.X., Wagner, M., Kumari, V., 2009. Sensorimotor gating depends on polymorphisms of the serotonin-2A receptor and catechol-O-methyltransferase, but not on neuregulin-1 Arg38Gln genotype: a replication study. Biological Psychiatry 66, 614–620.

Roussos, P., Giakoumaki, S.G., Bitsios, P., 2008a. The dopamine D(3) receptor Ser9Gly polymorphism modulates prepulse inhibition of the acoustic startle reflex. Biological Psychiatry 64, 235–240.

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

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

Svensson, L., 1990. The role of the dopaminergic system in the modulation of the acoustic startle response in the rat. European Journal of Pharmacology 175, 107–111.

Swerdlow, N.R., Hartman, P.L., Auerbach, P.P., 1997. Changes in sensorimotor inhibition across the menstrual cycle: implications for neuropsychiatric disorders. Biological Psychiatry 41, 452–460.

Swerdlow, N.R., Talledo, J.A., Braff, D.L., 2005. Startle modulation in Caucasian-Americans and Asian-Americans: a prelude to genetic/endophenotypic studies across the 'Pacific Rim'. Psychiatric Genetics 15, 61–65.

Swerdlow, N.R., Light, G.A., Cadenhead, K.S., Sprock, J., Hsieh, M.H., Braff, D.L., 2006. Startle gating deficits in a large cohort of patients with schizophrenia: relationship to medications, symptoms, neurocognition, and level of function. Archives of General Psychiatry 63, 1325–1335.

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., 2008. Impaired prepulse inhibition and habituation of acoustic startle response in Japanese patients with schizophrenia. Neuroscience Research 62, 187–194.

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

Venables, P.H., 1960. The effect of auditory and visual stimulation on the skin potential responses of schizophrenics. Brain 83, 77–92.

Vollenweider, F.X., Barro, M., Csomor, P.A., Feldon, J., 2006. Clozapine enhances prepulse inhibition in healthy humans with low but not with high prepulse inhibition levels. Biological Psychiatry 60, 597–603.

Weike, A.I., Bauer, U., Hamm, A.O., 2000. Effective neuroleptic medication removes prepulse inhibition deficits in schizophrenia patients. Biological Psychiatry 47, 61–70.

Wynn, J.K., Dawson, M.E., Schell, A.M., McGee, M., Salveson, D., Green, M.F., 2004. Prepulse facilitation and prepulse inhibition in schizophrenia patients and their unaffected siblings. Biological Psychiatry 55, 518–523.

Wynn, J.K., Green, M.F., Sprock, J., Light, G.A., Widmark, C., Reist, C., Erhart, S., Marder, S.R., Mintz, J., Braff, D.L., 2007. Effects of olanzapine, risperidone and haloperidol on prepulse inhibition in schizophrenia patients: a double-blind, randomized controlled trial. Schizophrenia Research 95, 134–142.