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Lack of relationship between acoustic startle and cognitive variables in schizophrenia and control subjects

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ABSTRACT

Measures of acoustic startle such as prepulse inhibition (PPI) and startle latency have been found to be impaired in schizophrenia, and are commonly thought to be related to cognitive deficits in this disease. However, findings about the relationship between startle variables and cognitive performance have been equivocal. In this study, we examined correlations between startle measures (baseline startle magnitude, latency, habituation and PPI) and cognitive performance (using the Benton Visual Retention Test, Conner's Continuous Performance Test, California Verbal Learning Test, Finger Tapping Test, and Wisconsin Card Sort Test) in 107 schizophrenia patients and 94 healthy controls. Overall, there was a lack of any significant relationship between these constructs in both populations when correcting for multiple comparisons. This suggests that alterations in startle measures seen in schizophrenia may not reflect elements of information processing that cause cognitive deficits in the disease.

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1. Introduction

The acoustic startle response is a reflex contraction of the skeletal muscles in response to a sudden acoustic stimulus (Landis and Hunt, 1939). Prepulse inhibition (PPI) is the inhibition of the startle reflex that occurs when a nonstartling stimulus is presented shortly before the startling stimulus (Hoffman and Searle, 1968; Graham, 1975). PPI is considered to be an operational measure of sensorimotor gating, the process of screening out excess or trivial stimuli in one's environment (Braff and Geyer, 1990). PPI is often impaired in schizophrenia, with patients showing reduced PPI compared to controls, although some studies have found no impairment, and other studies show a remediation by medication (Braff et al., 2001). Startle latency is the amount of time between the startling stimulus and the startle response. Latency can be measured during baseline startle (pulse alone) trials, and during PPI trials, where it exhibits a well-documented facilitation effect (Filion et al., 1998). Startle response latencies in schizophrenia have not been as thoroughly studied as PPI; longer latencies in the disease state have been reported previously (Braff et al., 1978; Geyer and Braff, 1982; Braff et al., 1999; Swerdlow et al., 2006), although not all studies have found this effect (Braff et al., 1992; Parwani et al., 2000).

It is often assumed that deficits in PPI are functionally associated with cognitive impairments in schizophrenia. Cognitive deficits in memory, attention and executive function are well-known features of this disease, and poor cognition is a predictor of poor functional outcome (Goldberg and Gold, 1995; Harvey et al., 1998; Green et al., 2004). The process of PPI is thought to reflect a gating of sensory input to the brain. In light of this, disruptions in PPI have been hypothesized to relate to sensory overload and cognitive fragmentation in schizophrenia (McGhie and Chapman, 1961; Braff and Geyer, 1990; Braff, 1993). Longer startle latencies sometimes reported in schizophrenia have not been as clearly interpreted, but could be expected to correlate with slower reaction times and poorer performance on cognitive tests, especially those that depend on speed of response. It is possible that longer startle latency is a reflection of a general slowing of neural processing and reflexes in the disease state.

Thus, while these aspects of the startle response are not specifically cognitive in nature, they are thought to reflect more basic facets of information processing that may underlie cognitive processes that are often disrupted in schizophrenia (Geyer, 2006). To date, most studies that have directly assessed this relationship have evaluated PPI only, and results have been inconsistent. Early work using a paradigm with uninstructed attention to startle probes (as in the present study) suggested that poorer performance on the Wisconsin Card Sort Test was

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associated with reduced PPI in a subgroup of patients (Butler et al., 1991). However, several subsequent studies using similar uninstructed paradigms found no association of PPI with performance on tests of executive function such as the Stroop Test (Swerdlow et al., 1995; Bitsios and Giakoumaki, 2005) and the Wisconsin Card Sort Test (Swerdlow et al., 2006). Three uninstructed PPI studies found that higher PPI is associated with superior planning abilities and execution time (Bitsios et al., 2006; Giakoumaki et al., 2006; Csomor et al., 2008); however, one study unexpectedly found that poorer planning was correlated with higher PPI (Bitsios and Giakoumaki, 2005). With regard to attentional capacity, when subjects were instructed to attend to the prepulse, higher PPI was related to better performance on the Continuous Performance Test when tested simultaneously (Rissling et al., 2005); however, two studies using similar instructions found no evidence for such a relationship (Hazlett et al., 2001, 2008). Finally, a study of a large cohort of schizophrenia patients found no relationship between 17 neurocognitive variables and PPI at 60-ms prepulse using an uninstructed paradigm (Swerdlow et al., 2006). To the authors' knowledge, no study to date has assessed the relationship of startle magnitude, habituation or latency to cognitive performance.

The discrepancies in the results summarized above, as well as the lack of data on the relationship of startle magnitude and latency to cognitive performance, provided impetus for the current study. We sought to directly assess the relationship between startle measures (baseline startle magnitude, habituation, latency, and PPI) and cognitive performance in a large sample of schizophrenia patients and healthy controls, with the hypothesis that subjects with the largest PPI deficits would have impaired cognition across a number of domains. Furthering our understanding of the nature of such a relationship will help researchers more clearly interpret startle deficits in schizophrenia and other clinical populations.

2. Methods

2.1. Subjects

A total of 120 adult schizophrenia patients (SCZ) and 114 healthy controls (CON) met study inclusion criteria and signed a consent form approved by the Institutional Review Board at Emory University and the Atlanta Veterans Affairs 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 et al., 2001), and symptoms were rated using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). The SCID-I (non-patient edition) was administered to CON subjects in order to rule out the existence of 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). 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 in the luteal phase express reduced PPI compared to men, but equivalent PPI to men during the follicular phase (Swerdlow et al., 1997; Jovanovic et al., 2004). Subjects who were smokers were not restricted from smoking before the study to avoid effects of nicotine withdrawal; however, most smoking subjects had not smoked for at least 1 hour prior to the startle session. Subjects were excluded from analysis for low startle response if their startle magnitude was zero on at least 2/3 of pulse alone trials in block 1 of the PPI session (see below). Thirty-three subjects were excluded from this analysis for low startle (SCZ, $n=13$; CON, $n=20$; distribution of subjects excluded for low startle between groups: $p=0.13$). Thus, the final sample included 107 SCZ and 94 CON subjects. Demographic information for all subjects, as well as medication status and symptom ratings for the SCZ subjects are shown in Table 1.

2.2. Acoustic startle measurement

Methodology for measuring the acoustic startle reflex was similar to that of Braff et al. (Braff et al., 1992), and to that used previously in our laboratory (Parwani et al., 2000; Duncan et al., 2003a; Duncan et al., 2003b; Jovanovic et al., 2004; Hasenkamp et al., 2008; Hasenkamp et al., 2010). Additional description of these methods is provided in Supplementary Methods. In short, PPI was measured at 30, 60 and 120-ms prepulse intervals from the right *orbicularis oculi* muscle. The main PPI session was preceded and followed by habituation blocks of six pulse alone (116 dB) stimuli each. The main part of the session consisted of three pulse alone trials and three prepulse trials (prepulse plus pulse) at each of the three designated prepulse intervals (30-, 60- and 120-ms), for a total of 12 startle stimuli. Three blocks of these 12 stimuli were presented in a pseudorandom order. Due to a large degree of habituation in blocks 2 and 3, only data from block 1 was analyzed for this study. (The main correlation findings were also examined using data from all blocks, and results presented in Supplementary Table 3. Similar results were found in this analysis).

Mean startle magnitude was calculated by averaging responses on pulse alone trials. Percent habituation (100×[average of first HAB block − average of second HAB block]/average of first HAB block) was calculated for each subject. PPI (100−[100×mean magnitude on prepulse trials/mean magnitude on pulse alone trials]) was calculated for each of the three prepulse intervals. Onset and peak latencies (as defined in Supplementary Methods) were determined for pulse alone and the three prepulse intervals by averaging the latencies acquired during the appropriate trials.

Table 1
Demographic and clinical information by group.

	CON ($n=94$)	SCZ ($n=107$)
Age (years, mean ± SE)[a]	37.6 ± 1.5	43.2 ± 1.1
Gender (percentage)[b]		
Male	54	74
Female	46	26
Ethnicity (percentage)[c]		
African American	36	48
Caucasian	48	46
Other	16	6
Smoker (percentage)[d]		
Yes	6	50
No	94	50
Handedness (percentage)[e]		
Right	90	90
Left	10	10
Medication (frequency)		
Atypicals	–	76
Typicals	–	8
Atypical + typical	–	11
No antipsychotic	–	12
PANSS rating (mean ± SE)		
Positive symptoms	–	17.8 ± 0.6
Negative symptoms	–	15.1 ± 0.5
Total	–	63.3 ± 1.6

[a] Age between groups (*t*-test): $t=-3.04$, d.f. = 1, $p=0.003$.
[b] Gender between groups (Chi-square): $\chi2=16.55$, d.f. = 1, $p<0.001$.
[c] Ethnicity between groups (Chi-square): $\chi2=6.71$, d.f. = 2, $p=0.04$.
[d] Smoking between groups (Chi-square): $\chi2=46.44$, d.f. = 1, $p<0.001$.
[e] Handedness between groups (Chi-square): $\chi2=0.03$, d.f. = 1, $p=0.87$.

2.3. Cognitive measures

Cognitive performance was assessed with five measures chosen to represent a wide range of cognitive function. The Benton Visual Retention Test (BVRT) Administration A (10 s exposure; Sivan, 1992) is a test of visual memory. Total number of correct trials was used as a measure of visual memory performance. Conner's Continuous Performance Test (CPT; Conners, 1992) was used as a measure of sustained attention. D-prime, a measure of the subject's ability to discriminate between target and non-target stimuli, was examined as an index of attention. The California Verbal Learning Test (CVLT) — Second Edition, Short Form (Delis et al., 2000) measures verbal memory; the composite immediate recall score was used in this study. The Finger Tapping Test (FTT; Halstrad, 1947) is a measure of simple motor speed. The raw number of dominant hand taps was used here. Finally, the Wisconsin Card Sorting Test, 64-card version (WCST; Kongs et al., 2000) was used to measure executive function; total perseverative errors was the variable used in the analysis.

2.4. Data analysis

Age, gender and smoking status were used as covariates for all between-group analyses. Mean startle magnitude and percent habituation were compared between groups by one-way ANOVAs. PPI, onset and peak latencies were compared between groups using a linear mixed model (repeated-measures) with a random intercept. Group differences in cognitive measures were assessed with one-way ANOVAs. Correlations between cognitive and startle variables were assessed with partial correlations controlling for age (dichotomous variables such as gender and smoking status cannot be included in partial correlations). To investigate the effects of gender on these relationships, correlations were also run separately for men and women. In addition, quartiles were constructed for each cognitive measure, and startle measures were compared between the highest and lowest quartile for each test using one-way ANOVAs. Alpha was set at 0.05 (uncorrected) for all analyses (Bonferroni correction for correlation analysis yielded a p-value of 0.0008).