PET Study of Greater Visual Activation in Schizophrenia

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Objective: The authors tested the hypothesis that photic visual stimuli cause a greater blood flow activation response in subjects with schizophrenia than in normal subjects. Method: Eleven medicated patients with schizophrenia and 10 normal subjects were studied with [^{15}O]H_2O positron emission tomography to measure perfusion during photic stimulation at four different rates. Results: The activation at three out of four rates of visual stimulation was greater for the patients with schizophrenia than it was for the normal subjects. Conclusions: Further investigation into the mechanisms of activation during sensory stimulation in schizophrenia is warranted.

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Elementary sensory processing in schizophrenia has not been well studied with functional neuroimaging techniques, in spite of behavioral evidence suggesting abnormal function in the first 500 msec of stimulus input (1, 2). Using functional magnetic resonance imaging (MRI), Renshaw et al. (3) found an enhanced hemodynamic response to visual stimulation in patients with schizophrenia. A follow-up study from their laboratory (4) suggested that this enhanced perfusion change could occur because of increased cerebral blood volume in the vasculature of the occipital cortex, which they observed by using dynamic susceptibility contrast MRI.

To cross-validate the initial functional MRI finding, we studied a similar group of medicated patients with the [^{15}O]H_2O positron emission tomography (PET) technique and a graded photic stimulus, which yields a "dose-response" relationship in the visual cortex between stimulation rate and blood flow (5). We also infused subjects with acetazolamide, which increases cerebral blood flow (CBF) by means of a nonneuronal mechanism (inhibition of carbonic anhydrase). We reasoned that if patients with schizophrenia have greater vascular volume, as suggested by Cohen et al. (4), then we would see a greater CBF increase during the acetazolamide infusion in patients with schizophrenia than in normal comparison subjects.

METHOD

We recruited 11 stable patients with schizophrenia. Four were inpatients who were to be discharged, and seven were outpatients. Four were women. The patients' diagnoses were established by structured interview (6) and were based on DSM-IV criteria. All of the patients were taking psychotropic medications (nine were taking clozapine). Their mean age was 36.1 years (SD=7.5), and their mean duration of illness was 13.4 years (SD=6.8). Ten comparison subjects were matched to the patients in age (mean=35.8 years, SD=6.2) and sex (four of the comparison subjects were women). The comparison subjects had no history of psychiatric illness, according to structured interview (6), and none reported any first-degree relatives with an axis I psychiatric disorder. After a complete description of the study, written informed consent was obtained from all subjects.

Subjects wore light-tight goggles that delivered a flashing visual stimulus by means of inset LED arrays at rates of 1, 3, 8, and 30 Hz. Subjects received a total of six scans; the four stimulation conditions and the one "null" condition (goggles on, no stimulus) were pseudo-randomized in the first five scans. Fifteen minutes before the sixth scan (a null stimulus), subjects received an intravenous infusion of 1 g of acetazolamide. Subjects were instructed to keep their eyes open for all scans.

PET scans were performed with a Siemens CTI 931/08-12 camera (CTI Inc, Knoxville, Tenn.). For each emission scan, subjects received an intravenous bolus injection of 66 mCi of [^{15}O]H_2O. Data were collected in a single 60-second frame beginning 5 seconds after the arrival of radioactivity in the brain. In seven normal subjects and five patients, arterial samples provided data for an input function and quantitative calculation of CBF.

An automated algorithm (7) transformed each reconstructed image to a standardized atlas system (8). Count data were proportionally normalized to the mean activity for gray matter voxels, and the images were averaged within each group. The mean difference for each voxel during the stimulation conditions compared with the null condition was expressed as a z score, and corrected probabilities for rejecting the null hypothesis of no activation were calculated (9). A 22.5-mm spherical region of interest was placed at the peak of striate cortex activation to permit between-group comparison of activation

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magnitude. Following the work of Worsley et al. (9), we obtained a measure of the extent of activation by counting all voxels with z>3.09 (uncorrected p<0.001) and transforming this number to "resels," or resolution elements, by dividing the volume of all analyzed voxels in each activation image by the three-dimensional spatial coherence of each activation image (estimated full width at half maximum from 11.7 to 14.7 mm). Resels reflect the number of potentially independent regions in the brain, permitting us to use the Poisson distribution to test the null hypothesis that there was no difference in the number of resels activated by each group (10).

RESULTS

Relative to the null stimulus, both groups showed significant activation for all stimulation conditions (maximum z scores >8.0). The patients with schizophrenia activated more resels at 1, 3, and 30 Hz (depicted in figure 1). Mean normalized magnitudes of activity in the striate cortex for the null, 1-Hz, 3-Hz, 8-Hz, and 30-Hz conditions were 1.44 (SD=0.06), 1.56 (SD=0.11), 1.66 (SD=0.11), 1.67 (SD=0.14), and 1.68 (SD=0.13), respectively, for the patients with schizophrenia, and 1.44 (SD=0.07), 1.56 (SD=0.08), 1.64 (SD=0.10), 1.64 (SD=0.10), and 1.64 (SD=0.13), respectively, for the comparison subjects. We excluded the data of one male patient with schizophrenia who found the stimulus too intense and closed his eyes. Because of technical difficulties, two patients with schizophrenia completed scans only for the null and 3-Hz conditions.

The CBF increase in the striate cortex following infusion of acetazolamide did not differ between the patients with schizophrenia (mean=40.8%, SD=35.5%) and the comparison subjects for whom we had quantitative data (mean=65.8%, SD=59.6%) (t=–0.83, df=10). Both groups showed the expected, global increase in CBF, and the patients with schizophrenia had a nonsignificantly smaller increase than the comparison subjects (mean=39.2%, SD=20.7%, versus mean=54.1%, SD=38.1, respectively) (t=–0.79, df=10).

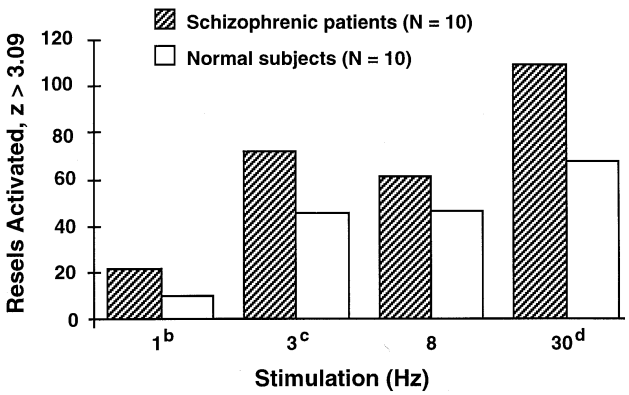
DISCUSSION

The larger extent of activation in the patients with schizophrenia confirmed our expectation of a greater activation response to the visual stimuli. We found no clear evidence that the stronger activation signal was more likely with any of the stimulation rates used. In contrast to the neuronally mediated visual activation response, the patients with schizophrenia showed a nonsignificantly smaller increase in CBF after the acetazolamide infusion. Although our study does not rule out abnormal cerebral vasculature in patients with schizophrenia, as suggested by Cohen et al. (4), our failure to find greater CBF increase in the striate cortex with acetazolamide suggests that abnormal vasculature cannot explain our results.

The medication status of the patients may have influenced the findings, although Siegel et al. (11) reported abnormally high occipital metabolism in unmedicated schizophrenic subjects during a visual attention task. The majority of our patients were taking clozapine, as were seven of the eight patients reported by Renshaw et al. (3). Our two patients not taking clozapine had activated striatal cortex at or above the group mean. Nevertheless, further studies in unmedicated patients will be necessary to directly rule out any effect of psychotropic medication.

Although our subjects viewed a simple stimulus and carried out a very minimal task (keeping their eyes open), the processing of this repetitive stimulus was not simple. Electrophysiological measurement of photic stimulation has found reduced "photic driving" in the power spectra of patients with schizophrenia (12). It is a question for further investigation whether subjects who show reduced photic driving in the EEG also show enhanced CBF activation. Event-related potentials in schizophrenia exhibit consistent abnormalities, both at early cortical stages of processing and at later stages of stimulus evaluation (13). Although we identified a regional abnormality in processing, additional work will be required to determine whether abnormal function originated in the visual cortex or in another region where stimulus evaluation and selection occurs, such as the thalamus or hippocampal/temporal structures. We conclude that further investigation of this phenomenon is warranted, particularly if activation paradigms are to evaluate the functional neuroanatomy of more complex tasks in patients with schizophrenia.

FIGURE 1. Extent of Activation in the Visual Cortex for Schizophrenic and Comparison Subjects During Photic Stimulation[a]



[a]Number of resels, or resolution elements, was determined by dividing the volume of all analyzed voxels in each activation image by the three-dimensional spatial coherence of each activation.
[b]Significant difference between groups (z=2.05, p<0.05).
[c]Significant difference between groups (z=2.40, p<0.01).
[d]Significant difference between groups (z=3.07, p<0.005).

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