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ORIGINAL ARTICLE

Prefrontal hyperactivation during working memory task in untreated individuals with major depressive disorder

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The prefrontal cortex, a part of the limbic-thalamic-cortical network, participates in regulation of mood, cognition and behavior and has been implicated in the pathophysiology of major depressive disorder (MDD). Many neuropsychological studies demonstrate impairment of working memory in patients with MDD. However, there are few functional neuroimaging studies of MDD patients during working memory processing, and most of the available ones included medicated patients or patients with both MDD and bipolar disorder. We used functional magnetic resonance imaging (fMRI) to measure prefrontal cortex function during working memory processing in untreated depressed patients with MDD. Fifteen untreated individuals with Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition recurrent MDD (mean age $\pm$ s.d. = 34.3 $\pm$ 11.5 years) and 15 healthy comparison subjects (37.7 $\pm$ 12.1 years) matched for age, sex and race were studied using a GE/Elscint 2T MR system. An echo-planar MRI sequence was used to acquire 24 axial slices. The *n*-back task (0-back, 1-back and 2-back) was used to elicit frontal cortex activation. Data were analyzed with a multiple regression analysis using the FSL-FEAT software. MDD patients showed significantly greater left dorsolateral cortex activation during the *n*-back task compared to the healthy controls ($P < 0.01$), although task performance was similar in the two groups. Furthermore, the patients showed significant anterior cingulate cortex activation during the task, but the comparison subjects did not ($P < 0.01$). This study provides *in vivo* imaging evidence of abnormal frontolimbic circuit function during working memory processing in individuals with MDD.
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Introduction

Major depressive disorder (MDD) is a major psychiatric illness with a lifetime prevalence of about 10–20% for women and 5–12% for men in community samples (Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV)-TR). MDD is associated with significant morbidity and economic cost to society, but its pathophysiology is not yet understood. The affected brain regions lie within the limbic-thalamic-cortical network. This network participates in the regulation of mood, cognition and behavior, and has been implicated in the pathophysiology of MDD.[1] Neuroimaging and neurocognitive studies[1,2] conducted over the past decade show that patients with MDD have cognitive disturbances and structural and functional abnormalities of some regions in this network. Abnormalities of prefrontal cortex in MDD patients have been demonstrated in functional, diffusion tensor, structural imaging and histopathological studies.[3–7] Subjects with MDD exhibit small gray matter volume in the lateral orbitofrontal cortex,[5] smaller neuronal size and lower neuronal and glial densities of the prefrontal cortex,[6] and microstructual abnormalities of the prefrontal cortex white matter compared to healthy comparison subjects.[7] Further, abnormalities of prefrontal cortex blood flow and metabolism are reported in subjects with MDD.[8–12]

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Recent evidence demonstrates frontal and limbic dysfunction in MDD patients during working memory processing. Many neuropsychological studies document working memory deficits in individuals with MDD.[13–18] MDD patients perform poorly on the *n*-back task, a working memory task, compared to healthy controls, and their performance on the *n*-back task is inversely correlated with the severity of their depression.[19] The *n*-back task performance of both depressed and remitted elderly MDD patients is significantly inferior to that of control subjects, suggesting that the impairment of working memory is a trait marker of geriatric depression.[17,20]

Available functional neuroimaging studies of working memory provide further evidence of frontal cortex involvement. Healthy individuals show bilateral activation of the dorsolateral prefrontal cortex (DLPFC), left inferior frontal gyrus[21,22] and anterior cingulate (ACC)[21] during *n*-back task performance. Furthermore, the DLPFC and left inferior prefrontal cortex activation to this task is positively correlated with working memory load in healthy individuals,[21] suggesting that the cortico-limbic network may regulate working memory.[23,24] In contrast, MDD patients show abnormal activation patterns marked by more pronounced activation on the left prefrontal cortex and the cingulate cortex during working memory tasks.[25–31]

However, all results are not consistent. Some studies suggest that patients with mood disorders show greater activation,[25,31] less activation[26–28] or no difference in activation within the regions of interest compared to healthy controls.[29,30] A functional magnetic resonance imaging (fMRI) study of MDD patients during an *n*-back task showed significantly lower activation in bilateral thalamus, right precentral gyrus and right parietal cortex compared to healthy controls.[27] Another study showed greater activation in the left inferior frontal gyrus, precentral gyrus, left middle frontal gyrus and ACC compared to healthy controls, and depressed patients also showed greater activity of the left middle frontal gyrus and ACC than healthy controls.[25] A problem with some available studies that may explain such discrepancies is that they included patients with both MDD and bipolar disorders,[26,29] and some included medicated patients.[25,27–31]

In this report, we describe the results of an fMRI study designed to compare the brain activity patterns elicited by a working memory task in a sample of unmedicated recurrent patients with MDD and a well-matched sample of healthy comparison subjects. The results support our hypothesis that MDD patients show hyperactivation of the prefrontal cortex and ACC during working memory load compared to healthy individuals.

Materials and methods

Subjects

Participants included 15 individuals with recurrent MDD and 15 healthy control subjects. There was no significant difference between MDD patients and the controls in age (mean $\pm$ s.d.; 34.3 ± 11.5 years, 37.7 ± 12.1 years, respectively), gender (male/female; 5/10, 6/9), education level or race. The MDD patients and healthy controls were recruited at hospitals and clinics and through advertisements broadcast in the community. This study was approved by the Institutional Review Board of The University of Texas Health Science Center at San Antonio, and written informed consent was obtained from all the participants after a complete description of the study was provided. All of the patients met DSM-IV criteria for recurrent MDD by the Structured Clinical Interview (SCID) for DSM-IV,[32] and healthy control subjects were screened for DSM-IV axis I disorders by the SCID nonpatient version.[33] The patients had a history of recurrent depressive episodes. The mean age of onset was 18.0 ± 10.4 (mean $\pm$ s.d.) years, and the mean length of illness was 15.3 ± 9.7 years. The mean number of depressive episodes in 12 of the 15 patients was 11.0 ± 9.6; the number of episodes was too numerous to count in the remaining two patients. All MDD subjects were in a depressed mood state, and had a score of 18 or more on the 21-item Hamilton Rating Scale for Depression[34] (mean $\pm$ s.d. $= 20.3 \pm 5.3$; range, 15–38). All of them were unmedicated (eight were drug-naive, seven were drug-free for mean $\pm$ s.d. $= 37.0 \pm 28.0$ months; 16–82 months). Seven patients had a history of psychiatric medication use. Four patients had taken only selective serotonin reuptake inhibitors (SSRIs; fluoxetine or sertraline), one had taken imipramine and nortriptyline or SSRIs, one had taken fluoxetine and bupropion and one had taken SSRIs and trazodone. The distribution of left and right handedness[35] was not significantly different between the MDD patients (right, 14; left, 1) and healthy controls (right, 12; left, 2; ambidextrous, 1). None of the MDD subjects had a history of psychosis, bipolar disorder, electroconvulsive therapy or a substance-dependence disorder within 6 months preceding the study. One patient had comorbid dysthymia and some had comorbid anxiety disorders; three had post-traumatic stress disorder, three had generalized anxiety disorder, two had specific phobia, one had obsessive compulsive disorder and one had agoraphobia without panic disorder. None of the healthy control subjects had current or past major mental disorders including psychotic disorders or mood disorders. No first-degree relatives of healthy control subjects had any Axis I psychiatric disorder. All participants received a clinical interview, laboratory tests and physical exam to rule out physical illnesses. Any participant with current endocrinological disease, history of head trauma with loss of consciousness, current or previous neurological disease, family history of hereditary neurological disorder or a current medical condition such as hypertension, diabetes, active liver disease, kidney problems or respiratory problems was excluded.

n-*Back task procedure*

We used the 0-, 1- and 2-back versions of the *n*-back task to impose a working memory load based on

Callicott *et al*.[24,36] The *n*-back task is often used as a working memory task[17,20] and is thought to evoke a number of working memory processes, including maintenance, monitoring, updating and manipulation of remembered information.[37] It requires the monitoring of a continuous sequence of numerical stimuli. For $n=0$, the task requires only a simple button press response to the stimulus displayed. For $n>0$, the task requires both the maintenance of the last *n* stimuli in memory and the updating of these remembered stimuli as each new stimulus is presented.[38] The target numerals 1–4 were randomly displayed at the corners of a square for a total duration of 30 s. Each numeral maintained a fixed position. Participants held a box with four arrow keys arrayed in the same configuration as the numerals on the screen, and they responded by pressing one of the four keys to match the target numeral. For example, in the 1-back task, participants were asked to press the key corresponding to the numeral that was displayed one trial before the current one. For the 2-back task, they were to press the key corresponding to the numeral presented two trials before the current one, and so on. Target numerals were presented every 12 s. Each task condition (0-back, 1-back and 2-back) was performed five times in psudo-random order for a total task duration of 645 s. All the participants received instruction from an experimenter (MP or PN) immediately before fMRI acquisition. The task was administered using E-prime script (http://step.psy.cmu.edu/scripts/) run on a Compaq Presario computer. Performance was recorded as percentage of correct responses and reaction time.

Image acquisition

Scanning was carried out on a 2T Prestige whole-body MRI scanner (General Electric Medical System/Elscint, Milwaukee, WI, USA). The subject's head was immobilized using a thermal plastic facial mask attached to a custom-designed head holder. All images were assessed for subject movement, and head movement was corrected using FSL-FEAT.[41] Functional imaging utilized a gradient echo-planar MR imaging sequence with sensitivity of the BOLD effect and was acquired as 24 axial slices (TR = 2000 ms, TE = 45 ms, flip-angle = 90°, voxel = 3.33 × 3.33 × 4.00 mm). To localize anatomical structures, 3D T1-weighted images were initially examined (TR = 25 ms, TE = 5 ms, flip-angle = 25°, voxel = 1 × 1 × 1 mm).

Image data analysis

After motion correction and smoothing, the data analyses were performed using FEAT (FMRI Expert Analysis Tool) Version 5.1, part of FSL[39] (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) and supplemented with utilities developed in house. Motion correction of each image was performed using spatial registration to the middle data point in the time series,[40] and smoothing was done by a nonlinear algorithm with 5 mm kernel. The data set was analyzed by a multiple regression model using a prewhitening technique accounting for the intrinsic temporal autocorrelation of BOLD imaging. Higher-level analysis was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects). The threshold of a *Z* (Gaussianised T/F) statistic image was estimated by clusters determined by $Z>2.3$ and a corrected cluster significance threshold of $P=0.01$.[41–43] *Z*-statistic images were created for each working memory condition (0-back, 1-back and 2-back), and three contrasts between 0-back, 1-back and 2-back conditions (1-back > 0-back, 2-back > 0-back and 2-back > 1-back) were performed. Multi-subject analysis utilized a mixed effects model and provided *Z*-images for each contrast reflecting activation patterns within each group and between groups. The threshold of these group maps was determined based on the magnitude ($Z=2.3$) and extent (cluster significance $P<0.01$) of activation. After limiting activation to brain regions nominated from the entire sample, we reduced the stringency of our thresholding to $Z=2.0$ and $P<0.05$.

Behavioral data analysis

The subject performance data were analyzed using nonparametric methods based on ranks with algorithms to calculate exact *P*-values because its distribution showed marked departure from normality. Between group differences on *n*-back task accuracy and reaction time for correct responses were assessed using the Mann–Whitney *U*-test. Comparisons among the 0-back, 1-back and 2-back tasks were performed using Friedman's test, and following a significant omnibus test, pairwise comparisons were examined using the Wilcoxon signed ranks test with Bonferroni adjustment for multiple comparisons.

Approximate activated regions were displayed using Talairach Daemon (http://ric.uthscsa.edu/td_applet/). The statistical analysis was done with the SPSS statistical software, version 12.0 for windows (SPSS Inc., Chicago, IL, USA). A *P*-value <0.05 was considered statistically significant.

Results

Behavioral performance

Valid performance data were available for only 10 healthy subjects and nine MDD patients owing to technical difficulties. There was no significant difference in either accuracy or reaction time between the MDD patient and the healthy subject groups (for reaction time $Z=0.08$, $P=0.97$ for 0-back; $Z=0.90$, $P=0.40$ for 1-back; $Z=1.7$, $P=0.10$ for 2-back, and for accuracy $Z=0.46$, $P=0.67$ for 0-back; $Z=1.24$, $P=0.23$ for 1-back; $Z=0.61$, $P=0.56$ for 2-back). A *post hoc* power analysis was performed to estimate the potential impact of the lost data on the conclusions. Assuming the effect sizes obtained from the available subjects, it is highly unlikely that any of the comparisons between the MDD patients and the healthy subjects would have been statistically significant with a sample size of 15 per group (power between 0 and

47% for all comparisons). As expected, *n*-back task accuracy declined as the delay interval increased (Friedman $\chi^2(2) = 9.5$, $P = 0.007$, Table 1). Response accuracy on the 2-back task was significantly inferior to that on the 0-back task ($Z = 3.29$, $P < 0.001$) and that on the 1-back task ($Z = 2.57$, $P = 0.01$), but the difference between the 0-back and 1-back was not statistically significant ($Z = 1.74$, $P = 0.13$ Bonferroni). Reaction time also varied as a function of task difficulty in the expected direction (Friedman $\chi^2(2) = 23.1$, $P < 0.001$, Table 1). Reaction time on the 2-back task was significantly longer than that on both the 0-back ($Z = 3.7$, $P < 0.001$) and the 1-back tasks ($Z = 3.8$, $P < 0.001$), but reaction time on the 1-back task was not significantly longer than that on the 0-back task ($Z = 1.4$, $P = 0.027$ Bonferroni).

Imaging data

Between groups comparison. The left middle frontal gyrus ($Z = 4.08$; $x = -34$, $y = 32$, $z = 28$; Brodmann Area (BA) 9) and left superior frontal gyrus ($Z = 4.55$; $x = -30$, $y = 52$, $z = 16$; BA10), parts of the DLPFC, showed significantly greater activation in the MDD patients than in the controls in the 2-back > 1-back contrast (Figure 1). The difference in activation between the two groups was not statistically significant for any other brain region or contrast.

Activation patterns within each group. In the MDD patients, the left and right frontal gyrus and the left cingulate gyrus were significantly activated in the 2-back > 1-back contrast (Figure 2). Table 2 showed significant activation in frontal region in each group. Similar results were obtained in the 2-back > 0-back and the 1-back > 0-back contrasts. In the healthy subjects, the left and right frontal gyri showed significant activation in the 2-back > 0-back and the 1-back > 0-back contrasts. In contrast to the patient group, the cingulate gyrus was not significantly activated in any contrast and no frontal or cingulate region was significantly activated in the 2-back > 1-back contrast. Parietal, temporal and occipital regions were significantly activated in both groups in the three contrasts.

Table 1 *n*-back task results

	Healthy subjects (n = *10*)		*MDD Patients* (n = *9*)	
	Mean	*s.d.*	*Mean*	*s.d.*
Reaction time (msec)				
0-back	810.3	49.2	807.3	75.0
1-back	842.7	62.7	811.3	75.3
2-back	910.6	34.2	894.0	17.6
Accuracy (%)				
0-back	92.5	16.5	96.4	4.7
1-back	89.4	19.5	82.7	26.0
2-back	71.5	24.0	75.0	27.7

Abbreviation: MDD, major depressive disorder.
There was no significant difference between MDD and control subjects on reaction time or accuracy.

Discussion

Untreated depressed individuals with recurrent MDD showed abnormally high activation of the left DLPFC (BA9/10) during a working memory task compared to the healthy control subjects, even though task performance was not significantly different for the two groups. It is noteworthy that the MDD subjects also showed significant activation of the ACC (BA24/32), whereas the control subjects did not show significant ACC activation. However, the mean group difference in ACC activation did not reach statistical significance. These results suggest that MDD patients show abnormal frontolimbic network hyperactivation involving the DLPFC and ACC during working memory.

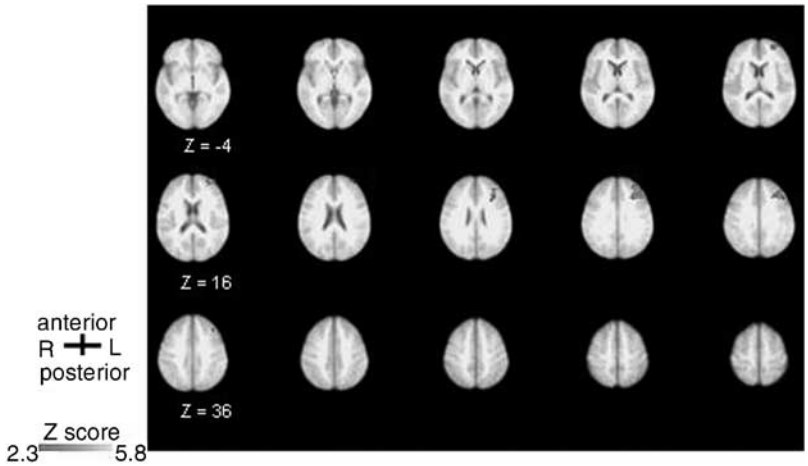

Figure 1 The difference in brain activation of the patients with MDD and the control subjects during the *n*-back working memory task (the 2-back > the 1-back). The MDD patients showed significantly greater activation of left DLPFC than the controls in this contrast.

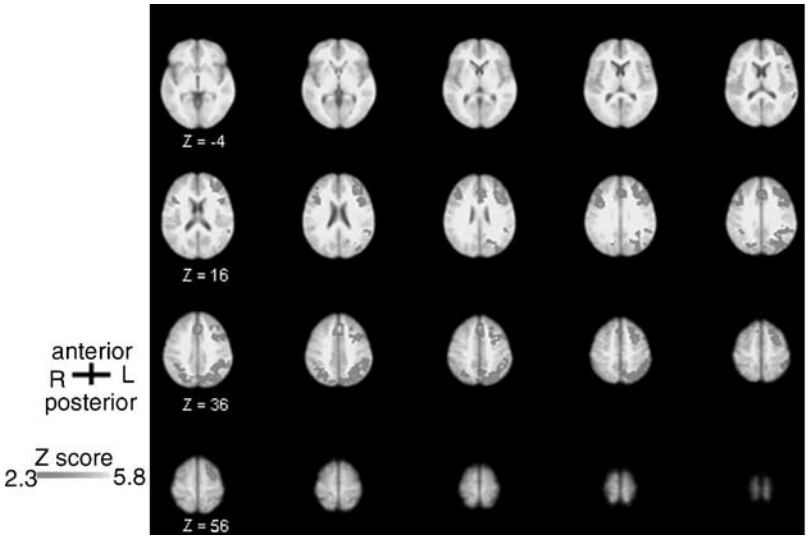

Figure 2 The MDD patients showed greater activation of the left and right DLPFC and ACC during the 2-back compared to the 1-back task.

Table 2 fMRI results

Anatomy (Brodmann area)	*Z[a] score*	*Talairach–Tournoux coordinates (mm)*		
		x	*y*	*z*
1-back > 0-back				
HC				
Lt. middle frontal gyrus[6]	6.23	−30	0	46
Lt. middle frontal gyrus[46]	5.59	−44	18	20
Lt. superior frontal gyrus[8]	5.63	−24	10	44
Rt. Middle frontal gyrus[46]	5.56	44	54	6
MDD				
Lt. middle frontal gyrus[6]	5.75	−30	0	48
Rt. precentral gyrus[6]	4.57	40	0	42
Lt. cingulate gyrus[24]	4.79	−16	0	42
2-back > 0-back				
HC				
Rt. Middle frontal gyrus[46]	6.51	44	34	20
Lt. middle frontal gyrus[6]	5.47	−26	0	44
MDD				
Rt. precentral gyrus[9]	5.63	42	4	30
Lt. middle frontal gyrus[6]	5.51	−26	0	48
Lt. cingulate gyrus[32]	6.95	−6	12	42
2-back > 1-back				
HC	—	—	—	—
MDD				
Lt. middle frontal gyrus[9]	5.83	−32	34	26
Lt. superior frontal gyrus[10]	5.19	−30	52	16
Rt. inferior frontal gyrus[9]	4.18	38	4	28
Rt. Middle frontal gyrus[9]	4.02	42	26	28
Rt. superior frontal gyrus[6]	3.56	2	14	48
Lt. cingulate gyrus[32]	5.6	0	20	40
Rt. cingulate gyrus[32]	3.95	6	22	34

[a]Determined from the voxel showing the local maxima.
HC, healthy control subjects; Lt., left; MDD, patients with major depressive disorder; Rt., right.

The DLPFC-striatum-thalamus circuit is thought to control cognitive and executive function, and the DLPFC is a primary center of this circuit.[44] The frontolimbic-subcortical circuit, including DLPFC, also is involved in the pathophysiology of MDD. Abnormal DLPFC function in MDD patients during working memory has been reported.[25,28] Neurochemical[45,46] and neuropathological[6] abnormalities of the DLPFC have also been noted. The theory of prefrontal cortex hypoactivation, that is, 'hypofrontality', in patients with mood disorders has been supported by various studies.[3] However, some recent investigations and the present results provide evidence of hyperactivation of prefrontal cortex or 'hyperfrontality' during working memory tasks in patients with mood disorder.[25,47] The association between task performance and frontal activation is not consistent. In some studies showing hypofrontality, the patients' cognitive or working memory performance was much poorer than that of the controls[28,30,48] and in the other studies the patients' performance was not significantly different from that of the controls.[26,49] One study demonstrating hyperfrontality showed poor performance in the patients on the *n*-back task ($n>0$) compared to controls,[47] and the other showed no difference in cognitive task performance between the patients and the healthy controls.[25] The MDD patients in our study showed this pattern of hyperfrontality without impaired cognitive task performance. It also is noteworthy that we found this abnormality in the left hemisphere. It is the left prefrontal cortex that is involved in cognitive and executive control rather than the right side. MDD patients show greater abnormalities of the left hemisphere than the right,[3] and transcranial magnetic stimulation applied to the left DLPFC has therapeutic effects on depressive symptoms.[50,51] In this context, our result supports the hypothesis that a DLPFC abnormality, which may be involved in the pathophysiology of MDD, is localized within the left hemisphere.

The ACC contributes to executive functions including attention, inhibition and resolution of cognitive conflict in executive processes.[38,52,53] It also plays a key role in emotional expression, affect regulation and cognitive processing, and it is an important region in the limbic-thalamic-cortical network that is involved in the pathophysiology of MDD.[54,55] ACC is activated in healthy individuals during working memory.[23,36] In the present study, MDD patients showed significant activation of the ACC during the *n*-back task, whereas healthy controls did not. Prior studies of patients with MDD demonstrated abnormal activation of the ACC during emotional stimuli[56,57] and during an *n*-back task.[25,27] Although ACC activation was not significantly different between MDD patients and controls in our study, the pattern of results is in line with other studies, which suggest excessive attention and executive control in MDD patients during working memory.

The 2-back > 1-back contrast showed that the cognitive task elicited greater DLPFC activation in MDD subjects compared to healthy controls, and that only the MDD patients showed significant ACC activation during task performance. However, behavioral performance measured by error rate and reaction time was similar for the two groups. In other words, the healthy subjects performed the 1-back and 2-back tasks with similar levels of frontal cortex activation, whereas the MDD patients needed greater DLPFC activation, and they also needed ACC activation, to maintain similar levels of performances on the two tasks. Since the 2-back task requires more effort and more activation of the frontolimbic network than do the 0-back and 1-back tasks,[24] our findings further suggest the vulnerability of this circuit in the process of working memory in MDD patients.

Hyperfrontality has been observed not only in patients with mood disorders[25,47] but in patients with schizophrenia as well.[58–60] Although its mechanism is not well known, two groups proposed similar hypotheses to explain the phenomenon;[61,62] patients show hyperfrontality under low working memory load and hypofrontality under high working memory load because fMRI response reaches the peak in low working memory load. No significant difference in DLPFC dysfunction between MDD and schizophrenia patients and a significant difference between the patients who had low psychomotor activity and those who had psychomotor activity were seen, suggesting that DLPFC dysfunction may be related to a behavioral deficit rather than a specific diagnosis.[9] Therefore, the hypothesis of hyperfrontality appears very relevant for the pathophysiology of MDD. Another speculative explanation is that the results of this study might reflect abnormal function of the dopaminergic system in MDD patients. Animal and human studies show that the dopaminergic system has an important role in modulating the prefrontal activation during working memory.[63–66] The dysfunction of the frontal cortex systems in subjects with MDD was reported in positron emission tomography and single photon emission tomography studies,[67–70] although there is no study, to our knowledge, that investigated the direct relation between the dopaminergic system and working memory in MDD patients. The dysfunction of the dopaminergic system in MDD patients may underlie the abnormal function of the frontolimbic network in the process of working memory reported in our present study and others.[67–70]

Our study has some methodological limitations, including the relatively modest sample size and the fact that our sample included patients with comorbid anxiety disorders. The ACC activation we observed in the MDD patients may include the influence of anxiety symptoms, because the anatomical pathophysiology of anxiety disorders involves the hippocampus, amygdala and ACC,[71–73] and patients with anxiety disorders also show a deficit of working memory.[74–76] However, we did not use any emotion processing task that would evoke anxiety symptoms, and we did not find any significant activation of hippocampus or amygdala during the task. Addition-

ally, working memory impairment in patients with anxiety disorders was reported to be greater than that in MDD patients and healthy controls.[76] However, our MDD patients with severe depressive symptoms showed no evidence of working memory impairment, as their *n*-back task performance was similar to that of the controls. Thus, the influence of anxiety comorbidity on the present results probably would be minimal. The performance data for the *n*-back task were not obtained from all participants due to technical difficulties. However, the performance of the available subjects clearly showed the expected pattern of superior performance on the easier tasks. Also, the investigator closely observed the subjects and verified that they understood the task and that they were performing the task during the imaging sequence. Among the available subjects, the performance of the patients was very similar to that of the healthy subjects, and *post hoc* analysis suggested that even had the full sample been available, the conclusions would likely remain the same. Therefore, we believe that the conclusion that the patients and controls showed equivalent performance on the memory task is correct.

With these limitations in mind, this study provides *in vivo* imaging evidence to support the hypothesis of impairment in brain pathways underlying working memory in individuals with MDD, and suggests that this impairment is involved in the pathophysiology of MDD.

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