Attention and Schizophrenia: Impaired Modulation of the Startle Reflex

Michael E. Dawson, Erin A. Hazlett, Diane L. Filion, Keith H. Nuechterlein, and Anne M. Schell

The startle reflex (SR) elicited by abrupt stimuli can be modified by attention to nonstartling stimuli that shortly precede the startle-eliciting stimulus. The present study of 15 recent-onset, relatively asymptomatic schizophrenic outpatients and 14 demographically matched normal control subjects demonstrated that attentional modulation of SR is impaired in schizophrenic patients. Specifically, the control group exhibited greater startle eye-blink modification following to-be-attended prestimuli than following to-be-ignored prestimuli, whereas the patients failed to show the attentional modulation effect. These results suggest traitlike attentional deficits in schizophrenia because the patients were relatively asymptomatic. The measurement of attentional modulation of SR may provide a nonverbal, reflexive, state-independent marker of the vulnerability to schizophrenia.

Schizophrenia has long been recognized as involving impaired attention and information processing (Bleuler, 1911/1950; Kraepelin, 1913/1919). However, there has been considerable disagreement regarding the nature of these impairments. Paradigms that allow isolation of elementary components of attention and information processing may help refine our understanding of these core schizophrenic impairments. The startle-reflex modulation paradigm is one such paradigm.

The startle-reflex modulation paradigm involves the modification of the acoustic startle reflex by innocuous environmental stimuli that precede the reflex-eliciting stimulus. For example, the size or latency of the eye-blink component of the human startle reflex to a sudden loud noise will vary depending on the stimulus events that immediately precede the startling noise. The amplitude of the startle reflex can be either inhibited or facilitated depending on the stimulus conditions, particularly the interval between onset of the first stimulus (prepulse) and onset of the startle stimulus. When the interval between the prepulse and the startle stimulus is short (i.e., between 30 and 300 ms), there is a reduction in startle amplitude compared with the response elicited in the absence of a prepulse. This phenomenon, called prepulse inhibition, is observed reliably in lower animals when measures of whole-body startle are used (Hoffman & Ison, 1980, 1992), as well as in humans when the eye-blink component of the startle reflex is measured (Anthony, 1985; Graham, 1975, 1992). Prepulse inhibition occurs with prepulses in various modalities, is unlearned (i.e., it occurs on the first trial), requires only midbrain and lower brain structures (Leitner & Cohen, 1985), and is evident in human adults even while they are asleep (Silverstein, Graham, & Calloway, 1980). For these reasons, short lead-interval prepulse inhibition has been hypothesized to reflect an automatic sensorimotor gating mechanism initiated by the prepulse to allow the early, preattentive stages of information processing of the prepulse to proceed relatively undisturbed by other stimulus events (Braff & Geyer, 1990; Graham, 1975, 1979, 1980).

In contrast to the short lead-interval prepulse inhibition effect, the amplitude of the startle blink is enhanced when a sustained prepulse in the same modality as the startle stimulus is used with a relatively long lead interval (e.g., 1000 ms or greater). The long lead-interval facilitation effect is hypothesized to at least partially reflect sensory enhancement associated with modality-specific selective attention (Anthony, 1985; Graham, 1979). In support of a selective attention model of long lead-interval startle eye-blink modification (SEM), it has been shown that blink amplitude is facilitated if attention is directed to the same modality as the startle stimulus, and that blink amplitude is inhibited if attention is directed to a modality different from that of the startle stimulus (see reviews by Anthony, 1985, and Putnam, 1990).

Evidence from recent studies indicates that the short lead-interval prepulse inhibition effect also can be modulated by selective attention, suggesting that it is not an entirely automatic process in all situations. These studies demonstrated that prepulse inhibition is enhanced by instructions to attend to the prepulse (DelPezzo & Hoffman, 1980; Filion, Dawson, & Schell, in press-a, in press-b; Hackley & Graham, 1987; Hackley, Woldorf, & Hillyard, 1987). Filion et al. (in press-a), for example, employed the SEM paradigm with normal college students within the context of an auditory selective attention paradigm that we had previously developed and validated (Dawson, Filion, & Schell, 1989; Filion, Dawson, Schell, & Hazlett, 1991). In this paradigm, subjects are presented with an
intermixed series of high and low pitch tones and are instructed to count the number of longer-than-usual occurrences (7 s rather than 5 s) of one particular pitch. The rationale for this paradigm is that the task requires subjects to discriminate between to-be-attended and to-be-ignored pitches and then sustain selective attention only to the to-be-attended pitch in order to determine its length. This paradigm has been shown previously to elicit differential orienting and attention in normal college student subjects (Dawson et al., 1989; Filion et al., 1991). Filion et al. (in press-a) found greater prepulse inhibition of the startle eye-blink reflex at a short lead interval (120 ms), and greater facilitation of the same reflex at a long lead interval (2000 ms), following the to-be-attended tone prepulse compared with the to-be-ignored tone prepulse. These results clearly demonstrate that the degree of both short lead-interval and long lead-interval SEM can be modulated by attention. Furthermore, the degree of startle inhibition at 120 ms and the degree of startle facilitation at 2000 ms following the to-be-attended prepulse were significantly correlated with the magnitude of skin conductance orienting responses (SCORs), indicating that subjects with the largest orienting responses to the prepulses show the greatest attentional modulation of SEM.

The measurement of SEM and its attentional modulation may have the potential to provide a sensitive nonverbal, nonvoluntary metric of either automatic or controlled attentional processes, depending on the stimulus conditions and task demands. In a paradigm without active attentional instructions, SEM at short lead intervals may index automatic preattentive processing of the prepulse. In an active attention paradigm SEM may index in addition to automatic processing both a rapid, controlled attentional modulation of early sensory processing at short lead intervals and a later sustained selective attention at long lead intervals. Moreover, startle blink is relatively free from voluntary control and requires only minimal cooperation from the subject.

These aspects of the SEM paradigm make it ideal for the study of pathological groups for whom attentional dysfunctions are hypothecized. Schizophrenic patients, for example, have been hypothesized to suffer from primary deficits in controlled cognitive processes (Callaway & Naghdi, 1982; Gjerde, 1983; Neale & Olteinans, 1980), perhaps because of reduced availability of controlled processing resources (Nuechterlein & Dawson, 1984). Other investigators have hypothesized primary impairments in the early preattentive stages of information processing following stimulus onset, particularly impairments in filtering of internal and external stimulation (Braff, Saccuzzo, & Geyer, 1992; McGhie & Chapman, 1961; Venables, 1984). Thus, for both practical and theoretical reasons, SEM may be a particularly useful tool for understanding the nature of the attentional dysfunctions in schizophrenia.

Despite these potential advantages, only three SEM studies have been published to date with schizophrenic patients. Braff et al. (1978), Braff, Grillon, and Geyer (1992), and Grillon, Ameli, Charney, Krystal, and Braff (1992) measured SEM in heterogeneous groups of hospitalized chronic and acute medicated schizophrenic patients. In Braff et al.'s (1978) study, a continuous innocuous tone served as the prepulse and was followed by a startling burst of loud white noise; in Braff, Grillon, and Geyer's (1992) study, a discrete mild white noise served as the prepulse and was followed by either a startling white noise or a startling air puff to the subject's neck; and in Grillon et al.'s (1992) study, a discrete white noise of varying intensity served as the prepulse and was followed by a startling burst of white noise. Subjects were not instructed to attend to any of the stimuli; hence, an uninstructed passive attention paradigm was used. In each of these studies, schizophrenic patients exhibited impaired short lead-interval prepulse inhibition relative to normal control subjects. The findings were hypothesized to reflect an impairment in automatic, preattentive central nervous system inhibition (sensorimotor gating; Braff & Geyer, 1990; Geyer & Braff, 1987). The deficiency in sensorimotor gating was interpreted as a "trait-linked longitudinal deficit in central inhibition and gating mechanisms" (Braff & Geyer, 1990, p. 187), which increases the vulnerability to cognitive fragmentation and disorganization in schizophrenia. Braff et al. (1978) also measured SEM at a long lead interval of 2000 ms and did not find significant facilitation in either the schizophrenic patient group or the normal control group, which may have been due to the lack of instructions to attend to the prepulses.

Unfortunately, it is not clear how much, if any, of the impairment of prepulse inhibition reported in the patients studied by Braff et al. (1978; Braff, Grillon, & Geyer, 1992) and by Grillon et al. (1992) was due to the patients' current symptomatic or medication status or to the long-term administration of various antipsychotic medications. It is unlikely that the current antipsychotic medication status was responsible for the deficit in prepulse inhibition given that animal studies indicate that antipsychotic medications do not induce such deficits (see Braff & Geyer, 1990); nevertheless, effects of long-term administration of such medications and the presence of psychotic symptomatology cloud interpretation of the SEM impairment. To clarify this situation, we now report for the first time SEM findings obtained from schizophrenic patients who (a) had a relatively recent onset of schizophrenia, thereby limiting the effects of a chronic illness and associated years of neuroleptic treatment and repeated hospitalizations, (b) were in relative symptomatic remission at the time of testing, so that we could be certain that SEM impairments were not secondary effects of concurrent psychotic symptoms, and (c) were on either low-to-moderate doses of a single antipsychotic medication with low anticholinergic effects or were off all antipsychotic medication.

It also is not clear in Braff et al.'s (1978; Braff, Grillon, & Geyer, 1992) and Grillon et al.'s (1992) studies how much, if any, of the schizophrenic impairment in prepulse inhibition may have been due to attentional factors. As we have noted, in normal individuals the degree of prepulse inhibition is enhanced by attention to the prepulse. The impaired prepulse inhibition found by previous investigators was presumed to reflect an automatic processing deficit because subjects were not instructed to attend to the prepulses. Nevertheless, it is possible that patients and normal controls assigned different attentional significance to the prepulses and that this contributed to the differences in prepulse inhibition. Therefore, in the present experiment we provided an explicit instructional manipulation of attention regarding the prepulses to both the schizophrenic patient group and the normal control group. All subjects were instructed to attend to one tone pitch (prepulse) and ignore another tone pitch. Thus, there were intermixed presentations of a
task-relevant to-be-attended prepulse and a task-irrelevant to-be-ignored prepulse. SEM to the to-be-ignored prepulse was expected to provide an estimate of predominantly automatic attentional processes, whereas SEM to the to-be-attended prepulse was expected to provide an estimate of automatic-plus-controlled attentional processes. Therefore, differential SEM to the to-be-ignored and the to-be-attended prepulses ought to reflect the controlled processing effect above and beyond the automatic processing of the to-be-ignored prepulse. Although startle latency also can be modified by the presence of a prepulse, SEM was measured in terms of changes in startle eyeblink amplitude, rather than latency, because latency has not shown consistent effects of attentional manipulations (e.g., Hackley & Graham, 1987), nor has it shown consistent impairments in schizophrenia (e.g., Brall, Grillon, & Geyer, 1992).

In addition, as in our previous investigations with this paradigm, we recorded SCORs to the to-be-attended and to-be-ignored prepulses. Our previous studies demonstrated larger SCORs to the to-be-attended prepulse than to the to-be-ignored prepulse. Thus, the SCOR can serve as an independent confirmation of differential attention to the prepulses.

Method

Subjects

A total of 15 schizophrenic patients and 15 matched normal controls (13 men and 2 women in each group) were recruited to serve as subjects. As explained in the Results section, the data of one of the normal controls were excluded from the final analyses, leaving 15 schizophrenic patients and 14 normal controls. The schizophrenic subjects were outpatients at the Afiercare Clinic of the University of California, Los Angeles, and were participants in a longitudinal study of the early phases of schizophrenia (Nuechterlein et al., 1992). The patients were diagnosed as having schizophrenia (n = 13) or schizoaffective disorder, mainly schizophrenic (n = 2), according to Research Diagnostic Criteria (Spitzer, Endicott, & Robins, 1978). The first psychotic episode began not longer than 2 years before entry into the main longitudinal project and occurred an average of 2.9 years (SD = 2.6 years) before testing in the present project. Thus, at the time of the present test the patients were relatively recent-onset and were without a long history of medication and institutionalization. The patients were either off all psychoactive medication or on a low-to-moderate dose of injectable fluphenazine decanoate (Prolixin) at the time of the present test session (1 patient had been off all medication for at least 5 months, 2 patients were receiving 6.25 mg, 11 were receiving 12.5 mg, and 1 was receiving 18.75 mg injections every 2 weeks). Although this procedure did not eliminate possible effects of the antipsychotic medications, it did produce standardization within a relatively narrow range of dosages. Antiparkinsonian medications were discontinued for at least 24 hr prior to testing for all but one of the patients in order to reduce their anticholinergic effects.

The patients were relatively asymptomatic at the time of their testing, as assessed by independent ratings on the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962). Total psychopathology scores on the 18-item BPRS ranged from 20 to 35 (M = 25.3, SD = 4.7, minimum possible rating = 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 (3 or less) with the exception of two patients, who received a rating of 4 on unusual thought content. More details regarding inclusions and exclusionary criteria, and regarding patient demographics, can be found in Nuechterlein et al. (1992) and Dawson, Nuechterlein, Schell, and Mintz (1992).

The matched normal controls also were drawn from participants in the longitudinal research project. These normal controls were matched to the schizophrenic outpatients on age, sex, race, and educational level. Thus, the final sample of patients (n = 15) and the matched controls (n = 14) did not differ in age (patients, M = 24.1 years, SD = 4.2; controls, M = 24.7 years, SD = 3.9) or years of education (patients, M = 12.3, SD = 1.8; controls, M = 13.1, SD = 1.6). As part of the longitudinal study, the control subjects were interviewed with an expanded lifetime version of the Present State Examination (FSE; Wing, Cooper, & Sartorius, 1974) to exclude those who themselves had a history of psychiatric illness or whose first-degree relatives had a major psychiatric illness.

Design

The study used a 2 X 2 X 4 mixed factorial design. The first variable consisted of two subject groups (schizophrenic patients vs. normal controls), the second variable consisted of two types of prepulses (to-be-attended vs. to-be-ignored), and the third variable consisted of four lead intervals (60, 120, 240, and 2000 ms following prepulse onset). Data analysis was first conducted with the to-be-ignored prepulse to test for predominately automatic cognitive effects and then was conducted with both the to-be-ignored and to-be-attended prepulses to test for controlled cognitive effects. All statistical analyses involving repeated measures with more than two levels used Greenhouse-Geisser epsilon corrections to adjust probabilities for repeated measures F values. We report the uncorrected degrees of freedom for these analyses and for t-tests that required correction because of heterogeneity of variance.

Procedure

Data reported here are based on the second of two test occasions conducted approximately 2 weeks apart in the Cognitive Psychophysiology Laboratory at the University of Southern California. Subjects gave informed consent before each of the two sessions. The first session involved the measurement of secondary reaction time during a selective attention task similar to the one reported here (Hazlett, Dawson, Filion, Schell, & Nuechterlein, 1991). The second experimental session began with attachment of electrodes for the recording of skin conductance and startle eyeblink. Subjects were then presented with audiotape instructions stating that their task was to listen to a series of high and low pitch tones presented through headphones, count silently the number of "longer than usual" high pitch tones, and simply ignore the low pitch tones (the to-be-attended pitch was counterbalanced across subjects). Subjects 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. Subjects received $5.00 if their count was correct, $4.00 if their count was off by one, and so forth.

After the instructions, a 5-min resting baseline was recorded, at the end of which subjects were given four warned presentations of the startle-eliciting burst of noise alone in order to adjust polygraph sensitivity. After the noise bursts, subjects were given one example of the high pitch tone and one example of the low pitch tone and were told that each of these examples was the standard 5 s in duration. At this time all subjects confirmed that they could discriminate between the high and low tones. After examples of the two tones were presented, the main portion of the experimental session began.

The main portion of the experiment consisted of a total of 48 tone
trials—24 high and 24 low pitch tones in a mixed, fixed semirandom order with intertone intervals ranging between 20 and 30 s (see Dawson et al., 1989, for further details). Of the 24 tones of each pitch, 16 included the startle-eliciting noise. Of these 16 trials, there were 4 presentations of the startle-eliciting noise at each of four lead intervals: 60 ms, 120 ms, 240 ms, and 2000 ms. The remaining 8 trials without startle-eliciting noises were intermixed so as to measure the SCORs to the tone prepulses without contamination by the noise. In effect, then, there was a to-be-attended prepulse and a to-be-ignored prepulse, each presented with the startling noise at three short lead intervals (60, 120, and 240 ms) and one long lead interval (2000 ms).

In addition to the startle noises presented at critical lead intervals, startle stimuli also were presented at prescheduled times during the intertone intervals to provide a baseline measure of startle amplitude. Specifically, startle noises were presented during 75% of the intertone intervals, with no more than one startle stimulus presented during any intertone interval. Startle-blink magnitudes to the loud noises presented during the intertone intervals served as baseline measures with which to compare blink magnitudes to the same startle stimuli presented at the critical lead intervals following the prepulses.

**Experimental Stimuli**

The to-be-attended and to-be-ignored prepulses consisted of 800 Hz and 1200 Hz tones presented at a volume of 70 dB(A). The tones were generated with a Fordham (FG-80) signal generator, with rise times controlled by a Coulbourn S48-04 rise/fall gate set at 25 ms. The startle stimulus consisted of a 100 dB(A) white noise that was 50 ms in duration. The startle 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 by a laboratory computer.

**Recording and Scoring of Dependent Variables**

The two primary dependent variables were the magnitude of the SCOR elicited by to-be-attended and to-be-ignored prepulses on trials without startling stimuli and the modification of the startle eye-blink magnitude produced during the to-be-attended and to-be-ignored prepulses at the four lead intervals.

SCORs were measured according to the standard procedures outlined by Dawson, Schell, and Filion (1990). Skin conductance was recorded from the volar surface of the distal phalanges of the first and second fingers of the nonpreferred hand with silver-silver chloride electrodes filled with 0.05 molar NaCl in a Unibase paste. Double-sided adhesive collars allowed a 10-mm contact area with the skin. A constant 0.5 V was applied across the electrodes, and the skin conductance signal was amplified by a Grass 7P1 preamplifier and a 7DAE driver amplifier. SCORs were computer scored off-line as increases in skin conductance beginning between 1.0 and 3.0 s following tone onset and having a minimum response amplitude of 0.05 μS. Startle eye-blink amplitude was measured as electromyographic activity (EMG) from two miniature electrodes (4 mm in diameter) placed over the orbicularis oculi muscle of the left eye, one electrode 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 integrator/preamplifier and a 7DAE driver amplifier. Eye blinks were recorded at full wave rectification and with integration at a time constant of 20 ms. The EMG signal was digitized at a rate of 1000 Hz for 300 ms following the presentation of each startle-eliciting loud noise. The startle eye-blink amplitude was then scored off-line with a modification of the program by Balaban, Losito, Simons, and Graham (1986). Startle-blink amplitude scores were converted to μV units, and differences were then computed between the mean baseline intertone interval eye-blink amplitude and the intratone eye-blink amplitudes. Because difference scores in absolute μV units are correlated with baseline startle-blink amplitude, the difference scores were converted to percentage change units, which removed the dependence on baseline in the present data. A positive SEM score indicates startle facilitation relative to baseline, whereas a negative SEM score indicates startle inhibition relative to baseline.

**Results**

**Skin Conductance Orienting Responses**

SCORs were measured as independent indexes of attentional processing of the to-be-attended and to-be-ignored prepulses on trials without presentation of the startle noise. Table 1 shows the mean SCOR magnitudes of the schizophrenic and normal control groups to the to-be-attended and to-be-ignored prepulses. A 2 (group) X 2 (prepulse type) analysis of variance (ANOVA) revealed significantly larger SCORs to the to-be-attended prepulse than the to-be-ignored prepulse, F(1, 27) = 7.46, p < .01. There was neither a significant group main effect nor a Group X Prepulse Type interaction. Thus, both the patients and controls responded more to the to-be-attended prepulse than to the to-be-ignored prepulse, consistent with previous results obtained with this paradigm with normal college students.

**Baseline Startle**

Analyses of the amplitudes of the startle eye-blink responses elicited during the intertone intervals (baseline) revealed a control subject whose score was more than 2 standard deviations above the nearest score in blink amplitude. Therefore, this subject was considered an outlier, and his data were discarded, reducing the control group sample to 14 subjects. No outlier subjects were identified with the baseline startle eye-blink measure in the patient group. Analyses of the mean startle eye-blink amplitude during the intertone interval revealed that the schizophrenic patients exhibited larger than normal responses, t(27) = 2.15, p < .05 (M = 26.67 μV and SD = 26.70 for the patients; M = 10.82 μV and SD = 9.82 for the control subjects). Therefore, we conducted analyses of covariance in parallel with the principal ANOVAs reported below, using the baseline eye-blink amplitude as a covariate, and confirmed the effects reported here. Thus, differences between schizophrenic and matched control

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Means and Standard Deviations of Skin Conductance Orienting Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>To-be-attended prepulse</td>
</tr>
<tr>
<td></td>
<td>M</td>
</tr>
<tr>
<td>Normal controls</td>
<td>.25</td>
</tr>
<tr>
<td>Schizophrenic patients</td>
<td>.19</td>
</tr>
</tbody>
</table>
groups in SEM scores are not due to differences in baseline startle reactivity.

**SEM to the To-Be-Ignored Prepulse**

Figure 1 presents the SEM scores of the patients and the controls for the to-be-attended prepulse and the to-be-ignored prepulse at all four lead intervals. As described earlier, it was anticipated that SEM to the to-be-ignored prepulse would provide an estimate of predominantly automatic attentional processes. Therefore, the SEM scores at the short lead intervals following the to-be-ignored prepulse were submitted to a 2 (group) × 3 (lead interval: 60, 120, and 240 ms) ANOVA. This analysis revealed a significant lead-interval main effect, $F(2, 54) = 4.04, p < .05$, indicating that prepulse inhibition was greater at the 60- and 120-ms intervals than at the 240-ms interval. However, there was no group main effect or interaction effect, indicating that the patients did not differ from normal subjects in prepulse inhibition following the to-be-ignored prepulse. Similarly, no difference between the groups was found in blink facilitation at the 2000-ms long lead interval following the to-be-ignored prepulse.

**SEM to the To-Be-Attended Prepulse**

As indicated previously, differences in SEM between the to-be-attended and to-be-ignored prepulses should provide an estimate of predominantly controlled attentional modulation of startle blink. To evaluate statistically these effects at the short lead interval, we performed a 2 (group) × 2 (prepulse) × 3 (lead interval) ANOVA on the SEM scores obtained at the three short lead intervals (the 60-, 120-, and 240-ms points in Figure 1). This analysis revealed a significant Group × Prepulse × Lead Interval interaction effect, $F(2, 54) = 3.42, p < .05$. This effect indicates that the patients and the controls differed significantly in their differential startle reactions following the to-be-attended and to-be-ignored prepulses at different lead intervals. Simple effects tests confirmed that the matched normal controls showed significantly greater blink inhibition following the to-be-attended prepulse than following the to-be-ignored prepulse at 120 ms, $F(1, 13) = 23.18, p < .001$, consistent with our previous findings with normal college students. However, as can be seen in Figure 1, the patients failed to show differential inhibition at any short lead interval. Thus, the normal controls demonstrated attentional modulation of prepulse inhibition of the startle reflex, whereas the patients showed a lack of attentional modulation of prepulse inhibition. In further support of this conclusion, we analyzed between-group differences at each lead interval. These analyses confirmed that, relative to the controls, the patients exhibited significantly smaller differential prepulse inhibition at 120 ms following to-be-attended and to-be-ignored prepulses, $t(21) = 2.37, p < .05$.

We next performed a 2 (group) × 2 (prepulse) ANOVA on the SEM scores at the long lead interval (the 2000-ms point in Figure 1). The Group × Prepulse interaction was significant, $F(1, 27) = 4.29, p < .05$, indicating that the groups differed in their differential blink modification to the to-be-attended and to-be-ignored prepulses. Simple effects tests confirmed that the normal controls exhibited significantly greater startle blink facilitation at 2000 ms following the to-be-attended prepulse than the to-be-ignored prepulse, $F(1, 13) = 11.48, p < .01$, again consistent with past findings with normal college students, whereas the schizophrenic patients failed to respond differentially. Thus, similar to the short lead-interval findings, only the normal control group exhibited significant attentional modulation of the startle blink at the long lead interval. A between-group comparison confirmed that, relative to the controls, the patients exhibited significantly less differential blink facilitation at the 2000-ms lead interval following the to-be-attended and to-be-ignored prepulses, $t(27) = 2.07, p < .05$. This long lead-interval finding suggests that the patients failed to maintain a strong selective attentional focus during the to-be-attended prepulse, at least at 2000 ms following onset of the to-be-attended prepulse.

![Figure 1](image.png)

*Figure 1.* Mean startle eye-blink modification scores as a function of prepulse type and lead interval for the demographically matched normal control subjects (left panel) and the schizophrenic patients (right panel). (Asterisks indicate significant differences between to-be-attended and to-be-ignored prepulses.)
Analyses of individual subject data, as opposed to group effects, were conducted to examine the individual consistency of the group effects. To assess the attentional modulation effect at the individual case level, we computed differences between the SEM scores for the to-be-attended and the to-be-ignored prepulses at the 120-ms and 2000-ms lead intervals for each individual subject. Negative difference scores indicate more inhibition following the to-be-attended prepulse, whereas positive difference scores indicate more facilitation following the to-be-attended prepulse. The difference scores for individual subjects at the 120-ms lead interval are shown in Figure 2. As can be seen, 13 of the 14 normal controls exhibited greater inhibition following the to-be-attended prepulse; the one exception was a subject who had 100% inhibition to both the to-be-attended and to-be-ignored prepulses. Thus, the number of normal control subjects responding in the predicted direction is highly significant (according to a sign test; \( n = 13, x = 0, p < .001 \)). In contrast, 9 of the 15 patients showed this direction of difference and, as can be seen in Figure 2, most of their difference scores hovered near zero. The number of patients who responded differentially in the direction of greater inhibition to the to-be-attended prepulses did not reach statistical significance (\( n = 14, x = 4, p = .09 \)).

Figure 3 shows the difference scores for individual subjects at the 2000-ms lead interval for normal controls and schizophrenic patients. As can be seen, 13 of the 14 normal controls exhibited greater startle blink facilitation following the to-be-attended prepulse than the to-be-ignored prepulse (\( n = 14, x = 1, p = .001 \)). Ten of the 15 schizophrenic patients responded in this direction, a nonsignificant effect (\( n = 15, x = 5, p = .15 \)). (Incidentally, the 2 patients whose startle eye-blink differential facilitation scores appear quite normal in Figure 3 are not the same 2 patients whose startle-blink differential inhibition scores appear normal in Figure 2.)

**Behavioral Performance**

As described earlier, the subjects’ task was to count the number of longer than usual (7 s rather than the usual 5 s) occurrences of one pitch tone and to simply ignore tones of the other pitch. There were 10 longer than usual occurrences of the to-be-attended pitch. The majority of both groups performed well on the task, with 9 of the 15 patients and 13 of the 14 controls giving answers that were within one of the correct answer. Nevertheless, the patient group’s average error score was significantly poorer than that of the controls (patients, \( M = 2.07, SD = 2.37 \); controls, \( M = 0.36, SD = 0.84 \)), \( t(27) = 2.62, p < .05 \). Therefore, we analyzed the SEM discrimination for the subgroups of the 9 patients and the 13 controls who performed well on the task. The mean differences between to-be-attended and to-be-ignored prepulses at the 120-ms and 2000-ms lead intervals remained significant (\( p < .01 \)) in the subgroup of normal controls, \( F(1, 12) = 24.98 \) and 9.40, respectively, and the SEM differences remained nonsignificant in the subgroup of schizophrenic patients. However, the difference between the normal and schizophrenic subgroups of good performers in differential SEM was no longer significant, unlike between the groups as a whole.

**Discussion**

Both group data and individual data clearly demonstrate for the first time that recent-onset, relatively asymptomatic schizophrenic patients have impaired attentional modulation of SEM.
at both short and long lead intervals. However, the schizophrenic patients did not exhibit a global deficit in SEM. That is, patients did not differ from normal in SEM following the to-be-ignored prepulse, nor did they differ from normal when SEM was averaged over to-be-attended and to-be-ignored prepu-

tures. Instead, the impairment was specific to the to-be-attended pre-
pulse. Inspection of Figure 1 suggests, and statistical analyses con-

mirmed, that the differences between the groups were significant for the SEM scores to the to-be-attended prepulse, and in their discrimination between attended and ignored prepu-
tures, at both the short 120-ms lead interval and the long 2000-ms lead interval. The normal control group showed significantly greater differential SEM to the to-be-attended and to-be-

ored prepu-
tures at both the 120-ms and 2000-ms lead intervals than did the schizophrenic group.

The overall pattern of SEM results across the four lead inter-

vals suggests a sequence of processes activated by this task, some of which are impaired in young, relatively asymptomatic schizophrenic patients and others of which are not. The four hypothetical sequential processes are as follows: (a) Premotor stimulus detection and evaluation operative shortly after stimu-

lus onset is the predominant influence at the 60-ms lead inter-

val; (b) stimulus discrimination and allocation of limited con-

rolled resources at approximately 100 ms following onset of the to-be-attended prepulse is an additional inhibiting influence during the to-be-attended prepulse at the 120-ms lead interval; (c) postdiscrimination transition from stimulus evaluation to the beginning of the time-judgment task is the predominant influence at 240 ms; and (d) sustained selective focusing of attention toward the to-be-attended prepulse in order to judge tone duration is the ongoing predominant influence at the 2000-ms lead interval. Thus, we posit that the dip seen in normal blink magnitude during the attended prepulse as one moves from a 60-ms lead interval to a 120-ms lead interval represents either the call for, or the actual allocation of, con-

rolled attentional resources to confirm the tentative preatten-
tive evaluation of this prepulse. This 120-ms dip represents a heighten-
ing of the gating process that screens out any competing stimuli, including those in the same modality as the to-be-

attended prepulse. The jump seen as one moves from the 120-

ms to the 2000-ms lead intervals represents the sustained allo-
cation of controlled attentional resources to perform the tone-length judgment task. The result of this sustained attention appears to be enhanced processing of all stimuli in the modality to which attention is directed. According to this hypo-

thesized sequence of events, relatively asymptomatic schizo-

phrenic outpatients are not measurably deficient in the early preattentive stimulus detection and evaluation process or in the transition to the time-judgment process; rather, they are defi-
cient in the allocation of controlled resources at 120 ms to evalu-

ate the to-be-attended prepulse and in focused, sustained con-

rolled attention at 2000 ms. Whether this hypothesis is correct or not, it should be emphasized that the differential SEM ef-
facts at 120 ms and 2000 ms are very robust in normal popula-
tions, as we have now replicated them in three additional groups of normal college students (Filion et al., in press-a, in press-b; Schell, Dawson, Hazlett, & Filion, 1993), in addition to the present group of demographically matched normal con-

The lack of group differences with respect to prepulse inhibi-
tion during the to-be-ignored prepulse suggests that the basic automatic sensorimotor gating mechanism may not be abnor-

mal in recent-onset, relatively asymptomatic schizophrenic pa-

tients under the present task conditions; rather, it is the con-

rolled attentional modulation of the gating mechanism that appears abnormal. This conclusion is consistent with informa-
tion processing models that specify that automatic processing of schizophrenic patients is normal but that controlled processing is deficient (e.g., Callaway & Nagdhi, 1982). However, the present conclusion does not appear consistent with results re-

ported by Braff et al. (1978; Braff, Grillon, & Geyer, 1992) and

Grillon et al. (1992), who found reduced overall prepulse inhibi-
tion in an uninstructed passive attention condition with chronic, symptomatic, and medicated patients, suggesting im-

paired automatic sensorimotor gating. The differences be-

 tween our results and those of these earlier studies may be due to differences in patient populations, medication status, or our imposition of an active attentional task.

The passive-versus-active task difference is theoretically inter-
esting because it highlights the distinction between automatic information processing and controlled information processing,
both of which have been hypothesized to be defective in schizo-

denia. Seen from this perspective, Braff et al's (1978; Braff, Grillon, & Geyer, 1992) and Grillon et al.'s (1992) results, ob-
tained in a passive nontask paradigm, suggest a possible auto-

matic processing impairment, whereas our results, obtained in an active task condition, suggest a controlled processing deficit. Our to-be-ignored prepulse might be expected to be predomi-
nantly automatically processed because it does not require per-
formance of the tone-duration task. However, processing the to-be-ignored prepulse was certainly not entirely an automatic process because subjects were performing a task that required stimulus discrimination, and sufficient attention had to be allo-
cated to the to-be-ignored prepulse to at least initially identify it as the task-irrelevant stimulus. Therefore, the to-be-ignored prepulse in an active attention paradigm probably is not pro-
cessed in the same manner as the nontask prepulse in a passive attention paradigm. This line of reasoning suggests that schizophrenia patients (and possibly college students at risk for schizo-

phrenia, see Simons & Giardina, 1992) are impaired in passive automatic processing, that superficial processing of to-be-ig-

ored stimuli in a task setting is not sensitive to schizophrenic deficits, but that focused and sustained attention to to-be-at-
tended task stimuli is sensitive to schizophrenic deficits. This is obviously a speculative hypothesis in need of testing. A particu-

larly important issue for future research is to clarify whether schizophrenic patients have deficits in automatic SEM as sug-
gested by Braff et al. (1978; Braff, Grillon, & Geyer, 1992) and

Grillon et al. (1992), or in controlled modulation of SEM as in-
dicated here, or whether there are different subgroups of pa-
tients, some with predominately automatic processing dis-
orders and some with predominately controlled processing dis-
orders.

Another important issue for future research concerns the state versus trait nature of the SEM deficits. The present results suggest that the controlled attentional impairment of SEM may be a traitlike vulnerability factor because the impairment was present in relatively asymptomatic outpatients. If the impair-
mment was solely related to the psychotic state, it would not be present in the relatively asymptomatic state (see Nuechterlein & Dawson, 1984; Nuechterlein et al., 1991). Another more definitive approach to determining the trait versus state nature of the SEM impairments for future research would be to test the same patients during the psychotic state and the remitted state. Still another line of evidence consistent with a trait interpretation are the findings among putatively at-risk college students of impaired SEM in a passive nontask paradigm (Simons & Giardina, 1992) and in an active task paradigm (Schell et al., 1993). These results are particularly important because the impairments in putatively at-risk college students cannot be due to the effects of medications or other secondary consequences of being diagnosed as having schizophrenia.

Also of interest is the apparent lack of concordance of the SEM results with task performance and the SCORs. The SCOR data did not significantly discriminate the patient and control groups and, although performance was abnormally poor in the patient group as a whole, SEM impairments were found in a subgroup of patients whose task performance was normal. This pattern of results suggests that the attentional modulation of SEM may be sensitive to subtle impairments that do not necessarily manifest themselves in other forms of behavior while the patients are largely asymptomatic. However, although the good performing patients failed to exhibit significant differential SEM following to-be-attended and to-be-ignored tones, it also is true that these well-performing patients did not differ significantly from controls in differential SEM. Clearly, more research is needed to better determine the relationship between deficits in behavioral performance and deficits in SEM.

In summary, although the startle eye-blink reflex is obligatory to certain rapid-onset stimuli, it can be modified by a variety of psychological processes at different levels of the central nervous system. Prepulse inhibition of the startle reflex is an automatic process mediated at the midbrain level (e.g., Leitner & Cohen, 1985), but it also can be modulated by a cortico–striato-pallidal–thalamic circuit (Geyer, Swerdlow, Mansbach, & Braff, 1990; Swerdlow & Koob, 1987). The present results obtained with normal subjects indicate that both the short lead-interval prepulse inhibition effect and the long lead-interval facilitation effect can be modulated by controlled cognitive processes, presumably mediated by top-down influences from the cortex. Thus, the absence of attentional modulation of SEM in young, relatively asymptomatic schizophrenic patients implicates a possible traitlike impairment at the cortical level. More broadly, the results suggest that the measurement of attentional modulation of SEM is useful in the detection and quantification of subtle controlled cognitive impairments, and it may provide a nonverbal, reflexive, state-independent marker of the vulnerability to schizophrenia.

References


Graham, F. K. (1992). Attention: The heartbeat, the blink, and the brain. In B. A. Campbell, H. Hayne, & R. Richardson (Eds.), Attention...
tion and information processing in infants and adults: Perspectives from human and animal research (pp. 3–29). Hillsdale, NJ: Erlbaum.


