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SENSORIMOTOR GATING DEFICITS AND HYPOFRONTALITY IN SCHIZOPHRENIA

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1. ABSTRACT

Patients with schizophrenia exhibit (a) deficient sensorimotor gating as indexed by impaired prepulse inhibition (PPI) of the startle eyeblink reflex suggesting abnormal automatic information processing and (b) abnormal attentional modulation of PPI suggesting impaired controlled information processing. Here we test the hypothesis of deficient attentional modulation of PPI in schizophrenia as a defect in the interrelationship between frontal lobe functions of planning and executive action and posterior function of processing of sensory stimulation using positron emission tomography (PET). Consistent with the literature, our findings indicate that unmedicated schizophrenia patients exhibit lower frontal/occipital ratios (termed "hypofrontality") compared with healthy controls (n=15 in each group) during a standard tone-length-judgment (attention-to-prepulse) task. Moreover, better attentional modulation of PPI was associated with higher frontal/occipital ratios in the control, but not the patient group. These findings extend animal models to humans by demonstrating the importance of frontal and occipital lobe coordination in the modulation of PPI.

2. SENSORIMOTOR GATING DEFICITS IN SCHIZOPHRENIA

Schizophrenia is characterized by deficits in attention and information processing, however, the nature of these deficits is poorly understood. The startle eyeblink modification (SEM) paradigm is a powerful psychophysiological tool that has the potential to integrate research across various domains of scientific inquiry such as cognitive science, clinical science, and neuroscience (1).

SEM has been well documented in both animals and normal humans 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. When the lead interval is short (approximately 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 (2-3). 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.

Numerous studies have reported PPI deficits in schizophrenia patients (see 4 for review) during an uninstructed passive attention condition. We have extended this line of investigation by studying attentional modulation of PPI in schizophrenia. Dawson and coworkers (5) tested medicated schizophrenia patients and age- and sex-matched healthy controls who were instructed to attend to one type of auditory prepulse (e.g., a high-pitched tone) and to ignore the other auditory prepulse (e.g., a low-pitched tone). The results showed that healthy 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 processing deficit in schizophrenia.

Animal models of PPI suggest that cortical-striatal-pallidal-thalamic circuitry plays a key role in modulating PPI in the rat (6-7). A key region within this neural circuitry is the prefrontal cortex. In order to test this hypothesis in humans, we examined simultaneous attentional modulation of PPI and glucose metabolism in the brain during the 30-minute uptake period for positron emission tomography with 18F-2-deoxyglucose in unmedicated schizophrenia patients and healthy individuals (8). In a task involving attended, ignored, and novel tones that served as prepulses, the healthy individuals showed greater PPI during attended than during ignored prepulses; the amount of PPI during novel prepulses was intermediate.

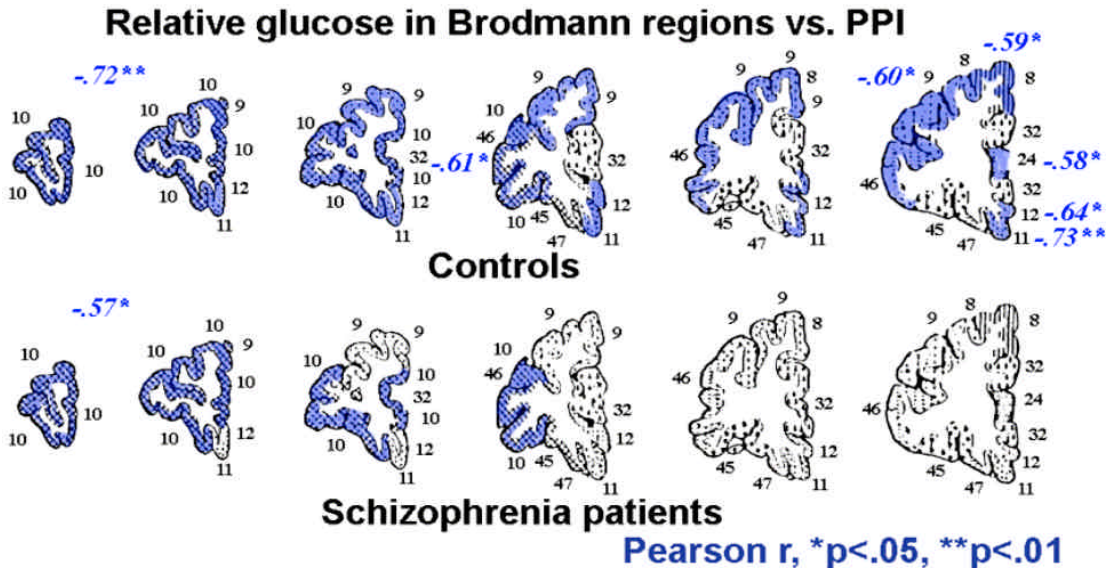

Figure 1. Frontal lobe coronal slices with Brodmann regions identified from Perry brain atlas used to evaluate glucose metabolism. Significant correlation coefficients between relative glucose metabolism and PPI during attended prepulse are shown for controls and patients in specific Brodmann regions. Note that in healthy subjects greater relative glucose metabolism in several key Brodmann regions within the frontal lobe is associated with better PPI (sensorimotor gating) during the attended prepulse. In contrast, patients showed this relationship in fewer regions. Perry and coworkers (9) provided a coronal atlas, composed of 33 coronal maps of the Brodmann areas, based on microscopic examination of one entire hemisphere of a post-mortem brain. A total of 33 evenly-spaced slices were identified such that the first slice began 1/34th of the distance from front to back.

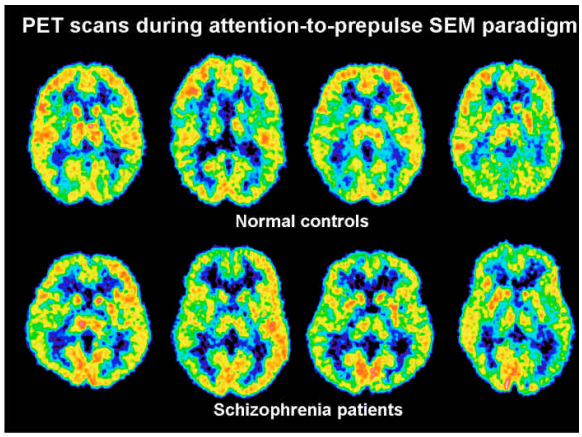

Figure 2. Individual axial PET scans during a standard startle eyeblink modification (SEM) paradigm are shown for four healthy individuals (top row) and four schizophrenia patients (bottom row). During the 30-min uptake period, subjects performed a task involving the presentation of attended, ignored, and novel tones that served as prepulses. Healthy individuals showed greater PPI during the attended than during ignored prepulses; the amount of PPI during the novel prepulses was intermediate. As can be seen, during performance on this tone-discrimination task, control subjects exhibited more relative glucose metabolism in the regions of the frontal lobe compared to those in the occipital lobe (note more red at top of scans than at bottom of scans). In contrast, patients showed a pattern of less relative glucose metabolism in frontal compared to occipital regions.

In contrast, the unmedicated patients failed to show differential PPI. For the control subjects, greater PPI during the attended prepulse was associated with higher relative metabolic activity rates in prefrontal (Brodmann Areas 8, 9, and 10 bilaterally) and lower in visual cortex (see Figure 1). Patients showed this relationship only for Area 10 on the left. During the attention-to-prepulse task, patients also had lower glucose metabolism in the superior, middle, and inferior frontal gyri, but not the precentral gyrus compared with the healthy controls (8). Figure 2 shows individual PET scans in schizophrenia patients and healthy individuals during the attention-to-prepulse paradigm. Consistent with animal models, our results demonstrate the importance of the functional integrity of prefrontal cortex to PPI modulation.

3. HYPOFRONTALITY IN SCHIZOPHRENIA

In the earliest functional brain imaging studies in schizophrenia (10), the ratio of the frontal and postcentral regions was computed and normal controls had higher ratios (1.10) than either older or younger groups of patients with schizophrenia (0.95 and 1.04, respectively). In this landmark article, the term “hypofrontality” was coined by Ingvar and Franzen to describe the anterior versus posterior cortical relationship. This early imaging data showed both frontal increases and posterior decreases rather than only frontal decreases. Prefrontal systems are identified as controlling intentional behavior and posterior structures are concerned with perceptual processes. Ingvar and Franzen (11) postulated “hypointentional” and “hypergnostic (perceptual processing)” dysfunction in schizophrenia. Interestingly, they suggest that mediothalamic-frontocortical projection

Table 1. Mean Frontal/Occipital Ratio Values in Unmedicated Patients and Age- and Sex-Matched Controls

	Controls		Patients	
	n=15		n=15	
Gyrus	Mean	SD	Mean	SD
Superior frontal	1.61	.17	1.58	.13
Middle frontal	1.71	.15	1.67	.20
Inferior frontal	1.78	.18	1.77	.18
Precentral	1.69	.11	1.75	.25

Group x Gyrus interaction T^2, F(3, 26)=3.53, p=.0286
Note: ratios calculated as (mean glucose metabolism in specific gyrus)/(mean glucose metabolism in Brodmann area 17, 18, and 19)

Table 2. Pearson Product-Moment Correlations Between Hypofrontality Ratios and Prepulse Inhibition During the Attended Prepulse

	Controls	Patients
	n=14	n=14
Gyrus		
Superior frontal	-.83*	-.41
Middle frontal	-.77*	-.39
Inferior frontal	-.84*	-.14
Precentral	-.50	-.25

Note: ratios calculated as (mean glucose metabolism in specific gyrus)/(mean glucose metabolism in Brodmann area 17, 18, and 19)

systems "which provide widespread activation of frontal structures, and also exert an inhibitory control upon afferent systems" might be responsible, although the cerebral blood flow studies could only image the cortex. In subsequent positron emission tomography (PET) studies carried out in 1981, low hypofrontality ratios were confirmed (12). Square regions of interest containing the striatum and anterior thalamus disclosed significant reductions in patients with schizophrenia (12). A follow-up study indicated the frontal/occipital ratio as the strongest separator of normals and patients (13). These findings are consistent with numerous studies supporting hypofrontality in schizophrenia (see 14 for review). As noted by Kim and colleagues (15), current studies have continued to find decreased blood flow in prefrontal areas "consistent with findings from the majority of previous studies reporting hypofrontality" (p. 546).

4. RELATING SENSORIMOTOR GATING ABNORMALITIES TO HYPOFRONTALITY IN SCHIZOPHRENIA

An important next step in this line of research is to relate impaired attentional modulation of PPI to hypofrontality in schizophrenia. This step would aid our understanding of the neural substrates of impaired startle modification in schizophrenia.

In the current paper, we extend our previous work (8) by conducting new analyses to directly test the hypothesis that schizophrenia-related deficits in the modulation of sensorimotor gating are associated with hypofrontality. We examined the ratio of glucose metabolic rate in superior frontal, middle frontal, inferior frontal, and precentral gyrus to occipital lobe regions (Brodmann area 17, 18, and 19). As can be seen in Table 1, the unmedicated schizophrenia patients had significantly lower frontal/ occipital ratios in superior, middle, inferior frontal gyrus regions compared with the healthy controls. However, the patients had higher frontal/occipital ratios in the precentral gyrus than the control subjects. These findings are consistent with numerous other reports of hypofrontality in schizophrenia during varied attentional tasks (14, 16-18).

Next, to examine the relationship between simultaneously recorded PPI and hypofrontality, we computed Pearson product-moment correlations. For the PPI measure, we focused specifically on the amount of PPI during the attended prepulse because theoretically, the greatest amount of modulation from cortical regions occurs during this stimulus condition than during the ignored prepulse condition. It is important to note that the range for PPI during the attended prepulse was similar in both the control and patient groups (controls: -100% to –21.9%; patients: -79.1% to 3.3%). PPI in controls during the attended prepulse showed a significant negative correlation with hypofrontality ratios for the superior, middle, and inferior frontal gyrus, but not the precentral gyrus (see Table 2). This pattern of correlations indicates that more PPI (i.e., better sensorimotor gating and screening out of irrelevant startle noise) during the attended prepulse is associated with increased frontal lobe and decreased occipital lobe relative glucose metabolism in healthy individuals (i.e., higher frontal/occipital ratios). In contrast, in the patient group, none of the hypofrontality ratios were correlated with PPI during the attended prepulse, suggesting a dysfunction in the key prefrontal cortex regions modulating SEM.

5. CONCLUSION

Taken together, the present findings indicate that hypofrontality in schizophrenia is associated with deficient attentional modulation of sensorimotor gating or PPI. This type of research is a critical next step if the measurement of startle modification is to realize its putative potential as an integrative-bridging paradigm across neuroscience, cognitive science, and clinical science (1). We are now extending this line of work using functional magnetic resonance imaging (fMRI) which is a powerful new methodology for the investigation of the neural circuits underlying the various attentional processes occurring during individual PPI conditions (e.g., attended, ignored) and the temporal characteristics of brain activation during these processes. The first fMRI study to examine PPI (19) further extends animal models to humans by indicating that the anterior and mediodorsal nuclei of the thalamus, each with unique frontal lobe connections, are involved in the modulation of PPI. Further work may elucidate other key structures in the circuitry underlying normal and aberrant PPI.

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