



Published in final edited form as:

Psychiatry Res. 2011 May 30; 187(3): 324–328. doi:10.1016/j.psychres.2011.02.011.

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.

Keywords

startle; PPI; latency; neuropsychology; cognitive; schizophrenia

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

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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, 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 associated with reduced PPI in a subgroup of patients (Butler, 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, 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 two 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, 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 one 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, 1992), 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). 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 Suppl. Table 3. Similar results were found in this analysis.)

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

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 second 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).

3. Results

3.1 Subject Demographics

Demographic variables are shown in Table 1. Age was differentially distributed across groups: the SCZ 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 CON group. The CON group contained more subjects of neither Caucasian nor African American ethnicity than the SCZ group. There was a higher percentage of smokers in the SCZ group than the CON group. Finally, no differences existed between groups in the distribution of handedness, with 90% of subjects in both groups being right-handed.

3.2 Group Differences in Startle and Cognitive Variables

Between-group differences on all startle and cognitive variables are shown in Table 2. We did not detect any differences between CON and SCZ subjects for baseline startle magnitude ($p=0.59$), habituation ($p=0.49$) or PPI ($p=0.92$). No main effect of group was found for onset latency ($p=0.31$) or peak latency ($p=0.35$). Age was a significant factor for baseline startle and latency measures. Gender was significant for baseline startle and onset latency, and smoking status was significant for habituation. As gender was not a significant covariate for PPI, it is not surprising that there were no group differences in PPI when analyzed separately among men ($p=0.76$) and women ($p=0.30$; data not shown).

SCZ subjects showed significantly poorer performance than CON subjects on all cognitive tests ($p\leq 0.004$), except a trend towards poorer performance on the WCST ($p=0.09$). Age was a significant factor in all analyses except FTT. Gender was a significant factor for CVLT,

WCST and FTT. Smoking status was not a significant factor for any measures of cognitive performance.

3.3 Correlation between Startle and Cognitive Variables

To investigate whether outcomes on startle and cognitive measures were related, we performed correlation analyses between mean startle magnitude, percent startle habituation, PPI at each interval, onset and peak latencies at each interval, and outcomes on each of the cognitive measures (Table 3). Because age was a significant factor in both startle and cognitive measures (see Table 2), partial correlations were used to control for age. We first performed these correlations separately in each diagnostic group; however, there were no significant differences between groups in any of the correlations (data not shown); thus, we collapsed the sample to contain all subjects (Table 3). Only four of the 65 correlations were significant at uncorrected alpha levels, and these relationships were all weak ($r < 0.3$). Moreover, none of these findings survived correction for multiple tests. Notably, the vast majority (49/65) of the correlation coefficients were $r < 0.10$, indicating that overall there was no strong relationship between these startle parameters and cognitive performance as measured by these tests.

Similarly weak r -values and lack of significance were found when correlations were performed separately by gender (Suppl. Tables 1 and 2), and with all subjects using data from all three blocks of the startle session (Suppl. Table 3).

Comparisons between the highest- and lowest-scoring quartiles of each cognitive performance also revealed no significant differences on any startle measure after correcting for multiple comparisons (Suppl. Table 4).

4. Discussion

The goal of this study was to determine whether there is a relationship between various startle measures and cognitive performance in schizophrenia patients and healthy controls. Several previous studies using uninstructed PPI paradigms like the one used presently have found no relationship between PPI and neuropsychological performance (Butler, 1991; Swerdlow et al., 1995; Hazlett et al., 2001; Bitsios and Giakoumaki, 2005; Bitsios et al., 2006; Swerdlow et al., 2006; Hazlett et al., 2008). This study agrees with these findings, and extends them to include PPI at multiple intervals, as well as measures of baseline startle, habituation and latency.

4.1 Baseline Startle Magnitude

No group differences were found in baseline startle magnitude between SCZ and CON subjects in this study. Startle magnitude was weakly correlated with performance on the WSCT, with lower startle correlating with a higher number of perseverative errors; however, the significance of this correlation did not withstand correction for multiple testing. This is the first study to report on the relationship between startle magnitude and cognitive performance on these tests. Overall, we conclude that there is little to no evidence of any such relationship.

4.2 Startle Habituation

Percent startle habituation over the session was very similar between groups in this sample. Furthermore, no cognitive variables were significantly correlated with habituation among the total population. Among women, performance on the BVRT was modestly correlated with less startle habituation, although this did not withstand correction for multiple testing.

4.3 Prepulse Inhibition

This study identified a very modest relationship between scores on the BRVT and PPI at the 120-ms interval; however, the significance of this relationship did not survive correction for multiple comparisons. The remaining correlations between PPI and cognitive variables were not significant, and r -values were near zero, indicating that these sets of variables were not related. It is interesting to note that the SCZ subjects in this study did not express PPI deficits compared to CON subjects. The majority (89%) of these SCZ subjects were on antipsychotic medication, and most were taking atypicals. While some studies have shown PPI deficits in schizophrenia 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; Duncan et al., 2003b), 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 et al., 2002; Kumari and Sharma, 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), which may be the case in the present sample. Importantly, despite a lack of PPI deficit, these SCZ subjects still showed robustly impaired cognitive performance. This discrepancy adds further weight to the conclusion that the neural circuitry underlying PPI does not directly map onto cognitive problems in schizophrenia. If the relevant startle circuitry for PPI was closely related to cognitive function, one might expect that SCZ subjects exhibiting PPI comparable to controls would also perform at levels similar to controls on cognitive tests.

4.4 Startle Latency

No group differences were found for onset or peak startle latency in this sample, in agreement with some previous work (Braff, 1992; Parwani et al., 2000). One hypothesis at the outset of this study was that slower neural processing (as indicated by slower startle latency) may underlie some of the cognitive deficits commonly reported in schizophrenia. If this were the case, we expected that longer startle latencies would relate to poorer cognitive performance. However, we found very limited evidence for this hypothesis, with only weak negative correlations between peak latency and scores on the CPT. Indeed, the significance of these correlations did not survive correction for multiple testing.

4.5 Conclusion

Overall, it appears that alterations in startle responses seen in schizophrenia do not reflect elements of information processing that are directly related to cognitive deficits in the domains measured here (visual and verbal memory, sustained attention, executive function and motor speed). Rather, startle and cognitive tasks may be tapping separate brain processes. Alternatively, the level of processing required for cognitive performance may be so complex that any contribution from the comparatively simple startle circuitry may be obscured in direct comparisons such as these. Recent work also suggests that the relationship of PPI and cognition may depend on attentional modulation (Scholes and Martin-Iverson, 2009; 2010). As this study used an undirected attention paradigm, the influence of attention cannot be assessed here. Regardless, the persistence of cognitive impairment in this schizophrenia sample despite the absence of PPI deficits further suggests that startle alterations and cognition are not closely related. This study has implications for future genetic studies of schizophrenia that attempt to use endophenotypes to narrow genetic heterogeneity of patient samples. Our finding suggests that impaired PPI and impaired cognition may define schizophrenia patients with non-overlapping sets of vulnerability genes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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.

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Table 1

Demographic and clinical information by group

	CON (n=94)	SCZ (n=107)
Age (years, mean \pm SE)^a	37.6 \pm 1.5	43.2 \pm 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 \pm SE)		
Positive Symptoms	-	17.8 \pm 0.6
Negative Symptoms	-	15.1 \pm 0.5
Total	-	63.3 \pm 1.6

^a Age between groups (t-test): $t=-3.04$, $df=1$, $p=0.003$

^b Gender between groups (Chi-square): $X^2=16.55$, $df=1$, $p<0.001$

^c Ethnicity between groups (Chi-square): $X^2=6.71$, $df=2$, $p=0.04$

^d Smoking between groups (Chi-square): $X^2=46.44$, $df=1$, $p<0.001$

^e Handedness between groups (Chi-square): $X^2=0.03$, $df=1$, $p=0.87$

Table 2

Between-group differences in startle and cognitive variables

	CON (mean ± SD)		SCZ (mean ± SD)		Effect of Group		Effect of Age		Effect of Gender		Effect of Smoking	
	mean	SD	mean	SD	statistic	p-value	statistic	p-value	statistic	p-value	statistic	p-value
STARTLE VARIABLES												
Baseline startle magnitude	117.8 ± 102.7		109.4 ± 97.5		F = 0.29	0.59	F = 8.59	0.004	F = 4.66	0.03	F = 0.01	0.94
Percent startle habituation	52.3 ± 27.5		52.7 ± 33.7		F = 0.48	0.49	F = 0.08	0.78	F = 0.43	0.51	F = 4.43	0.04
PPI^a					Z = 0.10	0.92	Z = -1.58	0.11	Z = 0.98	0.33	Z = 1.15	0.25
30-ms	10.9 ± 80.7		28.4 ± 61.2									
60-ms	43.6 ± 62.0		39.9 ± 61.5									
120-ms	57.1 ± 59.2		57.9 ± 43.3									
Onset Latency^a					Z = 1.02	0.31	Z = 4.61	<0.001	Z = 2.47	0.01	Z = -1.03	0.30
pulse alone	54.0 ± 15.3		56.7 ± 15.0									
30-ms	41.6 ± 13.1		45.9 ± 16.0									
60-ms	43.6 ± 13.2		43.3 ± 12.6									
120-ms	46.0 ± 12.7		50.0 ± 13.4		Z = 0.93	0.35	Z = 3.63	<0.001	Z = 1.24	0.22	Z = -1.24	0.22
Peak Latency^a												
pulse alone	83.9 ± 14.9		90.5 ± 15.4									
30-ms	66.0 ± 17.1		73.3 ± 18.0									
60-ms	65.0 ± 18.9		72.3 ± 21.5									
120-ms	71.1 ± 18.3		76.8 ± 18.4									
COGNITIVE VARIABLES												
BVRT (number correct)	7.5 ± 1.8		5.7 ± 2.0		F = 13.94	<0.001	F = 21.51	<0.001	F = 1.04	0.31	F = 0.18	0.67
CVLT (total correct)	29.1 ± 3.2		25.3 ± 4.8		F = 8.42	0.004	F = 12.54	0.001	F = 12.01	0.001	F = 0.02	0.88
WCST (perseverative errors)	9.3 ± 6.7		14.2 ± 10.3		F = 2.84	0.090	F = 28.14	<0.001	F = 8.75	0.003	F = 0.15	0.70
CPT (d-prime)	4.5 ± 0.8		3.7 ± 0.9		F = 16.35	<0.001	F = 7.25	0.008	F = 0.88	0.35	F = 0.10	0.76
FTT (total, dominant hand)	50.3 ± 8.8		43.7 ± 11.3		F = 17.81	<0.001	F = 3.65	0.06	F = 8.52	0.004	F = 2.38	0.13

^aPPI, onset and peak latency were assessed with a linear mixed model (repeated-measures) with a random intercept and age, gender and smoking as covariates.

Table 3

Correlations between startle and cognitive variables

	BVRT	CVLT	WCST	CPT	FTT
Baseline startle magnitude	-0.03	-0.06	-0.15*	-0.10	-0.13
Percent startle habituation	-0.14	-0.05	0.00	-0.13	-0.14
PPI (30-ms)	-0.08	-0.07	0.07	-0.08	-0.03
PPI (60-ms)	-0.09	-0.11	0.03	0.03	-0.01
PPI (120-ms)	-0.25**	-0.10	0.05	-0.05	-0.07
Onset latency (pulse alone)	-0.08	0.01	0.08	-0.08	-0.07
Onset latency (30-ms)	-0.07	-0.07	0.09	-0.04	-0.06
Onset latency (60-ms)	0.03	-0.09	0.08	-0.08	-0.01
Onset latency (120-ms)	0.02	-0.02	0.11	0.04	0.00
Peak latency (pulse alone)	-0.03	-0.02	-0.01	-0.28**	-0.08
Peak latency (30-ms)	-0.01	-0.04	-0.02	-0.04	-0.06
Peak latency (60-ms)	-0.04	-0.17	0.13	-0.20*	-0.02
Peak latency (120-ms)	0.18	0.08	0.05	-0.11	0.09

Values are Pearson's *r*, derived from partial correlations controlling for age.

* $p < 0.05$ uncorrected;

** $p < 0.005$ uncorrected.

Bonferroni correction for multiple comparisons yields a p -value of 0.0008.