An fMRI Study of Prefrontal Brain Activation During Multiple Tasks in Patients With Major Depressive Disorder

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Abstract: *Objective:* Previous research has provided conflicting information regarding the pattern of brain activation associated with cognitive performance in depressed people. We aimed to assess brain activation related to cognitive performance during planning and working memory tasks. *Method:* fMRI scans were conducted using a modified Tower of London task and a 2-back task in 13 patients with major depressive disorder and a matched control group. *Results:* Task performance was impaired in the depressed group on the Tower of London task but there were no differences between the groups in task performance on the *n*-back task. The patient group showed widespread increased brain activation in both tasks. There was considerable overlap in increased activation between the two tasks, especially in right prefrontal cortical regions. *Conclusions:* Patients with depression exhibit increased brain activation, especially in right prefrontal regions, across several types of cognitive task activity. Patients with depression may recruit greater brain regions to achieve similar or even poorer task performance than control subjects. *Hum Brain Mapp* 29:490–501, 2008. © 2007 Wiley-Liss, Inc.

Key words: depression; prefrontal cortex; fMRI; planning; working memory; brain activation

INTRODUCTION

Impaired cognitive function is clearly a common and disabling feature of major depressive disorder (MDD)

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although there is no widely accepted model that links cognitive impairment to the pathophysiology of MDD. A number of studies in recent years have used fMRI and other imaging techniques to study brain activation associated with cognitive activity in patients with depression. These studies have reported abnormalities in activation levels and blood flow across a number of brain regions. However, there is considerable heterogeneity in this literature giving conflicting results reflecting the fact that most studies have used different cognitive tasks and scanning methods.

For example, of fMRI studies published studying patients with unipolar major depression using a cognitive activation task; one used a mental arithmetic task [Hugdahl et al., 2004], one a verbal fluency task [Okada et al., 2003], one a emotional task involving the encoding of emotive pictures [Fahim et al., 2004], and three studies used variations of the *n*-back working memory paradigm [Barch et al., 2003;

Harvey et al., 2005; Rose et al., 2006]. In the study utilising the verbal fluency task, Okada et al. found a reduction in task-related activation in the left dorsolateral prefrontal cortex (DLPFC) [Okada et al., 2003]. This finding is relatively consistent with previous resting blood flow and metabolism studies that have reported a reduction in left frontal activity (for example [Bench et al., 1993; George et al., 1994]). However, a reduction in DLPFC activity was not seen in several of the other studies, except for the study of emotive encoding [Fahim et al., 2004]. Reduced activation was seen in right parietal regions with the mental arithmetic task [Hugdahl et al., 2004] and a 2-back working memory task using words and faces [Barch et al., 2003]. This latter study also reported reduced task-related activation in bilateral thalamus and the right precentral gyrus. Interestingly, two of the studies found increased task-related activation in prefrontal regions. This was found in bilateral Brodmann area (BA) nine with the mental arithmetic task [Hugdahl et al., 2004] and in left BA46 with a working memory task using letters [Harvey et al., 2005]. The latter study also found increased activation in other frontal regions and the anterior cingulate cortex [Harvey et al., 2005].

This variation in brain region activation is also present in earlier studies using PET and SPECT techniques. Several of these earlier studies reported decreased activity in depressed patients versus controls, for example in the anterior cingulate [Bremner et al., 2004; Goodwin, 1997], hippocampus [Bremner et al., 2004], ventromedial orbito-frontal cortex and caudate nucleus [Elliott et al., 1998], right parietal lobe [Philpot et al., 1993], and in widespread cortical and/or subcortical regions [Audenaert et al., 2002; Elliott et al., 1997]. The wide variation in these results is likely to reflect the differing clinical populations in the studies. For example, some studies included bipolar as well as unipolar depressed subjects [Goodwin, 1997] and some focused on specific groups such as the elderly [Philpot et al., 1993] or recent suicide attempters [Audenaert et al., 2002]. It is also likely to closely reflect differences in the brain areas activated with the cognitive tasks used in each study.

The aim of this study was to investigate task-related brain activation using two tasks previously utilized in imaging studies, a working memory (2-back) and a planning task (Tower of London), applied at the same time in the same population of patients with unipolar depression. By doing this we aimed to elucidate whether there were common areas of abnormal brain activation highlighted with both tasks that may prove to be more specific to the underlying pathophysiology of cognitive dysfunction in depression. In addition, given that previous studies have reported lateralized results (for example) [Okada et al., 2003]) and lateralized differences in brain activation have been used as the basis for novel therapeutic interventions such as repetitive transcranial magnetic stimulation [Fitzgerald et al., 2003], to allow us to study hemispheric differences we selected two tasks that have been shown to produce bilateral frontal activation. The Tower of London (TOL) task is a widely applied test of planning and executive function that requires sub-

jects to plan in mind the moves required to rearrange a series of colored balls. It has been used in PET and fMRI studies of normal cognition and produces activation of bilateral DLPFC [Elliott et al., 1997]. Working memory tasks have been repeatedly used in imaging studies of the DLPFC [Cabeza and Nyberg, 2000]. In *n*-back tasks, the subject is required to indicate whether or not an item matches an item that occurred one, two or more (*n*) items back in a continuous series. This requires short-term memory with continuous updating of memory content. This task also produces activation of bilateral DLPFC as well as more distributed brain regions.

METHODS

Subjects

Thirteen right-handed patients with a DSM IV diagnosis of major depression participated in the study as well as 13 healthy control subjects (Table I). The patients were recruited from the outpatient department of Alfred Psychiatry, Alfred Hospital, Melbourne, Australia and by referral from a number of private psychiatrists. Each patient had a DSM IV diagnosis of major depressive episode (M.I.N.I.) [Sheehan et al., 1998] and scored greater than 20 on the Montgomery-Åsberg Depression Rating Scale (MADRS) [Montgomery and Åsberg, 1979]. Eleven of the patients were on antidepressant medication at the time of the study.

TABLE I. Group characteristics

	Controls		Patients	
	Mean	SD	Mean	SD
Age	34.5	8.7	38.4	8.1
Sex (m/f)	5/8		8/5	
Years of education	13.4	2.0	12.7	4.2
MADRS			32.7	11.9
BDI			30.4	6.6
BPRS			19.1	4.5
GAF			49.6	16.5
CORE			8.8	8.1
TOL Planning				
Correct trials ^a	18.0	2.5	14.5	3.7
Incorrect trials	4.4	3.6	3.7	3.0
Reaction time (s) ^b	6.1	11.2	8.0	19.1
TOL Counting				
Correct trials	32.0	8.3	26.3	9.3
Incorrect trials	3.1	2.5	2.9	1.8
Reaction time (s)	4.1	0.83	5.0	1.4
<i>n</i> -Back: 0 back				
Correct trials	19.7	2.0	19.5	4.5
Incorrect trials	1.0	1.9	1.4	4.5
Reaction time (s)	0.52	0.08	0.56	0.11
<i>n</i> -Back: 2 back				
Correct trials	18.1	2.0	15.8	6.5
Incorrect trials	7.4	4.8	10.4	9.5
Reaction time (s)	0.74	0.15	0.79	0.26

^a $P < 0.05$.

^b $P < 0.01$.

Eight were taking a serotonin reuptake inhibitor, one a tricyclic antidepressant, and two mirtazapine.

Exclusion criteria included bipolar affective disorder or any concurrent other medical or psychiatric illness including substance abuse. Patients were not permitted to have had treatment with ECT in the preceding 12 months. Medically and psychiatrically well controls were recruited from hospital staff and contacts of the investigators.

All the patients were assessed with the MADRS [Montgomery and Asberg, 1979], the Beck Depression Inventory (BDI) [Beck et al., 1961], the Brief Psychiatric Rating Scale (BPRS) [Overall and Gorham, 1962], the CORE rating of psychomotor disturbance [Hickie et al., 1990], and the Global Assessment of Function (GAF) [American Psychiatric Association, 1994]. Handedness was recorded with the Edinburgh Handedness Inventory [Oldfield, 1971]. The control subjects were screened for psychopathology or a history of mental illness using the MINI [Sheehan et al., 1998].

Written informed consent was obtained from all patients and controls and ethics approval was obtained from the Human Research Ethics committee of the Alfred Hospital, Melbourne.

Imaging Procedure and Analysis

Stimuli

The task was explained and practiced outside the scanner room until subjects were comfortably able to perform both of the tasks (performance was not assessed prescanning).

Tower of London

The TOL task as adapted for the fMRI procedure was designed as a three-condition block sequence, with a planning condition, a counting condition, and a rest condition. During the planning condition, the participants were presented a baseline configuration and a target configuration on a single screen. Both configurations consisted of balls of different colors (blue, yellow, and red) placed on three vertical rods. The minimum number of necessary moves that were required to move the balls from the baseline to the target state had to be planned in mind. Answers were registered by pressing a button box held in the hand corresponding to the side of the screen where the correct answer was displayed. With the counting condition, participants were required to count the number of balls of two different colors, and choose the correct answer from two possibilities. During the rest condition, a fixation cross appeared on the screen and participants were instructed to relax. Each condition was presented in 40 second blocks appearing once per session. Within the blocks the tasks were presented in a self paced manner.

n-Back

The 2-back task involved presentation of a series of letters on a screen. The subjects were required to indicate with the

use of a button box when a particular letter appeared on the screen after it appeared on the screen 2 letters previously. This was compared with a control "0-back" condition when the subjects were required to indicate when a particular letter appeared on the screen. Each condition was presented in 32-second blocks.

Image acquisition

Gradient echo planar images were recorded using a 1.5 T G.E. Signa whole body scanner with the following imaging parameters: TR = 4,000 ms, TE = 60 ms, FA = 30°, FOV = 24 cm, matrix size 64 × 64, in-plane resolution 3.75 × 3.75 mm², 15 trans-axial slices to cover the entire brain with a slice thickness of 7.0 mm. To help with spatial normalization, a T₂ weighted image was acquired (15 trans-axial slices with 7-mm gap) in the same orientation as the echo planar images and a SPGR T₁ weighted image was acquired in the sagittal plane (124 slices, TR = 7.9 ms and TE = 1.78 ms, FA = 15°).

For the TOL task, each condition appeared once per session with 10 whole brain volumes acquired per condition. There were four sessions with each session lasting for 128 s, producing a total of 40 volumes per condition. For the *n*-back task, each condition appeared twice per session with 14 whole brain volumes acquired per condition. There were three sessions with each session lasting for 128 s producing in total 42 volumes per condition. The start of the stimulus presentation and the scanner acquisition were synchronized and the first two brain images were discarded in both TOL and *n*-back data in order to account for T₁ saturation effects.

Image analysis

Image analysis was performed using SPM99 (<http://www.fil.ion.ucl.ac.uk/spm/>) as the data analysis was commenced prior to the availability of the more recent versions of SPM. Prior to statistical analysis the images in each session were aligned to the first image using a six degrees of freedom rigid body transformation. The mean images after realignment of the two sessions for each subject were coregistered with the T₂ weighted image of the same subject. The T₂ weighted image was then normalized to the EPI template image in Talairach coordinate space using a nonlinear transformation based on discrete cosine basis functions (DCT 7 × 8 × 7 functions). The combined normalization matrix (obtained by multiplying the matrices calculated during the realignment, coregistration, and normalization step) was then applied to all EPI images for a given subject.

These images were then interpolated using a sinc function (9 × 9 × 9 voxels kernel) to produce resliced images with a voxel size of 2 × 2 × 2 mm³ in Talairach coordinate space and were spatially smoothed using an 8 mm Gaussian kernel. The statistical analysis was performed employing a high pass temporal filter with 88 sec cut off and the SPM99 canonical hemodynamic response function. Fixed effects analysis was performed for every subject where the regres-

TABLE II. Regions of greater activation in patients compared to controls in TOL task

Regions	Co-ordinates (mm)	Cluster size (mm ³)	Z-score	P_{FDR}
Right Frontal		1,747		
Inferior frontal gyrus	30 30 2		4.84	<0.016
Middle frontal gyrus	48 20 36		4.67	<0.032
	32 48 18		4.61	<0.040
	44 20 34		4.59	<0.045
Right angular gyrus/cuneus	42 -52 36	503	4.96	<0.009

sor modelled in the general linear model was based on the fixed response box-car function with temporal derivatives convolved with the SPM hemodynamic response function. We explicitly excluded task-related deactivations from our analyses by only reporting BOLD signal increases in the tasks of interest (2-back and planning) compared with the control conditions, and furthermore we only included positive t -values in the pooled random effects analysis. Our analyses were hypothesis driven and sought to establish whether BOLD signal increases were different between patients and controls. We did not examine signal reductions, nor differences in BOLD signal reductions between the groups, because of the difficulties in interpreting such differences.

Comparisons of BOLD signal response increases in planning compared with rest in the TOL task and 2-back compared with 0-back in the n -back task were computed. Correlation analysis between reaction times (RTs) and BOLD increases in planning compared with rest as well as between 2-back compared with 0-back was performed. In addition, we conducted correlations of MADRS scores with activations in the patient group.

Several secondary analyses were conducted. First, to allow us to further explore the issue of the laterality of changes reported in the primary analyses, hemispheric predominance during task performance was evaluated for controls and patients by flipping the spatially normalized data set 180° in the mid-sagittal plane such that they represent the “mirror” images of the first set. A fixed effect analysis was performed for each group separately and the contrast between unflipped and flipped images was calculated. Resulting statistical t -maps were thresholded at significant level $P_{FDR} < 0.05$ and the cluster sizes for the significantly activated regions were calculated using an extent threshold of $P_{uncorr} < 0.01$.

Second, given that we found some similarity and overlap in the areas of difference across the tasks, the TOL and n -back data were pooled to increase the statistical power to detect the differences in BOLD response between the two groups. A mean contrast image of planning compared with rest and 2-back compared with rest 0-back was generated for each subject, thresholded at $P_{uncorr} < 0.001$ ($t > 3.1$), and included in the random effects analysis of the pooled data. Significant regions of activation were identified using the SPM conjunction analysis model with a height threshold and an extend threshold of $P_{corr} < 0.001$.

Finally, to further explore the issue of “inefficiency” of activation, we calculated frontal efficiency ratios for patients and controls on each of the two tasks. This involved dividing task performance (TOL planning mean reaction time and 2-back number of total correct trials and mean reaction time) by the percentage signal activation in the right pre-frontal cortex voxel found to show the most significant difference between the groups (30,30,2 for the TOL and 28,18,54 for the n -back task). These ratios were then compared between the groups with independent sample t -tests (the TOL ratio required log transformation prior to parametric analysis).

RESULTS

Demographics and Clinical Characteristics

The two groups did not differ in mean age, sex or years of education (Table I). The clinical group exhibited moderate to severe depression with significantly impaired functioning (mean GAF <50).

Task Performance

Because of technical problems with the recording system, accurate performance data was not available on two control subjects and one patient (who were not excluded from the fMRI analysis).

TOL

There was a significant difference between the groups in performance on the TOL task (Table I). The control group completed a greater number of correct ($t(21) = 2.6$, $P < 0.05$) and total trials ($t(21) = 2.5$, $P < 0.05$), and had a significantly lower trial time ($t(21) = -2.9$, $P < 0.01$). There was no difference in the percentage of trials completed incorrectly ($t(21) = 0.2$, $P > 0.05$).

n -Back

The two groups did not differ in performance on the 2-back task in regards to response accuracy (controls 72.8%, patients 63.4% correct ($t(21) = 1.1$, $P > 0.05$) and response times ($t(21) = -0.55$, $P > 0.05$).

Figure 1.

Regions significantly activated in patients compared with controls in the TOL task (blue-green) and *n*-back task (red-yellow) as shown in neurological format (axial slices are $z = 34$ and 46 , coronal slice is $y = -10$ mm).

fMRI Activation

TOL

Both groups demonstrated activation of bilateral parietal cortex, bilateral precentral gyrus, bilateral frontal regions (including BA9 and BA46), and bilateral medial frontal/anterior cingulate. Comparing the groups, there was greater activation in the patients in the right inferior frontal, middle frontal gyrus (including BA9 and 46), and angular gyrus/cuneus (Table II, Fig. 1). There was no region in which greater activation was observed in controls compared with patients.

The RTs significantly correlated with left inferior frontal (including BA46) and right middle frontal (BA 46) activation for controls whilst for patients, significant correlations were found at parahippocampal, inferior frontal gyrus, insula bilaterally, right precuneus, and middle frontal gyrus (Table III, Figs. 2 and 3). Scatterplots were produced at the voxel of most significant correlation for patients ($-40, 2, 06$) and controls ($-44, 6, 26$).

There were no regions which correlated significantly with MADRS scores

n-Back

As in TOL, both groups significantly activated parietal regions, frontal regions (including BA9 and BA46), medial frontal/anterior cingulate, putamen, thalamus, and cuneus bilaterally. However, the patients' demonstrated significantly increased activity in middle, medial, inferior frontal gyri bilaterally, anterior cingulate gyrus, precentral gyrus, inferior parietal, middle temporal gyrus, cuneus/precuneus, and thalamus bilaterally compared with controls (Table IV, Fig. 1). There was no region in which greater activation was observed in controls compared with patients. There was no significant correlation observed between BOLD response signal increase and the RTs in either group. There were no regions which correlated significantly with MADRS scores.

Secondary Analyses

When the TOL and *n*-back data were pooled, the patients showed increased activity in right middle frontal and superior temporal gyrus, and left sylvian fissure compared with controls (significance $P_{\text{corr}} < 0.001$) (Table V, Fig. 4).

Figure 2.

Regions significantly correlated with the RTs in controls (blue-green) and in patients (red-yellow) during the performance of the TOL task for controls and patients, respectively. The images are displayed in the neurological format ($Z = -6, 24, 28$, and 48 mm).

TABLE III. Regions correlated with reaction times in controls and patients during TOL task

Regions	Coordinates (mm)	Cluster size (mm ³)	Z-score	P_{FDR}
Controls				
Left		855		
Inferior frontal gyrus	−44 6 26		5.42	<0.002
Middle frontal gyrus (BA46)	−42 38 20		4.46	<0.030
Right middle frontal gyrus (BA46)	44 36 28	205	4.36	<0.034
Patients				
Parahippocampal gyrus		3,477		
Left parahippocampal gyrus	−22 −36 −6		3.77	<0.047
Right parahippocampal gyrus	20 −36 −6		3.91	<0.042
Left		346		
Superior temporal gyrus/insula	−40 2 −6		4.74	<0.008
Inferior frontal gyrus	−38 22 −16		3.34	<0.048
Right		2,955		
Insula	36 0 −6		4.24	<0.020
Precuneus	20 −40 50	593	3.97	<0.037
Inferior frontal/precentral gyrus	50 0 22		3.90	<0.042
Left middle frontal gyrus	−44 4 48		3.80	<0.044

Comparison of hemispheric dominance during the n -back task showed significant activations predominantly in the right hemisphere (Table VI, Fig. 5a) in patients, whilst in controls significant activations were predominantly in the left hemisphere (Table VI, Fig. 5b). Hemispheric dominance during the TOL-task was similar to the n -back task (Table VII, Fig. 5c,d).

Frontal Efficiency Ratios

There was a significant difference between the controls and patients for the frontal efficiency ratios (FER) calculated

for the TOL task using the mean reaction time per subject (controls = 1.42 ± 0.09 , patients = 1.52 ± 0.12 , $P = 0.047$) but not for the n -back task with data calculated with either the response time or number of correct trials.

DISCUSSION

In this study we aimed to investigate task-related brain activation in patients with major depression using two separate cognitive tasks. The pattern of differences between the two groups was not the same using the two tasks but there was an overlap, particularly in regards to a pattern of

Figure 3.

Scatterplots showing the relationship between reaction times and percentage signal change/activation during the TOL task for controls [at $-44, 6, 26$: $r^2 = 0.56$, $P < 0.05$] and patients [$-40, 2, -6$: $r^2 = 0.42$, $P < 0.05$].

TABLE IV. Regions of greater activation in patients compared with controls in the *n*-back task

Regions	Coordinates (mm)	Cluster size (mm ³)	Z-score
Right frontal			
Middle frontal gyrus	28 18 54	7,767	>10
Inferior frontal gyrus	50 12 16		6.50
Medial frontal gyrus	6 10 4		>10
Anterior cingulate gyrus	6 12 42		7.75
Precentral gyrus	34 -8 54		7.56
Left frontal		3,440	
Medial frontal gyrus	-4 2 60		>10
Anterior cingulate gyrus	-2 8 46		>10
Precentral gyrus	-28 -54 48		>10
Middle frontal gyrus	-28 20 52		7.73
Inferior frontal gyrus	-52 24 16		7.59
Right parieto-temporal			
Inferior parietal lobule	50 -38 34	7,165	>10
Superior temporal gyrus	52 -52 28		>10
Precuneus	18 -66 42		7.22
Orbital gyrus	36 -80 24		>10
Left parieto-temporal			
Cuneus	-38 -62 36	1,979	>10
Inferior parietal lobule	-52 -46 32		6.35
Superior temporal gyrus	-46 -54 28		5.15
Middle temporal gyrus	-58 50 6	461	7.72
Right Thalamus	18 -10 10	971	5.75
Left Thalamus	-18 -14 12		7.29

All Z scores are significant at $P_{\text{corr}} < 0.001$.

greater activity in patients during the cognitive tasks in right prefrontal cortical regions. Using the TOL task, the major regional difference between the two groups was in right PFC with greater activation in the patient group. On the *n*-back task, the patients showed a more widespread pattern of activation compared with the controls with a large area of increased activation also in right PFC. When activation on the two tasks was pooled for an exploratory analysis, the major differences between the two groups was in right PFC. Interestingly, the more widespread activation on the *n*-back task corresponded to a normal level of performance on this task whereas the patients underperformed compared with the controls during the TOL task.

This is the first study of which we are aware that has utilized more than one cognitive task in the study of brain activation in patients with depression. It is also the first study to use fMRI in depressed patients to examine activation during the TOL task. This task has previously been applied to the study of cognitive activation in depression in a single study using PET [Elliott et al., 1997]. In that study, Elliott et al. reported a mixed pattern of increased and decreased brain activation in six depressed patients compared with six controls. Increased activation was found in the patient group in bilateral dorsolateral and rostrolateral PFC as well as bilateral thalamus and left anterior cingulate cortex. However, decreased activation in the patient group was also seen in bilateral medial PFC as well as superior temporal and right posterior cingulate cortex. Importantly, these

differences were seen on analysis of the planning versus counting conditions. In contrast, we did not see differences between planning and counting but the significant differences in our study were seen in the analysis of planning minus rest. Subtraction of the counting condition from the planning potentially allows us to study just planning specific elements of processing. However, this is likely to result in a lesser signal than the rest contrast. The implication of this is that the cognitive demand studied in our sample was likely to be less specific to brain regions involved in planning and more broadly reflect frontal executive activities associated with this task.

There were also differences in performance in the depressed patients in the two studies. In our study, the patients compared with the controls performed slower but with similar accuracy. In contrast, the patients in the study of Elliott et al. performed at similar speed but reduced accuracy, especially on the harder problems. These differences could reflect the small samples studied or subtle variations in the tasks. However the slower response speeds could also reflect a greater degree of melancholia in our patients who scored relatively highly on the CORE rating of psychomotor disturbance, although there were no differences in response times on the 2-back task. Evidence from motor tasks supports a reduction in response time in patients with melancholic symptoms as compared with nonmelancholic depressed subjects and controls [Rogers et al., 2002]. This could also reflect subtle differences in the clinical populations or task instructions in the two studies with the predominate strategies differing as to whether patients sacrificed accuracy to maintain speed rather than the opposite, a process which could be influenced by mood-related variables such as degree of task-related motivation or the way in which patients were coached to perform quickly.

Several previous studies have used fMRI to study brain activation in patients with depression using *n*-back methods. Barch et al. used an *n*-back design with faces and words and reported a generally decreased pattern of activation in patients versus controls in bilateral thalamus, right precentral gyrus and parietal cortex [Barch et al., 2003]. Interestingly, a different pattern of activation was seen between the two groups for the faces and word tasks. Controls, but not patients, activated right frontal cortex in the

TABLE V. Significant regions, at cluster level threshold $P_{\text{corr}} < 0.001$ observed in patients compared to controls for the pool data (mean TOL and *n*-back)

Regions	Co-ordinate mm	Cluster size (mm ³)	Cluster level threshold ^a
Right superior temporal gyrus	42 8 -16	1,891	<0.001
	50 -58 20	579	<0.001
Right middle frontal gyrus	44 24 48	1,049	<0.001
Left Sylvian fissure	-42 -32 22	679	<0.001

^aCorrected for multiple comparisons.

Figure 4.

Significant regions of activation (cluster level threshold $P_{\text{corr}} < 0.001$) comparing patients responses to controls for the pooled data (mean TOL and n -back). Axial slices correspond to $z = -16, 20$, and 48 mm are shown.

word n -back task. In contrast, right PFC was activated by the patients in the face n -back task. In a study more comparable to ours, Harvey et al. used a letter n -back task of varying task severity (1–3 back) [Harvey et al., 2005]. Consistent with our results, they found increased activation in the patient group with no areas of decreased activation compared with the controls. However, the pattern of activation was different with more areas identified on the left than the right including left inferior and middle frontal regions as well as dorsal anterior cingulate cortex. Differences in the findings of these three studies may well relate to task difficulty. As discussed by Harvey et al. [2005], a word n -back task is likely to be easier for subjects to perform than a face task. This could explain why increased activation in

Figure 5.

Hemispheric predominance during n -back task for (a) controls and (b) patients and the TOL task for (c) controls and (d) patients. The images are displayed in the neurological format and the z coordinate in millimeter is shown.

TABLE VI. Significant regions observed in controls and patients for the contrast unflipped > flipped during *n*-back task

Regions	Co-ordinates (mm)	Cluster size (mm ³)	Z-scores	<i>P</i> _{corr}
Controls				
Left				
Superior parietal lobule	-26 -60 48	3,096	>10	<0.001
Middle frontal gyrus	-18 -2 56	1,291	6.85	<0.001
Sylvian fissure	-26 22 4	201	4.90	<0.011
Right				
Middle frontal gyrus	28 24 54	323	6.26	<0.001
Medial frontal gyrus	8 32 44	335	4.77	<0.020
Patients				
Left				
Middle frontal gyrus	-52 2 34	1,665	7.31	<0.001
Superior temporal gyrus	-54 6 0	293	5.40	<0.001
Superior parietal lobule	-28 -62 50	224	6.46	<0.001
Right				
Middle frontal gyrus	40 42 24	476	>10	<0.001
Inferior parietal lobule	50 -44 38	3,405	>10	<0.001
Superior frontal gyrus	22 34 52	2,166	>10	<0.001
Precuneus	10 -74 50	937	6.22	<0.001

depressed subjects was seen in the two letter *n*-back studies, related to a need to activate greater cortical regions to achieve similar task performance. In our study, performance on the 2-back task was worse in the patient and control group than that seen in both of the other two studies. Although the difference between controls and patients was not significant, the patients performed worse than the control group suggesting that the difficulty of performance of the task may have been driving the greater area of activation in the patient group in our study. The pattern of involvement of prefrontal and cingulate cortical regions is consistent with the role of these areas in working memory function [Braver et al., 1997]. Of interest are also the results of this study of Rose et al. [Rose et al., 2006]. In this study, medial prefrontal-rostral anterior cingulate activation fell with increased task difficulty but fell less in patients with depression than controls. Therefore, this supports the notion of hyperactivity in depressed subjects but not a right localization.

In light of the differences in task performance between the two tasks, it is of considerable interest that we have demonstrated increased task-related activation, especially in right prefrontal regions, across both tasks. This occurred, to a greater or lesser degree, when patients performed at a similar performance level (*n*-back) and at an impaired performance level (TOL) as compared with controls. 'Hyperfrontality' has also been reported in depressed subjects in some other contexts. Increased bilateral middle frontal activation has been found in an fMRI study of mental arithmetic [Hugdahl et al., 2004] and increased activation in left PFC has been seen in one PET study using a STROOP task [George et al., 1997]. In the study of mental arithmetic, there was a significant component of having to keep task infor-

mation online, suggesting the possibility that these findings were also related to problems with working memory [Hugdahl et al., 2004]. These findings are in contrast to the results of several imaging studies using other cognitive activation tasks which have reported decreases in regional activation in depressed subjects. Studies using verbal fluency tasks have reported reduced activation in left PFC [Okada et al., 2003], right parietal cortex [Philpot et al., 1993] and widespread brain regions [Audenaert et al., 2002]. It is plausible that these differences relate to the degree of effort required across these tasks. The degree of effort required in the performance of the working memory and planning tasks may well exceed that required in a word generation task. More brain activation could be required to result in sufficient processing and performance in these more difficult tasks resulting in greater activation in the patient groups. These differences could also relate to the degree of laterality required on the performance of the tasks. Verbal fluency is considered to be predominantly a left hemisphere related task [Rogers et al., 2004] whereas, as shown in our control subjects and previous studies [Braver et al., 1997; Elliott et al., 1997; Rogers et al., 2004], both the TOL and *n*-back tasks elicit significant bilateral activation. Therefore, verbal fluency tasks may not be sensitive to abnormalities in right prefrontal cortex dysfunction in depression.

The calculated FER gives some further information in regards to the nature of the between group differences. As performance on the TOL task measure was reaction time and greater value reflects poorer performance, an increased FER indicated less cognitive performance per degree of brain activation. This supports the notion that the patient group is recruiting more brain resources in an attempt to maintain task performance. This concept has previously been discussed in the context of the physiology of normal

TABLE VII. Significant regions observed in controls and patients for the contrast unflipped > flipped during TOL

Regions	Co-ordinates (mm)	Cluster size (mm ³)	Z-scores	<i>P</i> _{corr}
Controls				
Left				
Middle frontal gyrus	-22 -4 54	585	6.14	<0.001
Middle occipital gyrus	-22 -84 22	645	5.82	<0.001
Inferior parietal lobule	-22 -50 46	314	5.51	<0.001
Right				
Precuneus	36 -80 42	1,727	>10	<0.001
Inferior parietal lobule	54 -36 54	332	5.33	<0.002
Patients				
Left				
Cuneus	-20 -84 22	1,430	5.86	<0.001
Right				
Parieto-Occipital cortex		2,614		
Superior occipital gyrus	34 -80 32		>10	<0.001
Inferior parietal lobule	54 -40 46		4.81	<0.019
Frontal cortex				
Superior frontal gyrus	6 20 50	509	5.56	<0.001
Medial frontal gyrus	10 28 36		4.72	<0.023

cognitive function and prefrontal performance in disorders such as schizophrenia (for example [Cairo et al., 2006; Calliott et al., 2003; Sayala et al., 2006; Tipper et al., 2005]) although we are unaware of any analysis of quantification of efficiency of activation in depression. The reduced efficiency in the patient group strongly supports the notion of a specific degree of right prefrontal dysfunction underlying these changes in task-related activation.

In addition to right prefrontal changes, areas of increased activation in the patients were identified in the superior temporal cortex - inferior parietal cortex regions bilaterally in the pooled analysis. The major contribution to this difference would appear to be the significantly increased activation in these regions that was seen in the 2-back task. Although significant differences in the TOL task alone were not seen in these regions, it is reasonable to propose that there was some degree of nonsignificantly greater activation in patients. This may well reflect altered working memory demands as the task does have a considerable requirement to keep information in mind during visual manipulation of the task components. Therefore, these findings could simply reflect the need for the greater activation of a variety of working memory-related brain regions to maintain functional performance, as reflected in the increased activation in a number of working memory related regions in the 2-back task analysis. This need for increased arousal of these regions could be secondary to the mood state of the subjects as emotional arousal has been shown to influence working memory performance [Li et al., 2006]. The support for the finding of increased task-related activation in the right hemisphere is in the context of a considerable history of research and theory development in regards to the role of the hemispheres in mood regulation and depression, most of which supports a considerable role for the right PFC. First, this literature indicates a clear role for the right PFC in the expression of, or modulation of, negatively valenced emotion and in the evaluation of emotional prosody (see review in [Shenal et al., 2003]). Second, a number of lines of research suggest that the right PFC is functioning more poorly in the depressed state [Liotti and Mayberg, 2001; Rotenberg, 2004]. This data includes deficits in a range of right hemisphere functions such as nonverbal expression and spatial abilities [Rotenberg, 2004], a slowing of reaction times to material presented to the left visual field [Liotti and Tucker, 1992] and less vivid imagery [Tucker et al., 1981]. This impaired performance, however, is accompanied by evidence of physiological hyperactivity predominately established with data from electrophysiological studies (for example [Henriques and Davidson, 1990; Jacobs and Snyder, 1996; Tucker et al., 1981]). In this context it seems logical to propose that the physiological hyperactivation seen either electrophysiologically at rest or related to a task in these imaging studies may result from a more fundamental right PFC localized functional deficit. At this stage we lack a sufficiently sophisticated understanding of the role of various subregions of the PFC to be able to propose with any sense of certainty where this deficiency may lie, if in

fact it is relatively anatomically localized. However, exploring differences in studies such as this that analyse the overlap in reported brain regions as well as quantitative meta-analytic approaches to imaging data in mood disorders (for example [Fitzgerald et al., 2006]) may provide some insight into these issues.

There are a number of limitations in the interpretation of the results of this study. Although our sample is larger than many of the previous imaging studies in depression, the sample size is still relatively small and this may have limited our capacity to find differences in some brain regions. In addition there was considerable variation in the medication treatment of the patients in the study. However, no research has suggested that medication will increase cortical activation in patients who remain depressed, although Mayberg et al. have shown changes in activation associated with clinical response to medication treatment [Mayberg et al., 2000]. Third, the use of SPM99 in our data analysis is worthy of comment. Because of logistical reasons were not able to reprocess all our data in SPM2 following commencement of analysis with the older version. It is recognized that "whitening filters" in SPM2 enhance statistical precision and lower the possibility of false positive results and that this has relevance to both event related and blocked study designs [Bianciardi et al., 2004]. Finally, the study does not allow us to make conclusions as to whether these findings are related to the depressive state or vulnerability to depressive illness. Although a number of studies have explored brain activation before and after treatment or in ill and remitted patients (for example [Davies et al., 2003; Mayberg et al., 2000; Michael et al., 2003]), the significant majority of these studies have scanned subjects at rest and we are unaware of any studies using the *n*-back or TOL tasks in this manner. Although the resting studies do suggest that there are significant alterations over time and that there are differences from controls that persist in the resting state, because of the fundamental differences in scanning approach it is not possible to extrapolate this to cognitive activation studies. Studies directly addressing this question are required.

CONCLUSIONS

In conclusion, the results of this novel investigation clearly suggest that cognitive performance in patients with depression is associated with increased cortical activation. This is especially noticeable in prefrontal regions, predominantly on the right. This supports the possible use of low frequency repetitive transcranial magnetic stimulation, a treatment technique that produces reduced brain activity and for which there is initial data suggesting clinical efficacy [Fitzgerald et al., 2003; Klein et al., 1999].

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