Probing attentional dysfunctions in schizophrenia: Startle modification during a continuous performance test

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Abstract

Startle eyeblink modification was measured in 20 relatively asymptomatic medicated schizophrenia outpatients and 18 matched controls in order to test for deficits in early and later stages of attentional processing during a memory-load version of the Continuous Performance Test. Participants viewed a series of digits and pressed a button after the digit 7 of each 3–7 sequence. On some trials, a startling noise burst was presented either 120 or 1200 ms following cues that a response might be needed soon (the digit 3) and also following noncues. Controls showed greater startle inhibition at 120 ms following cue than noncue prepulses, whereas patients showed equal inhibition to both, suggesting a deficiency in allocation of controlled attentional resources in early stages of processing. The patients, however, did show large startle inhibition at 120 ms when a distracting stimulus accompanied the task-relevant cue, unlike the controls, who ignored the distracting stimulus. In contrast, both groups showed equal startle inhibition 1200 ms following cue and noncue prepulses, indicating that later modality-specific attention processes are not impaired in patients during this paradigm. Both groups also showed equal inhibition at 120 ms during passively attended prepulses, suggesting that automatic attentional processes were not impaired in these patients.

Descriptors: Schizophrenia, Selective attention, Prepulse inhibition, Startle eyeblink modification, Continuous performance test, Controlled processing, Automatic processing

Continuous performance tasks (CPTs) are often used to index the attentional dysfunctions well known to be associated with schizophrenia (Nuechterlein, 1991). In such tasks, participants must detect and respond to target stimuli in a continuous train of rapidly and briefly presented stimuli, for instance by pressing a button whenever a “7” appears in a series of rapidly and randomly visually presented single digits. CPTs that add a working memory load to the task, such as instructing the participant to respond only when a “3” (cue) precedes a “7” (target), are more difficult than always responding to a single target (Beck, Bransome, Mirsky, Rosvold, & Sarason, 1956; Nuechterlein, Edell, Norris, & Dawson, 1986). Deficits in schizophrenia patients’ performance on memory-load CPTs occur during symptomatic remission and become more marked during a psychotic episode (Nuechterlein et al., 1992). This pattern of deficits, present in the remitted state and becoming greater in symptomatic states, suggests that the impairment is related to the vulnerability to schizophrenia and may reflect cognitive deficits that mediate symptom formation (Nuechterlein & Dawson, 1984a).

Memory-load CPTs are complex tasks involving a number of cognitive processes. Selective attention must be sustained on the sensory modality (usually visual) in which the stimuli are being presented, external distracting stimuli must be ignored, and the task instructions must be maintained in working memory. Each stimulus must be rapidly detected, encoded as a cue, an appropriate target (i.e., one that was preceded by the cue), an inappropriate target (one that was not preceded by a cue), a noncue or a nontarget. Thus, in the flow of information processing, both early predominately automatic processes (single stimulus detection) and later, predominately controlled processes (modality focus, discrimination between cue, target, and noncue/nontarget stimuli, and overall task instructions) must function effectively; impaired performance could result from a breakdown at any point. Cognitive impairments in schizophrenia have been hypothesized to involve automatic processes (Frith, 1979),
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controlled processes (Callaway & Naghdí, 1982), or both (Nu-echterlein & Dawson, 1984b). In the impaired CPT performance seen in schizophrenia, both early automatic processes such as those involved in stimulus detection and controlled processes such as those involved in cue/noncue discrimination and sustained focused attention may be dysfunctional.

The startle eyeblink modification technique can be used to identify individual processes that may be impaired. Startle eye- blink is a component of the general startle reflex elicited by any rapidly onsetting and intense stimulus, particularly a loud noise. This automatic reflex can be reliably modified by preceding the startle stimulus with a nonstartling stimulus, usually called a lead stimulus or prepulse. If the lead interval between the two stimuli is short (30–500 ms), the startle response is reliably attenuated, a phenomenon called prepulse inhibition (for reviews, see Blum-enthal, 1999; Graham, 1975). Prepulse inhibition (PPI), which typically maximizes 120–250 ms after prepulse onset, is thought to reflect protection of the processing of the prepulse from dis- ruption by the startle stimulus, or sensorimotor gating (Braff & Geyer, 1990; Graham, 1975). PPI occurs whether the startle stimulus and the prepulse are in the same sensory modality or different modalities. Although PPI is considered to be an automatic process, it can be modified by controlled selective attention. Directing attention to prepulses by making them task significant enhances PPI relative to that elicited by prepulses that are not task significant and that can be ignored (Delpezzo & Hof- man, 1980; Filion, Dawson, & Schell, 1993). In selective attention paradigms, the difference in PPI to attended versus ignored prepulses has been interpreted as reflecting controlled processing, or top-down modulation of the automatic PPI pro- cess (Dawson, Schell, Swerdlow, & Filion, 1997). On the other hand, PPI in passive attention tasks is thought to reflect predominately automatic processing (Braff et al., 1978; Braff, Grillon, & Geyer, 1992).

When the lead interval is longer (≥1000 ms), other startle modulation effects appear. In a passive attention task, long-lead interval facilitation is seen that is attributed to a simple arousal process (Graham, 1975). When attention is directed to the pre- pulse, controlled attentional processing may produce either startle facilitation or inhibition, depending on the experimental conditions. When participants are asked to attend to prepulses and the prepulse and the startle stimulus are in the same modality (usually auditory), startle is facilitated at long-lead intervals, more to an attended or task-relevant stimulus than to an ignored or task-irrelevant stimulus (Bohmelt, Schell, & Dawson, 1999; Filion et al., 1993; Jennings, Schell, Filion, & Dawson, 1996; Lipp & Hard- wick, 2003). However, when the prepulse and the startle stimulus are in different modalities and the task requires continuous, un- waver ing attention to the briefly and rapidly presented prepulse as in a CPT, as opposed to a discrete-trial task with relatively long prepulses and intertrial intervals, startle may be inhibited (Hazlett, Dawson, Schell, & Nuechterlein, 2001; Lipp & Neumann, 2004; Neumann, 2002; Rissling, Dawson, Schell, & Nuechterlein, 2005).

Several studies have found startle modification to be abnormal in schizophrenia and in persons at elevated risk for schiz- phrenia. PPI in a passive attention task, where participants are not specifically instructed to attend to prepulses, has been re- ported to be deficient in patients (Braff et al., 1978, 1992; Sverd- low et al., 2006), individuals with schizotypal personality disorder (Cadenhead, Geyer, & Braff, 1993; Cadenhead, Sverd- low, Shafer, Diaz, & Braff, 2000), and biological relatives of patients (Cadenhead et al., 2000). This finding has been inter- preted as a breakdown in sensorimotor gating processes in schizophrenia-spectrum disorders. Studies have indicated that passive PPI deficits in schizophrenia are associated with thought disorder (Perry, Geyer, & Braff, 1999) and both positive and negative symptoms (Braff, Sverdlow, & Geyer, 1999), whereas others have found no symptom correlates (Swerdlow et al., 2006). Wynn, Sergi, Dawson, Schell, and Green (2005) found that schizophrenia patients with lower PPI were poorer at detect- ing relevant social cues than patients with better PPI. Wynn et al. (2004) also reported reduced long-lead interval startle fa- cilitation in a passive-attention task with auditory prepulses and startle stimuli in both patients and first-degree relatives, theo- rized to reflect reduced orienting and reduced availability of cognitive processing resources.

We (Dawson, Hazlett, Filion, Nuechterlein, & Schell, 1993; Dawson, Schell, Hazlett, Nuechterlein, & Filion, 2000; Hazlett & Buchsbaum, 2001; Hazlett et al., 1998, 2007) have reported that attentional modulation of both PPI and long-lead interval startle modification is impaired in schizophrenia during an active-at- tention paradigm in which attended stimuli and startle probes were in the same (auditory) modality. Unlike healthy controls, patients failed to show greater PPI or long-lead interval facilita- tion following task-relevant attended auditory prepulses than following task-irrelevant ignored prepulses. We have also re- ported that deficient PPI during attended prepulses is correlated with heightened delusions, conceptual disorganization, and sus- piciousness (Dawson et al., 2000) and overall positive and neg- ative symptom severity (Hazlett et al., 2007). This failure to atten- tionally modulate startle has also been reported in individu- als with schizotypal personality disorder (Hazlett et al., 2003, 2007) and putatively at risk for psychosis as assessed by Chap- man scale scores (Schell, Dawson, Hazlett, & Filion, 1995).

Attentional modulation of startle can also be seen during the CPT. For example, Hazlett, Dawson et al. (2001) measured startle modification while college student participants performed a memory-load visual CPT in which they pressed a button whenever a “7” (the target) appeared following a “3” (the cue). The digits served as prepulses for an acoustic startle stimulus (white noise burst) that was presented at lead intervals of 120 and 1200 ms following some cue prepulses (“3”), noncue prepulses, and combinations of cue prepulses and distractor stimuli (tones). We found greater PPI 120 ms following cue than noncue pre- pulses, reflecting greater controlled processing of the more task-relevant stimuli of the CPT. At the long-lead interval, significant inhibition of acoustic startle was seen during both cue and non- cue prepulses, which we attributed to a strong focus of attention toward the visual modality and away from the auditory startle stimuli. PPI and long-lead interval startle modification did not differ between cue and cue + distractor trials, indicating an ability of the participants to prevent attention from being captured by the distractor stimulus.

The present study extends the methods previously used with college student participants (Hazlett, Dawson et al., 2001) to the study of CPT deficits in schizophrenia. The “3–7” memory-load CPT, adapted from Nuechterlein et al. (1986), was performed by schizophrenia patients and matched healthy controls while star- tle probes were delivered at both early (120 ms) and late (1200 ms) time points after digit prepulse onset. Using startle modification measures of attentional processing, we tested three hypotheses that, compared with the healthy controls, the schizophrenia pa- tients would (1) fail to attentionally modulate PPI during the CPT, (2) show reduced startle modification at long-lead intervals

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during the CPT, and (3) be less able to avoid attention capture by a distracting stimulus during the CPT. We also explored whether schizophrenia-related CPT deficits were associated with measures of startle modification.

Method

Participants
Twenty schizophrenia outpatients (17 men) and 18 age- and sex-matched healthy controls (15 men) comprised the final sample of paid volunteer participants in this study. Each was paid $25 for participation. Data from 2 additional controls were discarded from analysis because of equipment problems ($n = 1$) and excessive muscle artifact ($n = 1$). In addition, data from 2 patients and 3 additional controls were eliminated for failure to exhibit eyeblinks on over 25% of the baseline startle stimulus presentations.

The schizophrenia patients were outpatients from the UCLA Aftercare Research Program and participants in a longitudinal study of the early phases of schizophrenia (Nuechterlein et al., 1992). The patients met both Research Diagnostic Criteria (Spitzer, Endicott, & Robins, 1978) and DSM-IV criteria for schizophrenia ($n = 18$) or schizoaffective disorder, mainly schizophrenic ($n = 2$). The first psychotic episode began not longer than 2 years before entry into the main longitudinal project and occurred an average of 6.5 years ($SD = 4.1$ years) before testing in the present study. The patients were either off all psychoactive medication ($n = 1$), on a low-–to–moderate dose of the antipsychotic fluphenazine (Prolixin), injectable ($n = 16$) or oral ($n = 3$).

The outpatients were relatively asymptomatic at the time of their testing as assessed by independent ratings on the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962); the 18–item BPRS Total Psychopathology scores ranged from 18 to 43 ($M = 28.4, SD = 6.8$), where the minimum possible rating is 18. Ratings for the three psychotic symptom items of the BPRS (i.e., unusual thought content, hallucinations, and conceptual disorganization) were in the nonpathological range (i.e., $\leq 3$ on a 7-point scale) with the exception of 3 patients who received a rating of 4 on unusual thought content and 1 patient who received a 4 on conceptual disorganization. More details regarding the inclusionary and exclusionary criteria and patient demographics are found in Nuechterlein et al. (1992).

The healthy controls also were drawn from participants in the longitudinal research project. These participants were matched to the patients on age, sex, and educational level. Thus, the final sample of patients and the healthy controls did not differ in age (patients: $M = 30.6, SD = 6.3$; controls: $M = 28.3, SD = 5.3$, $t[36] = 1.2, p = .24$) or years of education (patients: $M = 13.2, SD = 2.1$; controls: $M = 13.2, SD = 1.6$, $t[36] = 0.04, p = .97$). The healthy controls were interviewed with a lifetime version of the Present State Exam (PSE; Wing, Nixon, Mann, & Leff, 1977) to exclude those with a history of significant psychiatric illness in self or first-degree relatives.

The psychophysiology research procedure was fully explained and participants read and signed an informed consent form that provided a general description of the study and the physiological responses being recorded and was approved by the Institutional Review Board.

Design
To examine the effects of different types of CPT prepulses, a $2 \times 3 \times 3$ mixed-design ANOVA was employed for the short (120 ms) and long-lead (1200 ms) intervals separately. The first variable consisted of group (healthy controls vs. schizophrenia patients), the second variable consisted of prepulse type (cue, noncue, and cue+distractor), and the third variable consisted of three CPT trial blocks. Data from the short- and long-lead interval responses were analyzed separately because they are thought to reflect quite different processes, PPI and arousal processes, respectively.

To examine the effects of the distractor stimulus when presented alone as a prepulse, a one-way ANOVA was employed for the short- and long-lead intervals separately, with startle responses at each lead interval being averaged over the baseline periods.

Procedure
The procedure for this experiment was identical to that published in our previous study of college students (Hazlett, Dawson, et al., 2001). The experimental session consisted of five phases: the audiologic test, electrode placement and task instructions, rest period, CPT practice, and the CPT-startle modification experiment. A brief audiologic test was performed to ensure that all participants had normal hearing within the frequency range of the 1000-Hz 70-dB(A) distractor tone. Participants were presented tape-recorded instructions that provided information about the nature of the stimuli to be used and a description of their task. They were instructed that their task was to concentrate on the numbers appearing on the screen, to press a response button every time they saw the digit 3 followed by the digit 7, and to refrain from pressing the button at any other time. Participants were also instructed that two types of auditory stimuli (a pure tone and/or a brief burst of static noise) would be presented occasionally throughout the experiment and that they should simply ignore these stimuli and concentrate on the visual task. Following detailed instructions regarding the task, 10 examples of the 3–7 sequence were shown to the participants. They were asked to practice pressing the button after each of these 3–7 sequences. Next, participants performed one block (160 trials) of the CPT, which served as practice to familiarize them with the visual task and ensure that they understood the task instructions. No distractors or startle stimuli were presented during this practice block. Participants were then given three warned examples of the startle stimulus. Following the examples of the startling noise bursts, the CPT-startle modification portion of the experimental session began.

The CPT-startle modification phase lasted 21.5 min and consisted of three CPT blocks with a baseline period preceding and following each block. Each CPT block consisted of 160 stimulus presentations or “trials” made up of 20 3–7 sequences (40 stimuli), 80 noncues, 20 3s not followed by a 7, and 20 7s not preceded by a 3 over a continuous observation period of approximately 4.5 min (interstimulus interval = 1.65 s). On 20% of the CPT trials in each block (32 trials), a tone distractor was presented through headphones simultaneously with a CPT stimulus (both cues and noncues). To measure eyeblink modification during the processing of the CPT stimuli, 12 preselected trials were “probed” with an acoustic startle-eliciting stimulus. Throughout the entire experimental session, participants were monitored through a one-way mirror for any movements.

A schematic of a portion of the trial sequence during the baseline and CPT periods is shown in Figure 1. To measure eyeblink modification effects to task-related stimuli without interference from the task motor response (see right portion of
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Figure 1. Schematic of a portion of the experimental session. During the baseline blocks, there were two stimulus conditions (startle probe alone, distractor tone with a startle probe presented at either the 120 ms or 1200 ms lead interval). During the CPT blocks, there were three stimulus conditions (cue, noncue, and cue + distractor tone) that had a startle probe presented at either the 120 ms or 1200 ms lead interval.

Figure 1), the startle-eliciting stimulus was presented at one of two possible lead intervals following the onset of the cue (digit 3) of a 3–7 trial sequence, while the participant was to press the response button after the digit 7 of the same sequence. Startle-eliciting stimuli were also presented at times following the digit 3 when the 3 was not followed by a 7. To determine eyeblink modification effects of noncue stimuli, the startle-eliciting stimulus was presented following the onset of noncue digits (i.e., 0s and 1s were chosen to be the least easily confused with the cues). Last, to determine the eyeblink modification effects of the presence of a distracting stimulus, startle-eliciting probes were presented on cue trials that had the simultaneously presented auditory distractor. In sum, during each CPT block, there were two startle-eliciting probes presented at both the short (120 ms) and long (1200 ms) lead intervals following the preselected cue, noncue, and cue + distractor stimuli (“prepulses”), yielding a total of 12 probe trials.

Six of the probe trials were presented during the first 80 CPT stimuli of each block and the remaining six were presented during the last 80 stimuli. The amount of time between the startle-eliciting probes varied from 13 to 36 s, with a mean interval of 24 s. The CPT trial sequence was varied across the three CPT blocks. The order of probed CPT trials was pseudorandom within each participant’s test session and did not vary across individuals. However, probe position (120 ms vs. 1200 ms) order was counterbalanced across participants.

Each of the CPT blocks was preceded and followed by a baseline period, which resulted in a total of four baseline periods (see left portion of Figure 1). The purpose of the 2-min baseline periods was twofold. First, to determine whether participants showed eyeblink modification during the distractor prepulse alone (i.e., tone prepulse without the presence of a visual CPT prepulse) during each baseline period, a startle probe was presented at both the short- and the long-lead interval following the onset of the distractor prepulse. PPI and long-lead interval startle modification data were averaged across the baseline periods for data analysis. Second, during each baseline period, two startle stimuli were presented at preselected times in the absence of a presale. Responses to these probes served as baseline measures with which to compare eyeblink modification produced by the prepulses. No stimuli were presented for at least 15 s before the distractor prepulses that contained probes or before the baseline probes.

To match arousal level during the baseline and CPT periods as closely as possible, CPT digits were presented during the baseline periods. These CPT digits usually had the same interstimulus interval as those presented during the CPT proper (1.65 s); however, occasionally there were relatively longer intersimulus intervals (ranging from 3 to 24 s with a mean interval of 13 s) to allow for the presentation of distractor plus startle stimuli and startle stimuli alone. There was no interruption between the baseline and CPT phases of the experiment, so from the participant’s point of view, the baseline period was identical to the CPT except for the occasional longer-than-usual gap between CPT stimuli. The participants were told that occasionally there would be brief periods where no numbers would appear, but they should continue to focus their gaze on the computer monitor and wait for the next number to appear. In sum, during each baseline period, there was one startle-eliciting probe presented at the short- (120 ms) and long- (1200 ms) lead intervals following the onset of the distractor tone and two startle probes presented in the absence of any presale stimuli, yielding a total of four probes.

Stimulus Materials and Apparatus

The CPT was administered using a computer with a NEC-Multiscan-3D monitor. The computerized version of the CPT used in this project was a modification of the 3–7 CPT program developed by Nuechterlein and Asarnow (1993). CPT stimuli consisted of a series of single digits (0–9) presented visually one at a time with an exposure time of 33 ms and an interstimulus interval of 1.65 s. The computer recorded correct target detections, false positive responses, and reaction time in milliseconds.

The auditory distractor stimulus was a 1000-Hz 70-dB(A) tone, 1400 ms in duration with a controlled rise/fall time of 25 ms with the frequency controlled by the VCO input to a Coulbourn noise generator. The startle-eliciting stimulus was a 100-dB(A) white noise burst 40 ms in duration with a near instantaneous rise/fall time generated by a Grason Stadler Model 901B noise generator. All auditory distractors and startle-eliciting stimuli were presented through headophones (Realistic NOVA-40 Model). The onsets, durations, and intervals between stimuli were controlled online by ASYST computer software.

Electromyographic (EMG) eyeblink responses were recorded using a Grass Model-7 polygraph equipped with a wide-band integrator/preamplifier (Model 7P3). Startle eyeblink was recorded as EMG from a pair of 4-mm silver–silver chloride electrodes filled with TECA electrode paste and placed directly over the orbicularis oculi muscle, the flexor muscle responsible for eyelid closure. These electrodes were placed just below and to the left of the lower left eyelid. All impedences were less than or equal to 5 KΩ. The EMG signal was recorded at full wave rectification with an integration time constant of 20 ms. The eyeblink responses were recorded and digitized at a rate of 1000 Hz for a period of 200 ms before to 300 ms following the presentation of each startle-eliciting stimulus.

Dependent Measures

The two primary dependent variables were the modification of eyeblink magnitude and behavioral performance on the CPT (indexed by a transformed A’ score). Startle eyeblink amplitude was measured under five stimulus conditions: probe-alone presentations (i.e., baseline magnitude) and probes presented at the two lead intervals following cue, noncue, cue + distractor, and distractor-alone presentations.

Eyeblink amplitude was computer scored off-line based on the criteria suggested by Balaban, Losito, Simons, and Graham...
(1986). Blink amplitude was scored in microvolt units for responses beginning within a latency window of 21–120 ms and reaching a peak within 150 ms of response onset. Scores for individual trials with an unstable prestimulus EMG baseline were replaced with the score for the nearest trial in the same condition. Outlier scores (any score greater than three standard deviations above the mean and greater than two standard deviations above the next highest score) were also replaced. Fewer than 1% of data points in either group were replaced.

To examine blink modification across the three CPT blocks, separate baseline blink amplitudes were calculated for comparison with each CPT block. Specifically, the two baseline probes preceding and following each CPT block were averaged together, which resulted in three baseline mean values (i.e., Baseline 1 = mean of probes presented during baselines 1 and 2, Baseline 2 = mean of probes presented during baselines 2 and 3, and Baseline 3 = mean of probes presented during baselines 3 and 4).

The magnitude of each startle blink elicited under a prepulse condition was expressed as a percent change score from the average response to the startle-alone stimuli presented during the appropriate baseline period, using the formula: percentage change = [(magnitude during prepulse – mean baseline)/mean baseline] × 100. A positive startle modification score indicates facilitation relative to baseline, and a negative score indicates inhibition relative to baseline.

To determine behavioral performance on the CPT, the hit rate and false alarm rate were used to calculate A’ (i.e., sensitivity; Grier, 1971) values across the three CPT blocks. In signal detection theory, “sensitivity” refers to an individual’s ability to discriminate the target (stimulus) stimuli from the non-target (noise) stimuli independent of any response bias (Green & Swets, 1966). When an individual has a high perceptual sensitivity score he/she typically has a relatively high hit rate (few errors of omission) and a relatively low false alarm rate (few errors of commission). Each participant’s A’ was transformed using the formula: 2 × arcsin (√A’) in order to create a more normally distributed variable (McNicol, 1972). In addition, this transformation creates a variable with a nearly linear relationship to d’, which is another commonly used index of sensitivity (McNicol, 1972). These transformed A’ scores were used in all subsequent data analyses to index behavioral performance on the CPT.

**Statistical Analyses**
Analyses involving repeated measures with more than two levels used Greenhouse-Geisser epsilon corrections to adjust probabilities for repeated measures F values. The uncorrected degrees of freedom for these analyses and for t tests that required correction due to heterogeneity of variance are reported.

**Results**

**Baseline Startle**
To determine whether there were group differences in baseline startle, we examined mean startle blink amplitude in response to the startle-alone stimulus that was presented during the baseline period. The healthy control and schizophrenia patient groups showed no difference in baseline startle amplitude (controls: \( M = 24.89, SD = 32.29 \) μV; patients: \( M = 19.98, SD = 19.79 \) μV; \( t[36] = 0.56 \)).

**Startle Modification during the CPT**

**Short-lead interval (PPI) effects.** Figure 2 shows the PPI scores for each prepulse type averaged over trial blocks for the patient and control groups. A 2 (group) × 3 (prepulse type) × 3 (trial block) mixed-design ANOVA on PPI during the CPT revealed no group effect, \( F(1,36) = 0.72, p = .40 \), indicating that the patients did not differ from healthy controls in overall PPI averaged over prepulse type and trial block. More important, this analysis revealed a significant Group × Prepulse Type interaction, \( F(2,72) = 4.02, p < .03, \) epsilon = .93. This effect indicates that the patients and controls differed significantly in their differential eyeblink responses to the different prepulse types averaged over trial blocks. Because the trial block effect, \( F(2,72) = 2.04, p = .15 \), Group × Trial Block interaction, \( F(2,72) = 1.17, p = .31 \), Prepulse Type × Trial Block interaction, \( F(4,144) = 1.62, p = .18 \), and Group × Prepulse Type × Trial Block interaction, \( F(4,144) = 1.59, p = .18 \), were all nonsignificant, the PPI scores were averaged over the three trial blocks for further analysis.

As can be seen in Figure 2, the matched controls showed significantly greater PPI following the cue prepulse than following the noncue prepulse at the short-lead interval, \( t(17) = 3.41, p < .004, d = 0.80 \). They also showed significantly greater eyeblink PPI following the cue+distractor prepulse compared to the noncue prepulse, \( t(17) = 2.40, p < .03, d = 0.57 \). The degree of eyeblink inhibition for the cue and the cue+distractor conditions did not differ significantly, \( t(17) = 0.70 \).

In contrast, the patients failed to show differential inhibition to the cue and noncue prepulses. Instead, the patients exhibited more eyeblink inhibition to the cue+distractor prepulse compared to the noncue prepulse, \( t(19) = 4.70, p < .001, d = 1.06 \) and compared with the noncue prepulse, \( t(19) = 4.34, p < .001, d = 0.97 \).

Between-group comparisons were conducted on the differential eyeblink inhibition scores (i.e., cue minus noncue and cue minus noncue+distractor difference scores). These analyses confirmed that the patients, compared to the controls, exhibited significantly less differential eyeblink inhibition between the cue and noncue prepulse, \( t(36) = 2.65, p < .02, d = 0.87 \). In addition, the patients compared to the controls exhibited significantly
greater differential eyelink inhibition between the cue and the cue + distractor prepulse, \( t(36) = 2.50, p < .02, \) \( d = 0.81 \). These findings demonstrate that the patients are capable of showing normal amounts of attentional modulation of PPI; however, the attentional modulation was driven by capture of attention by the distractor prepulse rather than the voluntary allocation of attention to the cue prepulse.

**Long-lead interval effects.** To determine whether patients exhibited deficits in controlled processing at the long-lead interval, the startle modification scores were submitted to a 2 (group) \( \times 3 \) (prepulse type) \( \times 3 \) (trial block) ANOVA. As seen in Figure 3, this analysis revealed that the overall effect of startle modification was significant, \( F(1,36) = 490.26, p < .001 \), with participants responding less to the startle stimulus during the CPT prepulses than during the startle alone baseline trials (overall mean = -63.4, \( SD = 31.8 \)). However, the group effect, \( F(1,36) = 1.82, p = .19 \), prepulse type effect, \( F(2,72) = 1.23, p = .29 \), trial block effect, \( F(2,72) = 1.44, p = .24 \), Group \( \times \) Prepulse Type interaction, \( F(2,72) = 1.26, p = .29 \), Group \( \times \) Trial Block interaction, \( F(2,72) = 0.84, p = .43 \), Prepulse Type \( \times \) Trial Block interaction, \( F(4,144) = 2.00, p = .10 \), and Group \( \times \) Prepulse Type \( \times \) Trial Block interaction, \( F(4,144) = 1.05, p = .38 \), were all nonsignificant. Thus, long-lead interval startle modification to the CPT prepulses did not differ between the patients and the controls, or between cue and noncue prepulses.

**Startle Modification during the Distractor Prepulse in Baseline Period**

**Short lead-interval (PPI) effects.** PPI during the distractor-alone prepulse presented during baseline when there was an occasional longer-than-usual gap between CPT stimuli was thought to provide a measure of predominantly automatic attentional processes to a passively attended stimulus. To determine if patients exhibited a deficit in automatic sensorimotor processing of the distractor prepulse, the PPI scores were submitted to a between-groups ANOVA. This analysis revealed that there was a significant overall level of PPI, \( F(1,36) = 303.38, p < .001 \), and no group main effect, indicating that both groups showed significant overall eyelink inhibition and patients did not differ from healthy controls (controls: \( M = -71.5, SD = 22.5 \); patients: \( M = -67.0, SD = 41.5 \), \( F(1,36) = 0.38, p = .54 \). These results indicate that during the baseline period, patients exhibited normal PPI during the passive distractor prepulse.

**Long-lead interval effects.** It was anticipated that startle modification to the distractor alone prepulse at the long-lead interval would provide a measure of predominantly automatic arousal processes (Graham, 1975). The long-lead interval startle modification scores for the distractor prepulse were submitted to a between-groups ANOVA which revealed startle modification was not significant (for either facilitation or inhibition) in either group at 1200 ms (\( M = -6.21 \) for patients, SD = 60.29, and \( M = 21.00 \) for controls, SD = 91.74; patients and controls did not differ, \( F(1,36) = 1.19, p = .28 \).

**Behavioral Performance**

As predicted, the groups differed significantly in CPT performance, \( t(36) = 2.46, p < .05, d = .79 \). The mean transformed \( A' \) score was 2.99 (SD = 0.09; range: 2.71–3.03) for the matched controls and 2.89 (SD = 0.15; range: 2.54–3.03) for the patients. It is noteworthy that 5 of the 20 patients had perfect \( A' \) scores.

**Relationship between Behavioral Performance and Startle Modification**

To test for relationships between performance on the CPT task and startle modification, we computed the Pearson correlation coefficients between \( A' \) and startle modification during the cue, noncue, and cue + distractor prepulses at 120 ms and 1200 ms, averaged over trial blocks, and cue minus noncue differences at 120 and 1200 ms averaged over trial blocks. Because of the limited variability of \( A' \) measures in the control group, correlations were computed separately for the two groups (eight correlations per group). No significant correlation was found between startle modification scores during any of the prepulse types or cue minus noncue difference scores and CPT performance in either group. Correlations among controls ranged between –.12 and .34 (\( df = 16 \)), and correlations among patients ranged from –.43 and .10 (\( df = 18 \)).

**Discussion**

**Startle Modification during the CPT**

The finding of performance deficits in the patient group is consistent with the CPT literature on schizophrenia (Nuechterlein, 1991; Nuechterlein et al., 1992). In particular, Nuechterlein et al. (1992) reported that signal/noise discrimination level (\( d' \) in a memory–load CPT similar to the one employed in the present study) was significantly lower in patients during remission and even more deficient during psychotic states compared to healthy controls. The present study extends these seminal findings by using a startle paradigm to shed light on the nature of attentional deficits observed during a memory-load CPT.
Our first hypothesis, that schizophrenia patients would fail to attentionally modulate PPI during the CPT, was confirmed. The healthy control group showed significantly greater PPI to the cue than to the noncue prepulse, whereas the patient group did not. Our second hypothesis, that patients would show reduced startle modification at long-lead intervals, was not confirmed, as patients and controls both showed significant startle inhibition that was not different across prepulse types. Our third hypothesis, that patients would be less able to avoid attention capture by the distractor prepulse, was supported for the short-lead interval measure. The patient group showed significantly greater PPI to the cue + distractor than to the cue prepulse, whereas the healthy control group did not. Finally, startle modification measures were found to be uncorrelated with schizophrenia-related CPT deficits.

Consistent with our earlier results with college student participants (Hazlett, Dawson, et al., 2001), the matched controls in the present study showed greater PPI to the cue than the noncue prepulses at the short-lead interval. This attentional modulation of startle at the short-lead interval indicates that approximately 120 ms following the prepulse, an early evaluation of the significance of the cue prepulse has occurred. This finding is consistent with other work showing that startle inhibition at short-lead intervals can be modulated by attention in healthy individuals in a discrete- vs. trial selective attention task (Bohmelt et al., 1999; Filion et al., 1993; Hawk, Pelham, & Yartz, 2002; Rissling et al., 2005). In contrast, the patients failed to show attentional modulation of PPI during the cue compared with the noncue prepulses. This result is consistent with previous research showing both medicated (Dawson et al., 1993, 2000) and unmedicated schizophrenia patients (Hazlett et al., 1998, 2007) exhibit deficient attentional modulation of PPI during an auditory selective attention task. Previous work suggests that attentional modulation of PPI at a lead interval of 120 ms reflects stimulus discrimination and greater allocation of limited controlled processing resources to a stimulus identified as task significant (Dawson et al., 1993, 1997). Thus, the finding in the present study of non-differential eyeblink inhibition to the cue and noncue prepulses in the patient group is interpreted as a deficit in controlled attentional processing, more specifically, the failure of voluntary modulation of an automatic process.

With respect to attention capture by the distractor prepulse, in the patient group, the greater PPI produced by the cue + distractor than by the cue alone demonstrates an inefficient allocation of attentional processing. In contrast to the patients, the controls appeared to effectively ignore the distractor as indicated by an equal amount of eyeblink inhibition to the cue prepulse and the cue + distractor prepulse. This finding is consistent with the hypothesis of Nuechterlein and Dawson (1984b) that CPT deficits in schizophrenia may be caused at least in part by devoting more of the available limited processing capacity to task–irrelevant stimuli. The fact that controls showed equal levels of PPI to the cue and the cue + distractor, both of which were greater than the PPI to noncues, suggests that their allocation of controlled resources to the cue + distractor is dominated by their voluntary controlled allocation to the cue, and this allocation represents a “there it is” response to a cue whose template has been maintained in working memory. The presence of the distractor does not cause any additional allocation of attentional resources. The fact that the patients show greater PPI to cue + distractor than to cue alone suggests that their processing of the cue + distractor reflects largely an automatic allocation of resources—a “what is that?” response that they cannot suppress. However, it is also true that PPI among both the controls and the patients during the cue + distractor is very strong (> 70% in both groups). It is possible that the failure of the controls to show greater PPI to the cue + distractor than to the cue alone may represent a ceiling effect on startle suppression.

At the long-lead interval, both patients and controls showed significant and nondifferential eyeblink inhibition. These results for the controls replicate the results of Hazlett, Dawson, et al. (2001) and Rissling et al. (2005). This finding suggests that this particular patient group may not be deficient in the later, modality specific attentional processes activated by the CPT. This finding differs from our prior work (Dawson et al., 1993, 2000; Hazlett et al., 1998, 2007) that found differences in attentional modulation of long-lead interval prepulse facilitation in a selective attention tone length-judging task, with controls showing greater facilitation to an attended than to an ignored stimulus, whereas patients did not. This result was interpreted as reflecting decreased sustained attention to the attended stimulus compared with the ignored stimulus among patients. However, this task employed discrete trials with relatively long interstimulus intervals (20–30 s) with both task-relevant and startle stimuli in the auditory modality and the tones to be judged as either 5 s or 7 s (5 s or 8 s in Hazlett et al. studies) in duration. In contrast, long-lead interval startle modification in the CPT task was measured while no task-related stimulus was physically present (CPT digits were 33 ms in duration). At this point, startle may be dominated by general (as opposed to cue-specific) modality-specific attention processes aimed at screening out cross-modality stimuli, processes in which these patients may not be deficient.

Taken together, these findings suggest that startle modification at the short- and long-lead intervals reflects a sequence of two processes activated by the CPT; one is impaired in the patient group and the other does not appear to be impaired. First, patients are deficient in the allocation of controlled resources involved in the encoding and discrimination of the cue and noncue stimuli at approximately 120 ms. This deficiency is reflected by the lack of differential eyeblink inhibition to the cue and noncue prepulses. Further, the finding of more eyeblink inhibition to the cue + distractor prepulse than to the cue alone in the patient group indicates that controlled resources are being inappropriately allocated to task–irrelevant stimuli, suggesting an inability to ignore distracting stimuli. Second, at the long-lead interval, a more general anticipatory attention process occurs while attention is focused on the visual modality following both cue and noncue prepulses. Both the controls and patients showed significant yet nondifferential eyeblink inhibition following the cue and noncue prepulses. According to this hypothesized sequence of events, relatively asymptomatic schizophrenia outpatients may not be deficient in the later modality-specific anticipatory attention process.

These results suggest that a major source of the schizophrenia patients’ impaired CPT performance has to do with encoding of the task-related stimuli and perhaps not with maintenance of the task instructions in working memory. At 120 ms following stimulus onset, the patients show no evidence of having discriminated the differential task relevance of the cue compared to the noncue. Normal participants, on the other hand, have made the discrimination between the cue and noncue and are inhibiting the startle reflex more following the cue. In contrast, at the long-lead interval following the cue, both patients and controls are exhibiting equal startle inhibition to both the cues and noncues. To the
extent that the startle modification at the long-lead interval reflects anticipation of the target following the cue, the patients are not abnormal in this anticipation and, therefore, do not appear abnormal in maintenance of task instructions and modality-selective attention.

**Startle Modification during the Distractor Alone**

In terms of the startle effects during the passively attended distractor prepulse, the patients did not differ from healthy controls at either the short-lead interval or the long-lead interval. In the present study, startle to the distractor alone is considered a measure of predominantly automatic processing to a passively attended prepulse, one that is presented when a task-relevant stimulus is not present. It is important to remember that these (auditory) distractor-alone prepulses were in a different modality from the primary visual vigilance task, and they did not require processing in order to perform the primary task. Thus, the finding that patients and controls did not differ in the amount of PPI produced by the distractor prepulse presented alone during the baseline period suggests that the patients do not have a deficit in automatic sensorimotor gating under these experimental conditions.

The finding of normal short-lead interval PPI in the patient group during these passively attended distractor prepulses contrasts with several previous findings (e.g., Braff et al., 1978; Braff, Geyer, & Swerdlow, 2001; Swerdlow et al., 2006). Across all of these studies employing passive attention paradigms, as well as in other studies, the schizophrenia patients exhibited impaired PPI compared with healthy controls. The failure of the present study to confirm previous observations of PPI deficits in schizophrenia to nontask stimuli may stem from some combination of the following factors.

First, several paradigmatic characteristics in the present study differ from those employed in previous research. Potentially important sources of variance include the use of explicit instructions regarding the nature of the prepulses in the present study, in contrast to an uninstructed passive attention paradigm that was most often previously employed. In addition, the distractor prepulses used in the present study were continuous 1000-Hz 70-dB(A) tones without imposed background noise, whereas previous reports of reduced PPI during a passive task utilized primarily brief discrete white noise prepulse stimuli (e.g., 75–90 dBA of white noise), which were presented over a constant background white noise of 70 dB(A), making the prepulses difficult to detect. Braff, Geyer, Light, et al. (2001) found that schizophrenia patient-control differences in passive PPI maximize when brief discrete white noise prepulses are used. Moreover, Hsieh, Swerdlow, and Braff (2006) have demonstrated that PPI is greater among normal participants (with an 86-dB(A) prepulse) when background noise is 54 dB(A) versus 70 dB(A), suggesting that discriminability of the prepulse is critical. Wynn et al. (2004) and Ford, Roth, and Pfefferbaum (1999), who did not use a background noise, failed to find passive PPI deficits in schizophrenia patients using brief white noise prepulses. PPI deficits in schizophrenia patients may appear only when the sensory gating system is in some sense taxed, either by prepulses that are difficult to detect or by the requirements of a selective attention task that requires top-down control of the process, and may not occur when single, easily detected prepulses are presented with relatively long intertrial intervals.

Second, the patient population in the present study differs from those tested in previous startle modification research using passive attention tasks. Specifically, the patients in the present study had a relatively recent onset of schizophrenia and were in a relatively asymptomatic period at the time of testing, whereas previous research with passive attention tasks involved more heterogeneous groups of patients in terms of chronicity of illness, years of neuroleptic treatment, number of hospitalizations, and concurrent psychotic symptoms. However, the findings of startle modification abnormalities similar to those seen in patients among persons with schizotypal personality disorder (Cadenhead et al., 1993, 2000) and relatives of schizophrenia patients (Wynn et al., 2004) raise doubt that differences between the present findings and those of previous research are due to lower levels of symptoms in the patients in the present study.

Startle modification to the distractor-alone prepulse at the long-lead interval was used as a measure of predominantly automatic processing. The long-lead interval facilitation of eyelink frequently seen in passive paradigms (e.g., Graham, 1975, 1979, 1980) is hypothesized to reflect what Graham (1975, p. 243) described as an automatic arousal effect that is considered to be independent of controlled processes. In an earlier study of startle modification during this CPT paradigm (Hazlett, Dawson, et al., 2001), college students showed significant eyelink facilitation during baseline periods to the distractor prepulse at the long-lead interval, which is consistent with the previous work employing passively attended prepulses at long-lead intervals. The failure of the patients and controls in the present study using the same paradigm to show reliable startle modification at this point may reflect a tendency of college students to show stronger orienting activity than the present participants, few of whom had attended college. The discrepancy between the previous findings with college students and the present results with patients and matched controls using the same paradigm may reflect a tendency of college students to show stronger arousal during the distractor-alone prepulse.

**General Conclusions**

Do schizophrenia patients have deficits in startle modification consistent with deficits in automatic processing, or deficits in controlled processing, or both? The present study included measures of automatic and controlled processing of startle during both “actively” and “passively” attended prepulses on a within-subject within-task basis. The results of this study suggest that during this task, patients exhibit deficits in predominantly controlled processes. Predominantly automatic sensorimotor gating processes appear to be normal in the patients under the present experimental conditions.

The finding that schizophrenia patients failed to show greater PPI to a task-relevant cue than to a noncue in the CPT task is consistent with our previous research using a continuous prepulse tone (Dawson et al., 1993, 2000; Hazlett et al., 1998, 2007) and suggests that patients are deficient in early stimulus encoding and discrimination and the allocation of controlled resources to task-relevant stimuli (Nuechterlein & Dawson, 1984a). The present study extends earlier work by showing that patients’ focus of attention is more vulnerable than that of controls when a task-irrelevant distracting prepulse is included in the paradigm. Specifically, the patients showed increases in PPI in response to the cue + distractor stimulus compared to the cue stimulus alone. This differential PPI suggests that differential automatic allocation of attention is possible for schizophrenia patients, but implies that allocation is not governed by task significance in a normal voluntary fashion.
A potential limitation in interpreting these data occurs because the patients (except for one) were receiving antipsychotic medication. However, recent work suggests antipsychotic medications may, if anything, improve PPI deficits, at least in passive attention tasks (Weike, Bauer, & Hamm, 2000; Kumari & Sharma, 2002; Quednow et al., 2006), thus reducing the appearance of patient-control differences. However, the improvement in PPI is much more marked with the atypical antipsychotics (e.g., Swerdlow et al., 2006), and the present patients were receiving a typical antipsychotic, fluphenazine. In addition, we have reported deficient attentional modulation of PPI in unmedicated schizophrenia patients during a tone discrimination paradigm (Hazlett et al., 1998, 2007). Whether the attentional modulation of PPI is also improved by atypical antipsychotic medication is a subject for future research. It is also clear that the CPT deficits in schizophrenia are, if anything, partially alleviated by antipsychotic medication (Orzack, Kornetsky, & Freeman, 1967; Sax, Strakowski, & Keck, 1998; Spohn, Lacoursiere, Thompson, & Coyne, 1977). Therefore, it is highly unlikely that medications can account for the present results.

Another limitation of the present study is that we probed the CPT process at only 120 ms and 1200 ms after the CPT stimuli. We felt that probing more often to include more probe latencies might have distorted the CPT process by focusing attention more on the probe stimuli and disrupting CPT performance. This study leaves open the question of whether development of PPI on the part of the patients simply lags that of controls, so that attentional modulation of PPI might have appeared at a later point. However, in our earlier studies of PPI in schizophrenia (e.g., Dawson et al., 1993, 2000), which found attentional modulation of PPI at 120 ms in controls but not in patients, we also probed at 240 ms after prepulse onset. PPI at this later point was reduced in both groups compared to that seen at 120 ms, and neither group showed attentional modification at this point, so the schizophrenia patients did not “catch up” to controls in terms of developing greater PPI to an attended than to an ignored prepulse. On the other hand, the prepulses in these studies were auditory, and PPI to visual prepulses shows a somewhat longer latency, so we cannot be sure that at a slightly longer probe latency, patients might not have shown attentional modulation in the present study. The startle probe paradigm could be fruitfully used in further research to more fully track the allocation of attentional resources throughout the sequence of stimulus presentation in the CPT.

In conclusion, the present startle modification results indicate that deficits in CPT performance may be caused by two different factors suggested by Nuechterlein and Dawson (1984b). First, as indicated by the lack of differential eyeblink inhibition to cue and noncue prepulses at the short-lead interval, the patients failed to allocate controlled resources appropriately to task-relevant cues. This would appear to reflect a failure of top-down controlled attention processes to modify what may be, in other circumstances, a largely automatic mechanism (basic PPI). Second, as indicated by greater eyeblink inhibition to the cue + distractor prepulse compared to the cue prepulse at the short-lead interval, the patients’ attention is captured by task-irrelevant stimuli that were not even in the same sensory modality.

Startle modification measures were not correlated with behavioral performance in either of the groups in the present research; nor did we find them to be correlated in our previous study (Hazlett, Dawson, et al., 2001) with college student participants. One factor that would mitigate against such a correlation is a restricted range of performance scores in both the patient and matched control groups, with performance being quite good in both groups, as it was with the college students. Rissling et al. (2005), on the other hand, found performance to be more variable in a more demanding CPT with perceptually degraded stimuli in college students and reported a significant correlation among normal participants, with greater PPI associated with better performance. The use of the more difficult perceptually degraded stimulus CPT with schizophrenia patients may also reveal a correlation between PPI and behavioral performance deficits. However, previous investigations have also failed to find correlations between schizophrenia-related PPI deficits and behavioral measures of neurocognitive functioning (e.g., Swerdlow et al., 2006).

The results of the present research suggest that the measurement of startle modification is a useful tool to quantify both automatic and controlled attentional impairments in schizophrenia. Previous startle modification research in schizophrenia has focused solely on discrete-trial paradigms. However, the results of this study offer encouragement to investigators interested in using startle modification to explore specific time-linked phases of attentional processing in continuous tasks known to reveal deficits in schizophrenia.

As we begin to understand the cognitive processes underlying CPT deficits in schizophrenia, it will also be important to understand the neural circuits that subserve these attention processes. Compared with healthy controls, FDG-PET scans in schizophrenia patients show abnormally low relative glucose metabolism in dorsolateral prefrontal cortex (DLPFC) and ventral caudate (Buchsbaum et al., 1990; Siegel et al., 1993), as well as, a lack of thalamo-cortical intercorrelations (Katz et al., 1996) during degraded stimulus CPT performance, suggesting circuitry dysfunction. More recent work using functional magnetic resonance imaging during a memory-load CPT similar to the one used in the current study confirms DLPFC and thalamic dysfunction in patients (e.g., Barch et al., 2001; Salgado-Pineda et al., 2003). These findings converge with animal (e.g., Swerdlow, Geyer, & Braff, 2001) and human (Hazlett et al., 1998; Hazlett, Buchsbaum, et al., 2001; Kumari et al., 2003) work indicating PPI is modulated by cortical-striato-thalamic circuitry. Thus, the observed deficiencies in controlled processing measured with startle modification and poor CPT performance in schizophrenia may have a common neural substrate. Given its known neurobiological substrates and genetic loading related to schizophrenia, a combined startle-CPT paradigm may be an excellent candidate measure to use in clinical studies to examine how different antipsychotics normalize these neural substrate deficits.

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