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Brain activation patterns during a selective attention test—a functional MRI study in healthy volunteers and patients with schizophrenia

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Abstract

Functional magnetic resonance imaging was used to compare cortical activation patterns in healthy volunteers with those in patients with schizophrenia during a modified verbal Stroop task. Healthy subjects ($n=13$) and patients with schizophrenia ($n=13$) on stable antipsychotic treatment, matched on demographic variables, were included. Patients were preselected on the basis of good performance on a selective attention test. Patients with schizophrenia showed a significantly increased pattern of activation in the left and right inferior frontal cortex and the anterior cingulate cortex. A significant negative correlation between activation of the left prefrontal cortex and accuracy in the modified Stroop test was observed for healthy controls but not schizophrenia patients. Although both groups recruited the prefrontal cortex during the modified Stroop task, for the schizophrenia patients this activation was bilateral, whereas for the controls this activation was primarily in the left hemisphere, suggesting that patients with schizophrenia recruited more prefrontal regions to perform the task with the same accuracy as healthy controls. Our findings of increased activity across multiple areas of the brain, including dorsolateral frontal cortex and anterior cingulate, in patients with schizophrenia who perform relatively well on a task of selective attention give further evidence that task performance may be a confounding factor in the interpretation of neuroimaging results.

Keywords: Functional magnetic resonance imaging; Schizophrenia; Stroop test; Task performance

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1. Introduction

Studies of patients with schizophrenia have repeatedly shown a wide range of neurocognitive disturbances, including deficits in working memory, executive function and attention (Gold and Harvey, 1993; Carter et al., 1996; Barch et al., 1999; Rund and Borg, 1999). Attentional deficits are among the earliest described and clinically most prominent cognitive deficits that are present in schizophrenia. These disturbances appear to be related to long-term outcome, disability and quality of life (Harvey et al., 1998; Bilder et al., 2000; Green et al., 2000; Oehl et al., 2000). Selective attention, the ability to reject irrelevant information while attending to a relevant input, is a fundamental cognitive capability that is essential for everyday functioning.

The Stroop paradigm (Stroop, 1935) is a widely used measure of selective attention and executive functioning (for an overview, see MacLeod, 1991). This task requires frontally mediated cognitive processes such as response inhibition, interference resolution, and behavioral conflict resolution. In the traditional Stroop task, subjects have to suppress the highly overlearned response of word reading in favor of the less automatic process of color naming. The cortical mechanisms underlying the inhibition of prepotent response tendencies in this task have been extensively studied in brain imaging studies. However, considerable variability exists in the brain regions observed to be activated in the Stroop task. Activations were reported in the anterior cingulate, lateral prefrontal cortex, inferior frontal gyrus, orbitofrontal area, inferior parietal lobule, premotor cortex, supplementary motor area, and putamen (Pardo et al., 1990; Corbetta et al., 1991; Bench et al., 1993; Carter et al., 1995, 2000; Taylor et al., 1997; Bush et al., 1999, 2000; Brown et al., 1999; Zysset et al., 2001; Tamm et al., 2002)

Hypofrontality has frequently been reported in patients when challenged with an executive 'frontal' task or working memory tasks at which they perform poorly (Berman et al., 1986; Weinberger et al., 1986, 1994; D'Esposito et al., 1995; Weinberger and Berman, 1996; Yurgelun-Todd et al., 1996; Callicott et al., 1998; Curtis et al., 1998; Fletcher et al., 1998; Stevens et al., 1998; Barch et al., 2001; Perlstein et al., 2001). Positron emission tomography (PET) studies (Carter et al., 1997) and functional magnetic resonance imaging (fMRI) studies (Yucel et al., 2002) have demonstrated that medicated patients with schizophrenia show a reduction in the anterior cingulate response to the incongruent Stroop condition.

Ramsey et al. (2002) suggested that the concept of hypofrontality in schizophrenia is too simple, and that both the characteristics of the cognitive task used during functional imaging and the level of performance in this task are essential for the interpretation of functional brain imaging experiments. Thus, whereas many studies in schizophrenia have reported reduced prefrontal cortex activation when patients perform poorly (Franzen and Ingvar, 1975; Weinberger et al., 1988, 1992; Callicott et al., 1998; Carter et al., 1998a; Fletcher et al., 1998; Stevens et al., 1998), others have reported that under carefully controlled conditions frontal activity is either normal (Frith et al., 1995; Mellers et al., 1998; Curtis et al., 1999) or even increased (Stevens et al., 1998; Manoach et al., 1999; Callicott et al., 2000) when patients' performance is near normal. Ramsey et al. (2002) concluded that the design and complexity of an attentional task is critical for the interpretation of functional brain imaging results in schizophrenia patients, as it determines to a large extent whether the patients are actually cognitively engaged in the task or not.

Implementation of the Stroop task, in its traditional form, is problematic for fMRI research. Verbal responses can introduce movement artifacts, and the use of covert responses limits evaluation of subjects' performance. We used a modified version of the Stroop task in which subjects responded to the printed color of a word via manual response. This modified Stroop task is similar in critical respects to more familiar response competition tasks (like the original Stroop task or go/no-go task) and engages cognitive control by requiring selective attention to the relevant stimulus dimension, the color. The main difference between the modified Stroop task and the traditional Stroop tasks is that subjects in the modified Stroop task compare two attributes

of a stimulus, whereas in the traditional Stroop task they generate a verbal response to match one attribute of a stimulus while suppressing the irrelevant dimension.

The primary object of the current study was to assess whether patients with schizophrenia and healthy control subjects differed in brain activation during performance of the modified Stroop task as assessed with fMRI.

2. Method

2.1. Subjects

Our study was carried out in 16 male patients with an ICD-10 diagnosis of schizophrenia and 15 healthy male subjects. Schizophrenia patients who displayed relatively high levels of global functioning and were able to perform the traditional Stroop task without any difficulties were selected for this study from the outpatient unit of the Department of Psychiatry of Innsbruck's University Clinics. Healthy subjects were selected from our healthy subject pool and were matched to the schizophrenia patients in age and years of education. The mean age of the healthy subjects was 30.0 years (S.D. = 5.6), and that of the patients was 32.7 years (S.D. = 5.9). All subjects were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). Volunteer subjects with a history of mental disorder, head injury, current alcohol/substance abuse, age >60 or <19, or with contraindications to MRI were excluded. All patients were treated with second generation antipsychotics (risperidone, olanzapine and clozapine) and had been on fixed doses for at least 1 month prior to testing. No patient received any concomitant medication. The patients had a mean duration of illness of 6.23 years (S.D. = 4.7). They had all been hospitalized on at least one previous occasion, experiencing positive symptoms. All patients had been clinically stable for at least 6 months before the study. Each subject was given information regarding the functional MRI procedure, and all signed an informed consent form. The study was approved by the Ethical Committee of the Medical Faculty of Innsbruck University. On the day of scanning, before the fMRI session, each subject was assessed by the same rater using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987).

2.2. Task

An adapted single-trial version of the color Stroop task was used. Subjects were presented with color words and were instructed to decide via button-press if the word and the color were color-congruent (e.g. the word RED printed in red) or color-incongruent (e.g. the word GREEN printed in red). The modified Stroop task consisted of 48 trials in which 50% of the trials were color-congruent and 50% were color-incongruent. The colored words were displayed for 1500 ms with an interstimulus interval of 1000 ms and subtended a visual angle of $2° \times 3°$. Stimuli in all blocks were presented in random order. Subjects responded with their right hand by pressing a yes/no button in response to color-congruent/color-incongruent targets. In-scanner accuracy data were obtained for all subjects. We were not able to record reaction time data during the scanning.

2.3. Stimulation

We used a blocked periodic design involving presentation of a rest condition for 40 s followed by a 40-s activation condition. This cycle was repeated three times over the course of 4 min. The resting baseline reference task was a standard condition during which subjects were instructed to lie still and remain quiet with their eyes open (Gur et al., 1982). For stimulation during the activation condition, we used a modified PC version of the Stroop test and projected the material on a screen placed in front of the MRI scanner, visible for the participant by means of an angled mirror placed above the head coil. The subjects were given no aural instructions during the scanning period. The noise from the scanner was reduced by the use of gradient damping headphones. To ensure that all subjects understood the study paradigm, general instructions for the tasks were reviewed with participants before they entered the magnet. This procedure was necessary to limit the vocalization and auditory stimulation in the scanner. No specific

stimuli were presented during the prescan instruction. To prevent head motions, additional foam pads and a special helmet fixed to the head coil were used.

2.4. Scanning procedure

Scanning was performed on a 1.5 Tesla whole body scanner (Magnetom VISION, Siemens, Germany) with an echo-planar capable gradient system (rise time = 600 μs, 25 mT/ms) and a circular polarized head coil (FOV = 250 mm). For fMRI, we employed T2* weighted single shot echo-planar sequences (TE/α = 64 ms/90°, matrix = 64×128, voxel dimension = 2.94×1.95×4.5 mm, 1.5 mm gap). We acquired 15 slices with a constant slice thickness of 3 mm parallel to the bicommissural plane (anterior commissure–posterior commissure line: AC–PC line), 14 axial slices above and 1 slice ventral to the AC-PC line. The AC-PC line was anatomically identified on scout images in the sagittal plane before echoplanar data acquisition.

During each cognitive task condition, a series of 60 sequential images was acquired, each consisting of 10 images during rest alternating with 10 images during stimulated states. Functional images were collected every 4 s.

2.5. Data analysis

Post-processing was done on a computer workstation with dedicated software (SPM99, The Wellcome Department of Neurology, University College London, UK). All conventional magnetic resonance images were interpreted by an independent neuroradiologist, and no clinical abnormalities were detected for any study subject. Firstly, 60 images of each condition were automatically realigned to the first image to correct for head movements between the scans (Friston et al., 1995). The data sets were then co-registered with a 3-D anatomical image and transformed into the standard stereotactic space corresponding to the atlas of Talairach and Tournoux (1988). Within this normalization, the voxels of the 3-D image were slightly smoothed to achieve an isotropic voxel size of 4×4×4 mm^3 (Poline et al., 1995). Voxels that had values greater than 0.8 of the volume mean in all the images were selected to restrict the analysis to intracranial regions. Low frequency artifacts arising from aliased cardiorespiratory and other cyclical components were removed with high pass filtering (0.5 cycles/min) of the time series. In order to present the overall pattern of activation across subjects, the stereotaxically transformed functional data sets from each subject were slightly smoothed with a Gaussian filter with a root-mean-square radius of 8 mm to compensate for inter-subject differences and to suppress high-frequency noise in the images. With these data, group activation maps were calculated by pooling the data for each condition across the patients and the control subjects. The alternating periods of baseline and activation were modeled using a simple smoothed delayed box-car reference vector to take account of the delayed cerebral blood flow changes after stimulus presentation. Significantly activated voxels were searched for by using the 'general linear model' approach for time–series data (Friston et al., 1995; Poline et al., 1995). Firstly, design matrices comprising contrasts testing for significant activations during Stroop activation vs. rest condition for the patients as well as for the control group were designed. In the comparisons within groups of patients or normal controls and for the comparisons between groups, an uncorrected threshold ($P < 0.001$; $k = 8$) was used. A second level random effects analysis was used to compare the two groups. For additional regression analysis (introducing the accuracy as an external covariate), an uncorrected threshold of $P < 0.01$ and $k = 8$ was used. For the purpose of attributing anatomical areas to activations, the coordinates of the Montreal Neurological Institute (MNI) template were transferred into a standardized stereotactic space (Talairach and Tournoux, 1988), using a Matlab 5.3.1 based program written by Brett et al. (2001), and clusters of activated voxels were assigned according to their center-of-mass activation. The behavioral data (age, education, prescanning Stroop task: accuracy and reaction time) were compared using a non-parametric statistic (Mann–Whitney *U*-test). A statistic was considered to be significant if its exact two-tailed probability value was < 0.05.

Table 1
Demographic data and clinical data

Subject characteristics	Controls ($n=13$)		Patients ($n=13$)		P-value
	Mean	S.D.	Mean	S.D.	
Age	30.0	5.6	32.7	5.9	0.226
Education (years)	14.6	3.6	12.4	2.8	0.097
Length of illness (years)			6.23	4.7	
PANSS total			48.9	12.1	
PANSS negative			14.2	5.0	
PANSS positive			11.4	5.9	
Mean total times (s) in pre-scanning Stroop test					
Stroop RCN	44.3	6.7	47.7	9.3	0.369
Stroop NCW	88.2	9.6	103.4	31.3	0.329
Accuracy (%)	98.8	0.8	98.9	0.9	0.704
Accuracy for the modified Stroop test during scanning					
Accuracy (%)	96.0	1.6	96.3	2.0	0.762

PANSS = Positive and Negative Syndrome Scale; RCN = mean total time of reading color names in black (neutral stimuli), and reading color names presented in its own color (congruent stimuli); and NCW = naming color of word, where the color of the print and the name of the word are different (incongruent stimuli).

3. Results

A total of 16 patients and 15 controls were scanned. Further analysis could not be done on two controls and three patients due to motion artifacts and problems during data acquisition, yielding a final sample of 13 patients and 13 controls. There was no significant difference between groups in age ($P=0.226$), years of education ($P=0.097$) and task performance in the original ($P=0.704$) and modified Stroop tasks ($P=0.762$). We found a significant positive correlation between the accuracy in the original Stroop task and the accuracy in the modified Stroop task (Spearman correlation, $P=0.005$). Demographic data and Stroop performance data are shown in Table 1.

3.1. fMRI data

3.1.1. Activation during the modified Stroop task

Locations of significant increase in BOLD signal during the modified Stroop task are shown in Table 2 and Fig. 1. Healthy subjects showed activation in the left inferior and middle frontal gyrus (BA 9, 44, 46), right anterior cingulate (BA 32), bilateral precuneus (BA 7, 19, 31), right superior parietal lobe (BA 7), right occipital cortex (BA 18), left caudate and bilateral insula. Patients with schizophrenia showed significant activations in bilateral inferior frontal gyri (BA 9, 47), right middle frontal gyrus (BA 9, 10), bilateral anterior cingulate (BA 24, 32), bilateral medial frontal gyri (BA 6), bilateral parietal cortices (BA 40), right temporal cortex (BA 39), left claustrum and left nucleus lentiformis.

Differences in task-related effects were examined by subtracting the activation values of patients from those of healthy subjects and vice versa. Patients with schizophrenia showed significantly more activation in the left and right inferior frontal gyrus (BA 9), the anterior cingulate (BA 24) and the right precuneus and temporal cortex (BA 7, 22), whereas healthy subjects showed a greater activation than patients with schizophrenia in the left temporal and occipital cortices (BA 19, 22, 39).

3.2. Correlation between brain activation and accuracy

Healthy subjects showed a positive correlation between accuracy in the modified Stroop task and brain activation in the left and right medial and superior frontal gyrus (BA 9, 10), bilateral anterior cingulate (BA 32), left middle frontal gyrus (BA 47) and right temporal cortex (BA 22) and hippocampus. A negative correlation between accuracy and activation of the left inferior and middle frontal gyrus (BA 44, 9), right precentral gyrus (BA 9) and left gyrus postcentralis (BA 3), right inferior parietal lobe (BA 40), left precuneus (BA 31) and left cuneus (BA 18), right thalamus, right insula and left claustrum was seen in healthy subjects. Patients with schizophrenia showed a positive correlation between accuracy and the activation in bilateral anterior cingulate (BA 31, 23), bilateral gyri parahippocampi and superior temporal gyri (BA 30, 29) and the left caudate. A negative correlation between accuracy and the activation of the left inferior and superior parietal lobe (BA 7, 40) and the right precentral gyrus

Table 2
Locations of significant increase of BOLD signal during the modified Stroop task for comparison subjects and patients with schizophrenia

Region	MNI coordinates			*Z* score
	x	*y*	*z*	
Controls				
Left inferior and middle frontal gyrus (BA 9, 44, 46)	−40	4	32	5.78
Right anterior cingulate cortex (BA 32)	12	12	40	4.03
Right superior parietal lobe (BA 7)	28	−56	44	4.06
Left precuneus, left precentral gyrus (BA 7, 19, 6)	−24	−64	36	5.73
Right precuneus (BA 31)	28	−72	20	5.89
Right middle occipital gyrus (BA 18)	28	−84	4	3.91
Left caudate	−20	16	16	3.81
Left insula	−28	20	−4	3.55
Right insula	40	20	20	3.53
Patients with schizophrenia				
Right inferior and middle frontal gyrus, precentral gyrus (BA 9, 10, 44, 47)	52	4	32	6.71
	32	28	−8	6.12
	28	44	16	4.37
Left and right medial frontal gyrus, anterior cingulate gyrus (BA 6, 24, 32)	−4	−8	56	5.08
	−16	8	32	3.60
Left postcentral gyrus, left inferior frontal gyrus, left inferior parietal lobule (BA 1, 9, 40)	−56	−28	40	7.43
Right middle temporal gyrus and right inferior parietal gyrus (BA 39, 40)	32	−68	28	5.67
Left lentiform nucleus and left claustrum	−20	8	−8	4.58
Left subthalam nucleus	−12	−12	−4	3.94
Schizophrenic patients minus control subjects				
Right inferior frontal gyrus (BA 9)	56	4	32	4.95
Left inferior frontal gyrus, left precentral gyrus (BA 9, 6)	−56	4	36	3.75
Anterior cingulate cortex, left medial frontal gyrus (BA 24, 6)	0	−8	40	4.83
Right precuneus (BA 7)	16	−76	36	4.07
Right superior temporal gyrus, right precentral gyrus (BA 22, 44)	56	−4	−8	3.92
Control subjects minus patients with schizophrenia				
Left middle and superior temporal gyrus (BA 37, 39, 22)	−44	−72	8	4.07
	−60	56	12	3.80
Left middle occipital gyrus (BA 19)	−40	−88	16	3.51

BA = estimated Brodmann's area.

(BA 6) was seen in patients with schizophrenia (Tables 3–4 and Fig. 2).

4. Discussion

The current study examined the functional activation pattern of a modified version of the Stroop task in a group of patients with long-standing and stable schizophrenia treated with novel antipsychotics, compared with a healthy control group.

As this current study utilized a different version of the Stroop task, it is somewhat difficult to compare the activation patterns to findings from previous fMRI studies. Nevertheless, the activation patterns detected in our study are in agreement with previous investigations of the original Stroop task, which reported increased signal intensity within the anterior cingulate cortex, lateral prefrontal cortex, parietal cortex and occipito-temporal cortex (Bench et al., 1993; Carter et al., 1995; Taylor et al., 1997; Peterson et al., 1999). While a growing number of neuroimaging studies have demonstrated that the dorsolateral prefrontal cortex and the anterior cingulate cortex are reliably acti-

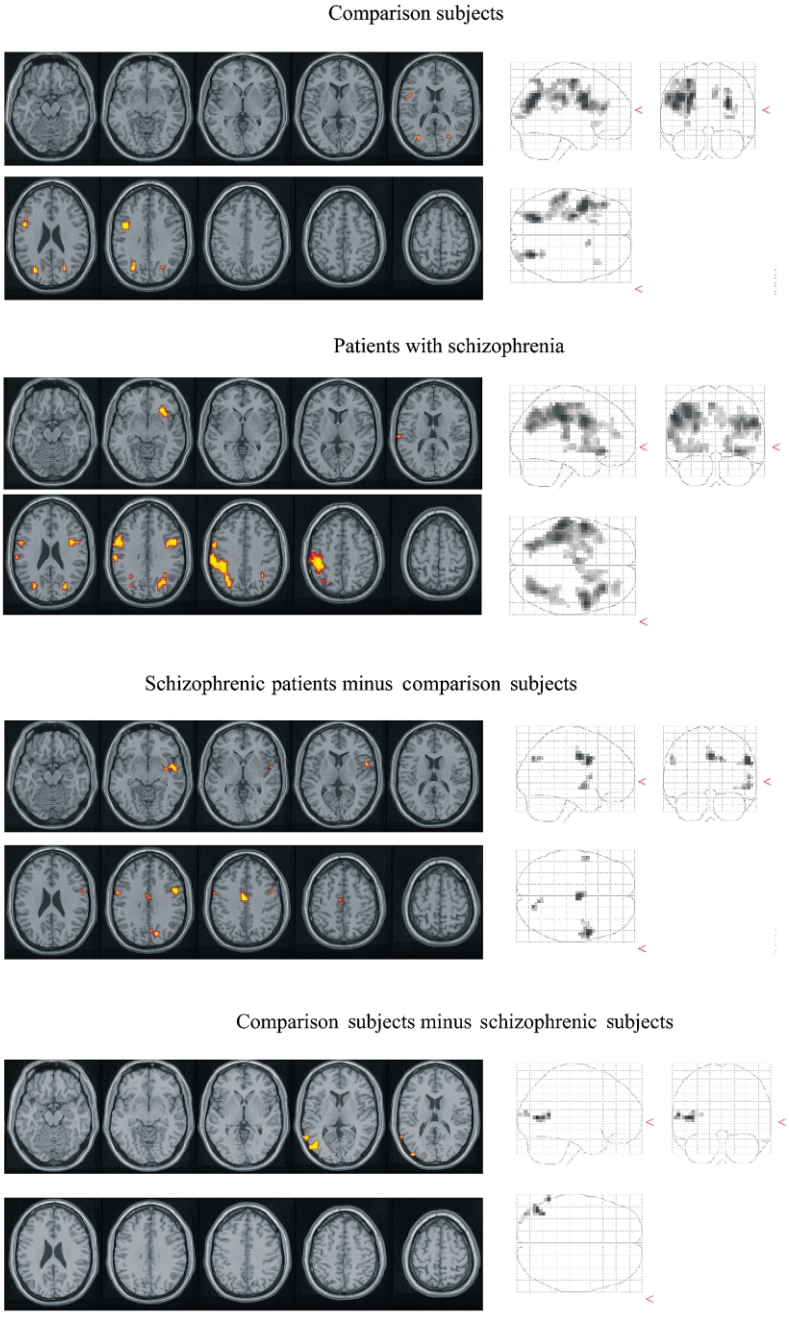

Fig. 1. Statistical parametric maps showing areas significantly activated by the modified stroop task in healthy controls and patients with schizophrenia. Colored pixels exceed the statistical threshold of $P<0.001$, uncorrected. For localization of activation see Table 2.

Table 3
Positive correlation with accuracy

Region	Coordinates			*Z* score
	x	*y*	*z*	
Healthy controls				
Left and right medial frontal gyrus and bilateral superior frontal gyrus (BA 9, 10)	−4	44	36	3.92
	20	48	28	2.65
Left and right anterior cingulate gyrus (BA 32)	−4	36	−8	3.13
Left middle frontal gyrus (BA 47)	−32	36	−8	2.98
Right hippocampus	28	−44	0	3.25
Left gyrus parahippocampi (BA 19)	−36	−52	0	3.50
Right superior temporal gyrus (BA 22)	48	−8	4	3.18
Patients with schizophrenia				
Left and right anterior cingulate gyrus (BA 31, 23)	0	−52	28	3.36
	−8	−24	28	2.76
Left caudate	−8	12	0	4.04
Left and right gyrus parahippocampi, superior temporal gyrus (BA 30, 29)	−20	−44	4	3.04
	20	−40	4	2.91

vated across a wide range of tasks that involve response conflict, such as the Stroop (Carter et al., 2000; Casey et al., 2000) and go-no/go tests (Casey et al., 1997), they indicate that the role of the dorsolateral prefrontal cortex is distinct from that of medial prefrontal regions. In particular, increased activation in the dorsolateral (BA 9, BA 46) and posterior inferior prefrontal cortex (BA 44) is assumed to be associated with increased top-down control via the representation and maintenance of an attentional set, whereas the anterior cingulate cortex seems to provide an evaluation of the degree of response conflict and signals when control needs to be more engaged (Botvinick et al., 1999; Banich et al., 2000; Carter et al., 2000; Liddle et al., 2001).

In the current study, patients with schizophrenia demonstrated a different pattern of activation in comparisons of task activity to rest than healthy subjects. Although both groups recruited the pre-

Table 4
Negative correlation with accuracy

Region	Coordinates			*Z* score
	x	*y*	*z*	
Healthy controls				
Left inferior and middle frontal gyrus (BA 44, 9)	−56	8	24	4.67
Right precentral gyrus (BA 9)	44	24	40	3.16
Left postcentral gyrus (BA 3)	−40	−24	40	2.74
Right inferior parietal lobe (BA 40)	44	−52	52	3.56
Left precuneus (BA 31)	−20	−60	24	2.86
Left cuneus (BA 18)	−4	−88	16	3.36
Right thalamus	8	−12	0	3.19
Right insula	36	8	20	3.49
Left claustrum	−36	−4	−4	3.36
Patients with schizophrenia				
Left inferior and superior parietal lobe (BA 7, 40)	−48	−40	48	3.97
	−28	−68	48	2.89
Right precentral gyrus (BA 6)	40	−12	48	2.80

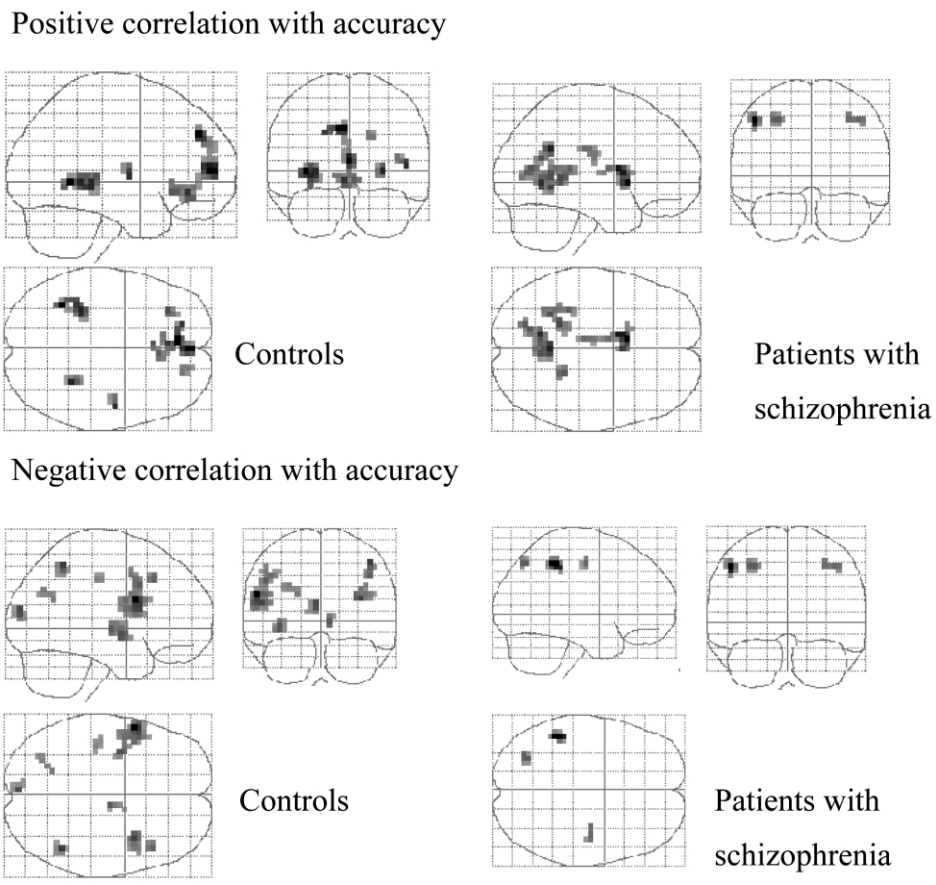

Fig. 2. SPM maps showing positive and negative correlation between brain activation and accuracy ($P<0.01$ uncorrected, $k=8$). Corresponding stereotactic coordinates are displayed in Tables 3 and 4.

frontal cortex (middle and inferior gyri) during the modified Stroop task, for the schizophrenia patients activation was bilateral, while for the controls activation was primarily in the left hemisphere. Further, a between-group comparison indicated that the patients with schizophrenia showed greater activation in the anterior cingulate cortex than controls. Thus, compared to controls, patients with schizophrenia recruited more prefrontal regions to perform the task, although behavioral data suggested that their performance was not significantly reduced compared to controls. This finding is not in line with other studies showing Stroop-related hypofrontality in patients with schizophrenia (Carter et al., 1997; Yucel et al., 2002). Our finding of overactivation may be explained by differences between studies. First, several authors pointed out that task performance can be a confounding factor in studies with schizophrenia patients and will typically result in a bias towards reduced brain activation in poorly performing patients (Frith et al., 1995; Price and Friston, 1999; Callicott et al., 2000; Perlstein et al., 2001; Ramsey et al., 2002). Underactivation in a poorly performing subject may therefore reflect failure to fully engage in the task when the task exceeds processing capacity (Bullmore et al., 1999; Price and Friston, 1999). The present study included patients pre-selected on the basis of high performance (accuracy and response time) on the original Stroop task. Our results are consistent with fMRI studies of patients who perform relatively

well on tests of working memory, indicating that under these circumstances, activity in the dorsolateral prefrontal cortex is not reduced, but tends to be increased for either slightly impaired or equivalent cognitive output in comparison with control subjects (Stevens et al., 1998; Curtis et al., 1999; Manoach et al., 1999; Callicott et al., 2000; Manoach et al., 2000). These results suggest that when patients are able to keep up with the processing demands, they do so less efficiently for a given level of performance accuracy.

Medication effects may also confound our results. Treatment with second generation antipsychotics may improve executive performance in patients with schizophrenia (for review, see Meltzer and McGurk, 1999; Sharma, 1999; Weiss et al., 2002), and some studies report a normalization of functional hypofrontality after symptomatic improvement. Honey et al. (1999) showed enhanced neural response levels in the prefrontal and parietal lobes of patients with schizophrenia during working memory performance after switching to risperidone compared with continued treatment with classical neuroleptics. Negative symptoms and cognitive deficits associated with schizophrenia may reflect a dysfunction of dopaminergic neural transmission at the level of the prefrontal cortex (Weinberger et al., 1988; Cohen and Servan, 1992). This hypodopaminergic model of prefrontal cortical functions in schizophrenia could explain the improvement in cognitive and negative symptoms associated with a normalization of the covariance between frontal and temporal task-relevant activations following antipsychotic drug treatment. Because our patients were treated with second generation antipsychotics when investigated, we cannot exclude that medication had an impact on the findings. One challenge for future studies will be to explore whether and to what extent cognitive dysfunctions in schizophrenia are caused, improved or worsened by medication. This calls for longitudinal studies that investigate patients before and after the beginning of treatment.

Secondly, the task design in the current study is quite different from the traditional Stroop task used in earlier studies that reported frontal hypofunction in schizophrenia (Carter et al., 1997; Yucel et al., 2002). In the traditional Stroop task, the two distinct pathways of color naming and word reading are competing for the response channel (vocalization). As pointed out above, verbalization can result in excessive head movements so that the original Stroop task is not an ideal task for fMRI experiments. We are aware of the fact that the elimination of a verbalized response would appear to alter the processes at work; nevertheless the modified Stroop task engaged a similar network of regional cerebral activity as the traditional Stroop task in healthy subjects, and a significant positive correlation between the accuracy in the original Stroop task and the accuracy in the modified Stroop task could be demonstrated. The modified Stroop task may be easier for patients with schizophrenia. If so, they may be able to keep up with the processing demands, but have to recruit extraneous neural activity to produce the correct response, reflected in an overactivation of the frontal cortex. Another potentially important source of variability in results was the use of a resting baseline reference condition compared to task activity condition in the current study. We are therefore not able to control for non-attentional functions (Star and Squire, 2001). However, several authors have examined the reproducibility of resting baseline measures with relatively unstructured conditions (i.e. eyes open, ears unoccluded, ambient noise kept to a minimum; for an overview, see Gur, 2000). These studies found very high reproducibility among healthy subjects (Gur et al., 1987; Warach et al., 1987) and patients with schizophrenia (Bartlett et al., 1991). In addition, the use of active reference conditions has the potential limitation of confounding the interpretation of activation effects if cognitive components interact between one or more reference tasks (Friston et al., 1996).

Furthermore, the dorsolateral prefrontal cortex seems to be coactivated with regions in the parietal cortex, consistent with the existence of reciprocal connections between lateral frontal cortex and parietal cortex that are well documented in primates (Pandya and Seltzer, 1982; Selemon and Goldman-Rakic, 1988). A number of studies have shown that parietal regions are activated during sustained attention, attention shifts, and when

attention is reflexively drawn to prominent features of a stimulus (see Cabeza and Nyberg, 2000, for review). In addition to playing a role in sustained attention, parieto-occipital activity may be associated with word reading (Buchel et al., 1998; Shaywitz et al., 1998; Brunswick et al., 1999) and visual attention processes (Carpenter et al., 2000). In our study, activation in the parietal lobe during the modified Stroop task was observed in parieto-occipital areas in agreement with previous studies (Bench et al., 1993; Carter et al., 1995; Peterson et al., 1999). Banich et al. (2001) postulated that this dosolateral/parietal circuitry is a source of attentional control, which is responsible for selecting and maintaining an attentional set that specifies the nature of task-relevant information.

Based on anatomical studies, investigations of handedness, and dichotic listening studies, cerebral and functional asymmetry seems to be reduced in patients with schizophrenia (DeLisi et al., 1994; Crow et al., 1996; Barta et al., 1997; Kwon et al., 1999; Sommer et al., 2001; Annett, 2002). This reduced lateralization can reflect two opposite types of functional states of the brain: a decreased activity of the left hemisphere or an increased activity in the right hemisphere. In the current study, patients with schizophrenia showed an increase in modified Stroop task-related activity in the right hemisphere. This finding is in agreement with other reports (Sommer et al., 2001; Ramsey et al., 2002). We did not find evidence of reduced activity in the left hemisphere, as reported by some authors (Lewis et al., 1992; Artiges et al., 2000; Yucel et al., 2002). In this context, Sommer et al. (2001) have pointed out that hypoactivity in the left hemisphere may be associated with impaired performance that has not been corrected for.

When correlations between accuracy and brain activation during performance of the modified Stroop task were examined, a significant negative correlation between activation of the left prefrontal cortex and accuracy in the modified Stroop test was observed for healthy controls but not schizophrenia patients. These results suggest that decreased activation in the dorsolateral prefrontal cortex corresponds to better optimization and decreased task difficulty in healthy subjects and leads to better performance in the modified Stroop task. A moderate negative correlation between parietal lobe activation and accuracy was found in both groups. These results are in line with other reports, showing that with practice of a cognitive task, performance improves while brain activity decreases (Buchel et al., 1999; Jansma et al., 2001).

Healthy controls and patients with schizophrenia showed a significant positive correlation between activation of the anterior cingulate and accuracy, indicating that better performance was associated with a higher level of activation in this area. Better task performance in both groups also paralleled an increased activation of the hippocampus and temporal lobe. This finding is in contrast with other reports showing a correlation between the total number of Stroop errors and anterior cingulate and hippocampal blood flow activation (Carter et al., 1997, 1998b; Kiehl et al., 2000; Nordahl et al., 2001). In the current study, the error rate was extremely low in both groups and because of the use of a block design, we were not able to trace the time course of regional brain activation during the course of individual error trials. Our results can tentatively be explained by the refined theory of performance monitoring by the anterior cingulate cortex (Carter et al., 1998b), suggesting that anterior cingulate activity is related to response competition, instead of monitoring errors per se. If the anterior cingulate activity is responding to response conflicts, its activation should also be present in correct trials, which was shown in some reports (Carter et al., 1998b, 2000; Botvinick et al., 1999; Cohen et al., 2000), suggesting that the anterior cingulate is one component of an error prevention network.

The results of this study need to be interpreted with some caution, mainly because the sample size is limited and all subjects were male. Since men and women may have different lateralization patterns (Shaywitz et al., 1995; Speck et al., 2000), further studies are needed to evaluate the transferability of the present finding to female patients. Additionally, we utilized a block design with regard to fMRI techniques as compared to event-related fMRI approaches. Event-related designs have the capacity to probe the time course of the signal change corresponding to interference

(Leung et al., 2000) and are less susceptible to habituation and changes in behavioral strategies within blocks than block designs (Bush et al., 1998). Supplementary investigations utilizing an event-related design are warranted to further explicate our findings.

Lastly, the study cannot directly be compared with previous studies using the original Stroop test, because we selected patients for good performance and used a modified version of the Stroop task. In conclusion, our findings of increased activity across multiple areas of the brain including dorsolateral frontal cortex and the anterior cingulate in patients with schizophrenia who perform relatively well on a task of selective attention provide further evidence that task performance may be a confounding factor in the interpretation of studies relating cognitive function to brain activation.

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