On the clinical and cognitive meaning of impaired sensorimotor gating in schizophrenia

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Abstract

Schizophrenia patients have been shown to have a defective sensorimotor gating process as indexed by impaired prepulse inhibition of the startle eyeblink reflex. Moreover, we have previously reported that schizophrenia patients have dysfunctional attentional modulation of prepulse inhibition. The present experiment combined our previous sample of 14 schizophrenia outpatients and 12 demographically matched control subjects with a new sample of 10 outpatients and 6 control subjects. All participants performed a tone-length judgement task that involved attending to one pitch of tone (the attended prepulse) and ignoring another pitch of tone (the ignored prepulse). During this task the acoustic startle eyeblink reflex was electromyographically recorded from the orbicularis oculi muscle. The results replicated the finding of impaired attentional modulation of prepulse inhibition in the new sample of schizophrenia outpatients compared to demographically matched control subjects. Specifically, the new control group exhibited greater startle modification during the attended prepulse, whereas the new patient group failed to show this differential effect. In addition, impaired prepulse inhibition following the attended prepulse was significantly correlated with heightened delusions, conceptual disorganization, and suspiciousness as measured with the expanded Brief Psychiatric Rating Scale. These correlations were significant with prepulse inhibition to the attended prepulse but not with prepulse inhibition to the ignored prepulse. Impaired prepulse inhibition was not correlated with negative symptoms. All in all, the results support the hypothesis that impaired attentional modulation of startle prepulse inhibition reflects basic neurocognitive processes related to thought disorder in schizophrenia. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Impaired sensory gating is hypothesized to be a frequent psychophysiological characteristic of schizophrenia (American Psychiatric Association, 1994, p. 280) that could theoretically lead to a variety of severe dysfunctions in perception, attention, and thinking (McGhie and Chapman, 1961). Specifically, deficits in the ability to selectively filter out irrelevant external and internal stimuli may produce misperceptions, a sense of sensory flooding, increased distractibility, and disorganized and fragmented thinking (Braff et al., 1992).

Prepulse inhibition (PPI) is a psychophysiological index of sensorimotor gating that has been used with schizophrenia patients. PPI is defined as the reduction of the amplitude of the startle reflex (usually the eyeblink reflex in human subjects) when a non-startling ‘prepulse’ precedes the startling pulse by an interval of approximately 30–300 ms (see review by Blumenthal, 1999). The reduction in the startle reflex is thought to be due to a momentary inhibitory sensorimotor gating process elicited by the prepulse that serves to protect the earliest stages of processing of the prepulse. In contrast, if a non-startling prepulse precedes the startle-eliciting stimulus by a longer lead interval (e.g. 2000 ms), the startle reflex is often enhanced (prepulse facilitation, PPF) (see review by Putnam and Vanman, 1999). PPF is thought to be due to a combination of arousal and sustained attention elicited by the prepulse. Thus, PPI and PPF represent different neurocognitive processes (Graham, 1975; Filion et al., 1998). Most relevant to the present article, the degrees of both PPI and PPF have been shown to be modulated in normal subjects by attention to the prepulse (for reviews, see Dawson et al., 1997; Filion et al., 1998).

Both PPI and PPF have been found to be impaired in schizophrenia patients. PPI abnormalities were first demonstrated in schizophrenia patients by Braff and his colleagues (Braff et al., 1978, 1992). In a passive paradigm in which attention to the prepulse was not manipulated, Braff et al. (1992) suggested that these results reflected an impairment in automatic, preattentive sensorimotor gating relevant to the vulnerability to schizophrenia.

More recent research has shown that the attentional modulation of PPI and PPF is impaired in medicated schizophrenia patients (Dawson et al., 1993) and unmedicated schizophrenia patients (Hazlett et al., 1998). In these studies, schizophrenia patients and normal control subjects were instructed to attend to one type of prepulse (e.g. high pitch tone) and not attend to another (e.g. low pitch tone). Both short lead intervals (60, 120, and 240 ms in Dawson et al.; 120 and 240 in Hazlett et al.) and long lead intervals (2000 ms in Dawson et al.; 4500 ms in Hazlett et al.) were studied. In both studies, normal control subjects showed greater PPI following the attended prepulse than the ignored prepulse only at the 120-ms lead interval, and greater PPF following the attended prepulse than the ignored prepulse at the long lead intervals. In contrast to the control subjects, the schizophrenia patients failed to show differential PPI and PPF during the attended and ignored prepulses. These results are consistent with five additional studies of normal participants (Filion et al., 1993, 1994; Jennings et al., 1996; Schell et al., 1995; Schell et al., in press 1995). The finding that attentional modulation of PPI occurs at the 120-ms lead interval, but not at 60 or 240 ms, suggests that the ‘attention to prepulse’ paradigm taps time-locked attentional processes in normal subjects. The patients, on the other hand, showed significant overall PPI and PPF but failed to respond differentially to the attended prepulse and the ignored prepulse at any lead interval. Dawson et al. (1993) and Hazlett et al. (1998) therefore concluded that schizophrenia patients were impaired in controlled attentional processes rather than automatic processes in the ‘attention to prepulse’ paradigm.

The first goal of the present study was to replicate in an independent sample of recent-onset schizophrenia outpatients the startle modification findings in the ‘attention-to-prepulse’ paradigm. A second broader goal of the present study was to
determine whether impaired startle modification is, as theorized, associated with certain schizophrenic symptoms. To date, only a few studies have examined this relationship with PPI in a passive paradigm, and no study has examined this relationship with PPI of startle blink in the ‘attention to prepulse’ paradigm.

Impaired PPI to a passively attended prepulse was recently reported to be significantly correlated with positive symptoms rated on the Positive and Negative Syndrome Scale (PANSS) (Weike et al., 2000). No significant correlations were found between the amount of PPI and negative symptoms. In contrast Braff et al. (1999) reported that impaired PPI in a passive paradigm was significantly correlated with both positive and negative symptoms measured with the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS). Employing a different approach, Perry and Braff (1994) and Perry et al. (1999) used a passive paradigm and found correlations between impaired PPI at a 120-ms lead interval in a passive paradigm with thought disorder measured in schizophrenic patients with the Rorschach Inkblot Test. All in all, the results suggest that impaired PPI may be related to positive symptoms (and possibly negative symptoms) in general, and thought disorder in particular in schizophrenic patients.

In the present study, key psychiatric symptom dimensions, particularly those related to thought disorder, were examined in schizophrenic outpatients in relation to PPI and PPF obtained in the ‘attention-to-prepulse’ paradigm. Symptoms were rated with an expanded 24-item version of the Brief Psychiatric Rating Scale (BPRS) based on information obtained in a brief semi-structured interview (Lukoff et al., 1986). The factor structure of the expanded BPRS in recent-onset schizophrenia outpatients, a population from which the present sample was drawn, has been reported by Ventura et al. (1999). There are four factors: (1) Positive Symptoms (e.g. unusual thought content, hallucinations, and conceptual disorganization); (2) Negative Symptoms (e.g. blunted affect, motor retardation); (3) Depression/Anxiety; and (4) Agitation/Hostility. This identified factor structure allowed us to investigate the specific domains of symptoms that might be related to a breakdown in sensorimotor gating, particularly positive symptoms vs. negative symptoms.

In summary, there were two specific goals of the present study. The first goal was to replicate the finding of impaired attentional modulation of PPI and PPF in a new sample of recent-onset schizophrenia outpatients, relative to demographically matched normal control subjects. The second goal was to determine the symptomatic correlates of impaired startle modification, and its attentional modulation, among schizophrenia patients. It was hypothesized that the original findings regarding impaired attentional modulation of PPI at 120 ms and PPF at 2000 ms in schizophrenia patients would be replicated, and that the impairments in PPI and its attentional modulation would be correlated with positive symptoms related to thought disturbance.

2. Methods

2.1. Participants

Data are reported for a total of 24 schizophrenia patients and 18 demographically matched normal control subjects. Data from an additional 15 participants (10 patients and 5 control subjects) were discarded because of either failure to blink on more than 1/3 of the presentations of the loud noise (n = 3), experimenter error (n = 1), equipment malfunctions (n = 8), drug abuse (n = 1), excessive muscle artifact (n = 1) or psychopathology in a control participant (n = 1).

Of the 24 patients, startle data are reported separately for 14 ‘old’ participants (i.e. those previously reported by Dawson et al., 1993), and for 10 ‘new’ patients added to test the replicability of the earlier findings. Of the 18 control subjects, startle data are reported separately for 12 ‘old’ participants and for 6 ‘new’ control subjects.

Symptomatic correlates, however, are reported for the combined ‘old’ and ‘new’ samples. The schizophrenia patients were outpatients at the UCLA Aftercare Program taking
part in a longitudinal study of the early phases of schizophrenia (Nuechterlein, et al., 1992). The patients were diagnosed as having schizophrenia \((n = 21)\) or schizoaffective disorder, mainly schizophrenic \((n = 3)\), by Research Diagnostic Criteria (Spitzer et al., 1978). All but one of the patients was on a low-to-moderate dose of injectable fluphenazine decanoate (between 6.25 and 18.75 mg of Prolixin) at the time of the test session (see Nuechterlein et al., 1992, for treatment details).

The normal control subjects were also participants in the longitudinal research project and were recruited primarily through newspaper and periodical advertisements. They had been interviewed with an expanded lifetime version of the Present State Examination (PSE) and family history questions to exclude those with a history of major psychiatric disorder in self or in their first-degree relatives. The present enlarged sample of patients (21 males and 3 females) and matched control subjects (14 males and 4 females) did not differ in age (patients: \(M = 27.2, \text{S.D.} = 6.3\); control subjects: \(M = 25.7, \text{S.D.} = 4.1\)), although the patients did have somewhat fewer years of education (patients: \(M = 12.2, \text{S.D.} = 1.7\); control subjects: \(M = 13.6, \text{S.D.} = 1.7\)), \(t (40) = 2.39, P < 0.05\).

2.2. Design

The study employed a \(2 \times 2 \times 4\) mixed factorial design conducted separately on the ‘old’ sample and ‘new’ sample. The first variable consisted of two groups (schizophrenia patients vs. normal control subjects), the second variable consisted of two types of prepulses (attended vs. ignored), and the third variable consisted of four lead-intervals (60, 120, 240, and 2000 ms).

2.3. Procedure

2.3.1. Symptom measures

Symptoms were rated on seven-point scales with the expanded 24-item version of the BPRS (Lukoff et al., 1986; Ventura et al., 1993). The BPRS was administered an average of 7.7 days (range 1–23 days) from the day of the startle modification test. The BPRS Total Psychopathology scores ranged from 26 to 54, \(M = 36.2, \text{S.D.} = 8.9\), with a minimum possible rating of 24.

2.3.2. Tone-length judgment task

Participants were instructed that their task was to listen to a series of high and low pitch tones presented through headphones, to attend to and count silently the number of ‘longer than usual’ tones of one pitch, and to simply ignore the tones of the other pitch (the attended pitch was counterbalanced across participants). The standard length was 5 s and the longer than usual duration was 7 s. Participants also were told that a brief loud noise burst would be presented occasionally throughout the tone-counting task, but that it was unrelated to the task and could be ignored. To emphasize the importance of the length–judgment task, a monetary reward was offered for a correct count of the longer than usual tones of the designated pitch.

All subjects were first presented samples of the high and low pitch tones and of the loud noise. The main portion of the test session then consisted of a total of 48 tone trials: 24 high and 24 low pitch tones in a mixed, fixed semi-random order with inter-tone intervals ranging between 20 and 30 s. Of the 24 tones of each pitch, 16 were followed by the startle-eliciting noise. Of these 16 trials, there were four presentations of the startle-eliciting noise at each of four lead-intervals: 60 ms, 120 ms, 240 ms, and 2000 ms. The remaining eight trials without startle-eliciting noises were presented in an intermixed order.

In addition to presentation of the startle noises at critical lead-intervals, startle stimuli were also presented at pre-selected points during the inter-tone intervals in order to provide a baseline measure of startle amplitude with which to compare blink amplitudes elicited during the prepulses. Specifically, startling noises were presented during 75% of the inter-tone intervals, with no more than one startle stimulus presented during any inter-tone interval.

2.4. Recording and scoring of startle modification

Startle eyeblink amplitude was measured as
electromyographic activity (EMG) from two miniature silver–silver chloride electrodes (4 mm in diameter), filled with TECA electrode paste, placed over the orbicularis oculi muscle of the left eye. One electrode was centered below the pupil and the other approximately 10 mm lateral to the first. The EMG signal was fed into a Grass 7P3 wide band preamplifier/integrator and a 7DA driver amplifier. Eyeblinks were recorded at full wave rectification and with integration at a time constant of 20 ms. The integrated EMG signal was digitized at a rate of 1000 Hz for 200 ms preceding and 300 ms following the presentation of each startle-eliciting loud noise. The startle eyeblink amplitude was then scored off-line with a modification of the program by Balaban et al. 1986. Startle eyeblink amplitude scores were converted to \( \mu \)V units, and differences were then computed between the mean baseline inter-tone interval eyeblink amplitude and the during-tone eyeblink amplitudes separately for each trial block. Because difference scores in absolute \( \mu \)V units were highly correlated with baseline startle blink amplitude, as we have found in previous studies Jennings et al., 1996, the difference scores were converted to percent of baseline startle amplitude, which removed the dependence upon baseline in the present data. A positive startle percent change score indicates startle facilitation relative to baseline PPF, whereas a negative score indicates startle inhibition relative to baseline (PPI).

2.5. Experimental stimuli

The attended and ignored prepulses consisted of 800-Hz and 1200-Hz tones, 5 s or 7 s in duration, presented at an intensity of 70 dB (A). The tones were generated using a Fordham (FG-801) signal generator, with 25-ms rise times controlled by a Coulbourn S48-04 rise/fall gate. The startling stimulus consisted of a 100-dB (A) white noise, 50 ms in duration. The startling noise was generated by a Grason-Stadler 901B noise generator and was gated at a near instantaneous rise time. All of the auditory stimuli were presented binaurally through headphones (Realistic NOVA-40 model). The onsets, durations, and intervals between stimuli were controlled on-line by a laboratory computer.

3. Results

3.1. Attentional modulation of PPI and PPF

In order to have a strong test of the independent replication of the earlier reported attentional modulation effects on PPI and PPF, the ‘old’ and ‘new’ samples were analyzed independently. Thus, a two (schizophrenic group vs. control group) × two (attended prepulse vs. ignored prepulse) ANOVA was computed on the percent change scores for each of the four lead intervals (60, 120, 240, and 2000 ms), separately for the ‘old’ and ‘new’ samples. Each lead interval was analyzed separately because different cognitive processes are hypothesized to be involved at each interval, with attention effects predicted only at 120 and 2000 ms and not at 60- and 240-ms lead intervals. Consistent with the predictions and with previous results, the ANOVAs conducted on the 60- and 240-ms lead intervals revealed neither significant Group effects, nor Attention main effects, nor Group × Attention interaction effects. Thus, there were no attentional modulation effects at 60 ms and 240 ms for either the patients or the control subjects in either the ‘old’ or ‘new’ samples.

In contrast, as shown in Fig. 1, there was significant attentional modulation of PPI at the 120-ms lead interval in both the ‘old’ and ‘new’ control samples. The 2 × 2 ANOVAs revealed significant Attention main effects in both the ‘old’ sample \( (F_{1,24} = 14.34, P < 0.001) \) and the ‘new’ sample \( (F_{1,14} = 5.74, P < 0.04) \). Most important, significant Group × Attention interaction effects were found in both samples \( (F_{1,24} = 6.10, P < 0.03, \) for the ‘old’ sample and \( F_{1,14} = 6.57, P < 0.03 \) for the ‘new’ sample). As can be seen in Fig. 1, the interaction effects reflect the finding that the control groups showed significantly greater PPI to the attended prepulse than to the ignored prepulse \( (t_{11} = 5.03, P < 0.001, \) for the ‘old’ sample and \( t_s = 3.35, P < 0.03, \) for the ‘new’ sample), whereas the patient groups failed to show signifi-
significant differential PPI. In fact, 17/18 control subjects exhibited greater PPI following the attended prepulse than the ignored prepulse, whereas only 12/24 schizophrenia patients showed this direction of differential responding. As suggested by inspection of Fig. 1, the major source of the difference between patients and control subjects was in their PPI to the attended prepulse and not to the ignored prepulse. Thus there was clear attentional modulation of PPI in both control samples, with enhanced PPI to the attended prepulse relative to the ignored prepulse, whereas such modulation was absent in both patient samples.

Similarly at the 2000-ms lead interval, as shown in Fig. 2, there is evidence of significant attentional modulation of PPF in both control groups, but not in either patient group. The $2 \times 2$ ANOVAs revealed significant Attention main effects in the ‘old’ sample ($F_{1,24} = 11.18, P < 0.003$), and in the ‘new’ sample ($F_{1,14} = 4.83, P < 0.05$). However, a significant Group $\times$ Attention interaction effect was found only in the ‘old’ sample, $F_{1,24} = 6.80, P < 0.02$. Although the interaction effect was not significant in the ‘new’ sample, it can be seen in Fig. 2 that attentional modulation of PPF was significant in both the ‘old’ and ‘new’ control samples ($t_{11} = 2.99, P < 0.02$ for the ‘old’ sample and $t_{2} = 2.83, P < 0.04$ for the ‘new’ sample), but not in either patient sample. Again, the major difference between patients and control subjects was in their response following the attended prepulse and not in their response following the ignored prepulse.

3.2. Symptomatic correlates of attentional modulation

We predicted that impaired PPI at the 120-ms lead interval following the attended prepulse would be related to the Positive Symptom factor of the BPRS. PPI at 120 ms following the ignored prepulse was also examined for exploratory purposes. PPF at 2000 ms following the attended prepulse also was abnormal in these patients and therefore was examined. However, as this abnormality may reflect a sustained attention process separate from sensorimotor gating, we did not hypothesize that PPF would be correlated with thought disturbance. In addition, the relationship of these PPI and PPF measures to other BPRS factors was examined to determine whether their influence would extend to symptom severity of all types.

Table 1 shows the intercorrelations between the PPI and PPF measures and the four BPRS symptom factors the means for the four factors were: Positive Symptoms 1.5; Negative Symptoms
Table 1
Correlations between BPRS factors and startle modification at 120- and 2000-ms lead intervals for attended and ignored prepulses

<table>
<thead>
<tr>
<th>Stimulus and lead interval</th>
<th>Positive symptoms</th>
<th>Negative symptoms</th>
<th>Agitation-hostility</th>
<th>Depression/anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI Attended (120 ms)</td>
<td>0.41*</td>
<td>−0.16</td>
<td>0.37</td>
<td>0.41*</td>
</tr>
<tr>
<td>PPI Ignored (120 ms)</td>
<td>0.14</td>
<td>−0.04</td>
<td>0.29</td>
<td>0.13</td>
</tr>
<tr>
<td>PPF Attended (2000 ms)</td>
<td>0.09</td>
<td>−0.13</td>
<td>−0.04</td>
<td>−0.13</td>
</tr>
<tr>
<td>PPF Ignored (2000 ms)</td>
<td>−0.06</td>
<td>−0.05</td>
<td>0.04</td>
<td>−0.10</td>
</tr>
</tbody>
</table>

*P < 0.05.

2.1: Depression/Anxiety 1.6; and Agitation/Hostility 1.3. Two of the correlations were statistically significant, and both involve PPI at 120 ms to the attended prepulse. As predicted, impaired PPI at 120 ms following the attended prepulse (more positive scores) was associated with heightened scores on the Positive Symptom factor. It was also correlated with higher scores on the Depression/Anxiety factor. Because we had previously hypothesized that the difference between the PPI to attended and ignored prepulses at the 120-ms lead interval specifically indexes controlled attentional processes (Dawson et al., 1997), we next correlated this difference score with the two BPRS factors showing significant correlations with the attended prepulse. The BPRS correlations with the attend–ignore difference scores revealed the same relationships as did the simple attended PPI scores, although only at the 0.06 probability level with the ‘Positive Symptoms’ factor. Thus, patients who exhibited a more normal difference score (PPI during the attended prepulse greater than PPI during the ignored prepulse) also exhibited lower scores on the Depression/Anxiety and Positive Symptom factors. None of the correlations at the 2000-ms lead interval, nor any of the correlations with PPI during the ignored prepulse, were significant.

We predicted that the strongest correlations with positive symptoms would be with PPI to the attended prepulse. The obtained correlations in Table 1 are consistent with this prediction. In order to determine if the correlation we predicted to be significant differed from the others not predicted to be significant, three specific one-tailed t-tests for differences between overlapping correlations were performed (McNemar, 1962). The correlation between PPI at 120 ms during the attended prepulse and positive symptoms was significantly larger than that for PPI during the attended prepulse and negative symptoms (t21 = 1.82, P < 0.05), for PPI during the ignored prepulse and positive symptoms (t21 = 2.66, P < 0.01), and for PPF at 2000 ms during the attended prepulse and positive symptoms (t21 = 2.44, P < 0.02).

To determine the specific items that accounted for the significant associations of PPI with the BPRS factors, we next correlated each of the items that loaded on the Positive Symptoms factor and the Depression/Anxiety factor with PPI to the attended prepulse. With the Positive Symptoms factor, two items were significantly correlated (r = 0.52, P < 0.01, for unusual thought content and r = 0.44, P < 0.05, for conceptual disorganization), and one approached significance (r = 0.38, P < 0.06, for suspiciousness). Thus the most delusional, disorganized, and suspicious patients exhibited the least amount of PPI to the attended prepulse. For the Depression/Anxiety factor, none of the individual items were significantly correlated with PPI, although they all showed weak-to-moderate correlations (r values ranged from 0.30 to 0.36).

3.3. Task performance data

The participants’ task was to count the longer than usual (7 s rather than the usual 5 s) occurrences of one tone pitch and to simply ignore the tones of the other pitch. There were 10 longer than usual occurrences of the attended tone pitch.
The majority of both groups performed well on the task, with 62% of all of the patients (15 of 24), and 89% of all of the control subjects (16 of 18) scoring within +/− 1 of the correct answer. However, the patients’ overall average error score was significantly greater than that of the control subjects (patients, M = 2.08, S.D. = 2.4; control subjects M = 0.67, S.D. = 2.3), t_{18.0} = 2.29, P < 0.03. In order to determine whether the impaired startle modulation simply reflected gross inattention to the prepulses, we next analyzed the PPI and PPF discrimination between attended and ignored prepulses for the subgroups of 15 patients and 16 control subjects who had performed well on the task (the ‘old’ and ‘new’ samples were combined for these analyses in order to have sufficiently large subsamples of good performers). For the good performing control subjects, the mean discrimination scores between attended and ignored prepulses remained significant for PPI at 120 ms and for PPF at 2000 ms, t_{14} = 5.97 and 3.26, P < 0.01. For the good performers among patients, the discrimination scores remained non-significant. Moreover, the difference between the PPI discrimination scores of the good performers among control subjects and patients was significant, t_{14} = 2.93, P < 0.01, and the PPF difference score approached significance, t_{14} = 1.97, P < 0.06. Thus, even for the subgroup that performed the tone-counting task well, schizophrenia patients showed impaired attentional modulation of PPI at 120 ms and PPF at 2000 ms.

4. Discussion

The two principal findings of the present study are: (1) impaired attentional modulation of PPI and PPF in schizophrenia outpatients was replicated in a new sample; and (2) impaired PPI to an attended prepulse was significantly correlated with higher levels of unusual thought content, conceptual disorganization, and suspiciousness. Each of these findings is discussed in turn below. First, the findings of Dawson et al. (1993) and Hazlett et al. (1998) were replicated, indicating that this sample of schizophrenia patients displayed normal PPI and PPF to ignored prepulses, but abnormal PPI and PPF to attended prepulses. These findings are important because they suggest that controlled attentional processes fail to modulate sensorimotor gating mechanisms following the task-significant attended prepulse in schizophrenia. Thus, we hypothesize that the normal enhanced protection of processing of the attended stimuli fails to occur in schizophrenia patients, which could lead to sensory overload at the most critical times. Moreover, sustained focused attention to the attended prepulse at 2000 ms also appears to be impaired in schizophrenia patients. These impairments are found even in the subgroup of patients who perform well on the tone duration judgment task, suggesting that the failures to attentionally modulate startle are more sensitive indexes of the underlying processes than is behavioral performance on the counting task. The present findings are also consistent with a recent report that schizophrenia patients exhibit impaired attentional modulation of inhibition of the R2 component of the electrically elicited eyeblink reflex when attention is focused on the reflex-eliciting stimulus (Meincke et al., 1999).

The lack of differences between normal control subjects and schizophrenia patients in PPI to the ignored prepulse suggests the possibility that the basic automatic sensorimotor gating mechanism is functioning normally in this group of patients. This conclusion is consistent with the conclusions of previous studies that employed the active ‘attention-to-prepulse’ paradigm (Dawson et al., 1993; Hazlett et al., 1998), but is contrary to conclusions reached in studies that employed a passive attention paradigm (e.g. Braff et al., 1992). Dawson et al. (1993) speculated that the differences between our results and those of Braff and colleagues could be due to the nature of the patient sample, the nature of the task, or stimulus parameter differences. For example, the patients studied by Braff et al. (1992) were older, had longer durations of illness, were more symptomatic, and were more heavily medicated than those studied here. Procedurally, Braff et al. (1992) did not require any attention to the prepulse, whereas the tone-length duration task employed here required at least enough processing of the ignored prepulse for it to be identified as the task-irrele-
vant stimulus. Potentially important stimulus parametric differences also exist between the laboratories. Braff et al. (1992) used short (20 ms) increases in a 70-dB background white noise as the prepulses, whereas we used long duration pure tones presented against an ambient background. All in all, Braff et al. (1992) presented difficult to detect prepulses to older chronic symptomatic patients without any instructions to attend to the stimuli. We, on the other hand, presented easy to detect prepulses to relatively young and relatively asymptomatic schizophrenic patients with instructions to attend to the stimuli. Any of these variables, or combination of variables, could conceivably account for the differences in results.

The second principal finding of the present study was that PPI to the attended prepulse, but not to the ignored prepulse, was significantly correlated with BPRS measures of disturbances in both content and form of thought. That is, PPI at 120 ms following the attended prepulse was most impaired in patients with higher levels of unusual thought content (delusions), conceptual disorganization, and suspiciousness as assessed by the expanded BPRS. Conceptual disorganization is rated high on the expanded BPRS when speech is confused, disconnected, or disorganized (Ventura et al., 1993). Conceptual disorganization (‘associative disturbance’) was hypothesized by Bleuler (1911/1950) to be a fundamental and primary dysfunction in schizophrenia, an emphasis that contemporary cognitive neuroscience has continued to support (Spitzer, 1997). Patients with poor sensorimotor gating, as indicated by impaired PPI, would be predicted to fail to inhibit irrelevant intrusions and therefore to display fragmented and disorganized speech (Braff et al., 1992). People with normal gating are able to inhibit irrelevant intrusions, whereas patients with severely impaired gating may be less able to do so. Thus, the correlation of PPI with conceptual disorganization is consistent with the view that PPI reflects sensorimotor gating and protection of cognitive processes, although the fact that this correlation is specific to PPI to the attended prepulse is not directly predictable from these conceptions.

Why in the present study do correlations occur specifically with impaired PPI to attended pre- pulses and not with ignored prepulses? It is hypothesized that PPI to attended prepulses reflects the ability to selectively protect the processing of important sensory information. According to this view, PPI to the attended prepulses reflects the ability to focus on what is important when it is important. Individuals who are less able to protect information processing when it is most needed would presumably show the greatest tendencies toward disconnected speech and perhaps delusional thought. In relatively remitted patients who are required to attend to easily detected prepulse stimuli, the deficit in PPI to the attended prepulse may represent a core dysfunction which correlates with residual symptoms of thought disorder. When patients are more symptomatic, the PPI abnormality may worsen to the point where it appears even with prepulses in a passive paradigm, particularly when the prepulses are brief and difficult to detect (e.g. Braff et al., 1992; and in a subsample of patients with more severe positive symptoms studied by Weike et al., 2000).

The association of PPI with delusions and suspiciousness is not as immediately interpretable as is the correlation with conceptual disorganization. Delusions are usually considered to be due to faulty inferential thinking. However, an alternative view is that delusions, especially paranoid delusions of the type exhibited by patients in the present study, are rationally developed beliefs to explain abnormal perceptual experiences (Maher, 1974). Maher hypothesized that patients with a disorder of sensory gating suffer from intense and confusing perceptual experiences that demand an explanation. The fact that these perceptual experiences do not seem to be shared by others raises the possibility that either other people are lying (which may lead to delusions of persecution) or that one is an extraordinary person selected to have these experiences (which may lead to delusions of grandiosity). Moreover, because no external cause of these unusual perceptual experiences is obvious, the patient may search for invisible mechanisms found in popular science (e.g. cosmic rays) or religion (demonic or divine power). Thus, the correlation of PPI with delusions and suspiciousness is consistent with Maher’s hypothesis.
that delusions arise from normal cognitive mechanisms used to explain unusual, intense perceptive experiences resulting from impaired sensory gating. The correlation of PPI with the Depression/Anxiety factor may similarly arise from deficit PPI indexing an inability to gate intrusive internal stimuli such as ruminative thoughts of guilt, failure, or loss in depression, or anxiety-provoking thoughts.

It is important to note that the absence of significant PPI correlations with some other BPRS factors and items should be interpreted with caution, as the range of some BPRS-rated symptoms was restricted in this sample of clinically stable outpatients. For instance, one cannot determine whether disorientation is associated with impaired startle modification because only one of the 24 patients had any degree of disorientation symptoms at the time of testing. However, the range of negative symptoms, which was not correlated with PPI, was actually greater than the range of positive symptoms, which were significantly correlated with PPI. Thus, the absence of significant correlations with negative symptoms in the present sample was not due to the restricted range of scores, but rather apparently to these symptoms not arising from the failure of gating processes.

An important next step is to relate impaired attentional modulation of PPI to signs and symptoms of schizophrenia in patients who exhibit a wider range of symptom severity, and also to relate impaired PPI with a range of laboratory cognitive measures. This step would aid our understanding of the clinical and cognitive significance of impaired startle modification in schizophrenia. Such research is a critical next step if the measurement of startle modification is to realize its putative potential as an integrative-bridging paradigm across neuroscience, cognitive science, and clinical science (Dawson et al., 1999).

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