Excessive recruitment of neural systems subserving logical reasoning in schizophrenia

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Summary
Schizophrenic patients generally perform poorly on tasks that address executive functions. According to several imaging studies, the dorsolateral prefrontal cortex is hypoactive in schizophrenic patients during these tasks. It is not, however, clear whether this finding is associated more with impaired performance than with the illness itself, as performance has not been taken into account. We examined brain activity associated with executive function in schizophrenia using an experimental fMRI design that reveals performance effects, enabling correction for performance differences between groups. As this approach has not been reported before, and because brain function can be affected by medication, the effect of antipsychotic medication was also investigated. A task was used that requires logical reasoning, alongside a closely matched control task. Performance was accounted for by including individual responses in fMRI image analyses, as well as in group-wise analysis. Effects of medication were addressed by comparing medication-naïve patients and patients on atypical antipsychotic medication with healthy controls in two separate experiments. Imaging data were analysed with a novel, performance-driven method, but also with a method that is similar to that used in earlier studies, which reported hypofrontality. A modest reduction in performance was found in both patient groups. Brain activity associated with logical reasoning was correlated positively with performance in all groups. In patients on medication, activity did not differ from that in controls after correcting for difference in performance. In contrast, performance-corrected activity was significantly elevated in medication-naïve patients. This study indicates that schizophrenia may be associated with excessive recruitment of brain systems during logical reasoning. Considering the fact that performance was reduced in the patients, we argue that the efficiency of neural communication may be affected by the illness. It appears that in patients on atypical antipsychotic medication, this neural inefficiency is normalized. The study shows that performance is an important factor in the interpretation of differences between schizophrenic patients and controls. The reported association between performance and brain activity is relevant to clinical imaging studies in general.

Keywords: brain function; executive function; fMRI; performance; schizophrenia

Abbreviations: DR = deductive reasoning; DSM = Diagnostic and Statistical Manual; GA = general activity; GLM = general linear model; WCST = Wisconsin Card Sorting Task; WM = working memory

Introduction
The notion that schizophrenia is characterized by deficient executive functions, particularly working memory (WM), seems well established (Goldberg et al., 1987; Park and Holzman, 1992; Goldman-Rakic, 1994a; Cohen et al., 1996; Morice and Delahunt, 1996; Heinrichs and Zakzanis, 1998; Riley et al., 2000; Weickert et al., 2000). Neuropsychological and functional neuroimaging studies indicate that executive functions are mediated primarily by frontal brain structures, as was shown in patients with frontal lobe lesions and in healthy subjects (Weinberger, 1993; Goldman-Rakic, 1994b). Following a study by Ingvar and Franszen (1974) who reported hypometabolism in the frontal cortex of schizophrenic patients, many neuroimaging studies have examined frontal lobe function in schizophrenia (for reviews see Spitzer, 1993; Goldman-Rakic, 1994a; Zakzanis and Heinrichs, 1999). Frontal hypofunction has frequently been reported in patients when they were engaged in cognitive tasks at which they perform poorly, particularly in tasks that
address WM (Weinberger et al., 1994; Weinberger and Berman, 1996; Yurgelun-Todd et al., 1996; Curtis et al., 1998; Fletcher et al., 1998; Stevens et al., 1998), such as the Wisconsin Card Sorting Task (WCST) (Milner, 1964; Berman et al., 1986; Weinberger et al., 1986) or other tasks that were designed to address WM function more explicitly (Cohen et al., 1994; d’Esposito et al., 1995; Callicott et al., 1998; Barch et al., 2001; Perlstein et al., 2001). However, with recent advances in task design for the study of WM, some studies suggest that the concept of hypofrontality in schizophrenia is too simple, and that both the characteristics of the cognitive task used during functional imaging, and also performance are essential for the interpretation of functional brain imaging experiments. Since these studies report that under carefully controlled conditions frontal activity is either normal (Frith et al., 1995) or even enhanced (Manoach et al., 1999; Callicott et al., 2000) in schizophrenic patients during engagement in WM tasks, the hypothesis of (selective) prefrontal cortex hypofunction may require revision. Authors noted that the results were associated with performance, in that equal (or enhanced) activity was observed when patients were capable of achieving a near-normal level of performance (Frith et al., 1995; Manoach et al., 1999). Callicott and colleagues (2000) also observed enhanced WM activity in schizophrenic patients, and provided evidence that it may be the result of physiological inefficiency due to prefrontal neuropathology, as measured with magnetic resonance spectroscopy. The design and complexity of a WM task is critical for the interpretation of functional brain imaging results in schizophrenic patients, as it determines to a large extent whether the patients are actually cognitively engaged in the task or not. If they are not, for instance because the task is too fast or complex, then brain activity is not necessarily associated with the function of interest, as the function was not invoked by the task. Performance data can be used to determine engagement in the task, and as such can provide essential information for the interpretation of neuroimaging results (Fletcher et al., 1998; Callicott et al., 2000).

Several groups have now presented methods of accounting for performance differences, which generally utilize the concept of a load-response function (Manoach et al., 1997; Callicott et al., 1998; Jansma et al., 2000; Perlstein et al., 2001), which in turn involves multiple levels of task difficulty in order to capture brain activity during both normal and deficient functioning. These tasks are, however, quite different from the executive function tasks, such as the WCST, which were used in the earlier studies that reported frontal hypofunction in schizophrenia, in that they target the WM component specifically. The current task targets the complex of functions that contribute to the process of solving problems by means of logical, deductive reasoning.

The present study was conducted to examine brain activity associated with executive function in schizophrenic patients from a new perspective. Recognizing that performance is a key issue in functional neuroimaging, and therefore in the interpretation of results obtained with schizophrenic patients, the contribution of performance played a critical role in experimental design and analysis of this study. We present data from a functional MRI experiment with a WCST-like task, but with a novel experimental design that incorporates performance variables. The performance issue is taken into account in several ways to clarify the association between executive functions and brain activity in schizophrenic patients (see Methods for a detailed description). Two questions are addressed with regard to cognitive brain function in schizophrenia: (i) is the relationship between performance and brain activity different for patients and controls?; and (ii) how is this relationship affected by medication? To address these questions an experimental design was chosen that accounted for performance differences at several levels (i.e. task, experiment and analysis). The task resembles the WCST in that it requires manipulation of internal and external information, and keeping information available (‘online’) in the process. It involves application of deductive reasoning to find a solution to a simple problem. As this experimental design differs from the design used in the previous schizophrenia studies with the WCST task, we also investigated the effect of medication. In separate experiments, patients on atypical antipsychotic medication and medication-naïve patients are compared with healthy controls.

### Methods

#### Subjects

Subject characteristics are shown in Tables 1 and 2. All subjects were right-handed as assessed with the Edinburgh

<table>
<thead>
<tr>
<th>Experiment 1</th>
<th>Experiment 2</th>
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<tbody>
<tr>
<td><strong>HC</strong></td>
<td><strong>PT</strong></td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>10</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>24.1 (5.0)</td>
</tr>
<tr>
<td><strong>Gender (male/female)</strong></td>
<td>7/3</td>
</tr>
<tr>
<td><strong>Handedness (EHI)</strong></td>
<td>0.90 (0.13)</td>
</tr>
</tbody>
</table>

HC = healthy controls; PT = patients; n = number of subjects; EHI = Edinburgh Handedness Inventory. Numbers in parentheses represent standard deviations.
Handedness Inventory (Oldfield, 1971). Subjects were screened by a psychiatrist using the Comprehensive Assessment of Symptoms and History, and History Schedule for Affective Disorder and Schizophrenia Lifetime version (Andreasen et al., 1992a). The severity of symptoms was assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Patients with a diagnosis of drug dependence (lifetime) or drug abuse (in the 3 months prior to entry into the study) were excluded. Healthy controls did not have any Diagnostic and Statistical Manual (DSM)-IV axis I diagnosis, and had no first-degree relatives with a psychiatric disorder.

In Experiment 1, 10 normal healthy controls participated, and 10 patients that had been treated with atypical antipsychotics for at least 4 weeks. All patients met DSM-IV criteria for schizophrenia or schizoaffective disorder. Ten healthy controls and 13 medication-naïve patients with schizophrenia participated in Experiment 2. Four of the patients were diagnosed as schizophreniform at the time of the experiment (DSM-IV code 295.4). At a follow-up diagnosis 6–12 months after the fMRI session, two patients did not meet the criteria for schizophrenia (new DSM-IV code 296.24, major depressive syndrome), and were therefore excluded. In the other two patients a diagnosis of schizophrenia (DSM-IV code 295.3) was confirmed.

All the subjects in this study gave their informed consent. The study was approved by the Ethical Committee of the University Medical Center of Utrecht in accordance with the Declaration of Helsinki.

**Task**

The cognitive task was a version of the XT-task conceived by Cicerone et al. (1983), modified for use in the MRI scanner, and addresses functions involved in logical, or more specifically deductive, reasoning. The task involves selection of one of two stimuli presented together. Stimulus pairs, one item at the left and one at the right side of the screen, are presented once every 3.6 s, and the response is fed back immediately as a circle around the selected stimulus (Fig. 1). At the end of each trial a message appears below the stimulus pair stating whether the response was correct or incorrect, for 600 ms. Failure to respond within 3.0 s after stimulus presentation is counted as incorrect. The stimuli consist of different coloured (blue or red) letters (X or T) that can be either large or small. Therefore, eight features (i.e. two different items in each of four categories/dimensions) are represented on each trial, i.e. large or small, red or blue, X or T, and left or right. Thus, the two stimuli of a pair always differ in all four dimensions. One of these dimensions is relevant to the task at any moment in the sense that the computer program dictates which feature is correct. The relevant feature changes after 10, 12 or 14 trials (mean 12 trials), without notice. During the experiment the relevant

### Table 2 Characteristics of patients

<table>
<thead>
<tr>
<th>Diagnosis (DSM-IV)</th>
<th>Experiment 1</th>
<th>Experiment 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>295.1</td>
<td>1 patient</td>
<td>1 patient</td>
</tr>
<tr>
<td>295.2</td>
<td></td>
<td>9 patients</td>
</tr>
<tr>
<td>295.3</td>
<td>6 patients</td>
<td></td>
</tr>
<tr>
<td>295.7</td>
<td>3 patients</td>
<td></td>
</tr>
<tr>
<td>295.9</td>
<td></td>
<td>1 patient</td>
</tr>
<tr>
<td>Time since first psychosis (median in months)</td>
<td>63</td>
<td>25</td>
</tr>
<tr>
<td>Antipsychotic medication at time of fMRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine, median 10 mg/day</td>
<td>5 patients</td>
<td>None</td>
</tr>
<tr>
<td>Clozapine, median 300 mg/day</td>
<td>5 patients</td>
<td>None</td>
</tr>
<tr>
<td>Total time on antipsychotic medication (months)</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Severity of positive symptoms (PANSS)</td>
<td>14.2 (4.3)</td>
<td>17.6 (2.7)</td>
</tr>
<tr>
<td>Severity of negative symptoms (PANSS)</td>
<td>16.8 (4.1)</td>
<td>17.3 (4.0)</td>
</tr>
</tbody>
</table>

PANSS = positive and negative syndrome scale. Numbers in parentheses represent standard deviations.

![Fig. 1](image)
rule changed 30 times. Each set of 10, 12 or 14 stimuli is referred to as an ‘epoch’.

The period during which the subject is searching for the rule is defined as the experimental condition (‘search’ condition). Performance is measured by the number of stimuli that is used before the rule is found. The control condition starts when the correct rule has been found. At this point, the rule simply has to be applied during the remainder of presented stimuli (until the task switches to a new rule that has to be found), effectively changing the task to a simple choice task which contains the same information input and response requirement. As the control condition only involves maintaining and applying the found rule, it is referred to as the ‘maintain’ condition. A similar approach has also been presented by Konishi et al. (1999) and Barcelo et al. (1997) as a method of separating executive functions from other cognitive functions. Performance was expressed as the number of items that were used during ‘search’ (i.e. the time it took to find the correct rule), averaged across all 30 epochs. With this task and system of coding, the best possible performance score averaged across epochs was calculated to be 4. The score that would be obtained with completely random responding was calculated to average 10.5.

fMRI scans
The study consisted of two experiments: one with medicated patients and healthy controls, and the other with medication-naïve patients and their healthy controls. The scan technique used for both was navigated BOLD (blood oxygenation level dependent)-sensitive 3D PRESTO (van Gelderen et al., 1995; Ramsey et al., 1998). Due to an upgrade of the MRI machine after the first experiment, the functional scan time was reduced by a factor of three, while the number of slices in the volume increased from 22 to 26. The upgrade resulted in better signal-to-noise ratio (better detection of BOLD signal change) and a larger volume covering more tissue of inferior visual, temporal and frontal cortices. Given this difference, the two experiments are analysed separately, comparing patients only with their corresponding controls. The details of scan procedures for Experiment 1 are shown below, with the values for Experiment 2 given in parentheses when they differed.

Scans were acquired in runs of 46 (138) with 3D PRESTO, on a Philips ACS-NT 1.5 Tesla Gyroscan with a PT1000 (PT6000) (Philips Medical Systems, Best, The Netherlands) gradient set (Ramsey et al., 1998). Scan parameters were: TE (echo time) = 36 ms, TR (repetition time) = 24 ms, flip angle = 10.5°, five (17) read-out echoes per TR, field of view (FOV) 183 × 225 × 77 mm (91), matrix 52 × 64 × 22 mm (26), voxel size 3.51 mm isotropic, scan time 7.25 s (2.42 s). Six runs were acquired during the task. This was followed by a functional scan with a 30° flip angle, which was used as the ‘anchor’ volume for co-registration of functional and anatomical volumes. The session was completed finally with an anatomical scan (3D-FFE, Fastfield Echo, TE = 4.6, TR = 30, matrix 128, FOV 256, flip angle 30°, slice thickness 1.2 mm, 130 slices). The anatomical scan was used to spatially localize the detected activity.

fMRI image registration
All registration procedures were applied to the dataset of each subject separately. Image resolution was preserved by means of tricubic spline interpolation (Thevenaz et al., 1998). The 30° flip angle functional scan (FA30 scan) was used for registration of the anatomical scan to the functional scans. The functional scans were each registered to the FA30 scan automatically as described previously (Ramsey et al., 1998).

Analyses of individual fMRI datasets
For each subject, the functional dataset was analysed with multiple regression in two ways: one where all scans acquired during task execution were contrasted with the scans acquired during rest [general activity (GA)], and one where the ‘search’ condition was contrasted with the ‘maintain’ condition [deductive reasoning (DR)]. In the GA analysis, no distinction was made between ‘search’ and ‘maintain’. This analysis corresponds to the classical block-wise analysis of WCST PET data, and was included to assess whether results obtained in this fashion would be replicated. In the DR analysis only the scans acquired during the task were analysed, therefore rest-scans were excluded. The experimental factor for the DR regression analysis was based on individual performance. For this, each scan was assigned to either ‘search’ or ‘maintain’, based on the correctness of the response given to the stimulus that was time-locked to that scan. Thus, an incorrect response resulted in coding of that scan as ‘search’. Additional factors were entered into the regression analysis to correct for signal trends. t-values were generated for the experimental factor for each voxel (Worsley and Friston, 1995), resulting in one GA and one DR t-map for each subject. Maps were thresholded at t = 4.5, which corresponds to a P-value of 0.05, Bonferroni-corrected for total number of scanned voxels in the brain (Ramsey et al., 1998). For each subject, the number of voxels exceeding the significance threshold was determined in 22 manually segmented volumes of interest (VOIs). These numbers were entered in the group analyses, which are described below.
Segmentation of anatomical scans

For each subject, the anatomical volume was manually segmented into 22 VOIs, 11 for each hemisphere. For outlining the VOIs an anatomical atlas was used (Duvernoy, 1991) to follow the division of Brodmann areas (Brodmann, 1909). Frontal cortex VOIs corresponded to cingulate gyrus (Brodmann area, BA 24/33), frontal pole (BA 10), ventrolateral inferior (BA 44/45), dorsolateral inferior (BA 9/46), middle (BA 8/9) and superior (BA 6) frontal cortex. Parietal VOIs corresponded to superior lobule (BA 7), supramarginal (BA 39) and angular gyrus (BA 40). Finally, the posterior cingulate (BA 23/29) and visual cortex (BA 17/18/19) were segmented.

To ascertain that segmentation did not bias group comparisons of activity, VOIs were tested by means of a general linear model (GLM) analysis with repeated measures (volumes of the set of 22 VOIs, divided by hemisphere), including data from both experiments. P-values are shown for the \( \epsilon \)-corrected \( F \)-tests. Significant effects of VOI \( \left[ F \left( 10, 370 \right) = 261.6, \ P < 0.001 \right] \), hemisphere \( \left[ F \left( 1, 37 \right) = 68.8, \ P < 0.001 \right] \) and experiment \( \left[ F \left( 1, 37 \right) = 16.7, \ P < 0.001 \right] \) were found, but there were no significant main or interaction effects involving \( \epsilon \)-corrected \( F \)-tests, indicating that there were no differences in segmentation between patients and controls.

Group-wise statistical comparisons of fMRI data

For comparisons between patients and controls, a GLM analysis (analysis of variance with repeated measurements) for repeated measures was performed, with the following parameter settings: within-subject factors area (11 VOIs per hemisphere) and hemisphere; between-subject factor illness and covariate performance (number of ‘search’ items). This design was applied separately to the GA and to the DR image data. Effects were assessed for significance with multivariate analysis, and are presented as \( \epsilon \)-corrected average \( F \)-tests. Voxel counts were first tested for normal distribution by means of a Kolmogorov–Smirnov test in each VOI. As the vast majority of VOIs showed normal distribution of voxel counts, further analyses were performed with parametric statistical procedures. As very low levels of activity in VOI would preclude detection of group-wise differences in brain activity levels (the ‘floor effect’), voxel counts in each VOI were tested (one-sample \( t \)-tests against zero) for each group, experiment and comparison (GA and DR) separately. Significant activity was present in almost all VOIs (except for BA 23/29), allowing for a meaningful comparison of volumes of activity between groups.

Results

The main variable for which groups were not matched was performance. To assess how performance affected reasoning-related brain activity, correlations were calculated between performance and total DR brain activity. Correlations were significant (patients and controls combined: Experiment 1, \( r = -0.55, \ P = 0.012 \); Experiment 2, \( r = -0.46, \ P = 0.036 \)). In the separate groups, this correlation was also present, albeit weakly (\( r \) ranged from \( -0.64 \) to \( -0.54 \), each \( P < 0.10 \)). Based on the effect of performance on brain activity, performance was included in all the GLM analyses as a covariate.

Experiment 1: patients on medication compared with healthy controls

Performance

Patients used slightly more items to find the rule than the controls, but this was not significant \( [t(18) = 0.75, \ P = 0.46] \) (Table 3). We noticed that one healthy control had performed near chance level and therefore qualified as an outlier (Shiffrin, 1988). When testing performance without this subject, a significant reduction in performance emerged for patients \( [t(17) = 2.44, \ P = 0.026] \). Individual performance determined coding of the fMRI scans of each subject, resulting in assigning, on average, 47% of the fMRI scans to the ‘search’ condition in controls and 51% in patients. The remaining scans were assigned to the ‘maintain’ condition.

Table 3 Summary of performance, volume of imaged brain and total volume of activated brain in all VOIs for the GA and the DR analyses

<table>
<thead>
<tr>
<th></th>
<th>Experiment 1</th>
<th>Experiment 2</th>
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<tbody>
<tr>
<td></td>
<td>HC (mean, SD)</td>
<td>HC (mean, SD)</td>
</tr>
<tr>
<td></td>
<td>PT (mean, SD)</td>
<td>PT (mean, SD)</td>
</tr>
<tr>
<td>Task performance</td>
<td>5.7 (0.5)</td>
<td>6.1 (0.3)</td>
</tr>
<tr>
<td>Analysed brain volume (cc)</td>
<td>742 (10)</td>
<td>764 (22)</td>
</tr>
<tr>
<td>Total GA activity (nvx)</td>
<td>318.5 (55.1)</td>
<td>181.5 (37.6)</td>
</tr>
<tr>
<td>Total GA activity (cc)</td>
<td>13.8 (2.4)</td>
<td>7.8 (1.6)</td>
</tr>
<tr>
<td>Total DR activity (nvx)</td>
<td>60.5 (10.6)</td>
<td>34.3 (10.7)</td>
</tr>
<tr>
<td>Total DR activity (cc)</td>
<td>2.6 (0.5)</td>
<td>1.5 (0.5)</td>
</tr>
</tbody>
</table>

HC = healthy controls; PT = patients; GA = general activity analysis; DR = deductive reasoning analysis; cc = cubic centimetres; nvx = number of activated voxels. Numbers in parentheses represent standard deviations.
Brain activity
In the GA analyses, activity was found bilaterally in frontal, parietal and occipital VOIs in both patients and controls (Fig. 2). No main effect of illness was found with GLM analysis comparing patients with controls. The analysis did reveal a significant interaction between area, hemisphere and illness \( [\text{multivariate } F(10,8) = 3.44, P < 0.05] \), but no other effects involving illness. Furthermore, performance was not significant as a main effect and did not interact with illness. Following up on the three-way interaction effect, univariate analyses were performed on each area, without performance as covariate (as it did not interact with illness effects). This revealed that brain activity was significantly reduced in patients in the following areas: left and right anterior cingulate \( [\text{BA 24/33, } F(1,18) = 5.32, P = 0.033 \text{ and } F(1,18) = 4.99, P = 0.038 \text{, respectively}] \), left posterior cingulate \( [\text{BA 23/29/30, } F(1,18) = 7.11, P = 0.016] \), left dorsolateral prefrontal cortex \( [\text{BA 9/46, } F(1,18) = 5.59, P = 0.030] \), left inferior frontal gyrus \( [\text{BA 44/45, } F(1,18) = 14.5, P = 0.001] \) and left superior parietal cortex \( [\text{BA 7, } F(1,18) = 10.81, P = 0.004] \). Thus, when analysing the fMRI data in a conventional way, i.e. disregarding the difference between ‘search’ and ‘maintain’, reduced activity was observed in frontal and parietal regions in the patients.

In the DR analysis, activity during ‘search’ was compared with activity during ‘maintain’ (Fig. 3). The main effect of area was significant \( [F(10,170) = 3.68, P = 0.007] \), indicating that activity was different across the VOIs. No effects were found for the hemisphere factor, and none of the interactions was significant \( (P > 0.20) \). The effect of the covariate performance was significant \( [F(1,17) = 6.74, P = 0.019] \). The main effect of illness, i.e. an apparent overall reduction, was not significant \( (P = 0.15) \) (Fig. 4), nor were interactions involving illness \( (P > 0.31) \). The effect of performance indicated a linear relationship between performance and summed brain activity, and in the absence of any effect of illness this relationship appears to be the same for both groups (Fig. 5). To check whether the one healthy control with exceptionally low performance affected the image data, the GLM analysis was conducted again without this subject. This did not alter the findings with regard to illness \( [\text{main effect } F(1,16) = 1.6, P = 0.23, \text{ interactions involving illness } P > 0.24] \).

To control for performance in an alternative way, the groups were matched for performance by excluding low performing patients and high performing controls. The GLM analysis was conducted again, without performance as covariate, but with seven subjects in each group matched for performance. The results confirmed the whole-group analyses in that there were no significant effects of illness (neither main nor interaction effects).

**Experiment 2: medication-naïve patients compared with healthy controls**

**Performance**
Mean performance for both groups is shown in Table 3. Medication-naïve patients used more items to find the rule than the controls \( [t(19) = 2.0, P = 0.06] \). Individual performance determined coding of the fMRI scans of each subject, resulting in assigning, on average, 52% of the fMRI scans to the ‘search’ condition in controls and 60% in patients. The remaining scans were assigned to the ‘maintain’ condition.
Brain activity

GA analysis did not reveal any differences between patients and controls in pattern or extent of activity (Fig. 6). Performance did not affect overall brain activity (no significant effect as covariate and no correlation with overall activity). Due to the more sensitive scan technique, activity levels were higher than those in Experiment 1 (see Table 3). As in Experiment 1, activity was equally present in both hemispheres (Table 3).

Analysis of the DR data revealed a main effect of illness \( [F(1,18) = 6.5, P = 0.02] \). As can be seen in Figs 7 and 8, patients exhibited increased activity during ‘search’ compared with controls. Overall, volume of activity was increased by 43% in patients relative to controls (Table 3). The main effect of the performance covariate (Fig. 9) was prominent \( [F(1,18) = 11.4, P = 0.003] \). In addition, a main effect of area emerged \( [F(10,180) = 3.0, P = 0.008] \), and of hemisphere \( [F(1,18) = 7.7, P = 0.012] \), indicating a differential pattern of activity. Several interactions were significant: hemisphere by performance \( [F(1,18) = 7.0, P = 0.017] \) and hemisphere by illness \( [F(1,18) = 5.6, P = 0.03] \). There was no interaction involving area and illness together. This indicates that illness did not affect any specific brain region, but it did affect the hemispheres differently. Following up on the hemisphere by illness interaction, the VOI voxel counts were combined within each hemisphere. Subsequent univariate analysis on each hemisphere showed that the strongest effect of illness occurred in the right hemisphere [main illness effect in right hemisphere \( F(1,18) = 8.7, P = 0.009 \), and in left hemisphere \( F(1,18) = 2.7, P = 0.12 \)]. The effect of performance remained significant in both cases \( [F(1,18) = 13.8, P = 0.002 \) and \( F(1,18) = 5.6, P = 0.03] \), respectively. Although the

GLM analysis did not indicate differential effects of illness on separate VOIs, we analysed the data from each VOI separately by means of a univariate GLM to assess in which regions the effect of illness was most pronounced. An effect of illness was significant in the right BA 24/33 \( [F(1,18) = 6.3, P = 0.02] \), right BA 8/9 \( [F(1,18) = 8.4, P = 0.01] \) and right BA 39 \( [F(1,18) = 4.9, P = 0.04] \).

To control for performance in an alternative way, the groups were matched for performance by excluding low performing patients and high performing controls. The GLM analysis was conducted again, without performance as covariate, but with seven subjects in each group matched...
for performance. The results confirmed the whole-group analyses with performance as covariate, in that there was a significant main effect of illness [$F(1,12) = 4.7, P = 0.05$]. The interaction effects were also the same: area [$F(10,120) = 9.3, P < 0.001$], hemisphere [$F(1,12) = 5.1, P = 0.04$] and illness by hemisphere [$F(1,12) = 6.0, P = 0.03$].

### Discussion

This study examined brain activity patterns associated with executive function involved in logical reasoning in schizophrenic patients with and without antipsychotic medication. In two separate experiments these patients were compared with healthy controls, using a novel task that allowed for separation of the effect of performance and the effect of illness. In patients as well as in controls, the level of task-specific brain activity was linearly dependent on level of performance. In both groups of patients, a modest reduction in performance was found, indicating a reduced efficiency of processing information relevant to the task as it took longer to find the rule, which may be related to perseverance (Sullivan et al., 1993) or to a WM deficit (Gold et al., 1997). In the first experiment, with patients treated with antipsychotic medication, the difference in performance explained the difference in level of brain activity associated with logical reasoning, indicating that if patients and controls were matched on performance, the brain activity patterns would be equal. In the medication-naïve patients, however, a significant elevation of brain activity associated with reasoning remained after partialling out the effect of performance. This finding indicates that although performance predicted brain activity, there was an increase in the level of activity that was independent of performance. As the current study examined volumes of active brain tissue, this performance-independent effect reflects an excessive utilization of neurones to accomplish the task. The enhanced activity was not specific for any of the regions associated with reasoning, but it was greatest in the right hemisphere. The fact that performance was not severely affected (16% reduction) confirms that the medication-naïve patients were effectively engaged in the task, and

![Fig. 5 Scatterplot showing the relationship between total brain activity (associated with reasoning, ‘DR’ analysis, ‘search’ versus ‘maintain’ as number of voxels in all VOIs) and performance on the XT task, for patients on medication and for healthy controls (Experiment 1). Total activity is the number of significant voxels ($t > 4.5$) summed over all VOIs. The lines represent the best linear fit obtained with regression analysis.](image)

![Fig. 6 Patterns of general brain activity (‘GA’ analysis, task versus rest) for medication-naïve patients and for healthy controls (Experiment 2). For each VOI the mean number of significant voxels ($t > 4.5$) is shown. Bars represent SEM. Each VOI is labelled with Brodmann area codes on the $x$-axis. F, P and O represent frontal, parietal and occipital cortex, respectively.](image)
that the neural systems subserving logical reasoning were operating productively. It appears from this study that atypical antipsychotics normalize this neural inefficiency, potentially by improving efficiency of communication within the network(s) that subserve executive functions. Furthermore, the schizophrenic patients (regardless of medication status) did not exhibit selective dysfunction of frontal brain structures as the patterns of brain activity, i.e. the distribution of activity across the brain, were not significantly different from those obtained from the healthy controls.

**Brain activity in medication-naïve patients**

The design of the present cognitive paradigm, in which task and control task are closely matched, has not been reported before and therefore the results cannot be related directly to other studies. In order to relate the current study to previous studies, particularly those in which the WCST was used, we compared the scans acquired during task execution to those acquired during a rest state, and tested for differences between patients and controls (GA analysis). In the medication-naïve patients no reduced activity was observed when comparing task activity to rest, in contrast with other reports with both medication-free and medication-naïve schizophrenic patients (Berman et al., 1986; Weinberger et al., 1986; Rubin et al., 1991, 1994; Andreasen et al., 1992b; Catafau et al., 1994; Parellada et al., 1994, 1998). In some of the WCST studies a cognitive control task was employed to control for brain activity not related to WM, and these generally report reduced activity in frontal structures (Berman et al., 1986; Weinberger et al., 1986), but activity was reduced in temporal and parietal regions also, although not significantly. The absence of an effect in the current study may be due to the fact that we did not perform a group-averaged map analysis. As has been argued by others (Weinberger and Berman, 1996; Manoach et al., 2000), activity may be more distributed within cortical regions in schizophrenic patients, leading to a failure to find overlapping regions of activity when images are smoothed and overlaid within groups, and consequently leading to a significant regional difference with controls. Alternatively, the patients in the current study may have been less cognitively impaired than those in the other studies.

**Fig. 7** Patterns of brain activity associated with reasoning (‘DR’ analysis, ‘search’ versus ‘maintain’) for medication-naïve patients and for healthy controls (Experiment 2). For each VOI the mean number of significant voxels ($t > 4.5$) is shown. Bars represent SEM. Each VOI is labelled with Brodmann area codes on the $x$-axis. F, P and O represent frontal, parietal and occipital cortex, respectively.

**Fig. 8** Plot of total brain activity as unstandardized residual activity (associated with reasoning, ‘DR’ analysis) for medication-naïve patients and for healthy controls (Experiment 2), after partialling out the effect of performance on the XT task by means of regression analysis.
the tasks address different sets of brain functions. Whereas the XT task requires both manipulation of information and holding it available (i.e. the sets of rules during ‘search’), the task used by Barch and colleagues mainly involves coding and maintaining information (Barch et al., 2001). Considering evidence of frontal pathology in various areas of schizophrenia research (Weinberger and Berman, 1988) on the one hand and the recent reports of enhanced activity of frontal cortex in schizophrenic patients (Manoach et al., 1999; Callicott et al., 2000) on the other, prefrontal cortex may be better described as dysfunctional rather than hypofunctional (Callicott et al., 2000).

**Brain activity in patients on antipsychotic medication**

When comparing the scans acquired during task execution with those acquired during a rest state (the GA analysis), a significant reduction of brain activity was found in patients on medication in prefrontal cortex, in accordance with other WCST studies (Berman et al., 1986; Weinberger et al., 1986; Andreasen et al., 1992b; Volz et al., 1997; Ragland, 1998). In addition, activity was reduced in anterior cingulate and parietal cortex. Anterior cingulate appears to be specifically involved when errors are likely to occur (Carter et al., 1998), which is the case during our ‘search’ condition. Reduced anterior cingulate activity in schizophrenia has been reported with a selective attention task that addresses this region specifically (Carter et al., 1997). Although parietal cortex involvement is not reported in most of the WCST neuroimaging papers, it has been shown to activate in healthy subjects, as measured by event-related potentials (Barcelo et al., 1997).

When comparing scans acquired during ‘search’ with those acquired during ‘maintain’ (the DR analysis), brain activity in patients on atypical antipsychotic medication did not differ from that in controls. Patients performed worse on the task than controls (excluding one outlier), but when corrected for the effect of performance on brain activity, brain activity patterns did not differ significantly between the groups. When taking these results together with the finding that task activity relative to rest (GA analysis) was reduced in patients on medication, it appears that activity in WM-related areas in these patients was reduced during both task conditions (‘search’ and ‘maintain’), while the difference in activity between the conditions was not affected.

**Relevance of performance for functional imaging of executive function**

The main difference between this study and some of the neuroimaging studies on executive function or on WM in schizophrenia is the emphasis on correction for performance effects. We argue that performance can be a confounding factor in patient studies on several levels (design of the task,
experimental design and analysis of fMRI data) 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). Poor performance can reflect two opposite types of functional state of the brain: an engaged brain system that fails to perform, and a brain system that is disengaged due to other causes of bad performance or to task design (Bullmore et al., 1999). Given that one state can not be differentiated from the other in many tasks (in both cases responses will reflect guessing), interpretation of reduced brain activity in poorly performing subjects is not straightforward (Bullmore et al., 1999) as it may well reflect failure to fully engage in the task.

Studies utilizing the WCST are also confounded by performance in another way. Scans are typically acquired during blocks labelled as the active condition, and are compared either with a rest-state (Rubin et al., 1991; Parellada et al., 1998) or with a separate control task (Berman et al., 1986; Weinberger et al., 1986; Buchsbaum et al., 1997). In doing so, however, activity during the two stages of the task (‘search’ and ‘maintain’) are combined, although the sets of functions that are involved are quite different. During ‘search’, all the rules have to be kept in memory, a strategy has to be applied to test each one of them, and decisions have to be made for each rule. These operations are regarded as complex executive functions, involving set-switching and re-routing of stimulus and response selection processes (Shimamura, 2000). During ‘maintain’, a simple rule has to be applied to each stimulus and no higher-order processing is required. In the typical block-design experiments, the executive functions that are engaged during ‘search’, and which are thought to be impaired in schizophrenia, are not then distinguished from functions involved in ‘maintain’. However, schizophrenic patients generally have no problem performing a simple task that can be performed by verbally rehearsing one rule, such as ‘maintain’ (Cohen et al., 1999).

**Distribution of brain activity**

An important question in the assessment of brain dysfunction in schizophrenia is whether it is regionally-specific or not (e.g. Cohen et al., 1996; Weinberger and Berman, 1996; Goldman-Rakic and Selemon, 1997; Andreasen et al., 1999). Whereas various previous studies indicate that schizophrenic patients exhibit a selective deficit in frontal structures, the present findings suggest that a more extended network of brain regions involved in logical reasoning, rather than a specific region, is affected in medication-naïve patients. In all groups, performance was correlated with total brain activity in the DR analysis, indicating that better performance was associated with higher levels of brain activity across the network. Thus, two effects were observed: (i) in all subjects performance benefited from higher levels of brain activity in the network; and (ii) performance in medication-naïve patients did not benefit from the performance-independent additional elevation of brain activity that was observed in this group. Whereas the first effect indicates that good performance requires extensive participation of brain systems in the task, the second indicates that in medication-naïve patients the excess of activity fails to result in better performance. We did not find clear evidence that either of these effects is regionally specific. We argue that the elevated activity in medication-free patients reflects a reduction of the efficiency with which the brain structures that constitute the network communicate with each other. Reduced efficiency in schizophrenia has been alluded to before (Callicott et al., 2000), and recent studies have examined the phenomenon of efficiency in more detail in healthy subjects, showing that with practice of a cognitive task, performance improves while brain activity decreases (Buchel et al., 1999; Jansma et al., 2001). This is reportedly associated with enhanced ‘effective connectivity’ (Buchel et al., 1999), in other words improved efficiency of communication (Jansma et al., 2001), between WM regions. In the light of this, excessive activity in medication-naïve patients may reflect a failure to accomplish efficient communication between the involved brain regions in (repeatedly) solving the problem of finding the new rule during the ‘search’ condition. The fact that excessive activity was predominantly lateralized to the right hemisphere is a little surprising given earlier studies that have implicated the left hemisphere in schizophrenia, but it does agree with one of our earlier studies on language lateralization in schizophrenic patients (Sommer et al., 2001). In that study we also noted the relevance of performance, and argued that hypoactivity in the left hemisphere, as reported in other papers, may be associated with impaired performance that has not been corrected for.

In order to investigate the whole network of brain regions involved in reasoning, the analysis included all the regions that have been indicated in WCST studies, i.e. prefrontal (Berman et al., 1986, 1995; Weinberger et al., 1986; Parellada et al., 1994; Rubin et al., 1994; Nagahama et al., 1996; Catafau et al., 1998; Tien et al., 1998), medial frontal (Catafau et al., 1998) and parietal (Berman et al., 1995; Nagahama et al., 1996; Tien et al., 1998) cortices. The consequence of this approach, as compared with separate tests within individual structures or voxels, is that sensitivity to small but consistent differences in activity across VOIs (i.e. a main effect) is enhanced at the expense of identifying differences in selective VOIs (i.e. interaction effects). Therefore, the finding of overall enhanced activity in medication-naïve patients does not disprove the notion that specific brain regions are affected more than others (Weinberger and Berman, 1988), even though no interaction effects were found.

**Medication effects**

Reduced efficiency of the network subserving logical reasoning was observed only in medication-naïve patients and not in patients who were stable on antipsychotic
treatment. Various theories on the psychopharmacology of schizophrenia stress the dopaminergic actions of antipsychotics, and state that a dysregulation of limbic and frontocortical dopamine systems may underlie the various symptoms of schizophrenia (Weinberger and Berman, 1988), including executive functions (Goldman-Rakic, 1996). Indeed, PET and single photon emission computed tomography studies have confirmed both abnormal basal, i.e. resting, levels of dopamine receptor levels (for a review see Laruelle, 1998), and abnormal responsivity to exogenous stimulation (Laruelle et al., 1999). The present finding that the disproportionate utilization of brain systems subserving reasoning was not observed in patients with atypical antipsychotic treatment, agrees with reports that brain functions are normalized with such treatment (Honey et al., 1999). Indirect enhancement of prefrontal dopamine activity by means of stress or a pharmacological challenge in monkeys proved to reduce WM performance selectively, lending further support to the role of dopamine in the organization of processes subserving this function (Murphy et al., 1996; Arnsten and Goldman-Rakic, 1998).

The results of the current study are affected by several limitations that need to be mentioned. First, comparison of the two experiments in the current study requires some caution, because different scanning parameters were used. The experimental design and the task were identical. The overall difference between the two experiments was limited to an overall increase in numbers of active voxels due to enhanced sensitivity with the upgraded scanner hardware. There was no indication, based on comparison of the two control groups, that the patterns of activity were affected by the upgrade (except for visual cortex where the upgrade enabled larger coverage of the visual cortex). The upgrade did not affect comparisons between patients and their controls. Secondly, although the results suggest an effect of atypical antipsychotic medication, this was not tested directly. A more firm conclusion would require a design where patients are tested twice, i.e. once ‘on’ and once ‘off’ medication.

Our finding of enhanced activity across multiple areas of the brain, including dorsolateral frontal cortex, in medication-naïve patients supports the notion of reduced capacity of a cognitive network, potentially due to excessive recruitment of neural systems and/or inefficient communication between brain regions, rather than the notion of a selective brain structure that fails to operate adequately. Furthermore, the fact that excessive recruitment was not observed in the patients on atypical antipsychotics suggests that such treatment may improve communication within the cognitive network. The current findings cannot be compared with previous studies directly, because in our study performance was taken into account, and the control condition (‘maintain’) was closely matched to the experimental condition (‘search’). The interpretation of our results, however, challenges the hypothesis of prefrontal hypofunction that has been supported by the previous WCST studies, both in medication-naïve patients and in patients on antipsychotics. The present study demonstrates that poor performance may be a confounding factor in the interpretation of neuroimaging results and, as such, deserves more attention. The hypothesis that some of the executive function deficits in schizophrenia result from neural inefficiency is supported by other studies (Manoach et al., 1999; Callicott et al., 2000) but requires more research. It is clear that the characteristics of the task used during scanning greatly influence the results. Considering that novel task designs used in healthy controls focus more on the dynamics of WM function (Buchel et al., 1999; Jansma et al., 2001), use of these tasks in schizophrenic patients will improve our understanding of the neural mechanisms underlying information processing deficits in schizophrenia.

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