Psychophysiology, 35 (1998), 186–198. Cambridge University Press. Printed in the USA.

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

ERIN A. HAZLETT, MONTE S. BUCHSBAUM, M. MEHMET HAZNEDAR, MELISSA B. SINGER, MARJA K. GERMANS, DAVID B. SCHNUR, EDWARD A. JIMENEZ, BRADLEY R. BUCHSBAUM, AND BILL T. TROYER

Department of Psychiatry, Mount Sinai School of Medicine, New York, USA

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, nonstartling 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.

This research was supported by a Young Investigator Award from the National Alliance for Research on Schizophrenia and Depression (NARSAD), Chicago, and NIMH grants MH56460 to E. A. Hazlett and MH40071 to M. S. Buchsbaum.

We gratefully acknowledge Drs. L. Shihabuddin, J. Edgar, and P. Powchik for patient recruitment, Jacqueline Spiegel-Cohen and Dr. Tse-Chung Wei for computer programming of software used in analysis of neuroimaging data, and Dr. Diane Filion for thoughtful comments on an earlier draft of this manuscript.

Address reprint requests to: Dr. Erin A. Hazlett, Department of Psychiatry, Box 1505, Mount Sinai School of Medicine, 1 Gustave L. Levy Place, New York, NY 10029-6574, USA. E-mail: hazlett@msvax.mssm.edu.

(1993) measured SEM in college students performing an auditory selective attention task. The students were presented an intermixed series of tones of two different pitches and instructed to count the number of longer-than-usual occurrences (i.e., 7 s vs. 5 s) of one tone pitch (e.g., high) and to ignore the other one (e.g., low). A brief burst of white noise was presented at short lead intervals of 60, 120, and 240 ms after the onset of each type of prepulse. Significantly greater PPI occurred during the attended prepulse than during the ignored prepulse when the lead interval between the tone prepulses and startle stimulus onsets was 120 ms. Thus, PPI can be modulated by controlled attentional processes.

When the lead interval is longer than ~800 ms, the amplitude of the startle reflex is enhanced in the presence of a prepulse in the same modality as the startle stimulus, especially if attention is directed toward the modality of the startle stimulus. In contrast, startle eyeblink amplitude is inhibited if attention is directed away from the modality of the startle stimulus (see reviews by Anthony, 1985; Filion et al., in press; Putnam, 1990). This long lead-interval 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 either a burst of loud white noise or a tactile stimulus as the startle stimulus; and Grillon, Ameli, Charney, Krystal, and Braff (1992) used a discrete mild white noise of varying intensity 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-pallidal-thalamic 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; Daviss & 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-prepulse 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.

Unusable eyeblink data were obtained for one patient and one control participant because of movement artifacts on critical tone trials that included the presentation of a startle stimulus. Unusable PET data were obtained for one patient who had extremely low gamma counts.

Procedure

PET ^{18}F-fluoro-deoxyglucose (FDG) uptake and SEM procedure. All participants had a PET scan with FDG. An intravenous line was inserted in the left arm for blood sampling and in the right arm for FDG injection. The left arm was warmed with a nonelectrical thermal pack for arterialization of the blood samples. Twenty-six 2-cc blood samples were drawn at baseline (just prior to FDG injection; $n = 1$), and at 30 s ($n = 14$), 3 min ($n = 4$), 5 min ($n = 4$), and 15 min ($n = 3$) postinjection until scan conclusion. Intravenous extension tubing was used to ensure that the participants were unaware of the injection and blood sampling procedures so as not to interfere with psychophysiological recordings. After the intravenous lines were in place, electrodes were attached for the recording of skin conductance and startle eyeblink, and the participant was moved to a comfortable chair in the testing room. Before the procedure began, participants were read standard instructions stating that their task throughout the FDG uptake period was to listen closely to a series of high- and low-pitched tones presented through headphones, to count silently the number of longer high-pitched tones, and to ignore the low-pitched tones (attended pitch was counterbalanced across participants). Participants were (a) told that the standard length tone was 5 s in duration and that the longer tone was 8 s in duration, (b) told that a brief noise burst would be presented occasionally throughout the task but that it was unrelated to the task and should be ignored, (c) not given any instructions about the novel tone, and (d) told to keep their eyes open and to focus their gaze toward the front of the room during the entire task. To emphasize the importance of the task, a monetary reward was offered for a correct count of the longer tones of the designated pitch. Participants were told they would receive $10.00 if their count was correct, $8.00 if their count was off by 1, and so forth.

After the instructions, a 3-min resting baseline was recorded, at the end of which participants were given three warned presentations of the startle-eliciting burst of noise alone to adjust and maximize polygraph sensitivity. After the noise bursts, participants were given one example of the high tone and one example of the low tone; they were told that each of these examples was the standard 5 s in duration. At this time all participants 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.

Participants began the task and were injected with the FDG tracer while seated in a sound-attenuated testing room ideally suited for psychophysiological recording. Similar to a standard room used for SEM testing, a low-light camera was mounted on the wall. The experimenter and all necessary psychophysiological equipment were 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 is 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 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 = 24 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, Spelbring, 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 midstriatal level and at an approximately matching PET slice using a semiautomated thresholding algorithm. Intertracer MR edging reliability with our method is high (intraclass correlation = .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 Buchsbaum 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,

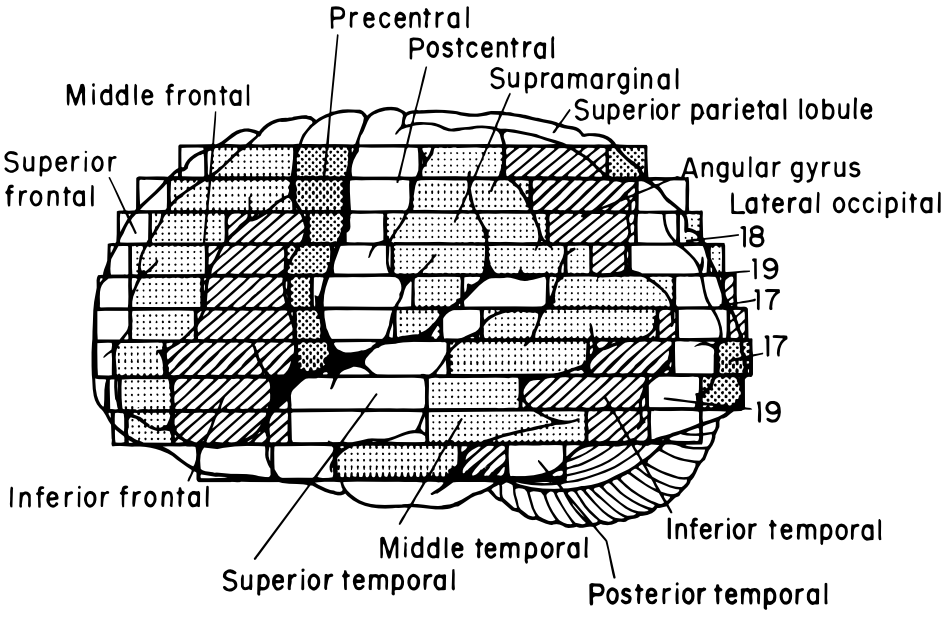

Figure 1. Lateral cortical surface reconstructed from the atlas of Matsui and Hirano (1978) with the use of their gyral identification. For each atlas slice, the perimeter was identified, and the percentage location of each sulcal division was recorded. For each PET scan, the perimeter was identified and the percentage location on the perimeter was used to calculate the mean glucose level within the sector of the cortical surface. An area-weighted average of each cortical region was then computed, resulting in the delineation of four separate major gyral divisions of the cortex within each of the four lobes: frontal (superior, middle, inferior, precentral), parietal (postcentral, supramarginal, angular, superior), temporal (superior, middle, inferior, posterior), and occipital (Area 19, Area 17, Area2 17, Area 18).

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

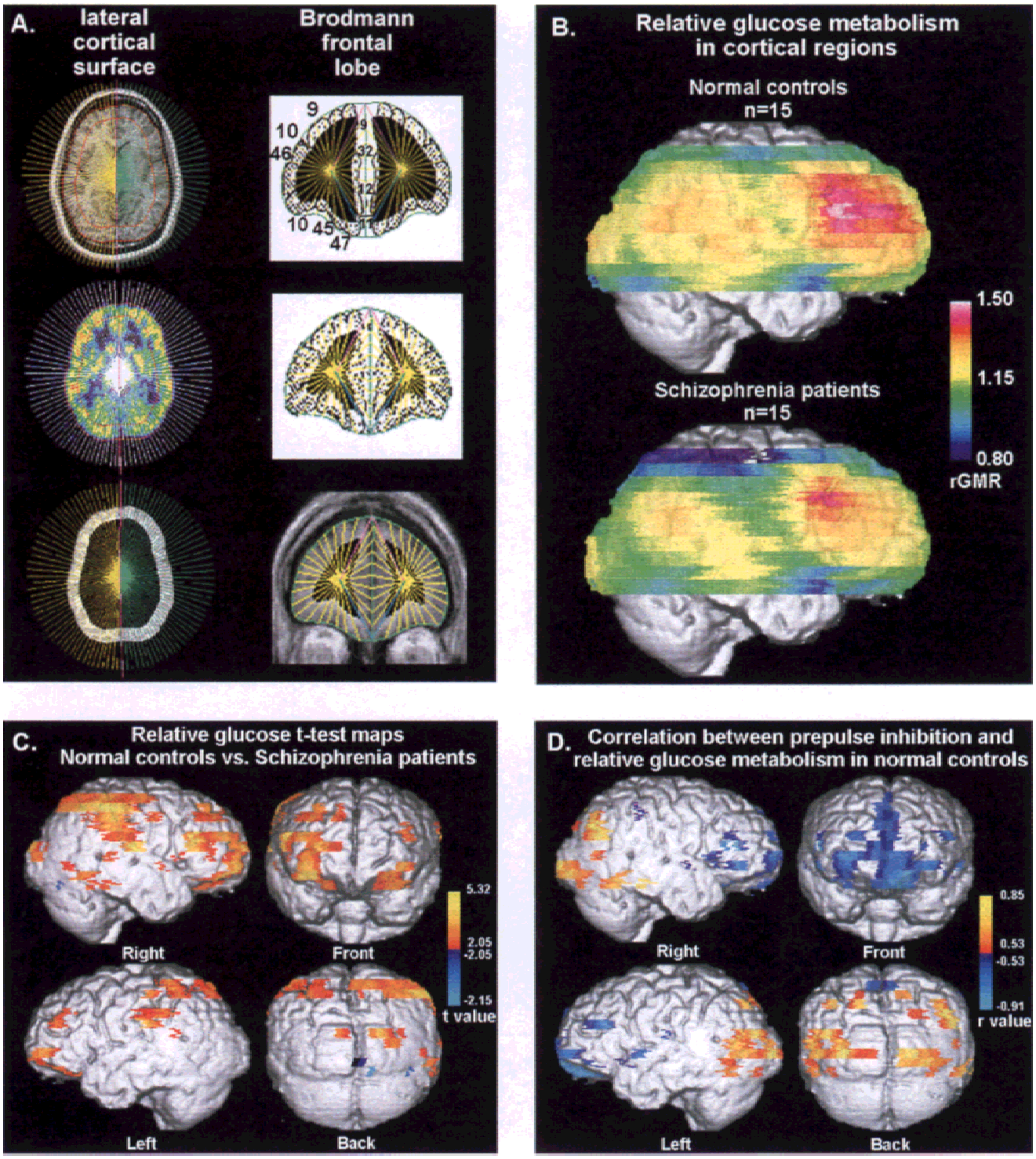

Figure 2. *See caption on facing page.*

drawings, and the specific sectors that covered each Brodmann area were identified.

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 × 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 × 2 mixed factorial design was employed for the 240-ms lead interval and consisted of two prepulse types (attended and ignored).

A 2 × 4 × 4 × 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(Group × Lobe × 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 × 2 × 3 × 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

Figure 2. (*facing page*) Cortical techniques and maps used to evaluate glucose metabolism. A. Lateral cortical surface technique used for axial PET slices and coronal slice technique used to obtain lateral, medial, and orbital Brodmann frontal lobe regions of interest is shown for one slice from one participant. Top left: Individual anatomical MR scan is outlined, nine anatomical midline points are located and midline is drawn through these points; slice is then warped to average outline and midline for the entire control group. Middle left: PET slice is coregistered with gray/white matter and CSF segmentation from matching MR scan slice. Bottom left: Gray/white brain matter segmentation is seen on MR, which is coregistered to PET slice. Top right: Perry, Oakley, and Perry (1996) coronal atlas of the frontal pole is shown with delineation of Brodmann areas (9, 10, 46, 45, 47, 32, 12, 11) for one slice. Middle right: Perry et al. atlas is warped to the contour of the average coronal MR image in our normal sample. Bottom right: Radial sectors are drawn on average MR image. Specific sectors are identified for each Brodmann area on all slices containing the area, and the average rGMR for pixels within each sector, which are coregistered to gray matter on the individual participant's gray/white matter and CSF segmented MR image, is then determined across the slices. B. Right hemisphere average cortical surface maps are shown for the healthy control group and schizophrenia patient group (see Table 1). The control group shows significantly higher relative glucose metabolism in lateral prefrontal and parietal cortex areas compared with the schizophrenia patients. The scale is metabolic rate relative to whole brain metabolic rate. C. Pixel-by-pixel cortical surface statistical probability maps of t-tests comparing relative glucose metabolism in control and schizophrenia patient groups. Yellow and orange indicate areas where the control group showed higher relative glucose metabolism compared with the schizophrenia patient group. This exploratory statistical probability mapping technique is consistent with more traditional ANOVA findings of a significant Group × Lobe × Gyrus interaction (see Table 1), indicating that patients showed lower relative glucose metabolism compared with controls in prefrontal and parietal cortex regions whereas similar glucose metabolism was observed for temporal and occipital lobe regions. D. Pixel-by-pixel cortical surface statistical probability maps of Pearson product–moment correlation coefficients between relative glucose metabolism and the amount of prepulse inhibition exhibited during the attended prepulse in the healthy control group. Purple and blue areas represent negative correlation coefficients, indicating that better PPI is associated with higher relative glucose metabolism. In contast, orange and yellow areas represent positive correlations, indicating that better PPI is associated with lower relative glucose metabolism. Thus, in the control group, individuals who exhibited better PPI during the attended prepulse activated their prefrontal cortex and not their visual association cortex. For $n = 14$, $r > .532$ produced a p value of $<.05$, therefore only r values which are less than or greater than .532 are displayed.

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, $t(1,27) = 2.78$, $p < .05$.

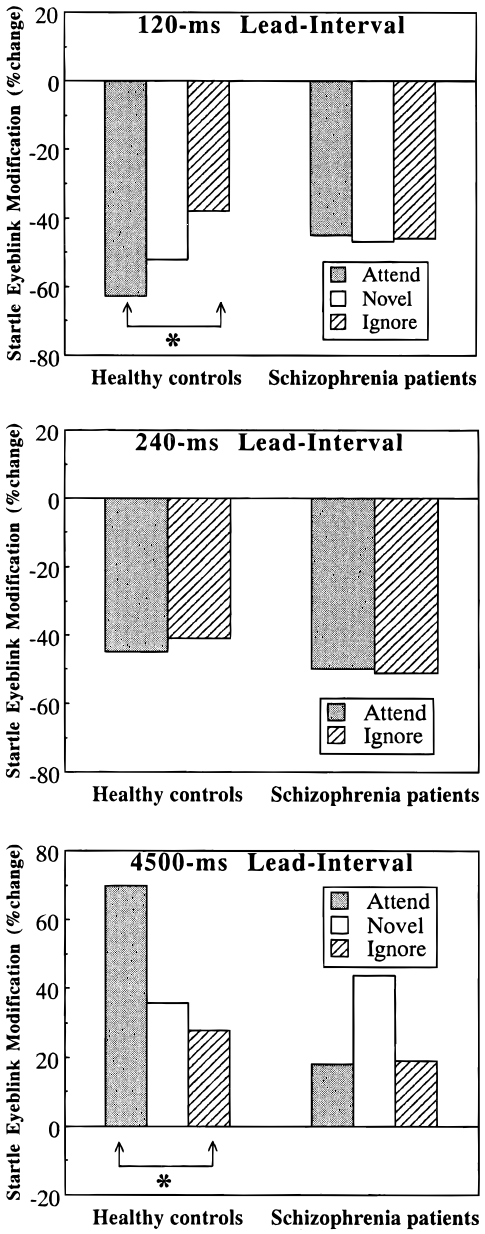

Figure 3. Mean startle eyeblink modification scores as a function of lead interval and prepulse type for the healthy controls and unmedicated schizophrenia patients. Asterisks indicate significant differences ($p < .05$) between the attended and ignored prepulses.

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 eyeblink 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 eyeblink 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 eyeblink 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 eyeblink 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 schizophrenia 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 gyrus 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.

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

	Controls ($n = 15$)		Schizophrenia patients ($n = 15$)	
Brain area[a]	*M*	*SD*	*M*	*SD*
Frontal lobe				
Superior frontal	1.19	.07	1.11*	.07
Midfrontal	1.26	.07	1.17*	.12
Inferior frontal	1.31	.09	1.24*	.07
Precentral	1.25	.09	1.23	.15
Entire lobe	1.25	.09	1.19*	.12
Parietal lobe				
Postcentral	1.19	.10	1.14	.14
Supramarginal	1.15	.07	1.04*	.13
Angular	1.16	.08	1.03*	.16
Superior parietal	1.05	.12	0.88*	.22
Entire lobe	1.14	.10	1.02*	.19
Temporal lobe				
Superior temporal	1.14	.06	1.11	.07
Midtemporal	1.22	.06	1.19	.07
Inferior temporal	1.13	.09	1.13	.10
Temporal posterior	1.08	.16	1.17	.20
Entire lobe	1.14	.11	1.15	.13
Occipital lobe				
Area 19	1.18	.09	1.14	.08
Area 17	1.07	.08	1.01	.14
Area2 17	1.18	.08	1.12	.10
Area 18	1.18	.11	1.13	.16
Entire lobe	1.15	.10	1.10	.13
Entire cortical surface	1.17	.11	1.12	.16

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, $F(9,252) = 2.80$, $p < .01$.
[a]See Figure 1.
*Significantly different from control group, $p < .05$, *t*-test.

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

	Hemisphere			
	Controls ($n = 14$)		Schizophrenia patients ($n = 14$)	
Brain area[a]	Left	Right	Left	Right
Frontal lobe				
Superior frontal	−.75**	−.70**	−.37	−.22
Mid-frontal	−.49	−.32	−.38	−.25
Inferior frontal	−.64*	−.64*	−.07	.13[b]
Precentral	.19	.15	−.28	−.02
Parietal lobe				
Postcentral	.34	.04	−.24	.00
Supramarginal	−.34	−.28	−.09	.02
Angular	−.25	−.15	.10	.02
Superior parietal	−.32	−.33	.17	.15
Temporal lobe				
Superior temporal	−.26	−.38	−.11	.22
Mid temporal	.36	.32	.03	.03
Inferior temporal	.60*	.54*	.09	.40
Temporal posterior	.34	.31	.19	−.04
Occipital lobe				
Area 19	.74**	.66*	.13	.10
Area 17	.66*	.66*	.07	.36
Area2 17	.33	.24	−.16	−.39
Area 18	.58*	.62*	.46	.29

[a]See Figure 1. [b]Significantly different from normal controls, $p < .05$.
*$p < .05$. **$p < .01$.

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

	Hemisphere			
	Controls (n = 14)		Schizophrenia patients (n = 14)	
Brodmann areas[a]	Left	Right	Left	Right
Lateral				
Area 10	−.72**	−.80**	−.57*	−.51
Area 46	−.61*	−.49	−.37	−.19
Area 8	−.59*	−.58*	−.43	−.34
Medial				
Area 9	−.60*	−.69**	−.26	−.33
Area 24	−.18	−.58*	.20	−.12
Area 32	−.50	−.49	−.13	−.31
Orbital				
Area 11	−.73**	−.44	−.20	−.05
Area 12	−.64*	−.44	−.44	−.52
Area 47	−.42	−.36	.10	.00

[a]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 nonparametric 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 (i.e., a more salient prepulse) in the current study (25 dB) compared with smaller ratios in earlier passive-attention studies (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 prepulses at 120 ms and in focused, sustained attention to attended prepulses at 4,500 ms. Further, patients tended to allocate excessive controlled attention at 4,500 ms to the novel prepulse.

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-prepulse 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 prepulses 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 prepulses 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 prepulse. 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 (Buchsbaum 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 prepulse 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 prepulses and, at 4,500 ms, focused on the task-irrelevant novel prepulses. 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

Akbarian, S., Kim, J. J., Potkin, S. G., Hetrick, W. P., Bunney, W. E., Jr., & Jones, E. G. (1996). Maldistribution of interstitial neurons in prefrontal white matter of the brains of schizophrenic patients. *Archives of General Psychiatry, 53,* 425–436.

Andreasen, N. C., Flaum, M., & Arndt, S. (1992). The Comprehensive Assessment of Symptoms and History (CASH): An instrument for assessing diagnosis and psychopathology. *Archives of General Psychiatry, 49,* 615–623.

Anthony, B. J. (1985). In the blink of an eye: Implications of reflex modification for information processing. In P. K. Ackles, J. R. Jennings, & M. G. H. Coles (Eds.), *Advances in psychophysiology* (vol. 1, pp. 167–218). Greenwich, CT: JAI Press.

Balaban, M. T., Losito, B., Simons, R. F., & Graham, F. K. (1986). Off line latency and amplitude scoring of the human reflex eyeblink with FORTRAN IV [Abstract]. *Psychophysiology, 23,* 612.

Bartels, P. H., & Suback, J. A. (1976). Significance probability mapping and automated interpretation of complex pictorial scenes. In E. Preston & M. Onoe (Eds.), *Digital proceedings of biomedical imagery* (pp. 101–114). New York: Academic Press.

Bleuler, E. (1950). *Dementia praecox or the group of schizophrenias* (J. Zinkin, Trans.). New York: International Universities Press. (Original work published 1911).

Braff, D. L., & Geyer, M. A. (1990). Sensorimotor gating and schizophrenia. *Archives of General Psychiatry, 47,* 181–188.

Braff, D. L., Grillon, C., & Geyer, M. A. (1992). Gating and habituation of the startle reflex in schizophrenic patients. *Archives of General Psychiatry, 49,* 206–215.

Braff, D., Stone, C., Calloway, E., Geyer, M., Glick, I., & Bali, L. (1978). Prestimulus effects on human startle reflex in normals and schizophrenics. *Psychophysiology, 15,* 339–343.

Braff, D. L., Swerdlow, N. R., & Geyer, M. A. (1995). Gating and habituation deficits in the schizophrenia disorders. *Clinical Neuroscience, 3,* 131–139.

Bubser, M., & Koch, M. (1994). Prepulse inhibition of the acoustic startle response of rats is reduced by 6-hydroxydopamine lesions of the medial prefrontal cortex. *Psychopharmacology, 113,* 487–492.

Buchsbaum, M. S. (1995). Charting the circuits. *Nature, 378,* 128-129.

Buchsbaum, M. S., & Hazlett, E. A. (in press). Positron emission tomography studies of abnormal glucose metabolism in schizophrenia. *Schizophrenia Bulletin.*

Buchsbaum, M. S., Ingvar, D. H., Kessler, R., Water, R. N., Cappelletti, J., van Kammen, D. P., King, A. C., Johnson, J. J., Manning, R. G., Flynn, R. M., Mann, L. S., Bunney, W. E., Jr., & Sokoloff, L. (1982). Cerebral glucography with positron emission tomography. *Archives of General Psychiatry, 39,* 251–259.

Buchsbaum, M. S., Nuechterlein, K. H., Haier, R. J., Wu, J., Sicotte, N., Hazlett, E., Asarnow, R., Potkin, S., & Guich, S. (1990). Glucose metabolic rate in normals and schizophrenics during the continuous performance test assessed by positron emission tomography. *British Journal of Psychiatry, 156,* 216–227.

Butler, R. W., Jenkins, M. A., Geyer, M. A., & Braff, D. L. (1991). Wisconsin card sorting deficits and diminished sensorimotor gating in a discrete subgroup of schizophrenic patients. In C. Tamminga & S. Schulz (Eds.), *Advances in neuropsychiatry and psychopharmacology: Vol. 1. Schizophrenia research* (pp. 163–168). New York: Raven Press.

Daviss, S. R., & Lewis, D. A. (1995). Local circuit neurons of the prefrontal cortex in schizophrenia: Selective increase in the density of calbindin-immunoreactive neurons. *Psychiatry Research, 59,* 81–98.

Dawson, M. E. (1990). Psychophysiology at the interface of clinical science, cognitive science, and neuroscience. *Psychophysiology, 27,* 243–255.

Dawson, M. E., Hazlett, E. A., Filion, D. L., Nuechterlein, K. H., & Schell, A. M. (1993). Attention and schizophrenia: Impaired modulation of the startle reflex. *Journal of Abnormal Psychology, 102,* 633–641.

Dawson, M. E., Schell, A. M., Swerdlow, N. R., & Filion, D. L. (1997). Clinical, cognitive, and neurophysiological implications of startle modification. In P. J. Lang, R. F. Simons, & M. Balaban (Eds.), *Attention and orienting: Sensory and motivational processes* (pp. 257–279). Mahwah, NJ: Erlbaum.

DelPezzo, E. M., & Hoffman, H. S. (1980). Attention factors in the inhibition of a reflex by a visual stimulus. *Science, 210,* 673–674.

Filion, D. L., Dawson, M. E., & Schell, A. M. (1993). Modification of the acoustic startle-reflex eyeblink: A tool for investigating early and late attentional processes. *Biological Psychology, 35,* 185–200.

Filion, D. L., Dawson, M. E., & Schell, A. M. (1994). Probing the orienting response with startle modification and secondary reaction time. *Psychophysiology, 31,* 68–78.

Filion, D. L., Dawson, M. E., & Schell, A. M. (in press). The psychological significance of human startle eyeblink modification: A review. *Biological Psychology.*

Friston, K. J., Frith, C. D., Liddle, P. F., & Frackowiak, R. S. J. (1991). Plastic transformation of PET images. *Journal of Computer Assisted Tomography, 15,* 634–639.

Graham, F. K. (1975). Presidential address, 1974. The more or less startling effects of weak prestimulation. *Psychophysiology, 12,* 238–248.

Grillon, C., Ameli, R., Charney, D. S., Krystal, J., & Braff, D. (1992). Startle gating deficits occur across prepulse intensities in schizophrenic patients. *Biological Psychiatry, 32,* 939–943.

Grillon, C., Courchesne, E., Ameli, R., Geyer, M. A., & Braff, D. L. (1990). Increased distractibility in schizophrenic patients. *Archives of General Psychiatry, 47,* 171–179.

Hackley, S. A., & Graham, F. K. (1987). Effects of attending selectively to the spatial position of reflex-eliciting and reflex-modulating stimuli. *Journal of Experimental Psychology: Human Perception and Performance, 13,* 411–424.

Hackley, S. A., Woldorff, M., & Hillyard, S. A. (1987). Combined use of microreflexes and event-related brain potentials as measures of auditory selective attention. *Psychophysiology*, *24*, 632–647.

Harris, G. J., Links, J. M., Pearlson, G. D., & Camargo, E. E. (1991). Cortical circumferential profile of SPECT cerebral perfusion in Alzheimer's disease. *Psychiatry Research: Neuroimaging*, *40*, 167–180.

Ison, J. R., & Hoffman, H. S. (1983). Reflex modification in the domain of startle: II. The anomalous history of a robust and ubiquitous phenomenon. *Psychological Bulletin*, *94*, 3–17.

Ison, J. R., O'Conner, K., Bowen, G. P., & Bocirnea, A. (1991). Temporal resolution of gaps in noise by the rat is lost with functional decortication. *Behavioral Neuroscience*, *105*, 33–40.

Jennings, P., Schell, A. M., Filion, D. L., & Dawson, M. E. (1996). Tracking early and late attentional processes with startle modification. *Psychophysiology*, *33*, 148–155.

Judd, L. L., McAdams, L., Budnick, B., & Braff, D. L. (1992). Sensory gating deficits in schizophrenia: New results. *American Journal of Psychiatry*, *149*, 488–493.

Knight, R. T. (1984). Decreased response to novel stimuli after prefrontal lesions in man. *Electroencephalography and Clinical Neurophysiology*, *59*, 9–20.

Knight, R. T., Hillyard, S. A., Woods, D. L., & Neville, H. J. (1981). The effects of frontal cortex lesions on event-related potentials during auditory selective attention. *Electroencephalography and Clinical Neurophysiology*, *52*, 571–582.

Knight, R. T., Scabini, D., & Woods, D. L. (1989) Prefrontal cortex gating of auditory transmission in humans. *Brain Research*, *504*, 338–342.

Koch, M., & Bubser, M. (1994). Deficient sensorimotor gating after 6-hydroxydopamine lesion of the rat medial prefrontal cortex is reversed by haloperidol. *European Journal of Neuroscience*, *6*, 1837–1845.

Kraepelin, E. (1919). *Dementia praecox and paraphrenia* (R. M. Barclay, Trans.). Edinburgh: E. & S. Livingston. (Original work published 1913)

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1990). Emotion, attention, and the startle reflex. *Psychological Review*, *97*, 377–395.

Matsui, T., & Hirano, A. (1978). *An atlas of the human brain for computerized tomography*. Tokyo: Igaku-Shoin.

McDowd, J. M., Filion, D. L., Harris, M. J., & Braff, D. L. (1993). Sensory gating and inhibitory function in late-life schizophrenia. *Schizophrenia Bulletin*, *19*, 733–746.

Nuechterlein, K. H., & Dawson, M. E. (1984). Information processing and attentional functioning in the developmental course of schizophrenic disorders. *Schizophrenia Bulletin*, *10*, 160–203.

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh Inventory. *Neuropsychologia*, *9*, 97–113.

Overall, J. E., & Gorham, D. R. (1962). The Brief Psychiatric Rating Scale. *Psychological Reports*, *10*, 799–812.

Paxinos, G., & Watson, C. (1986). *The rat brain in stereotaxic coordinates* (2nd ed.). Sydney: Academic Press.

Pelizzari, C. A., Chen, G. T., Spelbring, D. R., Weichselbaum, R. R., & Chen, C. T. (1989). Accurate three-dimensional registration of CT, PET, and/or MR images of the brain. *Journal of Computer Assisted Tomography*, *13*, 20–26.

Perry, R. H., Oakley, A. E., & Perry, E. K. (1996). *Coronal brain map and dissection guide: Localization of Brodmann areas in coronal sections*. Unpublished manuscript.

Putnam, L. E. (1990). Great expectations: Anticipatory responses of the heart and brain. In J. W. Rohrbaugh, R. Parasuraman, & R. Johnson, Jr. (Eds.), *Event-related brain potentials: Basic issues and applications* (pp. 109–129). New York: Oxford University Press.

Schell, A. M., Dawson, M. E., Hazlett, E. A., & Filion, D. L. (1995). Attentional modulation of startle in psychosis-prone college students. *Psychophysiology*, *32*, 266–273.

Schroeder, J., Buchsbaum, M. S., Siegel, B. V., Geider, F. J., Haier, R. J., Lohr, J., Wu, J., & Potkin, S. G. (1994). Patterns of cortical activity in schizophrenia. *Psychological Medicine*, *24*, 947–955.

Shihabuddin, L., Buchsbaum, M. S., Hazlett, E. A., Haznedar, M., Harvey, P., Newman, A., Schnur, D., Spiegel-Cohen, J., Wei, T., Machac, J., Knesaurek, K., Vallabhajosula, S., Singer, M., Ciaravolo, T. M., & Luu, C. (in press). Dorsal striatal size, shape, and metabolic rate in neuroleptic-naive and previously-medicated schizophrenic patients performing a verbal learning task. *Archives of General Psychiatry*.

Shimamura, A. P., Gershberg, F. B., Jurica, P. J., Mangels, J. A., & Knight, R. T. (1992). Intact implicit memory in patients with frontal lobe lesions. *Neuropsychologia*, *30*, 931–937.

Siegel, B. V., Jr., Buchsbaum, M. S., Bunney, W. E., Jr., Gottschalk, L. A., Haier, R. J., Lohr, J. B., Lottenberg, S., Najafi, A., Nuechterlein, K. H., Potkin, S. G., & Wu, J. C. (1993). Cortical-striatal-thalamic circuits and brain glucose metabolic activity in 70 unmedicated male schizophrenic patients. *American Journal of Psychiatry*, *150*, 1325–1336.

Silverstein, L. D., Graham, F. K., & Calloway, J. M. (1980). Preconditioning and excitability of the human orbicularis oculi reflex as a function of state. *Electroencephalography and Clinical Neurophysiology*, *48*, 406–417.

Swerdlow, N. R., Braff, D. L., Taaid, N., & Geyer, M. A. (1994). Assessing the validity of an animal model of deficient sensorimotor gating in schizophrenic patients. *Archives of General Psychiatry*, *51*, 139–154.

Swerdlow, N. R., Caine, S. B., Braff, D. L., & Geyer, M. A. (1992). Neural substrates of sensorimotor gating of the startle reflex: a review of recent findings and their implications. *Journal of Psychopharmacology*, *6*, 176–190.

Swerdlow, N. R., & Koob, G. F. (1987). Dopamine, schizophrenia, mania, and depression: Toward a unified hypothesis of cortico-striato-pallido-thalamic function. *Behavioral and Brain Sciences*, *10*, 197–245.

Swerdlow, N. R., Lipska, B. K., Weinberger, D. R., Braff, D. L., Jaskiw, G. E., & Geyer, M. A. (1995). Increased sensitivity to the sensorimotor gating-disruptive effects of apomorphine after lesions of medial prefrontal cortex or ventral hippocampus in adult rats. *Psychopharmacology*, *122*, 27–34.

Weinberger, D. R. (1987). Implications of normal brain development for the pathogenesis of schizophrenia. *Archives of General Psychiatry*, *44*, 660–669.

Weinberger, D. R., Berman, K. F., & Illowsky, B. P. (1988). Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia: III. A new cohort and evidence for a monoaminergic mechanism. *Archives of General Psychiatry*, *45*, 609–615.

(Received April 22, 1997; Accepted September 16, 1997)