Prefrontal cortex glucose metabolism and startle eyeblink modification abnormalities in unmedicated schizophrenia patients

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Abstract

Attentional modulation of the startle reflex was studied in 16 unmedicated schizophrenia patients and 15 control individuals during the $^{18}$F-2-deoxyglucose uptake period for positron emission tomography. In a task involving attended, ignored, and novel tones that served as prepulses, control individuals showed greater prepulse inhibition (PPI) at 120 ms and greater prepulse facilitation at 4,500 ms during attended than during ignored prepulses; the amount of PPI and facilitation during novel prepulses was intermediate. In contrast, patients failed to show differential PPI at 120 ms and tended to show greater facilitation at 4,500 ms during novel prepulses. For control individuals, greater PPI was associated with higher relative metabolic activity rates in prefrontal (Brodmann Areas 8, 9, and 10 bilaterally) and lower in visual cortex. Patients showed this relationship only for Area 10 on the left. Patients also had low metabolism in superior, middle, and inferior prefrontal cortex. Consistent with animal models, our results demonstrate the importance of the functional integrity of prefrontal cortex to PPI modulation.

Descriptors: Attention, Schizophrenia, Prepulse inhibition, Startle eyeblink modification, Positron emission tomography, Frontal lobe

Schizophrenia is characterized by significant deficits in attention and information processing that have been described since the time of Bleuler (1911/1950) and Kraepelin (1913/1919). The nature of these impairments, however, is still not clearly understood. Paradigms that can provide insight into the elementary operations or components that are involved in attention and information processing and the underlying neurophysiological mechanisms may further our understanding of core schizophrenia deficits. Startle eyeblink modification (SEM) is a powerful psychophysiological paradigm that may have the potential to integrate research across various domains of scientific inquiry such as cognitive science, clinical science, and neuroscience (Dawson, 1990).

SEM occurs when innocuous, non-startling stimuli (prepulses) are presented shortly before startle-eliciting stimuli; prepulses reliably inhibit or facilitate the amplitude of the startle reflex, including the eyeblink reflex. Different SEM effects are observed depending upon the temporal lead (preceding) interval between the onset of the prepulse and the onset of the startle stimulus (pulse). When the lead interval is short (~30–500 ms), there is a reliable reduction of the startle response amplitude compared with when the reflex is elicited in the absence of the prepulse. This short lead-interval prepulse inhibition (PPI) may reflect the action of an automatic sensorimotor gating system that is protective of early preattentive processing of the prepulse (Braff & Geyer, 1990; Graham, 1975). This phenomenon has been well documented in animals (see review by Ison & Hoffman, 1983) and normal humans (see reviews by Anthony, 1985; Filion, Dawson, & Schell, in press; Graham, 1975; Lang, Bradley, & Cuthbert, 1990). PPI occurs in 90–100% of normal individuals who show reliable eyeblink reflexes; the effect is quite robust, in the range of 50–100% inhibition (Filion et al., in press).

There is clear evidence that PPI is at least partially an automatic effect. For example, PPI is observed in decorticate rats (Ison, O’Conner, Bowen, & Bocirnea, 1991), in sleeping human adults (Silverstein, Graham, & Calloway, 1980), and on the first presentation of a lead stimulus—startle stimulus pairing (Graham, 1975). However, there is also evidence that PPI can be modulated by controlled attentional processes (e.g., DelPezzo & Hoffman, 1980; Filion, Dawson, & Schell, 1993, 1994; Hackley & Graham, 1987; Hackley, Woldorff, & Hillyard, 1987). For example, Filion et al.
Facilitation effect may reflect the sensory enhancement and inhibition associated with modality specific selective attention. In the active-attention tone-length-judgment paradigm, Filion et al. (1993) reported greater facilitation of the startle eyeblink reflex with a lead interval of 2,000 ms during the attended auditory prepulse than during the ignored auditory prepulse. Thus, similar to short lead interval PPI at 120 ms, long lead interval SEM can also be modulated by controlled attentional processes. Filion et al. (in press, p. 26) concluded that “further research is necessary to determine whether the attentional processes have effects that are modality specific, modality-independent, or both, depending upon the nature of the attentional task.”

In summary, a series of cognitive processes related to the present study are thought to modulate startle reflexes in the tone paradigm first employed by Filion et al. (1993). By the 120-ms lead interval, the discrimination between attended and ignored prepulses has occurred and the attended prepulse is receiving enhanced processing, reflecting controlled modulation of the gating process. By 240 ms, this additional protection is no longer present; information involved in early processing has been extracted from the significant prepulse, and a transition is beginning between stimulus discrimination and later processes involved in carrying out the task. At the long lead interval (e.g., 2,000 ms or 4,500 ms), because the prepulse is a continuous one and because the prepulse and the startle stimulus are in the same modality, facilitation occurs during both the attended and ignored prepulses. However, facilitation is greater during the attended prepulse, reflecting the allocation of greater controlled attentional resources to that stimulus (Dawson, Hazlett, Filion, Nuechterlein, & Schell, 1993; Schell, Dawson, Hazlett, & Filion, 1995).

Efforts to understand PPI deficits in schizophrenia have been pursued as two independent lines of investigation. The first involves clinical studies of schizophrenia patients and healthy control individuals that attempt to determine whether group differences exist and to specify the component processing deficits that contribute to group differences. Several investigators have examined PPI in medicated schizophrenia patients in an uninstructed passive attention condition. Braff et al. (1978) used a continuous mild tone as the prepulse and a startling burst of loud white noise as the startle stimulus; Braff, Grillon, and Geyer (1992) used a discrete mild white noise as the prepulse and a burst of white noise as the startle stimulus. In all three studies, patients exhibited impaired PPI compared with findings in healthy control individuals. Taken together, these PPI findings suggest that schizophrenia patients have poor automatic, preattentive sensorimotor gating that can lead to sensory overload, thought disorder, and cognitive fragmentation associated with severe psychotic symptoms (Braff, Swerdlow, & Geyer, 1995).

We have extended this line of investigation by studying attentional modulation of PPI in schizophrenia. Dawson et al. (1993) tested recent onset medicated schizophrenia patients and demographically matched control individuals who were instructed to attend to one type of auditory prepulse (e.g., a high-pitched tone) and to ignore the other auditory prepulse type (e.g., a low-pitched tone). They reported that control individuals exhibited greater PPI during the attended prepulse than during the ignored prepulse, demonstrating the expected attentional modulation of PPI of the startle reflex. In contrast, the patients failed to exhibit differential PPI during the attended and ignored prepulses. These findings suggest a controlled attentional processing deficit in schizophrenia. Dawson et al. (1993) also measured startle modification at a long lead interval of 2,000 ms. Similar to the PPI findings, only the control individuals exhibited significant attentional modulation of the startle reflex at the 2,000-ms lead interval. This finding suggests that the patients failed to maintain a strong selective attentional focus during the attended prepulse, at least 2,000 ms following onset of the attended prepulse.

The second line of investigation into PPI deficits in schizophrenia involves a neuroscience approach. Its focus has been to elucidate the neural substrates of impaired modulation of PPI in an animal model. PPI is indexed by whole body startle in the rat. Although the primary startle reflex circuit is located in the hindbrain and the basic PPI circuit appears to be located in the midbrain, forebrain structures such as the prefrontal cortex apparently can modulate PPI (reviewed by Dawson, Schell, Swerdlow, & Filion, 1997; Swerdlow, Caine, Braff, & Geyer, 1992). Because controlled attentional processing can modulate PPI, higher order brain regions should modulate PPI. Consistent with this view, Swerdlow and coworkers have demonstrated that cortical-striatal-pallidothalamic circuitry plays a key role in modulating PPI in the rat (Swerdlow, Braff, Taaid, & Geyer, 1994; Swerdlow & Koob, 1987). Both pharmacological and lesion manipulations of various brain structures within this circuitry cause impaired PPI (reviewed by Dawson et al., in press; Swerdlow et al., 1992). Taken together, there is compelling evidence to support the viewpoint that impaired PPI in the rat may be a valid animal model of deficient sensorimotor gating deficits in schizophrenia (Swerdlow et al., 1994). A key area within this neural circuitry is the prefrontal cortex. Several recent studies have shown that the medial prefrontal cortex modulates PPI in the rat (Bubser & Koch, 1994; Koch & Bubser, 1994; Swerdlow et al., 1995). Other relevant work by Knight, Scabini, and Woods (1989) has shown that patients with focal lesions in dorsolateral prefrontal cortex exhibit abnormally increased middle-latency auditory evoked potential amplitude, which is believed to index an early inhibitory mechanism that “gates” or controls input to primary auditory cortex regions. In addition, data from neuroimaging and postmortem studies suggest that frontal lobe dysfunction may be integral to the pathophysiology of schizophrenia (e.g., Akbarian et al., 1996; Buchsbaum et al., 1982; Davies & Lewis, 1995; Weinberger, 1987). Functional neuroimaging techniques such as positron emission tomography (PET) provide the capability to test in humans hypotheses derived from animal models of PPI by examining the relationship between brain function in...
key anatomical regions such as prefrontal cortex and psychophysiological measures such as PPI. However, the relationship between clinical human and animal PPI research to date has been a matter of informed speculation and inference rather than direct experimental investigation.

In the present study, we used PET to examine regional glucose metabolism during a carefully controlled attention-to-pulse paradigm to test the following hypotheses: (a) prefrontal cortex function will be associated with PPI in healthy volunteers; (b) unmedicated schizophrenia patients will show SEM abnormalities similar to those observed in medicated patients; (c) patients will also show SEM abnormalities during the presentation of a novel prepulse, and (d) PPI deficits in patients will be associated with abnormal prefrontal cortex function.

Method

Participants

Sixteen patients (11 men, 5 women; age [years]: M = 37, SD = 8.6, range = 28–51; education [years]: M = 12.3, SD = 2.3) were recruited from the Mount Sinai, Elmhurst, and Bronx VA hospitals. Fourteen patients were right handed, and two were left handed based on the Edinburgh Handedness Inventory (Oldfield, 1971). The patients were evaluated with the Comprehensive Assessment of Symptoms and History (CASH; Andreasen, Flaum, & Arndt, 1992) and diagnosed as having schizophrenia (n = 15) or schizoaffective disorder, mainly schizophrenic (n = 1), according to DSM-III-R and DSM-IV criteria. Patients were either never medicated (n = 3 men) or had been neuroleptic free for a minimum of 2 weeks (n = 13: 8 men, 5 women; shortest period of washout = 14 days; range = 14 days to 1 year, Mdn = 14 days). On the PET scan day, patients were assessed with the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962). Total psychopathology scores on the 18-item BPRS ranged from 27 to 58 (total M = 45.6, SD = 9.1, minimum possible rating = 18).

Fifteen normal volunteers (9 men, 6 women; age [years]: M = 31, SD = 10.4, range = 20–55; education [years]: M = 15.5, SD = 2.8) were recruited by advertisement. All of the normal volunteers received a CASH interview to exclude those characterized by a history of psychiatric illness in themselves or in their first-degree relatives.

All participants were screened by medical history, physical examination, and laboratory testing. Individuals with a history of substance abuse/dependence, neurological disorders, or head trauma were excluded. In addition, participants with a positive urine test for drugs of abuse on the day of the PET scan were eliminated. All participants provided written informed consent and were paid for their participation.

Usable eyeblink data were obtained for one participant and one control participant because of movement artifacts during the period when the radiolabeled sugar analog was taken up by the brain as a tracer of brain metabolic rate. The 32-min FDG uptake period coincided with the duration of the tone producing confines of the PET scanner itself. Only after completion of the main portion of the experiment was achieved without producing anxiety by having the psychophysiological equipment located just outside the room. Thus, continuous monitoring for movement artifacts during the procedure was achieved without producing anxiety by having the psychophysiological equipment in view of the participant. The main portion of the experiment took place during the period when the radiolabeled sugar analog was taken up by the brain as a tracer of brain metabolic rate. The 32-min FDG uptake period coincided with the duration of the tone SEM paradigm, a procedure similar to that used in our previous study with medicated schizophrenia patients (Dawson et al., 1993) and in the study of Filion et al. (1993) with college students. A particular advantage of the PET/FDG method for psychophysiological studies is that it permits task-related brain activity to be “labeled” while the participant is in a comfortable chair in a quiet testing room rather than in the claustrophobic, often anxiety-producing confines of the PET scanner itself. Only after completion of the 32-min period for FDG uptake and SEM stimuli presentation was the participant moved to the PET scanner. Thus, the brain activity patterns revealed during the scan represent the participant’s mental processes during the uptake period/psychophysiological paradigm and not during the scanning procedure itself.

The 32-min startle paradigm consisted of 52 tone trials: 22 high tones, 22 low tones, and 8 novel tones in a mixed, fixed semi-
random order with intertone intervals of 29–39 s \((M = 34\, \text{s})\). Of the 22 high or low tones, 12 included the startle-eliciting stimulus. Of these 12 trials, there were four presentations of the startle-eliciting noise at each of three lead intervals: 120 ms, 240 ms, and 4,500 ms. The remaining 10 trials without startle-eliciting noises were intermixed to measure the skin conductance orienting responses to the tone prepulses without contamination by the startle stimulus. Skin conductance data are not presented here. Given that previous work has shown that attentional modulation of SEM occurs at both the 120-ms and 4,500-ms lead intervals but not at the 240-ms interval and because we wanted to minimize the number of presentations of the novel tone, there were only eight presentations of the novel tone with four presentations of the startle-eliciting noise at each of two lead intervals: 120 ms and 4,500 ms.

In addition to the startle noises presented at critical lead intervals, startle stimuli were also presented at preselected times during the intertone intervals to provide a baseline measure of startle amplitude. Specifically, the startle stimulus was presented during 30 of the intertone intervals, with no more than one startle stimulus presented during any intertone interval. Startle eyeblink 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 during the prepulses.

**PET and magnetic resonance (MR) imaging.** PET scans were obtained with a head-dedicated scanner (model 2048, GE Medical Systems) with measured resolution of 4.5 mm in plane (4.2–4.5 mm across 15 planes) and 5.0 mm axially. PET images were reconstructed with a blank and a transmission scan for measured attenuation correction using the Hanning filter (width 3.15). Within 1 week of receiving their PET scan, all participants received an MR scan, which was used as an anatomical template. For each participant, the same individually molded thermoplastic face mask was used during both the PET and MR scans to keep the head stationary and permit accurate coregistration of PET and MR images. MR scans were acquired with a Signa 5× system (GE Medical Systems) with the following parameters: repetition time = 189 ms, echo time = 5 ms, flip angle = 40°, slice thickness = 1.2 mm, pixel matrix = 256 × 256, field of view = 23 cm. For each individual, our version of the surface-fitting method of Pelizzari, Chen, Spellbring, Weichselbaum, and Chen (1989) was used to coregister all PET scan slices to MR images in the axial, coronal, and sagittal planes. Brain edges were outlined without knowledge of diagnosis on an MR axial slice at midstromial level and at an approximately matching PET slice using a semiautomated thresholding algorithm. Intertracer MR edging reliability with our method is high (intraclass correlation \(r = .99\)) and has been reported previously (see Shihabuddin et al., in press, for more details). PET volume was translated \((x, y)\) and rotated on the center of mass to minimize sum of squared differences in edges. PET volume was translated and rotated in the sagittal plane with the atlas bone as the rotation point. The coronal plane was treated similarly, and the axial plane was redone as the last step. PET pixel size after coregistration was identical to the MR pixel size of 0.898 × 0.898 mm.

Once all the PET and MR images were coregistered, a new version of a lateral cortical surface technique (see Buchbaum et al., 1982; Harris, Links, Pearlson, & Camargo, 1991; Siegel et al., 1993) was used to obtain regions of interest. For each lobe of the brain, four separate major gyral divisions of the cortex were located on the lateral surface based on a brain atlas (Matsui & Hirano, 1978) (Figure 1). For each participant, mean relative glucose metabolic rate (rGMR) was then calculated with gray/white matter and cerebrospinal fluid (CSF) segmentation for each of the 16 areas, as an average across 10 slices (Figures 1 and 2A: left column). This new technique allows more accurate quantification of glucose metabolism in gray matter pixels while minimizing the contribution of CSF pixels with PET/MR image coregistration and MR segmentation. Thus, the confound of cortical atrophy and/or ventricular enlargement is minimized.

In addition, a more detailed Brodmann analysis of frontal lobe glucose metabolism was conducted on coronal slices using a digitized version of an atlas (Perry, Oakley, & Perry, 1996) that includes 33 coronal slice maps of Brodmann areas defined by microscopic examination of one entire postmortem brain. Thus,
this analysis complements the lateral cortical surface technique by allowing medial and orbital areas of the frontal lobe to be examined in addition to the lateral cortex. For each participant, the most anterior coronal slice that showed both left and right frontal lobe and the most anterior coronal slice showing the corpus callosum connecting the two hemispheres was determined. Next, six equidistant slices between these anterior and posterior boundary slices of the frontal lobe (to match the Perry et al. atlas proportionately) were outlined, and a midline was marked (see Figure 2A, right column). Finally, specific Brodmann areas of the lateral, medial, and orbital frontal cortex were delineated by proportional circumferential position. On each of the six coronal slices, the center of mass of each hemisphere was located, and 30 radii to the cortical surface were drawn. The same radii were drawn on the Perry

Figure 2. See caption on facing page.
The dependent measure for all PET data analyses was rGMR, expressed as the mean activity value (in nanocuries) for all gray matter pixels in each of the cortical regions of interest divided by the mean activity value for whole brain activity.

**Design**
The study used a $2 \times 3$ mixed factorial design for the 120-ms and 4,500-ms lead-interval SEM data. The first variable consisted of two participant groups (schizophrenia patients vs. controls); the second variable consisted of three prepulse types (attended, ignored, and novel as repeated measures). Data analysis was conducted for the 120-ms and 4,500-ms lead intervals separately. Similarly, a $2 \times 2$ mixed factorial design was employed for the 240-ms lead interval and consisted of two prepulse types (attended and ignored).

A $2 \times 4 \times 4 \times 2$ mixed factorial design was used for the rGMR data obtained in the lateral cortical surface analysis. The first variable consisted of two participant groups (schizophrenia patients vs. controls), and the remaining variables were all repeated measures and consisted of four lobes (frontal, parietal, temporal, occipital), four major gyral divisions within each lobe (1–4), and two hemispheres (left, right). Figure 1 illustrates these lobal and gyral demarcations. In addition to the a priori structured region of interest analysis of variance (ANOVA), statistical probability mapping was performed as an independent but complementary form of analysis. Statistical probability mapping has the advantage of averaging across smaller cortical regions and therefore allowing a more extensive exploratory survey of the entire lateral cortex. Thus, our statistical approach had two components: (a) specific a priori hypothesis testing with a single $F(\text{Group} \times \text{Lobe} \times \text{Gyrus})$ to control Type I error using the lateral cortical surface technique and (b) pixel-by-pixel statistical probability mapping (e.g., Bartels & Subach, 1976; Friston, Frith, Liddle, & Frackowiak, 1991) for comparability with other studies using this exploratory approach.

A $2 \times 2 \times 3 \times 3$ mixed factorial design was used for the Brodmann frontal lobe analysis. Similar to that described above, the first variable consisted of two groups, the second variable consisted of two hemispheres, the third variable consisted of three regions of the frontal cortex (lateral, medial, orbital), and the fourth variable consisted of three Brodmann areas within each of the three regions.

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 here the uncorrected degrees of freedom for these analyses and for $t$-tests that required correction because of heterogeneity of variance.

**Experimental Stimuli**
The startle-eliciting stimulus was a 104 dB SPL(A) white noise burst 40 ms in duration with a near instantaneous ($<1$ ms) rise/fall time. The startle noise was generated with a custom-built white-noise generator. The attended and ignored prepulses consisted of 70 dB SPL(A) 800-Hz and 1200-Hz tones that were 5 or 8 s in duration. The novel prepulse was a 70 dB SPL(A) 500-Hz tone 5 s in duration. The tones were generated with a BK Precision (model 3011B) function generator, with rise/fall times controlled by a Coulbourn S48-04 rise/fall gate set at 25 ms. Stimulus intensities were calibrated monthly with a digital sound level meter (Pacer model SL130). Frequencies of the tone stimuli were calibrated using the internal frequency meter in the function generator. All of the stimuli were presented binaurally through headphones (Realistic NOVA-40 model). The onsets, durations, and intervals between stimuli were controlled by a laboratory computer.

**Physiological Recording and Scoring**
Startle eyeblink responses were measured as electromyographic (EMG) activity from two miniature Ag/AgCl electrodes (3 mm in diameter) placed below the right eye over the orbicularis oculi muscle. One electrode was centered below the pupil, and the other was positioned approximately 10 mm lateral to the first. The EMG...
signal was fed into a Grass 7P3 wide band integrator/preamplifier and a 7DA driver amplifier. Eyeblinks were recorded at full wave rectification with an integration time constant of 20 ms. The EMG signal was digitized at a rate of 1000 Hz for a period of 250 ms after the onset of each startle stimulus. The startle eyeblink amplitude was then scored off line with a modification of the program by Balaban, Losito, Simons, and Graham (1986), which was used previously (Dawson et al., 1993). Startle blink amplitude scores were converted to microvolts, and differences were then computed between the mean baseline intertone interval eyeblink amplitude and the intratone eyeblink amplitudes. Because difference scores in microvolts 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. In addition, conversion to percentage change units allows comparison of these data with those of our previous SEM work with schizophrenia patients (Dawson et al., 1993), which also used percentage change units. By this method, a positive SEM score indicates startle facilitation relative to baseline, whereas a negative score indicates startle inhibition relative to baseline.

Results

Baseline Startle

Analysis of the mean startle eyeblink amplitude during the intertone interval showed no significant difference between the normal control group and the patient group (controls: $M = 67.7 \mu V, SD = 64.4 \mu V$; patients: $M = 39.7 \mu V, SD = 40.2 \mu V$), $t(27) = 1.42, p = .17$. However, where appropriate, we conducted analyses of covariance in parallel with the principal ANOVAs, using the baseline eyeblink amplitude as a covariate, and confirmed the effects reported here. Thus, differences between the schizophrenia and control groups in SEM change scores are not due to differences in baseline startle reactivity.

Short Lead Interval PPI

120-ms lead interval. Figure 3 presents the SEM scores for the patients and controls for the attended, ignored, and novel prepulses for the various lead intervals. To determine whether differential SEM occurred at the short lead intervals, a series of ANOVAs was performed. In addition, an orthogonal set of individual planned comparisons was then carried out to determine for each group at which lead intervals differential SEM had occurred. To evaluate these data at the 120-ms lead interval, we performed a 2 (group) $\times$ 3 (prepulse type: attended, ignored, novel) ANOVA. This analysis revealed a significant Group $\times$ Prepulse interaction, $F(2,54) = 3.34, p < .05, \epsilon = 0.9359$. This effect indicates that patients and controls differed significantly in their pattern of startle responses during the attended, ignored, and novel prepulses at the 120-ms lead interval. However, there was no group main effect, indicating that the patients did not differ from controls in overall PPI.

Differences in SEM between the attended and ignored prepulses at the 120-ms lead interval should provide an estimate of early predominantly controlled attentional modulation of the startle eyeblink during the attended prepulse. To evaluate this hypothesis, we performed a 2 (group) $\times$ 2 (prepulse: attended, ignored) ANOVA on the SEM scores at the 120-ms lead interval. Consistent with our previous findings in medicated schizophrenia patients (Dawson et al., 1993), this analysis revealed a significant Group $\times$ Prepulse interaction, $F(1,27) = 7.63, p < .05$. This effect indicates group differences in differential PPI to the attended and ignored prepulses at the 120-ms lead interval. Simple effects tests confirmed that the control group showed significantly greater inhibition of the startle eyeblink during the attended prepulse than during the ignored prepulse, $F(1,13) = 16.60, p < .01$, consistent with our previous findings with demographically matched normal controls (Dawson et al., 1993) and normal college students (Filion et al., 1993, 1994; Schell et al., 1995). In contrast, the schizophrenia patients failed to show differential inhibition of the startle eyeblink at the 120-ms lead interval (Figure 3). To confirm this interpretation, we examined between-group difference scores at the 120-ms lead interval. This analysis confirmed that the patient group exhibited significantly less differential PPI than did the control group at the 120-ms lead interval during attended and ignored prepulses, $t(1,27) = 2.78, p < .05$. 

Figure 3. Mean startle eyeblink modification scores as a function of lead interval and prepulse type for the healthy controls and unmedicated schizophrenia patients. Asterisks indicate significant differences ($p < .05$) between the attended and ignored prepulses.
240-ms lead interval. To examine differential SEM at the 240-ms lead interval, a 2 (group) × 2 (prepulse type: attended, ignored) ANOVA was conducted (Figure 3). This analysis showed there was neither a group main effect nor an interaction effect, indicating that patients did not differ from controls in PPI following the attended and ignored prepulses at the 240-ms lead interval. Thus, both the patients and controls showed nondifferential PPI during the attended and ignored prepulses at the 240-ms lead interval.

Long Lead Interval Prepulse Facilitation
The SEM scores for the 4,500-ms lead interval were subjected to a 2 (group) × 3 (prepulse type: attended, ignored, novel) ANOVA (Figure 3). Similar to the 120-ms lead interval effect, this analysis revealed a significant Group × Prepulse interaction, $F(2,54) = 6.10, p < .01, \epsilon = 0.9868$. This effect indicates that the patients and the controls differed significantly in their differential startle responses during the attended, ignored, and novel prepulses at the 4,500-ms lead interval. However, there was no group main effect, indicating that the patients did not differ from controls in overall prepulse facilitation averaged over the three prepulse types.

Differences in SEM between the attended and ignored prepulses at the 4,500-ms lead interval should provide an estimate of late predominantly controlled attentional modulation of the startle blink during the attended prepulse. To evaluate this hypothesis, we performed a 2 (group) × 2 (prepulse: attended, ignored) ANOVA on the SEM scores at the 4,500-ms lead interval. This analysis revealed a significant Group × Prepulse interaction, $F(1,27) = 6.69, p < .05$. This effect indicates group differences in differential prepulse facilitation during the attended and ignored prepulses at the 4,500-ms lead interval. In addition, the group main effect was also significant, $F(1,27) = 4.24, p < .05$, indicating that the patients exhibited less overall prepulse facilitation than did controls during the attended and ignored prepulses at the 4,500-ms lead interval (controls: $M = 70.4, SD = 17.5$; patients: $M = 27.7, SD = 18.7$). An orthogonal set of individual planned comparisons confirmed that the normal control group showed significantly greater facilitation of the startle blink response during the attended prepulse than during the ignored prepulse, $F(1,13) = 10.62, p < .01$, consistent with recent findings in college students (Jennings, Schell, Filion, & Dawson, 1996). In contrast, the patients failed to show differential facilitation of the startle blink response at the 4,500-ms lead interval during the attended and ignored prepulses (see Figure 3). To confirm this interpretation, we examined between-group difference scores at the 4,500-ms lead interval. This analysis also demonstrated that the patient group exhibited significantly less differential prepulse facilitation during attended and ignored prepulses than did the control group, $t(1,27) = 2.57, p < .05$.

SEM During the Novel Prepulse
Similar to the analysis conducted for the attended prepulse, differences in SEM between the novel and ignored prepulses at the 120-ms lead interval should provide an estimate of early predominantly controlled attentional modulation of the startle blink during the novel prepulse. To evaluate this hypothesis, we performed a 2 (group) × 2 (prepulse: novel, ignored) ANOVA on PPI at the 120-ms lead interval and on startle facilitation at the 4,500-ms lead interval. In neither of these analyses was the main effect of group or the interaction with group significant. However, because we hypothesized that the schizophrenic patients would be distracted by the novel prepulse, we proceeded with the orthogonal set of individual planned comparisons. Simple effects tests indicated that neither group exhibited differential PPI during the novel and ignored prepulses at the 120-ms lead interval. At the 4,500-ms lead interval, the control group did not exhibit differential startle facilitation during the novel and ignored prepulses. In contrast, there was a trend indicating that the patients exhibited more startle facilitation during the novel prepulse relative to the ignored prepulse at the 4,500-ms lead interval, $F(1,14) = 3.71, p = .07$. This effect, although marginally significant, suggests that the patients demonstrated controlled attentional modulation of prepulse facilitation during the novel prepulse. Moreover, in contrast to the controls, this finding suggests that the patients were maintaining a strong selective attentional focus during the novel prepulse instead of during the attended prepulse, at least at 4,500-ms following onset of the novel prepulse.

SEM During the Ignored Prepulse
In the present active attention paradigm, the closest equivalent to the prepulses used in passive attention paradigms would be our to-be-ignored prepulse, which is thought to provide an estimate of predominantly automatic attentional processes (Dawson et al., 1993). To evaluate this effect at the short lead intervals, the SEM scores during the ignored prepulse were examined with a 2 (group) × 2 (lead interval: 120 ms, 240 ms) ANOVA. This analysis revealed neither a group main effect nor an interaction effect, indicating that the patients did not differ from the controls in PPI during the ignored prepulse. The main effect of lead interval failed to reach significance, indicating similar amounts of PPI at the 120-ms and 240-ms intervals. Similarly, there was no difference between the groups in blink facilitation at the 4,500-ms lead interval during the ignored prepulse.

Cortical Glucose Metabolism
Table 1 shows mean rGMR in the 16 lateral cortex regions for the patient and control groups, and Figure 2B displays the complementary average cortical surface maps. To examine regional glucose metabolism during the SEM paradigm, rGMR values were submitted to a 2 (group) × 4 (lobe) × 4 (gyrus) × 2 (hemisphere) ANOVA. This analysis revealed a group main effect, indicating that average rGMR in the lateral cortex was lower in patients than in controls, $F(1,28) = 7.81, p < .01$. The lobe and segment main effects were highly significant, $F(3,84) = 19.50, p < .0001$ and $F(3,84) = 6.55, p < .001$, respectively; however, the hemisphere main effect did not reach significance. In addition, there was a significant Group × Lobe interaction, $F(3,84) = 4.09, p < .01$, $\epsilon = 0.0233$, indicating that although the patients had lower rGMR in the frontal and parietal lobes than did the controls, the two groups had similar rGMR in the temporal and occipital lobe regions (see Figure 2B). Of greatest interest was the significant Group × Lobe × Gyrus interaction, $F(9,252) = 2.80, p < .01$, $\epsilon = 0.0313$. Relative GMR was lower in patients than in controls in the superior, middle, and inferior frontal gyri but not the motor strip region (Table 1). In addition, rGMR was lower in the supramarginal, angular, and superior parietal lobe in the patients than in the controls (all $t > 2.58$, all $p < .02$).

Figure 2C illustrates the pixel-by-pixel statistical probability mapping of t-tests, which was used as a complementary form of analysis. This approach has the advantage of averaging across smaller cortical regions and therefore allowing a more extensive exploratory survey of the entire lateral cortex. Between-group t-test values were significant in lateral frontal and parietal cortex regions, indicating lower rGMR in patients than in controls. Thus, the statistical probability mapping findings are consistent with those of the more traditional ANOVA.
We next performed a more detailed analysis of the frontal lobe, which included lateral, medial, and orbital regions based on Brodmann area classification. A 2 (group) × 2 (lobe) × 3 (region: lateral, medial, orbital) × 3 (area: 1–3) ANOVA was performed on Brodmann areas within the frontal lobe. The three areas included in the lateral region were 10, 46, and 8; the medial areas were 9, 24, and 32; and the orbital areas were 11, 12, and 47. Consistent with the previous ANOVA, this analysis revealed a significant main effect of group, indicating that the patients had lower rGMR relative to the controls in the frontal lobe, \( F(1,28) = 5.90, p < .05 \). A visual inspection of the means for the two groups indicated that the patients had lower rGMR than the normal controls in all nine Brodmann areas bilaterally.

### Relationships Between PPI and Cortical Glucose Metabolism

The results just described revealed that the attended prepulse produced significantly greater SEM than did the ignored prepulse at both the 120-ms and 4,500-ms lead intervals in the control group. In contrast, the patients failed to exhibit this attentional modulation of SEM. Furthermore, patients showed significantly lower rGMR in several areas within the prefrontal cortex during the simultaneous recording of SEM. As previously reviewed, several animal studies of PPI have convincingly demonstrated that disturbances in the prefrontal cortex reduce the amount of PPI, and previous studies have shown maximal PPI in the attended prepulse, 120-ms lead interval condition (e.g., Filion et al., 1993, 1994). Thus, in the present study, if better PPI or sensorimotor gating in healthy individuals during the attended prepulse is associated with prefrontal cortex function, then PPI and rGMR in the prefrontal cortex should be correlated. In addition, because the range for PPI at the 120-ms lead interval during the attended prepulse was similar in both the control and patient groups (controls: −100 to −21.9; patients: −79.1 to 3.3) and because frontal lobe deficits in schizophrenia are heterogeneous, we also examined the relationship between PPI and prefrontal cortex function in the patient group.

To examine these relationships, Pearson product–moment correlations were computed. PPI in controls during the attended prepulse showed a significant negative correlation with rGMR in superior, middle, and inferior prefrontal cortex and as a significant positive correlation with visual association cortex regions in controls (Table 2; Figure 2D). This pattern of correlations indicates that more PPI during the attended prepulse is associated with increased frontal lobe and decreased occipital lobe rGMR in healthy individuals. The pixel-by-pixel statistical probability mapping of the correlation coefficients (Figure 2D) also confirmed these relationships in the control group. In contrast, none of the correlations in lateral cortical regions were significant in the patient group (Table 2). In addition, Table 3 (medial, orbital, and lateral cortex analysis) shows that higher rGMR in orbital and medial prefrontal regions is also significantly correlated with PPI during the attended prepulse in the control group. In the patient group, only Brodmann area 10 (frontal pole) on the left showed a significant negative correlation with PPI, indicating that more PPI during the attended prepulse is associated with increased rGMR in this isolated region of the prefrontal cortex in patients and in controls.

### Table 1. Relative Glucose Metabolism in Gray Matter During the Startle Eyeblink Modification Paradigm

<table>
<thead>
<tr>
<th>Brain area</th>
<th>Controls (n = 15)</th>
<th>Schizophrenia patients (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior frontal</td>
<td>1.19</td>
<td>.07</td>
</tr>
<tr>
<td>Midfrontal</td>
<td>1.26</td>
<td>.07</td>
</tr>
<tr>
<td>Inferior frontal</td>
<td>1.31</td>
<td>.09</td>
</tr>
<tr>
<td>Precentral</td>
<td>1.25</td>
<td>.09</td>
</tr>
<tr>
<td>Entire lobe</td>
<td>1.25</td>
<td>.09</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postcentral</td>
<td>1.19</td>
<td>.10</td>
</tr>
<tr>
<td>Supramarginal</td>
<td>1.15</td>
<td>.07</td>
</tr>
<tr>
<td>Angular</td>
<td>1.16</td>
<td>.08</td>
</tr>
<tr>
<td>Superior parietal</td>
<td>1.05</td>
<td>.12</td>
</tr>
<tr>
<td>Entire lobe</td>
<td>1.14</td>
<td>.10</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior temporal</td>
<td>1.14</td>
<td>.06</td>
</tr>
<tr>
<td>Midtemporal</td>
<td>1.22</td>
<td>.06</td>
</tr>
<tr>
<td>Inferior temporal</td>
<td>1.13</td>
<td>.09</td>
</tr>
<tr>
<td>Temporal posterior</td>
<td>1.08</td>
<td>.16</td>
</tr>
<tr>
<td>Entire lobe</td>
<td>1.14</td>
<td>.11</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Area 19</td>
<td>1.18</td>
<td>.09</td>
</tr>
<tr>
<td>Area 17</td>
<td>1.07</td>
<td>.08</td>
</tr>
<tr>
<td>Area 217</td>
<td>1.18</td>
<td>.08</td>
</tr>
<tr>
<td>Area 18</td>
<td>1.18</td>
<td>.11</td>
</tr>
<tr>
<td>Entire lobe</td>
<td>1.15</td>
<td>.10</td>
</tr>
<tr>
<td>Entire cortical surface</td>
<td>1.17</td>
<td>.11</td>
</tr>
</tbody>
</table>

**Note:** Group main effect, \( F(1,28) = 7.81, p < .01 \); Group × Lobe interaction, \( F(3,84) = 4.09, p < .01 \); Group × Lobe × Segment interaction, \( F(5,252) = 2.80, p < .01 \).

**See Figure 1.**

*Significantly different from control group, \( p < .05 \), t-test.

### Table 2. Pearson Product–Moment Correlations Between Relative Glucose Metabolism and Prepulse Inhibition at the 120-ms Lead Interval During Attended Prepulse

<table>
<thead>
<tr>
<th>Hemisphere</th>
<th>Controls (n = 14)</th>
<th>Schizophrenia patients (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior frontal</td>
<td>−.75**</td>
<td>−.70**</td>
</tr>
<tr>
<td>Midfrontal</td>
<td>−.49</td>
<td>−.32</td>
</tr>
<tr>
<td>Inferior frontal</td>
<td>−.64*</td>
<td>−.64*</td>
</tr>
<tr>
<td>Precentral</td>
<td>.19</td>
<td>.15</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postcentral</td>
<td>.34</td>
<td>.04</td>
</tr>
<tr>
<td>Supramarginal</td>
<td>−.34</td>
<td>−.28</td>
</tr>
<tr>
<td>Angular</td>
<td>−.25</td>
<td>−.15</td>
</tr>
<tr>
<td>Superior parietal</td>
<td>−.32</td>
<td>−.33</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior temporal</td>
<td>−.26</td>
<td>−.38</td>
</tr>
<tr>
<td>Mid temporal</td>
<td>.36</td>
<td>.32</td>
</tr>
<tr>
<td>Inferior temporal</td>
<td>.60*</td>
<td>.54*</td>
</tr>
<tr>
<td>Temporal posterior</td>
<td>.34</td>
<td>.31</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Area 19</td>
<td>.74**</td>
<td>.66*</td>
</tr>
<tr>
<td>Area 17</td>
<td>.66*</td>
<td>.66*</td>
</tr>
<tr>
<td>Area 217</td>
<td>.33</td>
<td>.24</td>
</tr>
<tr>
<td>Area 18</td>
<td>.58*</td>
<td>.62*</td>
</tr>
</tbody>
</table>

*See Figure 1. bSignificantly different from normal controls, \( p < .05 \).

*Significantly different from normal controls, \( p < .05 \).
Relative Glucose Metabolism and Prepulse Inhibition

Table 3. Pearson Product–Moment Correlations Between Relative Glucose Metabolism and Prepulse Inhibition During Attended Prepulse

<table>
<thead>
<tr>
<th>Brodmann areas(^a)</th>
<th>Lateral</th>
<th>Medial</th>
<th>Orbital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (n = 14)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>-.72**</td>
<td>-.60*</td>
<td>-.73**</td>
</tr>
<tr>
<td>Right</td>
<td>-.80**</td>
<td>-.69**</td>
<td>-.44</td>
</tr>
<tr>
<td>Schizophrenia patients (n = 14)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>-.57*</td>
<td>-.26</td>
<td>-.20</td>
</tr>
<tr>
<td>Right</td>
<td>-.51</td>
<td>-.33</td>
<td>-.05</td>
</tr>
</tbody>
</table>

*See Figure 2A.
*\(p < .05\), **\(p < .01\).

Performance on Tone–Length–Judgment Task
For each participant, we recorded the accuracy of the count made of longer attended prepulses to determine if there were differences among the groups in the motivation or ability to perform this selective attention task. There were six longer occurrences of the attended pitch. Several individuals in each group performed well on the task; 6 of the 16 patients (38%) and 11 of the 15 controls (73%) gave answers that were within 2 of the correct answer. However, the average error score for the patient group was significantly higher than that for the control group (patients: \(M = 8.2, SD = 6.9\), range = 0–19 errors; controls: \(M = 2.0, SD = 2.1\), range = 0–8 errors), \(H(1) = 4.16, p < .05\), Kruskal-Wallis non-parametric test.

Discussion

SEM in Controls and Unmedicated or Drug-Naive Schizophrenia Patients
A number of SEM findings in the control group replicate and extend previous work with attention-to-prepulse paradigms. First, by the 120-ms lead interval, attended and ignored prepulses had been discriminated, and attended prepulses received enhanced processing. This finding of controlled modulation of PPI replicates previous studies in normal volunteers (Dawson et al., 1993; Filion et al., 1993, 1994; Jennings et al., 1996; Schell et al., 1995). Second, at 240 ms, the additional protection was no longer present, and the amount of differential PPI during attended and ignored prepulses was nonsignificant, also replicating previous work (Dawson et al., 1993; Filion et al., 1993, 1994; Jennings et al., 1996; Schell et al., 1995). Third, at 4,500 ms, facilitation was significantly greater during attended than during ignored prepulses, reflecting the allocation of greater controlled attentional resources as consistent with previous work with students (Jennings et al., 1996).

In addition, in controls, the amount of PPI at 120 ms and prepulse facilitation at 4,500 ms during novel prepulses was intermediate between that of attended and ignored prepulses. At both early and late lead intervals, controls showed a linear relationship between the task significance of the three prepulse types and the amount of controlled attentional processing during each. Specifically, ignored prepulses elicited few if any controlled resources, novel prepulses elicited some, and attended prepulses elicited additional controlled processing resources. In support of the cognitive framework proposed by Dawson et al. (1993), the present findings confirm that SEM is a useful measure for determining the degree of controlled attentional processing during various prepulses, each associated with a different level of task significance.

The present study demonstrates for the first time that unmedicated or drug-naive schizophrenia patients have impaired attentional modulation of PPI. Compared with controls, the unmedicated patients failed to show differential PPI during attended and ignored prepulses at 120-ms lead intervals. Consistent with previous studies of medicated patients (Dawson et al., 1993; McDowd, Filion, Harris, & Braff, 1993), the finding suggests that unmedicated schizophrenia patients are deficient in the allocation of controlled resources at 120 ms to evaluate attended prepulses.

At 4,500 ms, unmedicated patients failed to exhibit the normal pattern of differential prepulse facilitation during attended and ignored prepulses. This finding is consistent with our previous finding at a 2,000-ms lead interval in medicated patients (Dawson et al., 1993). Further, in contrast to the controls, unmedicated patients showed a trend toward greater prepulse facilitation during novel prepulses than during ignored prepulses. Thus, patients were inefficiently allocating their attentional resources to a task-irrelevant stimulus (the novel prepulse). This conclusion is consistent with the view that available processing resources for task-relevant cognitive operations are deficient in schizophrenia patients because processing resources are deployed to task-irrelevant stimuli (Grillon, Courchesne, Ameli, Geyer, & Braff, 1990; Nuechterlein & Dawson, 1984).

Also consistent with our previous findings in medicated patients (Dawson et al., 1993), unmedicated patients and controls did not differ with respect to the ignored prepulses at all three lead intervals. This finding appears to be inconsistent with results reported by Braff et al. (1978, 1992) and Grillon et al. (1992), who found reduced overall PPI in an uninstructed passive-attention paradigm, suggesting impaired automatic sensorimotor gating. Several key methodological differences may account for the apparent discrepancies, including the imposition of an active attentional task and different stimulus characteristics. For example, patients may have benefited from the larger prepulse-to-background ratio (e.g., 15 dB of Braff et al., 1992). It is also possible, as Dawson et al. (1993) suggested, that the basic automatic sensorimotor gating mechanism may not be abnormal in patients during the active attention paradigm.

At the 240-ms lead interval, patients did not differ from controls, consistent with our previous work (Dawson et al., 1993). Both groups showed nondifferential PPI during attended versus ignored prepulses. According to the cognitive framework proposed by Dawson et al. (1993), patients do not differ from normal individuals at this 240-ms transition point between stimulus discrimination and later processes involved in carrying out the tone–length–judgment task.

In sum, in support of a previously hypothesized cognitive sequence of events (Dawson et al., 1993), our SEM findings indicate that unmedicated patients do not differ from normal individuals in...
automatic sensorimotor gating mechanisms in an active-attention condition or in the transition period at 240 ms. They are deficient, however, in the allocation of controlled resources to evaluate attended pre puples at 120 ms and in focused, sustained attention to attended pre puples at 4,500 ms. Further, patients tended to allocate excessive controlled attention at 4,500 ms to the novel pre pulse.

Cortical Glucose Metabolism During the SEM Paradigm

Both the a priori structured region of interest ANOVAs and statistical probability mapping provided convergent evidence of abnormalities in rGMR in bilateral prefrontal and parietal cortex of unmedicated or drug-naive schizophrenia patients. Although patients exhibited lower rGMR in the superior, middle, and inferior frontal gyrus and parietal cortex compared with controls, the two groups did not differ in frontal motor region (precentral gyrus), temporal cortex, and occipital cortex. This anatomical pattern suggests that the observed deficits in SEM measures of information processing are not due to functional abnormalities in auditory or visual association areas. Instead, it underscores the importance of the prefrontal cortex in attention. Our findings of low rGMR in prefrontal and parietal cortex in unmedicated patients during the attention-to-pre pulse SEM paradigm are consistent with many earlier PET studies of schizophrenia patients, particularly those which required participants to perform an attentional task (e.g., Buchsbaum et al., 1990; see review by Buchsbaum & Hazlett, in press). In a canonical discrimination analysis, Schroeder et al. (1994) showed that a hypofrontality and parietal cortex glucose metabolism factor separated a large group of schizophrenia patients from healthy controls who were performing a sustained attention task. However, some previous studies failed to confirm hypofrontality in schizophrenia patients, especially those studies that involved a resting or passive attention paradigm (reviewed by Buchsbaum & Hazlett, in press).

The present findings bear a striking topographic resemblance to those observed in a conceptually related electrophysiological study by Judd, McAdams, Budnick, and Braff (1992). They used a two-stimulus evoked potential paradigm to examine the inhibition of the P50 wave that occurs in the epoch ~50 ms after stimulus onset. Similar to PPI, the second stimulus typically evokes a P50 wave that is inhibited or gated by the effect of the first stimulus. Schizophrenia patients showed significant P50 sensory gating deficits at frontal, central, and parietal electrode placement sites, with a tendency for the deficit to be most prominent in frontal lobe areas.

Cortical Glucose Metabolism Correlates of Normal and Impaired PPI

The present results provide the first direct evidence from healthy humans that greater PPI during attended pre pulses is significantly correlated with higher rGMR in dorsolateral (Areas 8 and 10 bilaterally), medial frontal (Area 9 bilaterally), orbital prefrontal (area 11 on the left), and cingulate (Area 24 on the right) cortex areas. Moreover, in controls, greater PPI is significantly correlated with decreased rGMR in visual association areas. In patients, better PPI during attended pre pulses is associated with higher rGMR in a much smaller portion of the prefrontal cortex, with only area 10 on the left reaching significance.

Our Brodmann area findings in the medial prefrontal cortex (Area 9 bilaterally) and anterior cingulate cortex (Area 24 on the left) for the control group are consistent with three recent studies of PPI in rats. Bubser and Koch (1994) showed that depleting the prefrontal cortex of dopamine caused a loss of PPI in rats similar to the deficient PPI we observed in unmedicated schizophrenia patients during the attended pre pulse. This line of research was extended by Koch and Bubser (1994) in a more detailed exploration of the three areas of the prefrontal cortex that may be involved in PPI. They concluded that prelimbic cortex (a square region labeled “cingulate cortex, area 3” and “infralimbic cortex” in their reference atlas, Paxinos & Watson, 1986) was more involved in PPI than were dorsolateral and anterior cingulate cortex. The prelimbic cortex region described by Koch and Bubser in rats parallels our Brodmann medial area findings in controls. More recently, Swerdlow et al. (1995) reported that low doses of a dopamine agonist, apomorphine, significantly disrupted PPI in rats with medial prefrontal cortex lesions. Taken together, these three studies appear to be consistent with the present findings in unmedicated schizophrenia patients because they indicate that medial prefrontal cortex modulates PPI. Other findings relevant to the present study are those of Knight, Hillyard, Woods, and Neville (1981), who showed that evoked potentials of patients with lesions of the dorsolateral prefrontal cortex showed less attention-related negativity than did those of controls.

Schizophrenia patients had a significantly lower correlation than controls (~0.64 vs. 0.13) in the right inferior prefrontal area (Table 2); this exact area showed the strongest normal versus schizophrenia differences in another group of patients doing a visual continuous performance task (Buchbaum et al., 1990). However, only one of the cortical areas within the frontal lobe (Tables 2 and 3) was confirmed as significantly different between controls and patients and the p level was not significant after Bonferroni correction.

Our results suggest that the pattern of functional organization in the cortex (e.g., frontal–occipital lobe) is important in schizophrenia and attention. Control participants who exhibited the greatest PPI during the attended pre pulse were using their prefrontal cortex and suppressing occipital lobe function, suggesting that frontal and occipital lobe coordination is critical in the attentional modulation of PPI. In contrast, schizophrenia patients who showed greater PPI used their prefrontal cortex to a much lesser extent and failed to suppress their occipital lobe function.

Consistent with our findings, Butler, Jenkins, Geyer, and Braff (1991) reported that paranoid schizophrenia patients with the greatest number of perseverative responses on the Wisconsin Card Sorting Test (WCST) also showed the greatest loss of tactile PPI. Because the perseverative response measure of the WCST has been reported to be correlated with frontal lobe damage (e.g., Weinberger, Berman, & Illowsky, 1988), Butler et al. speculated that defective sensorimotor gating may result from impaired frontal lobe inhibitory function.

Based on work with lesion patients, Knight (1984) suggested that the prominent features of prefrontal cortex damage, including poor selective attention and perseveration, may be linked to problems in inhibitory control. Knight further suggested that prefrontal gating deficits may extend from early sensory gating to late stages of processing. Consistent with this hypothesis, schizophrenia patients in our study failed to focus on attended pre pulses and, at 4,500 ms, focused on the task-irrelevant novel pre pulses. Similarly, an inability to suppress previous incorrect responses on the WCST may underlie the poor performance of patients with dorsolateral lesions (Shimamura, Gershberg, Jurica, Mangels, & Knight, 1992).

One shortcoming of the present study is the small sample size. Clearly, more research in larger numbers of schizophrenia patients is needed to evaluate possible subgroup differences in PPI deficits. For example, several patients did not exhibit PPI deficits. It would
be valuable to determine the characteristics (e.g., prefrontal cortex functioning, SEM, clinical symptoms) of subgroups of patients with good and poor PPI. There is much to be learned about the neural circuitry that modulates PPI in healthy individuals and schizophrenia patients. In the present study, we did not examine all of the regions within the cortical-striatal-pallidal-thalamic circuitry thought to modulate PPI. Deficits in PPI probably are a result of aberrant connectivity between key brain regions rather than a result of dysfunction in a single region. More research is needed to address these issues.

It could be argued that PET with FDG is not an optimal functional neuroimaging technique for the study of SEM because of poor temporal resolution. Functional MRI (fMRI), for example, provides better time resolution (for flow in the 2–6 s range) but is currently incompatible with the presentation of acoustic startle stimuli because of distracting noise generated by the scanner itself. Moreover, until technical improvements can be made to eliminate artifacts of signal loss in the orbital frontal cortex due to adjacent bone and air, the entire frontal lobe cannot be examined systematically. Another technique, $^{15}$O PET, lacks the particular limitations of fMRI but has other disadvantages. Its temporal resolution, superior to that of FDG PET and inferior to that of fMRI, is measured in seconds to minutes, a time frame that does not match the shorter periods (milliseconds) in the various components of the SEM paradigm. In exchange for the improved (but still inadequate) temporal resolution provided by $^{15}$O PET, there is a loss of spatial resolution compared with FDG PET. This shortcoming would detract from the detailed examination of subcortical structures within the cortical-striatal-pallidal-thalamic circuitry thought to modulate PPI such as the thalamus and anterior cingulate gyrus, which can be studied in three dimensions with FDG PET (Buchsbaum, 1995).

Overall, our results support those for animal models, which suggest that prefrontal cortex plays an important role in the modulation of PPI. They also underscore the importance of the frontal lobe in tasks involving stimulus discrimination and novelty and further suggest that PPI measures provide an index of the integrity of frontal lobe function. Thus, the study of SEM in conjunction with functional neuroimaging has the potential to enhance our understanding of the cognitive and neuroanatomical basis of normal and disordered information processing.

REFERENCES


