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Article *in* NeuroImage · August 2005

DOI: 10.1016/j.neuroimage.2005.02.048 · Source: PubMed

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Cognitive control and brain resources in major depression: An fMRI study using the *n*-back task

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Received 2 December 2004; revised 16 February 2005; accepted 21 February 2005
Available online 8 April 2005

Several neuroimaging studies have reported 'hypofrontality' in depressed patients performing a cognitive challenge compared to control subjects. Hypofrontality in depression is likely associated with an impaired behavioral performance. It is unclear whether this impaired performance is the consequence or the cause of hypofrontality. Consequently, we proposed to compare the cerebral activity of depressed patients and healthy subjects while controlling for the level of performance. Ten individuals meeting DSM-IV criteria for Major Depression and 10 healthy controls were tested with a verbal version of the *n*-back task during fMRI scanning. The working memory load was manipulated across the experiment (1,2,3-back) to increase the cognitive demands. fMRI data were acquired on a 1.5-T GE scanner and analyzed using SPM99 software. We did not find any difference between groups in both performance and reaction times for each level of complexity of the *n*-back task. Depressed patients and control subjects showed bilateral activation of the lateral prefrontal cortex, anterior cingulate and parietal cortex. Activation of these regions was modulated by the complexity of the task. Within this *n*-back neural network, depressed patients showed greater activation of the lateral prefrontal cortex and the anterior cingulate compared to healthy subjects. This study provides evidence that depressed patients need greater activation within the same neural network to maintain a similar level of performance as controls during a working memory task. Our findings suggest that depression may impair the cognitive capacity of depressed patients by recruiting more brain resources than controls during cognitive control.

Keywords: Major depression; *n*-back task; Cognitive control; Magnetic resonance imaging; Prefrontal cortex; Hyperfrontality

Introduction

Many neuroimaging studies on depression have reported functional abnormalities in the prefrontal cortex (PFC). For instance, resting state studies using PET frequently identify increased metabolism in regions such as medial and orbital PFC (MPFC; OPFC) (Drevets, 2000). Moreover, abnormalities in dorsal and lateral parts of the PFC have also been observed at rest, with hypometabolism in dorsolateral prefrontal cortex (DLPFC) (Baxter et al., 1989; Sackeim et al., 1990) and anterior cingulate cortex (ACC) (Galynker et al., 1998). In addition to resting state studies, some imaging experiments have been conducted with depressed patients performing various cognitive tasks. However, findings obtained from these experiments are still inconsistent. Two independent studies using two different cognitive tasks (*n*-back Task and Wisconsin Card Sorting Test) did not find any difference in frontal activity between depressed patients and control subjects (Barch et al., 2003; Berman et al., 1993), while three other studies showed decreased activity in the DLPFC using the Tower of London and verbal fluency tasks (Elliott et al., 1997; Okada et al., 2003) and in the ACC using a standard Stroop task (George et al., 1997). A recent functional MRI (fMRI) study using an arithmetic task even found hyperfrontality in the DLPFC in depressed patients compared to normal subjects (Hugdahl et al., 2004).

A confound within the cognitive activation studies that found hypoactivity in depression was the impaired behavioral performance of depressed patients compared to normal subjects. One could argue that the impaired performance is a *cause* of the cerebral discrepancies between groups instead of being a *consequence*. This problem has been underlined in schizophrenia by two studies showing that hypofrontality is not present during performance of a cognitive task when patients' performance is balanced with that of controls (Fletcher et al., 1996; Frith et al., 1995). Similar to these studies on schizophrenia, we proposed to compare the cerebral activity between depressed patients and healthy subjects while controlling for the level of performance.

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Available online on ScienceDirect (www.sciencedirect.com).

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doi:10.1016/j.neuroimage.2005.02.048

The purpose of this study was to assess with fMRI the cerebral activity of depressed patients who perform a cognitive task at normal levels.

Since depressed patients have problems with tasks requiring effort and executive control (Hartlage et al., 1993), we believe that the identification of a cerebral abnormality in depression must be achieved by using an effortful task. Thus, our challenges were, on the one hand, to focus on a cognitive function that would involve effortful processing for depressed patients and, on the other, to recruit depressed patients that could allocate enough resources in order to reach the level of performance of normal subjects.

We used a verbal variant of the *n*-back task that allows us to parametrically manipulate the workload/complexity within working memory (WM). An increasing amount of evidence suggests that depressed patients are impaired on tasks involving WM (Harvey et al., 2004; Porter et al., 2003). A recent fMRI study on schizophrenia used the *n*-back task to demonstrate that hyperfrontality arises as patient performance approaches that of healthy subjects, while low-performing patients are uniformly hypofrontal (Callicott et al., 2003). Callicott et al. (2003) suggested that schizophrenic patients with a normal performance at the *n*-back task are less efficient when processing information and this is reflected by an abnormal hyperfrontality. Based on Callicott's findings, we hypothesized that normal behavioral performance in depressed patients performing the *n*-back task would be also associated with hyperactivity in the dorsal and lateral regions of the PFC compared to control subjects.

Materials and methods

The study was approved by the Ethics Committee for Biomedical Research of the Pitié-Salpêtrière Hospital.

Participants

Ten right-handed inpatients (7 females; 19–45 years of age) fulfilling the DSM-IV criteria for a nonpsychotic major depressive episode (unipolar depressive disorder) were recruited at the Pitié-Salpétrière hospital. Diagnoses were made using the MINI International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) by two psychiatrists (PF and GL). Patients were excluded on the basis of these criteria: history of manic/hypomanic episode, neurological illness, medical disorders or medication likely to affect cognition, current and/or past diagnosis of substance abuse or ECT in previous 12 months. Severity of depression was assessed using the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) and the Beck Depression Inventory (BDI) (Beck et al., 1961). Only subjects with MADRS scores of 20 or more were selected. The Tyrer anxiety scale (Tyrer et al., 1984) was also administered. The verbal IQ was measured by the Wechler Adult Intelligence Scale-Revised (WAIS-R). All patients were taking SSRIs antidepressant and were tested within 2 weeks of first receiving their treatment. Prior to being included in the fMRI study, patients performed twenty-eight training blocks of the *n*-back task (seven per level of complexity). We emphasized the importance of effort and commitment to the task. Two conditions had to be fulfilled. First, we set a performance cutoff for each level of complexity [mean performance obtained by healthy subjects in a previous behavioral study (Harvey et al., 2004) minus one standard deviation for each level]. Thus, for every subject, all practice blocks for each level were averaged and cutoff performances to reach were: 0-back = 96%; 1-back = 92%; 2-back = 76%; 3-back = 72%. Secondly, subject's performance (response accuracy in %) for each level of complexity had to be stable across the seven blocks. Consequently, subjects with unstable performance were excluded. Twenty-two depressed patients performed the training *n*-back session and ten patients have fulfilled the conditions for the fMRI study. The 10 selected patients were comparable to the twelve non-selected patients regarding age, verbal IQ (WAIS-R), education and depressive symptoms intensity.

Ten right-handed control subjects (5 females; 18–42 years of age) were recruited from the community. They were interviewed with the MINI and were excluded if there was any evidence of psychiatric history, neurological history, psychoactive substance abuse, family history of depression or use of medication which might have influenced their cognition. The presence of depression and anxiety symptoms was assessed. Written informed consent was obtained for each subject.

Task design

Subjects performed a letter variant version of the *n*-back tasks (Braver et al., 1997). These tasks require maintenance and permanent update of relevant pieces of information in WM. Load and mental manipulation within WM were modified by using three levels of complexity: 1-2-3-back tasks. Subjects also performed a control task (0-back) in which they were required to identify a single prespecified letter (i.e., an "X"). Briefly, subjects were asked to indicate whether a letter presented on a screen (the "target" stimulus) matched a letter previously presented (the "cue" stimulus). In order to reduce visual and phonological strategies, we used phonologically closed letters with upper and lower case. Thus, only the following letters were presented: b, B, d, D, g, G, p, P, t, T, v, V. Subjects were told to ignore the case of the letters. They responded either by pressing the right or the left button if the target was identical or different from the cue, respectively. All blocks consisted of a pseudo-random sequence of 12 consonants varying in case. The total duration of a given block, from instruction (4 s) to performance feedback (4 s), was 42 s. A 4 s blank delay separated the instruction from the appearance of the first letter. Letters were presented for 0.5 s and were separated from one another by a 2-s delay. Blocks were separated from one another by a 8-s interval. Four runs of seven blocks were presented to subjects (seven blocks per condition). The different condition blocks were also presented pseudo-randomly. The *n*-back task administered in this study was performed with rewarded and non-rewarded blocks, using the procedure reported by Pochon et al. (2002). Before each block, subjects were informed as to the type of cognitive task (0, 1, 2 or 3-Back) to be performed and the reward at stake. The symbols "$$$" and "0" indicated respectively that the block would be with or without monetary reward. To avoid the mental calculation of their gains, subjects were not explicitly informed about the precise amount of money associated with the "$$$" symbol. However, they were told that their performance accuracy would determine the amount of money they would win and that they could earn up to 305 Euros (≈270 U.S. Dollars). Rewarded blocks were pseudo-randomly distributed among all the blocks. Each *n*-back condition had 4 rewarded blocks and 3 nonrewarded blocks.

fMRI

Visual stimuli were projected using an active video projector and presented on a screen viewed through mirror glasses. Two buttons connected to a PC running *EXPE6* software were given to the subjects.

Functional images were acquired on a 1.5-T whole-body scanner (SIGNA, GE, Milwaukee, WS, USA), using T2*-weighted gradient echo, echo-planar imaging sequence, sensitive to blood oxygen level-dependent (BOLD) contrast (repetition time 2000-ms, echo time 40-ms, flip angle of 90°, matrix 64 × 64, field of view 220 × 220 mm). Four functional runs of 178 contiguous volumes were acquired. Volumes comprised 14 axial slices of 5-mm thickness and were obtained every 2 s. Each run lasted 356 s. The first three volumes of each run were discarded to reach signal equilibrium. High-resolution T1 weighted images [3-D fast gradient-echo inversion recovery sequence, T1 (inversion time) = 400-ms, repetition time = 1600-ms, echo time = 5-ms, matrix 256 × 256 × 128, field of view 220 × 220 mm, slice thickness = 1.5-mm] were acquired for anatomical localization.

Statistical analysis

Clinical and neuropsychological data were compared using Student's *t* tests. For the *n*-back tasks, response accuracy (%) and reaction times (ms) were recorded. Repeated-measures ANOVAs (2 × 3) were used for comparisons between groups, with a within-subjects complexity factor (3 levels) and a between-subjects group factor (2 levels). Student *t* tests (two-tailed) were used to compare groups for the 0-back condition.

fMRI data were processed using the SPM99 software (Friston et al., 1995). Functional scans, corrected for slice timing and subject motion, were normalized using the same rigid transformations and smoothed with a 10-mm full-width half-maximum Gaussian filter. Then, statistical parametric maps (SPMs) were computed for all subjects individually using the general linear model with separate hemodynamic basis response function modeling MR signal responses of each period of the task. High and low pass filters were applied to discard signals of no-interest. Contrast images on estimates of interest were obtained for each subject (1-back vs. 0-back, 2-back vs. 0-back, 3-back vs. 0-back and *n*-back (1-2-3-back) vs. 0-back).

To identify the main effect of WM for both populations, we first conducted a one-sample *t* test on the resulting contrast images obtained for the *n*-back (1 + 2 + 3-back) vs. 0-back comparison (10 images for each group). Using a statistical threshold of $P = 0.001$ uncorrected, we obtained a SPM of the WM network (WMN) involved in every *n*-back tasks. The regions observed were comparable to the regions obtained in other studies using verbal *n*-back tasks (Braver et al., 1997; Pochon et al., 2002). Schematically, the WMN that we found included, bilaterally, both parietal [Brodmann's areas (BAs) 7/39/40] and frontal (BAs 6/8/9/32/44/45/46) regions. Then, using MRIcro software (Version 1.36), we drew a mask using the SPM{T} map obtained from the previous *t* test as the frame of the WMN. The result was a large WMN mask, which included the entire regions of BAs 9 and 46. Analyses concerning the effects of reward outside the WMN and related to other periods of the task (instruction and feedback) will be described elsewhere. Within the mask, we examined the main effect of reward with a one-sample *t* test that included all subjects and that compared all rewarded blocks to all non-rewarded blocks. No region within the WMN mask showed a significant effect related to reward, for either the Reward vs. No-Reward or No-Reward versus Reward contrast. We also tested for a Group × Reward interaction by performing a two-sample *t* test that compared control subjects and depressed patients for the effect of reward within the WMN. No significant difference between groups was observed.

Based on this first observation, we decided to pool together rewarded and non-rewarded blocks for all other subsequent analyses. In the present paper, we report the effects of the *n*-back tasks within the WMN and related to specific contrasts of interest [1-back vs. 0-back, 2-back vs. 0-back, 3-back vs. 0-back and *n*-back (1-2-3-back) vs. 0-back]. The resulting set of images was used for a second level of analysis where subjects were treated as a random variable. This analysis allowed us to explore between-group comparisons (two-samples *t* tests). We focused specifically on the *n*-back (1-2-3-back) vs. 0-back contrast for the comparison between groups. For every *t* tests, activations are reported if they exceeded $P < 0.001$ (uncorrected) on the single voxel level and $P < 0.05$ (corrected) on the cluster level (cluster size cutoff of 10 voxels).

Lastly, signal-to-time curves were extracted for regions that showed a significant difference between groups. Voxels with the highest *T* value in these specific regions were selected as the center of 5-mm radius spherical volumes of interest (VOIs), in which the mean signal-to-time was calculated. Curves were obtained by averaging the data point values of a specific level of complexity within the subject's VOI signal at different time point. A mean curve was therefore obtained for every subject and for each level of complexity. These curves were then averaged across subjects to get a mean group time-course of fMRI signal for each level of complexity. Mean values of each curve were compared between groups using a Student's *t* test (0-back) and a repeated-measures ANOVA (2 × 3) (1-2-3-back).

In a previous investigation by Pochon et al. (2002), results showed that increased cerebral activity in DLPFC was associated with a decreased activity in the MPFC. Therefore, we have also extracted and analyzed the signal-to-time measure in the MPFC. In order to select the VOI in the MPFC, we conducted a one-sample *t* test including all subjects using the 0-back vs. *n*-back contrast. Again, the voxel with the highest *T* value was selected as the center of a 5-mm radius spherical VOI. The statistical analyses were then applied.

Results

Demographic and clinical measures

The two groups did not differ in terms of age ($t = 1.26$, $df = 18$, $P = 0.22$), verbal IQ ($t = 0.65$, $df = 18$, $P = 0.56$), years of education ($t = 0.1$, $df = 18$, $P = 0.92$) and sex ratio ($x^2 = 0.79$, $df = 1$, $P = 0.37$) (Table 1). Clinical data suggest that patients were moderately to severely depressed with a history of recurring depressive unipolar disorder.

n-back performances

Compared to control subjects, depressed patients were not significantly different at the 0-back task for both response accuracy ($t = 0.24$, $df = 18$, $P = 0.81$) and reaction times ($t = -0.66$, $df = 18$,

Table 1
Demographic and clinical characteristics and *n*-back performance of depressed patients and control subjects (given values are means with standard deviations in parentheses)

	Depressed patients (N = 10)	Control subjects (N = 10)
Age (years)	33.8 (8.4)	29.0 (10.1)
Verbal IQ (WAIS-R)	98.7 (5.5)	103.1 (17.1)
Education (years)	14.7 (1.5)	14.6 (2.9)
Sex ratio	7F/3M	5F/5M
Beck scale	17.8 (3.4)	0.0 (0.0)
MADRS total score	26.7 (4.6)	0.0 (0.0)
Tyrer anxiety scale	12.8 (4.4)	0.1 (0.3)
Mean duration of illness (years)	9.7 (7.1)	
Mean duration of index episode (months)	8.6 (10.6)	
Mean number of depressive episodes	2.6 (1.1)	
Mean number of hospitalizations for depression	2.2 (1.6)	
0-Back		
Accuracy (%)	98.9 (2.2)	99.1 (1.9)
Reaction times (ms)	589.0 (131.1)	634 (173.7)
1-Back		
Accuracy (%)	93.6 (5.9)	96.0 (4.0)
Reaction times (ms)	812.2 (199.2)	777.9 (187.9)
2-Back		
Accuracy (%)	78.7 (11.6)	80.9 (9.7)
Reaction times (ms)	1122.9 (229.3)	1065.5 (199.2)
3-Back		
Accuracy (%)	74.6 (7.9)	75.6 (5.4)
Reaction times (ms)	1157.9 (218.9)	1088.1 (149.2)

P = 0.52). Concerning the *n*-back task per se, repeated-measures ANOVAs did not reveal any differences between groups for both response accuracy (main effect of group: F(1,18) = 0.28, P = 0.60) and reaction times (main effect of group: F(1,18) = 0.41, P = 0.53). Thus, depressed patients had a normal behavioral performance. Increasing the complexity prompted a significant decrease in accuracy (main effect of complexity: $F(2,17) = 63.91$, $P < 0.001$) and an increase in the reaction times (main effect of complexity: $F(2,17) = 84.65$, $P < 0.001$). No significant Group × Complexity interaction appeared for either accuracy ($F(2,17) = 0.13$, $P = 0.88$) or reaction times ($F(2,17) = 0.23$, $P = 0.80$) (Behavioral data in Table 1).

fMRI data

n-back task activations

Control subjects. We first examined the brain activation related to the main effect of the *n*-back task by subtracting the activity of the 0-back task from activation for all levels of complexity (*n*-back vs. 0-back comparison). Five parietal and five frontal clusters (698 voxels overall) passed the P threshold and cluster size cutoff. These regions were located bilaterally in the superior parietal lobules (BA 7), right inferior parietal lobule (BAs 39/40), bilateral middle frontal gyri (BAs 9/46), left inferior frontal gyrus (BA 45) and ACC (BA 32) (see Table 2 and Fig. 1). To explore the contribution of each level of complexity, the 1-back, 2-back and 3-back tasks were separately compared to the 0-back task. The 1-back vs. 0-back contrast revealed only one cluster situated in the inferior and middle frontal gyri, which overlap BAs 45 and 46. The 2-back vs. 0-back and 3-back vs. 0-back contrasts showed similar activations, with 10 and 11 clusters respectively that passed the

Table 2
Significant activation within the Working Memory Network for both control subjects and depressed patients during the *n*-back task (1-2-3-back vs. 0-back task contrast)

Brain area	Hemisphere/BA	Stereotaxic coordinates			T score	Cluster level	
		x	y	z		P	k
Control subjects							
Superior parietal lobule	L/7	−33	−45	42	7.13	0.003	51
	L/7	−12	−69	48	6.30	0.001	60
	R/7	15	−60	42	5.88	0.043	21
Inferior parietal lobule	R/40	51	−30	36	13.23	0.000	75
	R/39	42	−63	36	7.64	0.002	54
Anterior cingulate	R/32	9	39	33	8.44	0.029	25
Inferior frontal gyrus	L/45	−45	18	21	10.91	0.000	202
Middle frontal gyrus	L/46	−39	45	6	7.69	0.000	146
	R/46	39	45	9	7.55	0.013	33
	R/9	48	39	24	5.74	0.016	31
Depressed patients							
Superior parietal lobule	R/7	42	−51	48	10.32	0.000	113
Inferior parietal lobule	L/40	−36	−51	36	8.86	0.000	114
Anterior cingulate	L/32	−6	24	39	6.88	0.000	116
Inferior frontal gyrus	L/45	−45	18	27	14.75	0.000	326
	R/44	51	15	24	5.94	0.026	27
Middle frontal gyrus	L/46	−36	48	15	9.77	0.000	166
	R/46	33	6	48	6.72	0.002	56
	R/9	39	45	21	6.40	0.016	31

Activations are reported if they exceeded $P < 0.001$ (uncorrected) on the single voxel level and $P < 0.05$ (corrected) on the cluster level. Stereotaxic coordinates represented the peak height voxel of the cluster; k = number of voxels per cluster.

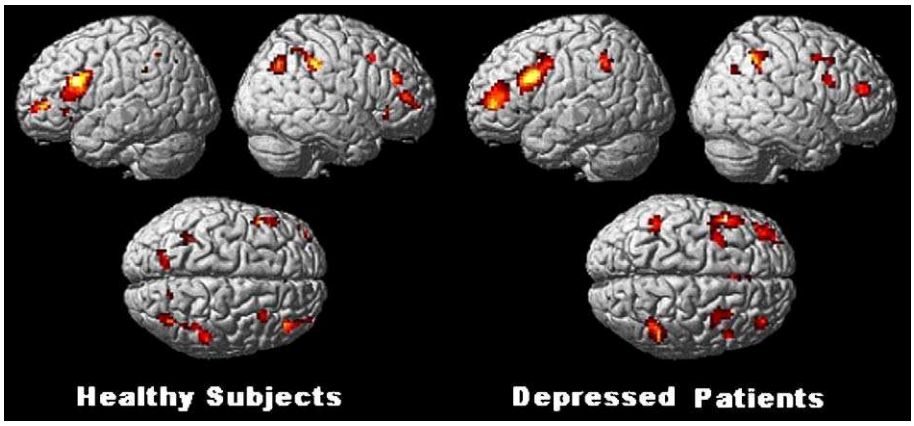

Fig. 1. Brain activations during the *n*-back working memory task (1-2-3-back vs. 0-back) in healthy subjects (left) and depressed patients (right). Statistical parametric maps of brain regions (one-sample *t* test for each group of 10 subjects) showing significant activation at a statistical threshold of $P < 0.001$ (uncorrected) on the single-voxel level and $P < 0.05$ (corrected) on the cluster level. For coordinates related to the peak voxel of each cluster, see Table 2.

P threshold and cluster size cutoff. Regions involved in the 2-back vs. 0-back contrast included bilateral superior and inferior parietal lobules (BAs 7 and 40), left middle frontal gyrus (BA 46), bilateral inferior frontal gyri (BAs 45/44) and right ACC (BA 32). In addition to these regions, the 3-back vs. 0-back contrast also showed right inferior and middle frontal gyri (BAs 9 and 47). The total number of voxels that passed the *P* threshold increased across the levels of complexity (1-back vs. 0-back: $k = 166$; 2-back vs. 0-back: $k = 558$; 3-back vs. 0-back: $k = 929$), which suggests an increased recruitment of the WMN with increasing cognitive demands.

Depressed patients. For the *n*-back vs. 0-back contrast, two parietal and six frontal clusters (949 voxels overall) passed the *P* threshold and cluster size cutoff. Similar to control subjects, significant regions were located in right superior parietal lobule (BA 7), left inferior parietal lobule (BA 40), bilateral middle frontal gyri (BAs 9/46), bilateral inferior frontal gyri (BAs 44/45) and ACC (BA 32) (see Table 2 and Fig. 1). Unlike control subjects, who showed only one significant cluster for the 1-back vs. 0-back contrast, depressed patients analysis yielded five significant clusters. These clusters were situated in the ACC (BA 32), bilateral inferior frontal gyri (BA 45), left middle frontal gyrus (BA 46) and in the superior parietal lobule (BA 7). Two parietal and four frontal clusters were significant for the 2-back vs. 0-back contrast, comprising the inferior parietal lobules bilaterally, left middle frontal gyrus (BAs 6/46), left inferior frontal gyrus (BAs 44/45) and ACC (BA 32). Finally, the 3-back vs. 0-back contrast showed significant activations in eight clusters, including bilateral inferior parietal lobules (BAs 39/40), bilateral inferior frontal gyri (BAs 8/44/45), bilateral middle frontal gyri (BAs 9/46) and ACC (BA 32). Similar to the control subjects, the total number of voxels that passed the *P* threshold increased across levels of complexity (1-back vs. 0-back: $k = 176$; 2-back vs. 0-back: $k = 627$; 3-back vs. 0-back: $k = 1452$).

Between-groups comparisons

To examine whether there were any regions within the WMN that showed group differences, we conducted two-sample *t* tests using the *n*-back vs. 0-back contrast. For control subjects, relative to the depressed patients, no voxels reached statistical significance. When depressed patients were compared to control subjects, three significant frontal clusters were isolated: left inferior frontal gyrus and precentral gyrus (BAs 6/44), left middle frontal gyrus (BA 46) and ACC (BA 32) (Fig. 2).

Hemodynamic responses to complexity

Signal-to-time curves were extracted in regions that showed more activation for depressed patients, compared to control subjects (see Fig. 3). In all three VOIs, the increase in task complexity prompted an increase of the fMRI signal [Complexity Effect: left inferior frontal gyrus (BA 44): $F(2,17) = 23.87$, $P < 0.001$; left middle frontal gyrus (BA 46): $F(2,17) = 4.67$, $P = 0.024$; ACC (BA 32): $F(2,17) = 20.12$, $P < 0.001$]. In the left middle frontal gyrus (BA 46), the increase of the fMRI signal was significantly greater for depressed patients compared to control

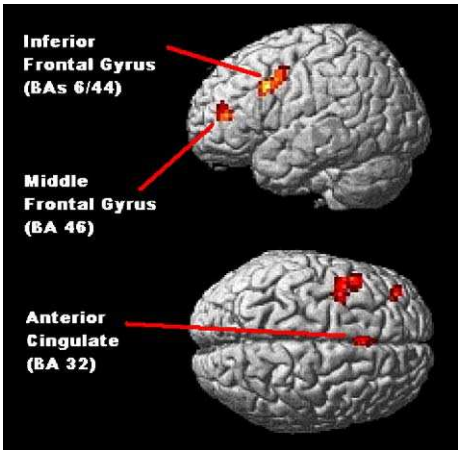

Fig. 2. Statistical parametric maps of brain regions (two-sample *t* test; *n*-back vs. 0-back) showing significantly more activation in depressed patients compared to healthy subjects during the *n*-back task. The coordinates and *t* values for maximal activation in these clusters were $x = -45$, $y = 12$, $z = 33$ ($t = 4.89$) for the left inferior frontal gyrus, $x = -36$, $y = 42$, $z = 12$ ($t = 4.84$) for the left middle frontal gyrus and $x = -3$, $y = 24$, $z = 39$ ($t = 4.12$) for the ACC. Statistical threshold of $P < 0.001$ (uncorrected) on the single-voxel level and $P < 0.05$ (corrected) on the cluster level.

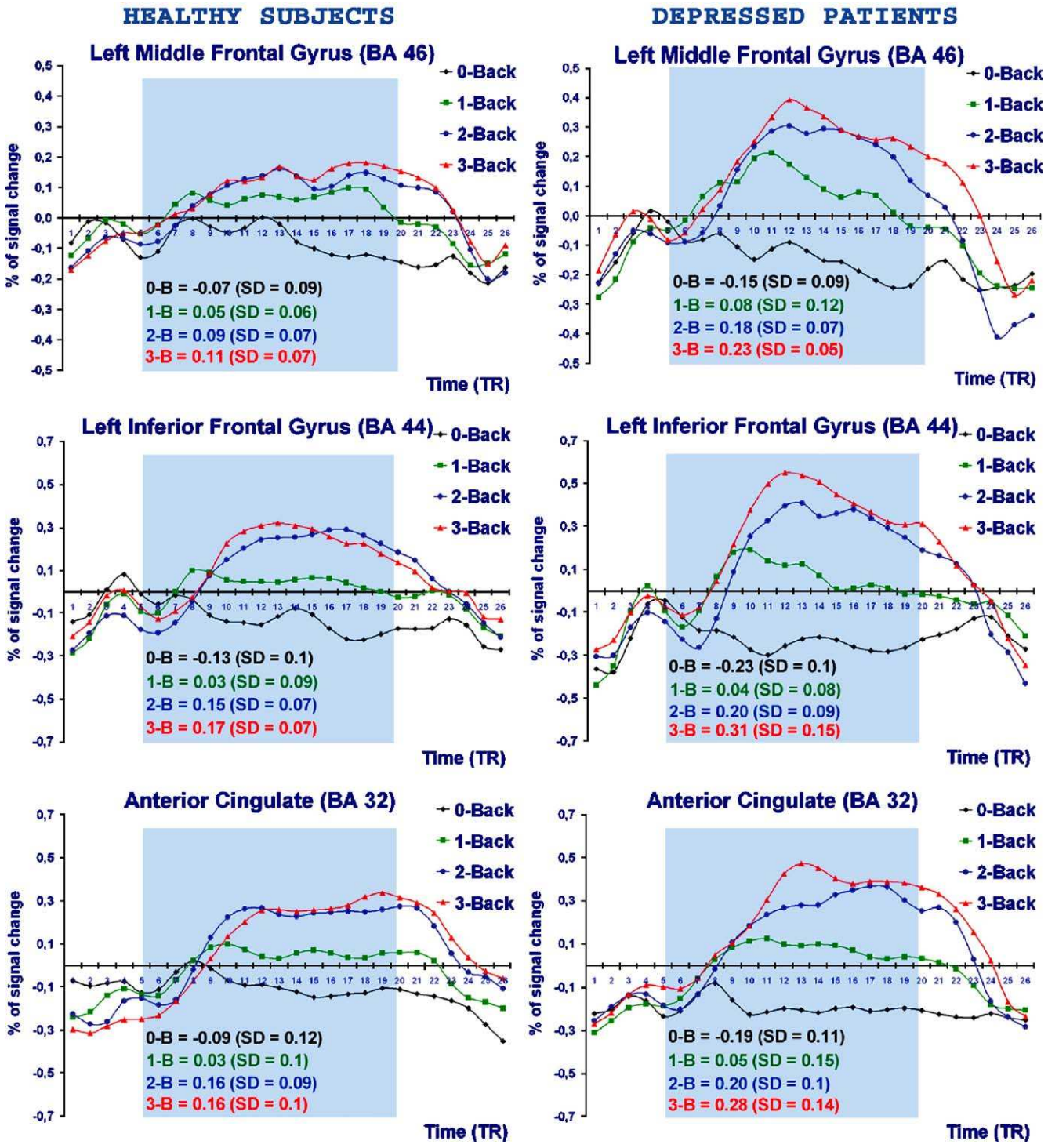

Fig. 3. Averaged fMRI signal time-course curves for regions that showed significantly more activation in depressed patients compared to control subjects. For each region, the peak voxel was selected as the center of 5-mm radius spherical volume of interest (VOI), in which the mean signal-to-time was calculated. Blue area corresponds to the *n*-back period per se. The time-scale unit is expressed as TR (repetition time; 2 s per TR). Black curve = 0-back; green curve = 1-back; blue curve = 2-back; red curve = 3-back. The mean signal values are shown for each condition.

subjects [main effect of group: $F(1,18) = 5.32$, $P = 0.033$], while no significant Group × Complexity interaction was observed [$F(2,17) = 0.79$, $P = 0.47$]. We did not find a significant main effect of group for both left inferior frontal gyrus (BA 44) [$F(1,18) = 3.44$, $P = 0.08$] and ACC (BA 32) [$F(1,18) = 1.1$, $P = 0.31$], however we observed for both VOIs a significant Group × Complexity interaction [LIFG: $F(2,17) = 6.81$, $P = 0.007$; ACC: $F(2,17) = 3.79$, $P = 0.04$]. For these two VOIs, the interaction was explained by a significant difference at the 3-back condition, with depressed patients showing a greater increase of the fMRI signal (*post hoc* t tests: LIFG: $t = 2.64$, $df = 18$, $P = 0.017$; ACC: $t = 2.01$, $df = 18$, $P = 0.037$). Finally, Student t tests did not reveal any

differences between groups concerning fMRI signal changes at the 0-back condition within each VOI (LIFG: $t = -1.87$, $df = 18$, $P = 0.1$; left middle frontal gyrus: $t = -1.42$, $df = 18$, $P = 0.17$; ACC: $t = -1.76$, $df = 18$, $P = 0.11$).

Post hoc analyses in the MPFC revealed a significant effect of complexity [$F(2,17) = 22.59$, $P < 0.001$], with the fMRI signal showing a gradual decrease of activity as the task became more difficult (Fig. 4). The main group effect did not reach significance, although a trend was found for a greater decrease of activity in control subjects [$F(1,18) = 3.60$, $P = 0.07$]. No significant result was found for both Complexity × Group interaction [$F(2,17) = 0.63$, $P = 0.55$] and 0-back condition ($t = -1,48$, $df = 18$, $P = 0.16$).

Discussion

The main goal of this study was to examine the brain activity associated with the normal execution of a WM task in depressed patients and healthy subjects. Consistent with our hypothesis, depressed patients exhibited hyperactivity within the WMN while performing the *n*-back task. To our knowledge, this is the first study that demonstrates hyperactivity in depressed patients who perform an effortful cognitive task at normal levels.

Hyperactivity of the dorsal ACC and the lateral PFC in depression

When compared to control subjects, depressed patients exhibited two hyperactive regions in the lateral PFC: the left inferior frontal gyrus (BA 44/6) and the left middle frontal gyrus (BA 46). Hyperactivity of the dorsal ACC (BA 32) was also observed in depressed patients. Within the well-defined neural architecture of the WMN, these three regions have been linked to complementary cognitive functions, such as a subvocal rehearsal system mediated by the left inferior PFC (BA 44/45), an executive component mediated by the DLPFC (BA 9/46) and an error monitoring and/or attentional processing system supported by the ACC (BA 24/32) (Braver et al., 1997; Carter et al., 1998; Postle et al., 1999; Smith and Jonides, 1999). At odds with our results, some neuroimaging studies involving a cognitive challenge did not find any differences between depressed patients and healthy subjects in the PFC (Barch et al., 2003; Berman et al., 1993). Barch et al. (2003) used a version of the *n*-back task, which included both verbal and spatial conditions. Their depressed patients did not show any cerebral abnormalities within the PFC, although they performed as well as control subjects. With respect to our study, this discrepancy might be explained by two main differences in task complexity: the use of letters instead of words as stimuli and the inclusion of a 3-back condition. Firstly, the words used by Barch et al. (2003) appear to be easier to remember than letters. This can be observed by comparing the mean accuracy obtained by their depressed patients in the 2-back task (96%) with our patients' accuracy at the same condition (78.7%). Secondly, their *n*-back version involved only one level of complexity (2-back) whereas ours included three levels, the last being a difficult 3-back condition. The inclusion of this last condition is relevant since hemodynamic curves analyses conducted within dorsolateral and inferior PFC and ACC show a progressive increase in the cerebral activity following the parametric increase in load and manipulation of information. The modulating effect of task difficulty on the cerebral activity of prefrontal cognitive regions has been shown in other studies (Braver et al., 1997; Gould et al., 2003; Pochon et al., 2002). In our study, statistical significance was specific to the 3-back condition in both the left inferior frontal gyrus (BA 44) and the ACC (BA 32). Taking these differences into account, it is possible that Barch et al.'s task was not effortful enough to prompt hyperfrontality in their patients.

Hyperfrontality in schizophrenia and depression

Hyperfrontality has also been demonstrated in schizophrenic patients performing a cognitive challenge (Callicott et al., 2003; Manoach et al., 2000). Callicott et al. (2003), using a theoretical model of the fMRI response to WM load, suggested that schizophrenic patients are hyperfrontal at relatively normal performance (smaller WM load) and hypofrontal when performance is impaired (higher WM load). Specifically, their model describes an inverted U-shaped load-response curve that is shifted

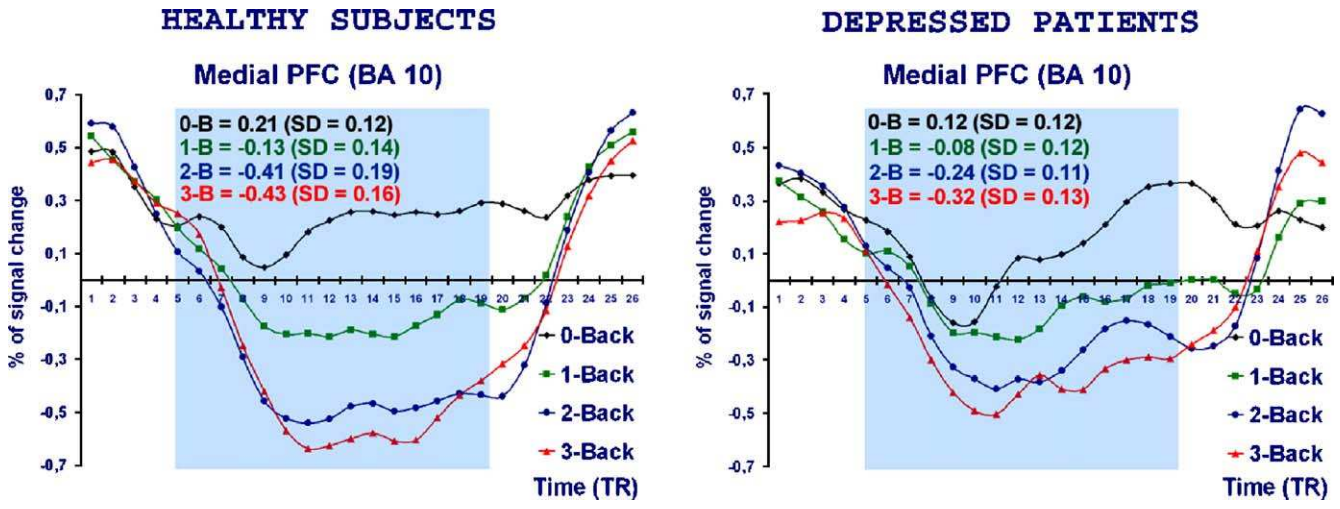

Fig. 4. Averaged fMRI signal time-course curves for the medial PFC. The peak voxel (x = 0, y = 54, z = 3) was selected as the center of a 5 mm-radius spherical volume of interest (VOI), in which the mean signal-to-time was calculated. Blue area corresponds to the *n*-back period per se. The time-scale unit is expressed as TR (repetition time; 2 s per TR). Black curve = 0-back; green curve = 1-back; blue curve = 2-back; red curve = 3-back. The mean signal values are shown for each condition.

to the left in schizophrenia, which suggests an early recruitment of the PFC. Although our results do not clearly demonstrate an early recruitment of the PFC in our depressed patients compared to controls, they fit the Callicott's model since they show a general hyperfrontality in depressed patients performing an effortful task at normal levels. A recent study found hyperactivity in PFC in depressed patients performing an arithmetic task (Hugdahl et al., 2004). Like our *n*-back task, their arithmetic task involved an online monitoring of continuously presented stimulus materials. In contrast to our results, this hyperactivity was associated with an impaired behavioral performance rather than normal performance. Despite the absence of a clear explanation for this hyperfrontality, these authors pointed toward dissociation between behavioral performance and activated brain areas. Indeed, we cannot rule out the possibility that the hyperfrontality and aberrant activation in depression is more influenced by the amount of effort invested in a task than by the patients' behavioral performance per se. Increased amount of effort, which includes cognitive control and attentional processes, could be the cause of hyperfrontality. Hugdahl et al.'s results are not incompatible with ours since they probably refer to the same brain adaptations to difficulty.

Unlike Callicott et al.'s findings in schizophrenia, the aberrant activity of the DLPFC (BA 46) in depressed patients was associated with hyperactivity of the dorsal ACC (BA 32). Many researchers have identified the ACC as an important component of attentional networks and several studies suggest that both dorsal ACC and lateral PFC operate together during tasks that involve high levels of mental effort and control (Bush et al., 2000). Taken together, fMRI findings in schizophrenia and depression suggest that neither hypofrontality nor hyperfrontality per se is a sufficient explanation for cognitive impairments. Both are complementary and refer to different ways of adaptation to cognitive challenge.

Depression, cognitive control and brain resources

The aberrant activation of the DLPFC and the ACC associated with normal performance in depressed subjects may reflect several interrelated problems: (1) an inefficiency of a task-related neural network reflecting a difficulty in organizing neural activity; (2) an excess of cognitive control or subject's task engagement.

(1) Depression is likely the result of maladaptive functional interactions among a network of limbic–cortical regions (Mayberg, 1997). The limbic–cortical model is related to emotion regulation, in which cortical deactivations play a critical role. Some cortical regions involved in specific cognitive functions such as DLPFC (BA 9/46) and dorsal ACC (BA 32) would inhibit emotional responses through efferent connections to limbic–paralimbic targets, such as MPFC, insula and OPFC (Liotti and Mayberg, 2001). Therefore, a plausible explanation for the hyperfrontality observed in depression could be related to a lack of deactivation in limbic structures. Past neuroimaging studies involving a cognitive challenge have shown that besides the increased activity in cognitive regions, some other regions (i.e., MPFC) show simultaneous decreases in activity in healthy subjects (Pochon et al., 2002). These authors propose that a dynamic interplay is created between activated lateral and dorsal areas necessary to maintain a high level of performance and deactivated ventral and medial areas. This capacity to deactivate limbic regions and maximize the activity in the processing regions would create an activity gap between cortical and limbic regions that would likely increase as the task increases in difficulty (Fig. 5—left upper and lower graphics). In depression, the fact that some patients with an impaired performance exhibit hypoactivity in task-related areas could be partly linked to an inability to properly deactivate limbic areas (MPFC), taking into account that these regions usually show abnormal activation in depression (Mayberg, 1997). The activity gap between dorsal cortical and limbic regions would be notably decreased compared to control subjects and this in turn could affect the processing efficiency (Fig. 5—right upper graphic). According to this theoretical model, hyperfrontality would occur to counter the lack of deactivation in limbic regions, in order to keep an effective activity gap and thus a normal behavioral performance (Fig. 5—right lower graphic). To test this hypothesis, we examined in a post hoc analysis the hemodynamic response to complexity in the MPFC (Fig. 4). Although we did not find significant results, a trend is suggestive of a dysfunction of the cortico-limbic network in depression. Further studies will clarify these cortico-limbic relationships and their specific association with hyperfrontality in depression.

(2) The dorsal ACC activation may reflect the cognitive control and the intentional amount of effort that a subject uses in a task. It has been proposed that goal-directed behaviors involve an adaptive cognitive control system for selecting contextually relevant information (Ridderinkhof et al., 2004 for a review). Carter et al. (1998) suggested that the contribution of the dorsal ACC to executive processes is the on-line detection of processing conflicts that may be associated with deteriorating performance. Moreover, the involvement of the dorsal ACC in performance monitoring is enhanced in tasks using monetary reward and performance feedback (O'Doherty et al., 2001; Ullsperger and von Cramon, 2003), two factors that were present in our protocol. Two general roles have been associated with the dorsal ACC: (1) the monitoring of errors and conflicts and (2) the performance adjustments in association with the lateral PFC. As we controlled for the behavioral performance of our subjects, the hyperactivity of the dorsal ACC observed in depressed patients cannot be explained by an increased number of errors or negative feedbacks for the patients. However, even with a comparable number of errors in both groups, it is possible that our *n*-back task elicits different types of performance adjustments in depressed patients compared to healthy subjects. Ridderinkhof et al. (2004) proposed two different types of trial-to-trial performance adjustments that could be supported by the dorsal ACC: (1) shifts in the trade-off between the speed and accuracy of responding that place the cognitive system in a more cautious mode and (2) increases in control that improve the efficiency of information processing. Changes in the speed/accuracy ratio would not likely explain by itself the dorsal ACC hyperactivity in our depressed patients since the reaction times measured in both groups were statistically comparable. Alternatively, depressed patients might need greater cognitive control in order to process information as efficiently as nondepressed subjects. Ridderinkhof et al. (2004) suggested that changes in control and efficiency of information processing, induced by effortful trials (3-back task for instance), could be associated with the capacity to reduce interference from distracting information. This is entirely consistent with the theoretical model of dorsal cortical and limbic interactions, in which hyperfrontality in depression could represent changes in cognitive control in response to greater interference. Consistent with the strong connections between ACC and DLPFC, the dorsal ACC activation might signal the need for controlled processing, which the DLPFC would be critical in initiating (Davidson et al., 2002).

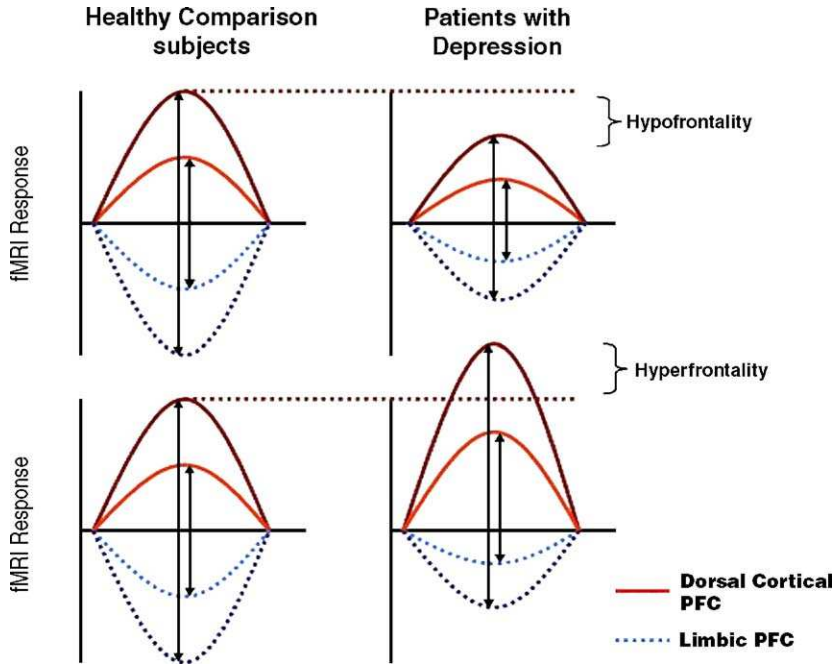

Fig. 5. Theoretical model of hemodynamic responses to increasing difficulty in dorsal cortical (DLPFC) and limbic (MPFC) PFC, in healthy comparison subjects and in patients with depression. Time course is represented on the *x* axis with the theoretical fMRI response on the *y* axis. Continuous curves (above *x* axis) illustrate the gradual augmentation of the activity within dorsal cortical PFC with increasing difficulty. Dotted curves (below *x* axis) illustrate the gradual deactivation within limbic PFC with increasing difficulty. Vertical arrows illustrate the activity gap between dorsal cortical and limbic PFC, that is, the capacity to deactivate counterproductive regions and maximize the activity in the processing regions. It is supposed that a large gap favors the processing efficiency. Upper right graphic illustrates a hypofrontality context, in which depressed patients are not able to counter the lack of deactivation in limbic PFC. The result is hypofrontality in dorsal cortical PFC and likely an impaired performance at the hypothetical task. Lower right graphic illustrates a hyperfrontality context, in which depressed patients counter the lack of deactivation in limbic PFC by enhancing the activity of the dorsal cortical PFC, in order to maintain the same "activity gap" compared to the healthy comparison subjects. The result is hyperfrontality in dorsal cortical PFC and a normal behavioral performance at the hypothetical task.

Taken together, these explanations could suggest that more brain activation is needed in the processing regions in depression to get "normal" functioning during effortful tasks. Repeating such cognitive efforts may place heavy demands on the brain resources of depressed patients and the progressive exhaustion of cognitive resources would precede the deficits. At a clinical level, this is consistent with depressed patients subjectively reporting problems with activities that demand a continuous effort such as organizing and planning serial activities and remembering information.

Caveats and limitations

This study has limitations that should be considered. Our findings are limited by the small group size and medication effects. Further studies should test a larger group of unmedicated depressed patients to confirm our results. However, although it has been shown that medication contributes to metabolic increases in dorsal cortical regions while recovering from depression (Mayberg et al., 2000), it is unlikely that medication alone would generate hyperfrontality compared to healthy subjects, considering that our patients were in an acute episode of depression, instead of being in a period of recovery. Three patients were also taking benzodiazepines. Thus, some side-effects including drowsiness cannot be excluded for these patients, although they did not receive benzodiazepine on the experiment day. Secondly, our inclusion process allowed us to recruit patients that were able to allocate enough efforts to achieve a normal cognitive performance. Our 10 selected patients could likely represent a sub-group of depressed patients with no apparent cognitive dysfunction. Thus, we cannot generalize our results to the whole depressive population. However, we believe that one of the important and innovative aspects of this article is to demonstrate that these depressed patients are not as cognitively intact as their behavioral results suggest. This way, our study contributes to a better understanding of the depressive illness by observing a cognitive abnormality from another perspective.

Acknowledgments

This study was supported by NARSAD and by scholarships to POH from Fondation pour la Recherche Médicale. Thanks to Matthew Menear and Hazel M. Sutton for useful comments.

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