Anterior Cingulate Gyrus Dysfunction and Selective Attention Deficits in Schizophrenia: [15O]H2O PET Study During Single-Trial Stroop Task Performance

Cameron S. Carter, M.D., Mark Mintun, M.D., Thomas Nichols, B.S., and Jonathan D. Cohen, M.D., Ph.D.

Objective: Attentional deficits are a prominent aspect of cognitive dysfunction in schizophrenia. The anterior cingulate gyrus is proposed to be an important component of frontal attentional control systems. Structural and functional abnormalities have been reported in this region in schizophrenia, but their relationship to attentional deficits is unknown. The authors investigated the function of the anterior cingulate gyrus and the related neural systems that are associated with selective attention in patients with schizophrenia. Method: While subjects performed multiple blocks of a single-trial Stroop task, [15O]H2O positron emission tomography scans were obtained. Fourteen patients with schizophrenia were compared with 15 normal subjects matched for age, gender, and parental education. Results: The patients with schizophrenia responded at the same rate but made more errors in color naming during the color-incongruent condition. Consistent with the authors' hypothesis, patients with schizophrenia showed significantly less anterior cingulate gyrus activation while naming the color of color-incongruent stimuli. Conclusions: Patients with schizophrenia fail to activate the anterior cingulate gyrus during selective attention performance. This finding adds to the understanding of the functional significance of the structural and metabolic abnormalities in schizophrenia that have been previously reported in this region of the brain.

(Am J Psychiatry 1997; 154:1670-1675)

Selective attention, the ability to enhance the processing of information relevant to our goals and limit the processing of that which is irrelevant, is a fundamental cognitive capability that is essential for everyday functioning. Disturbances of selective attention are among the earliest described and most clinically apparent cognitive deficits that are present in schizophrenia (1), and these disturbances appear to be related to behavioral disorganization in this illness (2).

With the advent of functional brain imaging it has become possible to investigate the neural substrates of selective attention deficits. Positron emission tomography (PET) studies that employ continuous performance tasks have reported decreased metabolism in lateral and medial prefrontal cortex in patients with schizophrenia (3, 4). These studies used continuous performance tasks to stabilize the subjects’ psychological state and place demands upon systems involved in vigilance and attention. These studies did not include control tasks or seek to establish specific relationships between abnormal attentional processes and the metabolic response of neural systems.

With the development of the [15O]H2O PET brain mapping technique, in which repeated scans are performed during different psychological states, it has become possible to design experiments that associate discrete neural system responses with specific cognitive processes. This involves constructing control tasks that match activation tasks on sensory, motor, and cognitive processes that are not specifically of interest. Comparisons of regional cerebral blood flow (CBF) between activation and control states isolate the regional CBF responses that are related to the specific processes of interest. A recent application of this technique used a dichotic listening task to show impaired task-appropriate modulation of blood flow in the superior temporal gyrus in patients with schizophrenia (5).

In studies of attentional processes analyzed by human brain mapping, considerable emphasis has been placed upon the role of the anterior cingulate gyrus (6). The anterior cingulate gyrus is activated when subjects
divide their attention across more than one feature of a stimulus (7) but not when they attend to a single feature. During the Stroop task (8), a paradigmatic measure of selective attention in which subjects must avoid reading a word (a pre- potent response) while naming its color, anterior cingulate gyrus activation has been reported in three independent studies (9–11); the precise rostro-caudal location of activation varied with the particular stimulus parameters employed (11). In contrast, the dorsolateral prefrontal cortex and parietal cortex, but not the anterior cingulate gyrus, were activated when subjects maintained attention for the occurrence of visual and somatosensory stimuli (12). It has been proposed that anterior cingulate gyrus activation is associated with the selection of one of several competing responses (6, 13) and that it has an executive role in the control of selective attention (6, 10).

Anterior cingulate gyrus abnormalities have been reported in morphometric and histopathological studies of schizophrenia (14, 15). Medial frontal hypometabolism was found in patients at rest (16) and during performance of a continuous performance task (17, 18). Decreased medial frontal activation, probably in the anterior cingulate gyrus, was seen in patients during performance of the Tower of London task (19), and impaired activation was seen in the anterior cingulate gyrus during paced verbal fluency, compared to word repetition, tasks in patients with schizophrenia (20). We recently reported decreased activation in the anterior cingulate gyrus, dorsolateral prefrontal cortex, and superior temporal gyrus during supra-span memory performance (21). Liddle and colleagues reported significant correlations between anterior cingulate gyrus regional CBF and disorganization in chronically symptomatic subjects (22). Together these studies suggest that there are behaviorally relevant structural and functional anterior cingulate gyrus abnormalities in patients with schizophrenia. However the relationship between these abnormalities and specific functional deficits, such as impaired selective attention, remains unknown. The present study sought to address this question by using [15O]H2O PET and a single-trial Stroop task.

METHOD

Subjects

The study was approved by the University of Pittsburgh biomedical institutional review board. All subjects gave written informed consent after the procedure was fully explained to them. Fourteen patients with schizophrenia and 15 healthy comparison subjects participated. All were right-handed (determined by their response to the first three questions of the Edinburgh Inventory [23]), had normal or corrected-to-normal vision that could discern color, and were native English speakers. The comparison subjects were matched as a group with the patients with schizophrenia on age (patients with schizophrenia: mean 35.7 years, SD = 4.4; comparison subjects: mean 34.3, SD = 9.1), gender (patients with schizophrenia: six women, eight men; comparison subjects: eight women, seven men), and years of parental education (patients with schizophrenia: mean 12.0, SD = 1.6; comparison subjects: mean 12.5, SD = 1.8). Regional CBF data from the normal comparison group, analyzed by using an earlier version of Statistical Parametric Mapping, have been reported elsewhere (11). All patients met DSM-IV criteria for chronic schizophrenia (N = 12) or schizoaffective disorder, bipolar type (N = 2), and had been clinically stable on fixed-dose antipsychotic regiments for a minimum of 3 months. Two patients were being treated with clozapine, and two were receiving risperidone. The rest were being treated with a variety of conventional antipsychotics. Schizophrenic symptoms were rated on the day of study by using the Positive and Negative Symptom Scale (24). We examined correlations among symptoms, performance, and regional CBF responses by combining items from the Positive and Negative Symptom Scale to produce three syndromes. The positive syndrome consisted of the symptoms of hallucinations and delusions. Blunted affect, emotional withdrawal, passive social avoidance, motor retardation, and lack of spontaneity were combined to form the negative syndrome. Finally, the symptoms of conceptual disorganization, difficulty abstracting, and poor attention comprised the disorganization syndrome. Alphas for these syndromes were 0.85, 0.87, and 0.78, respectively.

Procedures

PET images were obtained with a Scitens ECAT 951i 31 camera. Subjects' heads were immobilized by using an individually molded thermoplastic mask. The PET gantry was rotated and tilted so that the lowest imaging plane was parallel to, and approximately 1 cm above, the carotid bifurcation. A 10-minute transmission scan that used three rotating "pin" sources of 68Ge/68Ga for the purpose of calculating attenuation factors preceded the blood flow studies. Brain activity was measured after an intravenous injection of 50 mg of [15O]H2O in 5–7 ml of saline. Twenty seconds after injection, a 60-second emission scan was acquired and reconstructed to approximately 10 mm full width at half maximum to create a map that is highly proportional to CBF (25). In subsequent sections we will follow the convention of referring to these data as regional CBF.

The Stroop task was programmed by using PsyScope (26) on a Macintosh IIfi computer. Subjects began the task 40 seconds before injection and continued for 3 minutes. Each trial began with a central fixation cross for 500 msec that was followed by the stimulus (a colored word) for 1250 msec. Subjects' responses were registered by using a voice-activated relay and timing device with millisecond accuracy. Responses were also tape recorded to measure accuracy. In the two previous PET studies of single-trial Stroop performance that included color-congruent stimuli, these stimuli comprised an entire block of trials (9, 10). In discussing these studies, Taylor et al. (13) pointed out that when subjects are presented with a block of color-congruent trials they may change strategy and read the word rather than name the color. To control for this, we mixed neutral stimuli in with the color-congruent and color-incongruent stimuli. Facilitation blocks consisted of trials in which 50% of the stimuli were color-congruent (e.g., the word RED printed in red), and 50% were neutral (e.g., the word DOG printed in black). Interference blocks consisted of trials in which 50% of the stimuli were color-incongruent (e.g., the word RED printed in green), and 50% were neutral. Neutral blocks consisted of animal name words that were printed in color. Stimuli in all blocks were presented in random order. Subjects were instructed to fixate on the center of the monitor and ignore the words while naming their colors as quickly and accurately as possible. Subjects performed each of the three experimental conditions three times. The order was counterbalanced across subjects. While in the PET scanner, but before the first regional CBF scan, subjects received one practice block of the condition that they had been randomized to receive first during the PET study.

Data Analysis

Individual PET images were registered by using an automated algorithm to correct for small head movements (27); then registered to the individual subject's MRI scan (28). Spatial normalization was accomplished by registering these data to a standard MRI that had been previously transformed to the coordinates of the atlas of Talairach and Tournoux (29). PET images were then analyzed by using Statistical Parametric Mapping (30) software. Data were normalized to an average value of 50 ml/100 ml/minute by using analysis of covariance (ANCOVA). A gaussian filter (12 mm full width at half maximum) was applied to the data to reduce the effects of high frequency noise and
FIGURE 1. Extent and Location of the Difference Between Normal Comparison Subjects and Patients With Schizophrenia in Anterior Cingulate Gyrus Regional CBF Response to Naming the Color of Color-Incongruent Stimuli.

4Results are rendered onto a T1-weighted structural MRI scan that has been spatially transformed to the coordinates of the atlas of Talairach and Tournoux (29).

individual differences in anatomy. The mean difference between the color-incongruent and the neutral conditions was compared between the patients with schizophrenia and the healthy subjects by using a split plot ANCOVA. The resulting image of t statistics was transformed to z scores to allow the associated display to be independent of the degrees of freedom. The comparison of patients with schizophrenia and normal subjects was undertaken in two steps. The first analysis was hypothesis driven and focused on the anterior cingulate gyrus. The critical threshold for this comparison was a z score of 2.32, which corresponded to a p value of 0.01. The second comparison was exploratory and sought to identify other regions throughout the brain in which activation in patients with schizophrenia was less than that of comparison subjects during performance of the Stroop task. The critical z score for this comparison was 3.09, which corresponded to a p value of 0.001.

RESULTS

Task Performance

Because of initial technical difficulties in measuring verbal responses in the scanner, reliable reaction time data were available for only nine comparison subjects and 10 patients with schizophrenia. Accuracy ratings, scored from taped responses, were obtained for all but one subject in each group. Both groups were able to maintain the pace of responding to a stimulus every 1750 msec without omissions. Hence, differences between the groups' regional CBF response cannot be due to reduced rates of responding, which is a frequent confound in mapping studies of cognitively impaired subjects.

As in previous studies of single-trial Stroop task performance (31), the patients with schizophrenia did not show greater interference, as measured by the difference in reaction times for color-incongruent stimuli (patients with schizophrenia: mean=958.6 msec [SD=186.4], comparison subjects: mean=902.3 msec [SD=229.4]) and neutral stimuli (patients with schizophrenia: mean=855.9 msec [SD=171.0], comparison subjects: mean=805.3 msec [SD=192.3]) (F=0.03, df=1, 17, p<0.87). In the error analysis, overall error rates were low, which confirms that subjects understood the task and were performing as instructed. The patients with schizophrenia showed a larger increase in errors with color-incongruent stimuli (mean=11.1%, SD=9.2%) than with neutral stimuli (mean=2.2%, SD=1.9%) than did the comparison subjects (mean=1.9% [SD=3.4%] and mean=0.5% [SD=0.9%], respectively) (F=7.9, df=1, 25, p<0.01). These errors invariably consisted of reading the word rather than naming its color. This greater error interference remained significant whether the comparison was made for all subjects or just those with reaction time data. Pearson's correlation coefficients between reaction times and error rates for color-incongruent stimuli for the whole group (r=0.10, df=18, p<0.34), the comparison subjects (r=0.36, df=8, p<0.34), and the patients with schizophrenia (r=0.02, df=9, p<0.34) were not significant. The nonparametric Spearman's rank order correlation showed a similar result (whole group: r_s=0.14, N=19, p=0.26; comparison subjects: r_s=0.42, N=9, p<0.26; patients with schizophrenia: r_s=0.12, N=10, p<0.26). Hence, the higher frequency of errors was not simply due to a speed-accuracy tradeoff by the patients with schizophrenia. Rather, the greater number of errors in the color-incongruent condition indicates attentional dysfunction in the patients with schizophrenia, which reflects a greater influence of the irrelevant dimension of the stimulus (the word) over naming the color (32).

Performance during color-congruent blocks did not reveal differences between the patients with schizophrenia and the comparison subjects in either reaction times (color-congruent mean=723.7 msec [SD=209.7] and 665.7 msec [SD=160.0], respectively; neutral mean=790.8 msec [SD=218.5] and 751.2 msec [SD=176.2], respectively) or errors (color-congruent mean=0.1% [SD=3.3%] and 0.0% [SD=0.0%], respectively; neutral mean=1.4% [SD=1.2%] and 0.6% [SD=1.1%], respectively). Comparison subjects showed more reaction time facilitation than patients, but this was not significant. This would be expected if patients with schizophrenia have a deficit in the control of selective attention, since in the current design the color-congruent condition was a mix of neutral and color-congruent stimuli. Comparison subjects would be better able to strategically allow more reading, thus taking advantage of the presence of color-congruent color names to improve performance.

Regional CBF

The regional CBF analysis focuses on the comparison of the two groups' responses to color-incongruent versus neutral conditions, since it is in this comparison that
patients showed significant evidence of impaired selective attention.

Consistent with our hypothesis, patients with schizophrenia showed significantly less activation than comparison subjects in the right anterior cingulate gyrus (pixel maxima at Talairach coordinates 12, 46, 4) \((z=2.88, N=29, p<0.002)\). The location and extent of this group difference is shown in figure 1.

Figure 2 shows other regions of the brain that increased less in patients with schizophrenia than in normal comparison subjects in response to naming the color of color-incongruent stimuli. Differences are seen in the left precentral gyrus (Talairach coordinates −26, −14, 52) \((z=3.24, N=29, p<0.001)\), and right hippocampal gyrus (Talairach coordinates 12, −38, 4) \((z=3.45, N=29, p<0.001)\). Orthogonal projection views of these group differences in activation are shown in figure 2.

Group differences in the magnitude of regional CBF responses seen in the anterior cingulate gyrus, left precentral gyrus, and right hippocampal region were not due to greater variability in these regions. The patients with schizophrenia showed smaller and generally less variable responses than comparison subjects in the anterior cingulate gyrus (patients with schizophrenia: mean change=1.2% [SD=2.4%]; comparison subjects: 2.4% [SD=3.4%]) and the precentral gyrus (patients with schizophrenia: mean=−0.2% [SD=2.2%]; comparison subjects: mean=3.3% [SD=3.4%]). The hippocampal gyrus difference reflected a region that decreased more in the patients with schizophrenia (mean=−2.4%, SD=3.7%) than in the normal comparison subjects (mean=0.3%, SD=4.3%).

Correlations Between Regional CBF Response and Behavior

Pearson’s product moment correlation coefficients were calculated between errors in the color-incongruent condition and regional CBF response in the anterior cingulate gyrus. This correlation was positive and approached significance at a trend level in both groups (comparison subjects: \(r=0.48, df=13, p<0.09\); patients with schizophrenia: \(r=0.48, df=12, p<0.10\)). To evaluate the specificity of this finding, correlations were computed between errors and the regional CBF response at the two other regions that distinguished patients with schizophrenia from comparison subjects: the left precentral gyrus (patients with schizophrenia: \(r=−0.52, df=12, p<0.07\); comparison subjects: \(r=−0.23, df=13, p<0.16\)) and the right hippocampal region (patients with schizophrenia: \(r=0.44, df=12, p<0.14\); comparison subjects: \(r=−0.40, df=13, p<0.16\)).

Within the schizophrenia group correlation coefficients were computed for anterior cingulate gyrus activation and positive, negative, and disorganization syndrome scores. None of these correlations approached significance. The correlation between errors in the color-incongruent condition and disorganization, which we have found in studies of larger groups of patients (33), was also not significant.

DISCUSSION

Consistent with our hypothesis, patients with schizophrenia showed significantly less anterior cingulate gyrus activation than normal comparison subjects during the color-incongruent condition of the Stroop task. This is consistent with previous studies that suggested abnormal medial frontal physiology in schizophrenia (16–22). Because of our experimental design we are able to attribute functional relevance to this finding. We compared regional CBF under attentionally demanding conditions (response competition) to a state in which sensory, motor, and cognitive components unrelated to resolving this competition were identical. Hence, we conclude that failure to activate the anterior cingulate gyrus in the color-incongruent condition is related to the selective attention demands of the task.

The primary purpose of this study was to test a focal hypothesis: patients with schizophrenia would fail to activate the anterior cingulate gyrus during selective attention performance. Our results confirm this hypothesis while also showing that other regions respond abnormally to task performance in patients with schizophrenia. This
result is consistent with recent PET findings that suggested
that patients with schizophrenia fail to modulate cortical
activity in distributed networks in a task-appropriate
manner (5, 34). One hypothesis that has been invoked
to account for these findings is that corticocortical or
corticostriatal-thalamic connectivity is disturbed in schizo-
phrenia (5, 35). The caveat to this interpretation is that a
failure to activate a region involved in executive control
would also have widely distributed ramifications within
a neural network engaged by the task. The design of pre-
vious studies as well as the current one do not allow us
to draw firm conclusions regarding which of these two
interpretations is more accurate. Further studies with
novel designs and quantitative methods for evaluating
connectivity are needed to resolve these two competing
views regarding the underpinnings of abnormal patterns
of cortical activation during cognitive performance in
schizophrenia.

In both groups, anterior cingulate gyrus activation cor-
related with errors in the color-incongruent condition.
Similar correlations between poor performance and an-
terior cingulate gyrus activation have been previously re-
dported during a Stroop-like task (13) and during a re-
sponse inhibition task (36). A baseline level of task-related
activation, with incremental increases with increasing er-
ror rates, is consistent with the hypothesized role of the
anterior cingulate gyrus in monitoring for or detecting
errors and in strategically reactivating selected circuits
to compensate for their occurrence (37, 38). Such a function
would reflect the connectivity between the anterior cin-
gulate gyrus and both the cortical systems involved in
cognition and the limbic regions involved in emotion and
motivation. Physiological dysfunction in this region could
result in the lower regional CBF response and greater
number of color-naming errors seen in patients in the cur-
rent study, with preservation of the correlational relation-
ship between these two measures.

The relationship between impaired selective attention
performance and disorganization reported in other stud-
ies (2, 31) was not found. There were no significant rela-
tionships between symptoms and cingulate regional CBF
response, which may reflect a restricted range of patient
symptoms. All patients were mildly ill and clinically stable
outpatients.

All patients in the study were treated with neuro-
leptics. It is possible that the failure of the anterior cin-
gulate gyrus to activate during Stroop performance in
the patients with schizophrenia reflects the effects of
antipsychotic medications rather than processes related
to the pathophysiology of schizophrenia. Decreases in
resting anterior cingulate gyrus regional CBF and me-
tabolism have been reported 3–4 weeks after neuro-
leptic withdrawal in patients with schizophrenia (39,
40), which confirms that increasing dopamine tone in-
creases resting cingulate blood flow and metabolism.
However, since previous studies that reported reduced
anterior cingulate gyrus activation during Tower of
London performance (19) and verbal fluency (34) found
this result in unmedicated patients, we believe
that this account of our results is unlikely. A definitive

conclusion on this point must await a replication in an
unmedicated group of patients.

The locus of the reduced regional CBF response asso-
ciated with naming the color of color-incongruent stimuli
is within the rostral anterior cingulate gyrus. Similar loci
of activation have previously been reported during Stroop
performance (10). On the basis of animal studies and a
limited review of human PET studies (41), it has been
proposed that within the anterior cingulate gyrus the more
caudal region is involved with cognition and the more
rostral region with emotions. The results of this and other
Stroop studies suggest that a role in attention extends to
the pregenual portion of the cingulate. Reports of caudal
anterior cingulate gyrus activation in response to pain
(42) are also inconsistent with a simplified functional di-
vision of ventral and dorsal regions along cognitive versus
emotional lines. Of course, one can always argue that
activation associated with pain reflects attention to this
sensation and that activation during a cognitive task refl-
cts an emotional response. However, the association
between performance and anterior cingulate gyrus activ-
ation in the present study, as well as those of Taylor et
al. (13) and Casey et al. (36), argues against a nonspecific
emotional response driving anterior cingulate gyrus activ-
ation. More functional imaging studies that focus on this
region are needed before we will have a clear under-
standing of the nature of functional specialization within
the human anterior cingulate gyrus.

While the precise pathophysiological mechanisms that
underlie a failure to increase regional CBF in the anterior
cingulate gyrus during selective attention in schizophrenia
are unknown, recent histopathological studies have re-
ported findings that may begin to illuminate this issue.
Benes (15) reported greater numbers of vertical glutama-
teric fibers in layer II of the anterior cingulate gyrus in
postmortem schizophrenic brains along with a reduction of
GABAAergic interneurons and up-regulation of post-
synaptic GABA receptors. Benes proposed a model of a
disturbed intrinsic circuitry of the anterior cingulate gyrus
in which an increase in excitatory input and a reduction in
GABAAergic inhibition within layer II cause unmodu-
lated pyramidal cell activity in this region and its distant
projection sites. A similar model that emphasized distur-
bances in glutamatergic, dopaminergic, and GABAAergic
neurotransmission in the cingulate in schizophrenia has
been also proposed by Olney and Farber (43).

In the present study we found that patients with
schizophrenia showed significantly less activation in the
anterior cingulate gyrus, which was associated with im-
paired selective attention. This suggests that the func-
tional significance associated with histopathological
and physiological abnormalities that have been pre-
viously reported in this region of the brain in schizo-
phrenia includes a relationship with deficits in selective
attention. These results demonstrate the utility of the
Stroop task as an activating procedure in functional im-
aging studies and invite further studies that evaluate the
relationship of anterior cingulate gyrus function, atten-
tional deficits, and associated clinical manifestations in
schizophrenia.
REFERENCES


16. Tamminga CA, Thaker GK, Buchanan R, Kirkpatrick B, Alphs LD, Chase TN, Carpenter WT: Limbic system abnormalities identified in schizophrenia with fluorodeoxyglucose and neocortical alterations with the deficit syndrome. Arch Gen Psychiatry 1992; 49:522-530


32. Cohen JD, Servan-Schreiber D: Context, cortex, and dopamine: a connectionist approach to behavior and biology in schizophrenia. Psychol Rev 1992; 99:45-77


43. Olney JW, Farber NB: Glutamate receptor dysfunction and schizophrenia. Arch Gen Psychiatry 1995; 52:998-1007