Prepulse Facilitation and Prepulse Inhibition in Schizophrenia Patients and Their Unaffected Siblings

Jonathan K. Wynn, Michael E. Dawson, Anne M. Schell, Mark McGee, Dustin Salveson, and Michael F. Green

Background: Deficits in schizophrenia patients and their first-degree relatives have been reported in prepulse inhibition (PPI), a phenomenon that measures an early stage of information processing (sensorimotor gating). It is less clear whether these information processing deficits extend to prepulse facilitation (PPF), which measures a later stage of generalized alerting or orienting.

Methods: This study examined three separate issues: first, whether schizophrenia patients have deficits in PPI and PPF; second, whether the siblings of patients show deficits in these processes; and third, whether prepulse duration influences the degree of the deficits. These issues were examined in 76 schizophrenia patients, 36 of their siblings, and 41 normal control subjects.

Results: Patients and siblings did not differ from control subjects in PPI, perhaps due to the use of different procedural parameters compared with other laboratories that have consistently found PPI deficits in schizophrenia patients. Patients and their siblings produced significantly less PPF than control subjects. For both PPI and PPF, prepulse duration was not a significant factor.

Conclusions: These results imply that PPI deficits reveal a generalized alerting or orienting deficit that is present in both schizophrenia patients and their siblings, suggesting that this deficit may be tapping an endophenotypic vulnerability factor.

Key Words: Startle, prepulse inhibition, prepulse facilitation, orienting, schizophrenia, endophenotypic marker

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tartle eyeblink modification (SEM) is a powerful tool for studying information processing by examining how a startle eyeblink is modified by a preceding, nonstartling stimulus (prepulse). When the prepulse precedes the startle pulse by a short interval (known as the lead interval), for example, less than 500 msec, the startle eyeblink is inhibited, a phenomenon known as prepulse inhibition (PPI). When the lead interval is longer, for example, greater than 1000 msec, the startle eyeblink is facilitated, particularly if the prepulse and startle stimulus are in the same sensory modality, a phenomenon known as prepulse facilitation (PPF). Investigators have used SEM to study information processing deficits in schizophrenia for many years (Braff et al 1978; Cadenhead et al 1997; Dawson et al 1993; Hazlett et al 1998). More recently, PPI has been used with schizotypal individuals (Cadenhead et al 1993) and first-degree relatives of schizophrenics (Cadenhead et al 2000) as a possible endophenotypic marker. This article examines both PPI and PPF in schizophrenia patients, their first-degree relatives (siblings), and normal control subjects.

It is thought that PPI and PPF reflect two separate mechanisms: PPI is believed to index an automatic sensorimotor gating mechanism or a protection of processing mechanism (Braff et al 1992; Graham 1980) whereby the processing of the prepulse gates out the sensory information of the startle stimulus. Deficits in PPI could theoretically lead to cognitive overload and fragmentation, traits exhibited by some pathologic populations such as schizophrenia patients (Braff and Geyer 1990). In contrast, PPF in a passive attention paradigm is thought to reflect a classical activating effect (Graham 1975), indicating alerting or attention or automatically elicited generalized orienting (as opposed to specific orienting during a task that requires attention to be paid to specific stimuli; Graham and Hackley 1991). Prepulses appear to cause subjects to orient to incoming information, thus enhancing the subsequent amount of eyeblink to the startle burst, if the prepulse and startle burst are in the same modality (Graham 1980). Deficits in orienting have been related to deficits in allocation of processing resources to external stimuli and a reduction in available processing resources, traits also exhibited by schizophrenia patients (for a review, see Nuechterlein and Dawson 1984). Moreover, deficits in orienting have been shown to be stable trait markers for schizophrenia patients (Dawson et al 1994; Spohn et al 1989) and at-risk populations (Simons 1981).

Although PPI is thought to be automatic, several studies have shown that by directing attention toward the prepulse, PPI and PPF can be enhanced (Dawson et al 1993, 2000; Hawk et al 2002; Hazlett et al 1998; Schell et al 2000). Some investigators (e.g., Braff et al 1992; Cadenhead et al 2000) interpret the PPI deficits exhibited by schizophrenia patients as reflecting automatic sensorimotor gating deficits during a passive attention task. Others (e.g., Dawson et al 1993, 2000) suggest that PPI deficits exhibited by schizophrenia patients are in the controlled attentional modulation of PPI during an active attention task; however, differences in the methods used to elicit PPI and PPF can have substantial impact on the results. The methods used in our study differ in several ways from those of laboratories that consistently find absolute PPI deficits in schizophrenia patients, for example, differences in level of background noise (which makes the prepulse less easily detectable), recording electromyogram (EMG) from the right eye, and the use of different types of prepulses.

This study addressed one parameter that could lead to differences in findings across laboratories. Specifically, laboratories that find deficits in absolute, automatic PPI in a passive attention paradigm in schizophrenia patients and at-risk subjects use discrete white noise prepulses (which begin and end before startle onset), whereas those that find deficits only in attentional modulation of PPI and PPF use continuous pure-tone prepulses (which begin and continue up to and beyond startle onset) in an...
active attention paradigm. Our study included both types of prepulses in a passive attention paradigm.

In passive attention paradigms, PPI has been proposed as a vulnerability indicator for schizophrenia. Those presumably at risk for developing schizophrenia (psychometrically defined; e.g., Simons and Giardina 1992) and those diagnosed with schizotypal personality disorder (Cadenhead et al 1993) have exhibited PPI deficits. Only one published study, to our knowledge, examined PPI in first-degree relatives of schizophrenia patients (Cadenhead et al 2000). In this study, deficient PPI in first-degree relatives was found under a specific condition—namely, measuring PPI from the right (but not left) eye at a 30-msec lead interval, but not at lead intervals of 60 or 120 msec.

Although there have been numerous studies on PPI in schizophrenia, schizophrenia-spectrum populations, and at-risk populations, the literature concerning PPF deficits is sparse. There is only one published study, to our knowledge, that examined PPF in a passive paradigm in schizophrenia. Braff et al (1978) examined both PPI and PPF in schizophrenia patients. Although the patients were deficient in PPI, they did not show any PPF differences from normal control subjects. Other studies have found PPF attentional modulation deficits during an active attention task (i.e., failure to produce more PPF during a to-be-attended prepulse) in both schizophrenia patients (Dawson et al 1993, 2000) and subjects putatively at risk based on the Chapman scales (Schell et al 1995).

Our research examined three separate issues. First, we tested whether schizophrenia patients have deficits in PPI and PPF with the parameters used in this study. Second, we tested whether the siblings of patients show deficits in these processes. If SEM is a genetic vulnerability marker for information processing deficits in schizophrenia, patients and their nonpsychotic siblings should show deficits in SEM. We hypothesized that both schizophrenia patients and their siblings would show reduced PPI as well as reduced PPF. The third issue this study addressed was whether the use of two types of prepulses, discrete white noise pulses or continuous pure tones, in the passive paradigm would partially explain the differences in findings among laboratories. We hypothesized that with the discrete white noise prepulses in a passive attention task patients and their siblings would show reduced PPI compared with normal control subjects, and that with the continuous-tone prepulses patients and their siblings would show normal levels of PPI compared with normal control subjects.

Methods and Materials

Participants

Participants initially included 90 schizophrenia patients, 48 of their siblings (sharing both biological parents of the schizophrenia proband), and 47 nonpatient control subjects. Subjects were drawn from a larger study of Early Visual Processing in Schizophrenia (principal investigator: M.F. Green); schizophrenia probands were recruited from outpatient clinics at the Greater Los Angeles Veteran’s Administration (VA) Healthcare System and through presentations in the community. Nonpatient control subjects were recruited through flyers posted at the University of California-Los Angeles (UCLA) and the VA medical centers and through newspaper advertisements. Siblings were contacted with permission from the schizophrenia proband. All participants gave written informed consent after the procedures were fully explained according to the procedures approved by the UCLA and VA Institutional Review Boards. Patients met criteria for schizophrenia based on the Structured Clinical Interview for DSM-IV (SCID; First et al 1996b). All patients with useable startle eyblink data (see Subject Exclusions) were receiving antipsychotic medication at the time of testing: 43 were on atypical antipsychotics, 22 were on typical antipsychotics, and 11 were on mixed or unknown (e.g., blinded) antipsychotics.

Psychiatric symptoms were assessed in the patient group using the 24-item Brief Psychiatric Rating Scale (BPRS; Ventura et al 1993). Interviewers were trained to a minimum intraclass correlation of .80 on ratings. Table 1 provides the means and standard deviations of the items (range 1–7) for the patients on the thinking disturbance, or positive symptom (unusual thought content, hallucinations, and conceptual disorganization) and on withdrawal-retardation, or negative symptom (emotional withdrawal, blunted affect, and motor retardation) factors of the BPRS (Overall et al 1967), as well as the total BPRS score.

Nonpatient control subjects were screened with the SCID and SCID-II (First et al 1996a) and were excluded if they met criteria for any psychotic disorder, bipolar mood disorder, recurrent depression, substance dependence, or paranoid, schizoid, borderline, avoidant, or schizotypal personality disorders. Control subjects were also excluded if there was any history of any psychotic disorder among first-degree relatives.

To remove the possible effect of psychosis on SEM measures, we excluded from analysis siblings with a history of psychosis. Of the original 48 siblings assessed with the SCID and SCID-II, five were excluded for a history of a psychosis (3 with schizophrenia, 1 with schizoaffective disorder, and 1 with delusional disorder). None of the remaining siblings were taking any antipsychotic medication. Seven additional siblings were excluded because they were nonresponsive to the startle stimulus, leaving 36 siblings in all further analyses. Of these siblings, two received an Axis II disorder diagnosis (not otherwise specified and paranoid). Eight siblings had a history of drug or alcohol abuse, four a history of a depression, and four a history of both substance abuse and depression. All siblings with a history of an Axis I disorder were in remission.

Additional exclusion criteria for all patients and control subjects included age < 18 or > 55 years, active substance use disorder in the past 6 months, identifiable neurologic disorder, mental retardation, or seizure disorder. Diagnostic interviewers were trained to a minimum kappa of .75 for rating psychotic and mood symptoms by the Diagnostic and Psychopathology Unit of

### Table 1. Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenia</th>
<th>Siblings</th>
<th>Controls</th>
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<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>39</td>
<td>18</td>
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<tr>
<td>F</td>
<td>37</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>42.70 (8.46)</td>
<td>38.23 (9.61)</td>
<td>35.64 (7.96)</td>
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<tr>
<td><strong>Range</strong></td>
<td>20–55</td>
<td>18–55</td>
<td>21–50</td>
</tr>
<tr>
<td><strong>Sex (M:F)</strong></td>
<td>74:2</td>
<td>17:19</td>
<td>19:21</td>
</tr>
<tr>
<td><strong>Antipsychotic Medication</strong></td>
<td>22:43</td>
<td>29:21</td>
<td>20:29</td>
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<tr>
<td><strong>BPRS</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Total</strong></td>
<td>47.78 (10.67)</td>
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<tr>
<td><strong>Thinking Disturbance</strong></td>
<td>2.95 (1.15)</td>
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<tr>
<td><strong>Withdrawal-Retardation</strong></td>
<td>2.30 (1.10)</td>
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<tr>
<td><strong>Baseline Startle (μV)</strong></td>
<td>17.34 (28.82)</td>
<td>20.12 (22.34)</td>
<td>12.89 (14.43)</td>
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</tbody>
</table>

Data are Mean (SD).

*Schizophrenia patients significantly older than controls, p < .001.

*Siblings of patients significantly older than controls, p < .01.

For patients on known medications.
the UCLA Clinical Research Center for the Study of Schizophrenia (principal investigator: R.P. Liberman).

Procedure

Subjects were seated in a comfortable chair. Two miniature (4-mm) Ag–AgCl electrodes were placed on the surface of the skin beneath the left eye, the first under the pupil and the other approximately 1 cm lateral to the first. A ground electrode was placed on the left mastoid. Electrical resistances between electrodes were less than 5000 Ohms. Eyeblinks were recorded as EMG activity using a Coulbourn (Allentown, Pennsylvania) S75–01 bioamplifier and digitized for later analysis. The EMG activity was filtered with an 8-Hz high-pass filter and a 1000-Hz low-pass filter, along with a 60-Hz notch filter. The data were collected as raw EMG at 2000 Hz beginning 200 msec before startle stimulus onset and 300 msec after startle stimulus onset. Discrete prepulses were 20-msec presentations of 75 dB(A) white noise bursts (20–20,000 Hz) with a near-instantaneous rise–fall time. Continuous prepulses were 5000 msec presentations of 75 dB(A) 1000 Hz tones, with a rise–fall time of 25 msec. The startle stimulus consisted of a 50 msec, near instantaneous rise–fall time, 105 dB(A) white noise burst (20–20,000 Hz). There was no imposed background noise. Auditory stimuli were digitized on a computer and presented through the computer’s sound card binaurally through headphones. Decibel levels were recorded with a Realistic sound level meter using a Quest Electronics earphone coupler.

The experimental session consisted of 24 trials, presented in a mixed, pseudorandom order, split into two blocks (12 trials in each block). We assessed PPI using a lead interval of 120 msec and PPF using a lead interval of 4500 msec. Of these 24 trials, there were four startle-probed trials presented for each combination of prepulse duration and lead interval, resulting in four discrete prepulses with a 120 msec lead interval, four discrete prepulses with a 4500 msec lead interval, four continuous prepulses with a 120 msec lead interval, and four continuous prepulses with a 4500 msec lead interval (there were four unprobed prepulses for each prepulse type as well to make the presentation of prepulse plus startle unpredictable). Averages for each of the two prepulse trials for each condition in each block were computed and used in the analyses. There were also 15 intertrial interval (ITI) startle probes presented throughout the experiment, varying from 8–11 sec into the ITI. Responses to the first 8 ITI startle bursts were averaged and used to compute PPI and PPF for the first block and the last 7 ITI startle bursts were averaged to compute PPI and PPF for the second block. The ITIs varied from 30–36 sec.

Eyeblinks were scored offline using the raw, rectified EMG signal. Prestartle EMG activity was defined as occurring 100 msec before startle stimulus onset. Peak startle activity was defined as a 20 msec average of the peak activity (10 msec pre-, 10 msec postpeak) occurring within a window of 20–120 msec after startle stimulus onset. Eyeblink amplitude was the difference between the peak startle activity and the prestartle EMG activity. Startle eyeblink modification scores were then calculated as percent change scores: [(prepulsed startle – startle alone) / (startle alone)] * 100. Thus, a negative percent change score indicates PPI, whereas a positive percent change score indicates PPF. Percent change units are preferred over difference scores because difference scores in absolute µV units are correlated with baseline startle blink amplitude, whereas percent change scores are not, removing any dependence on baseline startle amplitude (Jennings et al 1996).

Results

Subject Exclusions

Before any statistical analysis, subjects with blink amplitudes less than an average of 2.0 µV to startle-alone trials (based on the average of all 15 ITI startle-alone trials) were considered nonresponders and were excluded from further analysis (14 patients, 7 siblings, and 6 control subjects met this criterion). The following number of subjects comprised each group after exclusions: 76 (2 female) patients, 36 (19 female) siblings, and 41 (22 female) normal control subjects.

Demographic Data

Descriptive data on the demographics of the schizophrenia patients, siblings, and control subjects are presented in Table 1. The groups differed in age [F(2,150) = 9.69, p < .001]; siblings and control subjects did not differ in age, nor did patients and siblings, but schizophrenia patients were older than the control subjects. Although there were significant age differences across groups, age, which ranged from at least 21–50 years in each group, did not correlate with any of the dependent variables in any group (p > .30 in all cases). Therefore, it appears that SEM is unrelated to age in the age range of these subjects, and it is unlikely that age can explain any group differences. There were also significant gender differences across the three groups, with the schizophrenia patients having a higher proportion of men than the siblings or control subjects (X² = 48.50, p < .001). The gender distributions were comparable for the siblings and the control subjects. Possible effects of gender differences are discussed later. There were no significant correlations between PPI and PPF with BPRS scores. There was also no significant effect of patients’ type of medication (i.e., atypical vs. typical antipsychotics) on PPI or PPF.

Baseline Startle Amplitude

Baseline startle amplitude and habituation for the 15 ITI startle-alone presentations were examined to determine if the groups differed. Greenhouse–Geisser corrections (ε) were used to adjust for Type I error probabilities. We report the uncorrected degrees of freedom and the Greenhouse–Geisser corrected probability levels for all analyses that have more than two levels of repeated measures. Results of a repeated measures analysis of variance (ANOVA) revealed no significant group differences (F < 1; an a priori significance level of .05 was used in this and all other analyses). Results also showed a significant effect of block [F(14,2100) = 17.14, p < .001, ε = .635], indicating that startle reactivity decreased throughout the session; however, the block effect did not interact with group, suggesting that all three groups showed equal habituation. The mean and SD baseline startle amplitude for each group are seen in Table 1.

Prepulse Inhibition

The PPI scores were analyzed with a 3 (group) × 2 (prepulse duration) × 2 (block) mixed ANOVA. Results showed a main effect of prepulse duration [F(1,150) = 49.46, p < .001], and a main effect of block [F(1,150) = 19.93, p < .001]. There were no other main effects or interactions. The main effect of prepulse duration was due to discrete prepulses producing significantly greater prepulse inhibition (~65.44%) than continuous prepulses (~49.36%). The main effect of block is due to greater PPI seen in the first block (~63.33%) versus the second block (~51.47%). Although there were few women in the patient sample, there were adequate numbers in the sibling and control groups, and gender was included as a separate group factor. Results revealed
no significant gender main effects or interactions. Group means, averaged over trial block, for PPI can be seen in Figure 1. All three groups produced PPI that was significantly different from zero ($p < .05$ in all groups).

**Prepulse Facilitation**

The PPF scores were analyzed with a 3 (group) × 2 (prepulse duration) × 2 (block) mixed ANOVA. Results showed a main effect of prepulse duration ($F(1,150) = 9.66, p < .01$), a main effect of block ($F(1,150) = 12.94, p < .001$), and a significant group effect ($F(2,150) = 5.74, p < .01$). There were no significant interactions.

The significant block effect was due to greater PPF in the later (24.76%) versus earlier trial block (1.59%). During the first block, PPF was not significant (i.e., significantly different from zero) overall or in any individual group. This effect was expected based on a block effect in a previous study of normal college students (Schell et al. 2000) that used the same procedures as our study. Therefore, the data were reanalyzed only for the second block, where significant overall PPF occurred. There was a significant main effect of prepulse duration ($F(1,150) = 6.93, p < .01$) and a significant group effect ($F(2,150) = 5.14, p < .01$). The prepulse main effect was due to continuous prepulses generating significantly larger prepulse facilitation (36.60%) than discrete prepulses (12.92%). The significant group effect can be seen in Figure 1. Using Duncan’s Range test for multiple comparisons, the normal control subjects produced significantly greater PPF (47.00%) than either the patients (9.21%) or the siblings (18.06%); patients and siblings were not significantly different. Only the normal control subjects ($t(40) = 3.49, p < .05$) and siblings ($t(35) = 2.15, p < .05$) produced PPF that was significantly different from zero. As with the PPI data, gender was added as a group variable; there were no main effects or interactions with gender.

To further explore possible effects of gender, we analyzed the data of the second block for the siblings and control subjects only because these groups had comparable gender distributions with larger group × gender sample sizes. We found no significant gender effects or interactions with gender. Therefore, it is unlikely that the group differences observed are due to a gender effect.

**Discussion**

The three major findings of this paper are the following: 1) deficient PPF was found in schizophrenia patients and their siblings; 2) intact PPI was found in schizophrenia patients and their siblings, a finding contrary to many published studies finding PPI deficits in such groups; and 3) these findings were obtained regardless of the duration of the prepulse (i.e., discrete white noise vs. continuous tone).

The principal new finding of this study was the deficient PPF exhibited by both schizophrenia patients and their siblings. We believe this is the first study to show PPF deficits in these groups. Both patients and siblings showed significantly less PPF than control subjects, and the patients and siblings did not differ in their amount of PPF. These results suggest that the deficit in PPF in schizophrenia is not due solely to the clinical presence of the disease. Instead, the deficient PPF in patients and siblings suggests a deficit in generalized alerting or orienting that may be a possible vulnerability marker for schizophrenia. If these findings are replicated, PPF may be another example of a psychophysiological endophenotypic markers for schizophrenia, similar to P50 gating (Siegel et al. 1984), P300 (Turetsky et al. 2000), mismatch negativity (Michie et al. 2002), smooth-pursuit eye tracking (Iacono et al. 1992), and perhaps PPI (Cadenhead et al. 2000).

Orienting deficits are seen widely in schizophrenia patients, in response systems as diverse as skin conductance (Bernstein et al. 1982; Dawson et al. 1994) and mismatch negativity (Shelley et al. 1991). Deficits in orienting may point to deficiencies in the ability to process salient environmental stimuli (Dawson and Nuechterlein 1984); however, these deficits have rarely been studied using PPF as an index of orienting. The failure to find PPF deficits in schizophrenia patients in the only prior study that examined PPF (Braff et al. 1978) may have been due to several important experimental differences, such as lead interval (2000 msec as opposed to 4500 msec) and how startle was measured (by potentiometer as opposed to EMG). Our study demonstrates that it is possible to detect deficits in PPF in schizophrenia patients, even in the absence of PPI deficits. It also demonstrates the need to gain a better understanding of the experimental conditions under which PPF deficits can be observed and replicated and whether PPF reflects deficits in generalized orienting and alertness. For instance, we observed significant PPF among control subjects only in the second trial block, which does not seem consistent with the view that PPF reflects generalized orienting or alertness processes.

Despite the notable findings with PPF, we were unable to find PPI deficits in schizophrenia patients and their siblings using either discrete white noise or continuous-tone prepulses. Other studies with schizophrenia patients have found PPI deficits at the 120-msec lead interval, as well as shorter intervals (e.g., Braff et al. 1992, 2001; Cadenhead et al. 2000; Kumari et al. 2000). The failure to find PPI deficits in schizophrenia patients does not seem to be due to major differences in subject characteristics (e.g., age and illness duration) between our studies and others that have yielded positive results (e.g., Braff et al. 1999, 2001); however, as mentioned previously, many of the studies reporting positive findings of PPI deficits in patients, and the one study of siblings, used experimental procedures that differed from those used in our experiment. We measured EMG from the left eye, whereas most studies that have found PPI deficits in schizophrenia measured startle eyelink from the right eye (e.g., Braff et al. 1992, 1999; Cadenhead et al. 2000; Kumari et al. 2000 but for an
exception see Grillon et al 1992). Also, we did not use any imposed background noise, whereas studies that have reported PPI deficits in schizophrenia patients (Braff et al 1991, 2001; Cadenhead et al 2000) have typically used a relatively strong background noise (i.e., 70 dB) with short duration prepauses (20 msec) that usually were 8–16 dB increases over the imposed background noise. Based on studies from our laboratory and others (e.g., Ford et al 1999), it appears that background noise may make the auditory prepauses difficult to detect, especially when they are short-duration discrete changes. The possibility that PPI deficits in schizophrenia are seen primarily when prepauses are near threshold levels was suggested by Judd et al (1992).

The study by Cadenhead et al (2000) found PPI deficits in siblings under one specific condition, while using a 30-msec lead interval, measuring EMG from the right eye, and using a constant background noise. Our study only had one early lead interval (120 msec), measured EMG from the left eye, and had no background noise. Cadenhead et al (2000) suggested that measuring PPI from the right eye taps into a left temporal lobe deficit that is seen in other different measures (e.g., Gur and Chin 1999; Salisbury et al 1998). It is entirely possible that we would have found PPI deficits in patients and their siblings had we used the same experimental procedures as Cadenhead and colleagues.

These results indicate the value of further explorations using PPI and PPF to study schizophrenia and as endophenotypic markers for schizophrenia. We found for the first time deficits in PPF in schizophrenia patients and their siblings. These results point to the possibility that PPF deficits may be an additional index of a vulnerability factor for schizophrenia. It is also important to note that PPF deficits, similarly to PPI deficits, may not be unique to schizophrenia, and these findings should be studied in other psychiatric control subjects. It is possible, indeed likely, that PPF is seen only under certain experimental conditions, similar to PPI. This study strongly encourages further examination of the specific experimental conditions under which PPI and PPF deficits are seen in schizophrenia and at-risk populations.

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