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Structural and cognitive deficits in remitting and non-remitting recurrent depression: A voxel-based morphometric study

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ABSTRACT

Remission is the optimal outcome for major depressive disorder (MDD), but many patients do not improve appreciably despite treatment with medication. Treatment-resistant patients may experience deterioration in cognitive functions. Research has reported structural abnormalities in certain brain areas that may contribute to a poor clinical response. We hypothesize that there will be structural differences between patients able to achieve remission and those responding poorly to antidepressants. In the first voxel-based morphometric (VBM) study comparing remitting with non-remitting MDD, we investigated gray matter volume (GMV) differences between depressives to determine which structural abnormalities existed, and correlated these with diminished cognitive functioning. Of 44 adults with recurrent MDD, 19 had full remissions and 25 were non-remitters after a 6-week trial with antidepressant treatment. Remission was defined by 17-item Hamilton Depression Rating Scale scores of ≤ 7 for at least 2 weeks. VBM and neuropsychological studies were conducted on all patients and 25 healthy controls. The patients who remitted revealed milder visual attention deficits than did controls. This correlated with reduced GMV in the left postcentral gyrus (Brodmann area, or BA, 3) and the bilateral medial/superior frontal gyrus (BA 6). The non-remitting patients had reduced GMV in the left dorsolateral prefrontal cortex (DLPFC, BA 9), and impaired acoustic and visual attention associated with GMV differences in several cortical regions, thalamus and amygdala/parahippocampal gyrus. These findings indicated that patients whose MDD remitted were cognitively and morphologically different from non-remitters. Voxel-based structural deficits in the left DLPFC may characterize a subgroup of people with recurrent MDD who respond poorly to antidepressants.

Major depressive disorder (MDD) is increasingly recognized as a chronic, deteriorating illness with high comorbidity (Krishnan, 2003; Lee et al., 2008; Roose et al., 2001; Trivedi et al., 2007). Without sufficient treatment, residual symptoms of depression can lead to worsening outcomes, including higher relapse rates, suicidality (Kennedy and Paykel, 2004; Tranter et al., 2002; Trivedi et al., 2008), and diminished quality of life and psychosocial functioning (Hays et al., 1995; Kennedy and Paykel, 2004; McCall and Dunn, 2003). For depressives without early symptomatic remission, some researchers have reported that a greater number of previous episodes and a longer duration of untreated illness lead to poorer cognition in MDD (Fossati et al., 2002; Kessing, 1998; Paradiso et al., 1997). This is why remission without residual symptoms, rather than a 50% improvement on a depression rating scale, is now regarded as an optimal outcome in treating depression (Bakish, 2001; Israel, 2006; Kocsis et al., 2007). However, many patients do not improve appreciably despite several medication trials (Fekadu et al., 2009; Little, 2009). Those who are resistant to treatment account for most of the overall burden caused by depression (Little, 2009).

Patients with abnormal structures in depression-related brain networks show a decreased response to antidepressant medications; for example, structural abnormalities of the hippocampus, amygdala and frontal lobe were found to correlate with poor clinical response (Frodl et al., 2008, 2004; Janssen et al., 2007; Macqueen et al., 2008). Most of these findings were within the limbic-thalamo-cortical circuit, which is proposed as a critical neural network in depression, and impaired reciprocal functional relationships between the cortical (e.g., dorsolateral and medial prefrontal cortex) and limbic (e.g., amygdala) structures would result in emotional dysregulation and

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depression (Drevets et al., 2008; Mayberg, 2002). Although structural neuroimaging studies in depressed subjects have identified several anatomical abnormalities, most of these findings failed to be replicated consistently (Konarski et al., 2008). One possible reason for this is the heterogeneity of the selected study populations across studies. For example, some studies focused only on MDD patients with or without prior antidepressant exposure, while others selected only MDD patients with or without symptomatic remission. Another possibility is the variability of methodology. Although most of previous studies used region-of-interest measurement, the inherent variability and inconsistent validation in defining regions of interest across studies could be vulnerable to criticism (Konarski et al., 2008).

Voxel-based morphometry (VBM) is a voxel-by-voxel technique that enables us to make a detailed "visit" into brain structures (Ashburner and Friston, 2000). Some VBM studies reported anatomical abnormalities in patients with MDD (Leung et al., 2009; Taki et al., 2005; Tang et al., 2007; Vasic et al., 2008; Yuan et al., 2008). By using VBM measurement, several regions of potential gray matter abnormality have been identified as correlating with ratings of depressive symptoms. These regions include the dorsolateral and medial prefrontal cortex, inferior frontal gyrus, precentral and postcentral gyrus, anterior cingulate cortex, superior and inferior temporal gyrus, hippocampus, amygdala and thalamus. However, the results so far have not been consistent, and this may still be a result of the heterogeneity of the depressed population. Findings of structural deficits in more homogenous depressed populations were more similar. For example, from studies involving mostly non-remitting depressed patients, gray matter reduction of the left prefrontal cortex in adult patients (Vasic et al., 2008) and in geriatric males with MDD (Taki et al., 2005) have been identified using VBM methodology. The left dorsolateral prefrontal cortex (BA 9, 10 and 46) was found to have abnormal metabolism in depression (Brody et al., 2001; Drevets, 1999, 2001; Drevets et al., 2002, 2008; Siegle et al., 2007), and was also an effective target for treating medication-resistant depression with repetitive transcranial magnetic stimulation (Su et al., 2005). We speculate that only those patients with structural deficits in certain brain areas, such as the dorsolateral prefrontal cortex, may have a diminished capacity to respond to antidepressants. However, there has been no study comparing depressed patients who responded well to antidepressant treatment with those who do not experience remission after receiving medication.

In the present study, we investigated whether there would be structural differences between remitting and non-remitting patients, and whether patients who could experience remission after treatment had less abnormal brain structures. In addition, there are only a few VBM studies so far that have investigated the relationship between brain structure and cognitive function in adults with MDD (Leung et al., 2009; Vasic et al., 2008). One study (Vasic et al., 2008) found a negative correlation between attention deficits and the size of the right inferior frontal gyrus in depressed patients. The other (Leung et al., 2009) reported that attention biases towards negative stimuli were positively correlated with reduced gray matter in the right superior frontal, anterior cingulate, and fusiform gyri in female patients. These studies utilized small samples ($N = 15$–17), included only patients without remission, and had inconsistent results. To examine the clinical implications behind structural differences, we also investigated which structural abnormalities in remitting and non-remitting depressives correlated with severity of depression and diminished cognitive functioning.

Material and methods

Study subjects

Forty-eight recurrent MDD outpatients (13 males, 35 females) were recruited at Taipei Veterans General Hospital from July 2007 to June 2008. The diagnoses were established by structured history-taking and administration of the Mini International Neuropsychiatric Interview (MINI), based on the *Diagnostic and Statistical Manual for Mental Disorders (DSM-IV)* criteria (American Psychiatric Association, 1994). Patients were recruited for the study only if they were 21 to 65 years of age, and had no alcohol or substance abuse history, no major physical or neurological illness, and no comorbidity with schizophrenia, bipolar disorders, other major psychoses, obsessive–compulsive spectrum disorders, post-traumatic stress disorder, or Cluster B personality disorders.

After screening, subjects received open-label antidepressant treatment (SSRIs, SNRIs or bupropion) for the next 6 weeks. The patients were further divided into remitting and non-remitting MDD groups, according to the severity of their depression after antidepressant treatment. Remission was defined by 17-item Hamilton Depression Rating Scale (HDRS-17) scores ≤ 7 for at least 2 weeks (Frank et al., 1991). However, patients were excluded if they required extraordinarily high doses of antidepressants (e.g., fluoxetine ≥ 60 mg/day) or benzodiazepines (e.g., lorazepam ≥ 4 mg/day) during the 6 weeks of treatment. After MINI screening, a group of age-, gender-, and handedness-matched healthy controls ($n = 25$; 19 female subjects) also participated in the study. Those with a family history of an axis I disorder including schizophrenia, major depression or bipolar disorder in first degree relatives were excluded. The study was performed in accordance with the Declaration of Helsinki and was preapproved by the local Ethics Review Committee. All participants provided written informed consent.

Procedures

A thorough history was taken to obtain demographic and clinical characteristics for all participants. Individual assessments of pre- and post-treatment mood were done by an experienced psychiatrist (T.-P. Su). These included ratings with the Hamilton Depression Rating Scale-17 (HDRS-17) and Young Mania Rating Scale (YMRS). After antidepressant treatment, we arranged neurocognitive tests, which were done by a trained research assistant and a VBM imaging study.

Neurocognitive testing

Attention

Attention functions were measured by Tests for Attentional Performance (Zimmermann, 1997). We chose an acoustic task for evaluating auditory attention and a Go/No-Go task for assessing visual attention. In the acoustic attention task, participants had to detect irregularity within an alternating sequence of high and low tones (i.e., successions of two high or two low tones) and were asked to respond as quickly as possible. In the Go/No-Go task, subjects were asked to respond as quickly as possible after the × symbol appeared. They were not to press the key when the + symbol appeared. During the testing process, subjects were seated in a comfortable chair with arm rests. The tasks were generated on a 12.5-in. computer screen (32-cm diagonal screen length) with a viewing distance of 60 cm. Subjects were asked to press a key in the front, center area of the keyboard with their right index finger as quickly as possible according to the given testing instructions. To ensure that subjects understood each task, all tasks provided pretest trials. After subjects completed the pretest with all correct responses, the formal test was then administered to record their reaction times (mean and standard deviations), omissions and false alarms. Reaction time (median), false alarm and omission frequencies of acoustic and Go/No-Go tasks were recorded for further analysis.

Memory

Memory function was measured by the Word Lists Test for verbal memory function and the Face Test for visual memory function

(Wechsler, 1997). The word list task was in two parts. During the first part of the test, subjects were asked to recall what they had heard immediately after listening to 12 words (List A) for four trials. The first score of recalling list A (word lists I recall) measures immediate recall ability for unstructured material that is repeated during learning. The second testing of delayed recall (word lists II recall) assesses information retention by asking the subject to recall those 12 words (List A) after a delay of 25–35 min. High scores indicate efficient learning and recall, while low scores indicate weakness or deficit in learning and recall. The faces test contains 48 pictures of faces, including 24 target faces and 24 distracters. The score for face recognition I was the number of correctly differentiated distracters and target faces from among all the 48 face pictures immediately after one repeated visual exposure to the 24 target faces. For assessing delayed facial recall, subjects were asked to do the test again by differentiating target faces from 48 mixed pictures after 25–35 min delay. The correct number was recorded as the score of face recognition II.

Executive function

The Wisconsin card sorting test (WCST) was used to evaluate executive function during the time between the immediate word/face recall test and the delayed word face recall test. The Wisconsin Card Sorting Test (WCST) utilized the 128 card procedure, administered according to instructions in the manual (Heaton et al., 1993). The WCST consists of 4 stimulus card and 2 identical decks of 64 response cards (a total of 128 response cards). The response cards display figures of varying forms (crosses, circles, triangles or stars), colors (red, blue, yellow or green) and number of figures (one, two, three or four). The stimulus cards are always presented from the participant's perspective in a standard left-to-right order: the one red triangle, the two green stars, the three yellow crosses and the four blue circles. The participant is then given a stack of response cards and asked to match each one to one of the stimulus cards. The subject is not told how to match the cards (by the rule of color, form or number), but is told whether a particular match is right or wrong. Three WCST indices were used for analysis: (1) percent (%) errors, (2) % conceptual level responses, and (3) categories completed.

Imaging studies

Magnetic resonance imaging (MRI) data acquisition

All MRI scans were performed on a 1.5 T MRI system (Excite II; GE Medical Systems, Milwaukee, WS, USA). T1-weighted images (T1-images) were acquired parallel to the anterior commissure–posterior commissure line by using a three-dimensional fluid-attenuated inversion-recovery fast spoiled gradient recalled echo (FLAIR-FSPGR) sequence. The imaging parameters were: TR = 8.548 ms, TE = 1.836 ms, TI = 400 ms, flip angle = 15°, field of view (FOV) = 26 × 26 cm, matrix size = 256 × 256, and 124 contiguous slices with the slice thickness = 1.5 mm.

Data processing for VBM

An optimized VBM protocol (Ashburner and Friston, 2000; Good et al., 2001) was used. All preprocessing and analyses of images were performed with statistical parametric mapping (SPM2; Wellcome Department of Imaging Neuroscience, London, UK available online at http://www.fil.ion.ucl.ac.uk/spm), (Friston et al., 1995a,b) and involved the following steps:

Creation of group-specific templates and priors. A group-specific template of images was established directly from the datasets of the subjects in order to reduce any bias in template selection. With the priors provided in SPM2, the normalized T1-images were segmented into cerebrospinal fluid (CSF), gray matter, and white matter compartments. The normalized T1W, CSF, and gray/white matter images were separately averaged and smoothed with an 8-mm Gaussian kernel to generate group-specific T1-images template and priors which then served as the standards for further processing. The image of the skull was stripped from the normalized T1-images before segmentation using the Brain Extraction Tool (compiled in FSL 4.0; FMRIB Image Analysis Group, Oxford, UK; available online at www.fmrib.ox.ac.uk/fsl) to improve the quality of segmentation (Smith et al., 2002).

Derivation of optimized normalization parameters. The native T1-images were again segmented based on the group-specific priors, then the segmented images were precisely normalized to the group-specific gray/white matter priors separately in order to obtain the optimal normalization parameters for each tissue type. The normalization included affine transformations and linear combination of smooth basis functions modeling global non-linear shape differences (Ashburner and Friston, 1997, 2000).

Optimized normalization and segmentation. The parameters acquired, as described in the previous section, were applied to normalize the native T1-images into standard space. This step afforded the optimal spatial transformation of gray/white matter and reduced any contribution from non-brain voxels. These optimal-normalized T1-images were finally segmented into CSF, gray/white matter partitions and resliced to 2 * 2 * 2 mm^3 for the voxel-wise group comparisons.

Correction of volume changes. The Jacobian determinants derived from the spatial normalization were introduced in nonlinear spatial transformations which modulated the regional differences of partitioned gray/white matter on images from relative to absolute amounts (volume). Before the voxel-wise group comparisons, all normalized, segmented, and modulated images were smoothed with an 8-mm Gaussian kernel.

Group comparisons of VBM. ANCOVA was chosen to compare the gray matter volumes among the groups. The total intracranial volume (TIV), ages, and degrees of education were set as the covariates. Since one available VBM study in comparing depressed patients in remission with normal controls had shown significantly reduced gray matter volume in the right superior frontal cortex and left postcentral cortex (Yuan et al., 2008), an uncorrected P-value < 0.005, as well as a cluster size that included more than 20 contiguous voxels (if not otherwise specified), were determined to putatively detect significant differences between groups. Given a concern about multiple comparisons, the significant clusters were further used to perform Small Volume Correction (SVC) with an anatomically defined regional mask in the relevant gray matter area. Only the clusters meeting a SVC-FWE-corrected P-value of <.05 were reported. Peak localizations of group comparison results were derived from the coordinates from the Montreal Neurological Institute (MNI) template. We used a non-linear algorithm, provided by Matthew Brett (MRC Cognition and Brain Sciences Unit, Cambridge, UK), to transform MNI into Talairach coordinates. The localization of the peak coordinates was identified on the basis of the Talairach and Tournoux atlas (Talairach and Tournoux, 1988).

Statistics

Statistical analysis was performed by using SPSS 11.5 software (SPSS Inc, Chicago, IL). One-way ANOVA (or Student's t-test) and the Chi-square test were applied to compare the continuous and categorical variables among groups, respectively. With regard to cognitive testing, continuous variables were compared among the three groups by ANOVA, followed by post-hoc LSD analysis to determine which groups accounted for significant between-group differences (P<0.05). Univariate ANCOVA for all three group comparisons, using age and education as covariates, was then performed for

only those variables found to have trend significance ($P<0.10$) in the ANOVA. The partial correlation test (two-tailed) was chosen to examine the relationship between clinical variables and GMV, controlling for age, education, and TIV. $P<0.05$ was deemed to be statistically significant. To elucidate the neuroanatomical correlates of individual differences in cognitive performance, partial correlation analyses with age, education and TIV as confounding covariates were performed to correlate the cognitive testing scores with the regional brain volumes. The regional gray matter volumes were extracted from the peak coordinates showing a diagnostic effect. The threshold for statistical significance was set at $P<0.05$ with correction for multiple comparisons.

Results

Clinical characteristics and cognitive profiles among groups

In all, we tested 19 MDD patients in remission and 25 in non-remission after antidepressant treatment. Four patients, two each with remission and non-remission, were excluded because they required high doses of benzodiazepines for insomnia during the treatment trial. Twenty-five normal controls were tested for comparison. Eighteen patients had a comorbid dysthymic disorder (Non-remitter: Remitter (N) = 12:6); 16 had panic disorder (N = 11:5); 13 had generalized anxiety disorder (N = 9:4) and 7 had social phobia (N = 5:2). Except for a lower education level ($F(df=2, 66)=6.90$; $P<0.05$), no significant differences involving pre-treatment mood ratings and other clinical variables, such as age, age of onset, illness duration and depressive episodes, were found between patients with remitting and non-remitting MDD (Table 1). This suggests that the patient's responses to antidepressants were not definitely determined by their duration of illness or previous depressive episodes. After treatment, the non-remitting subjects maintained more severe depressive symptoms than did remitting MDD patients (post-treatment HDRS: 16.3 (6.0) vs. 3.4 (2.0); $P<0.01$; see details in Table 1).

The non-remitting patients performed significantly worse in attention than did those in the other two groups. The non-remitters had a longer reaction time for the acoustic attention task (median, $F(2, 64)=3.77$; $P<0.05$), although the scores on the omission and false alarm items of acoustic attention task did not differ much among groups. Both the non-remitters and remitters presented significantly more false alarms for the visual attention task than did healthy controls ($F(2, 66)=5.36$; $P<0.05$). These results suggest that non-remitting patients had slower responses to acoustic stimuli. In addition, both remitting and non-remitting depressives had a higher potential for misinterpreting what they saw in the environment. With regard to memory performance, the

Table 1
Demographic and clinical characteristics among patients with non-remitting depressives, remitting depressives, and healthy controls.

	Non-remitting MDD[a] ($n=25$)	Remitting MDD[a] ($n=19$)	Healthy control[a] ($n=25$)	F/t value	ANCOVA $F(df=2,64)$
Gender (n = male/female)	5/20	6/13	6/19	0.79 (χ^2)	–
Age[b] (years)	46.5 (10.4)	42.6 (13.0)	40.6 (12.7)	1.53	–
Educational level[b] (years)	10.5 (5.5)	14.2 (2.8)	13.7 (3.0)	6.90*	–
Handedness (n = right/left)	23/2	19/0	25/0	3.63 (χ^2)	–
Age of onset[c] (years)	36.5 (13.2)	33.6 (14.4)	–	0.69	–
Illness duration[c] (years)	9.4 (8.5)	9.0 (7.9)	–	0.15	–
Past depressive episodes[c] (times)	4.8 (3.2)	3.5 (2.6)	–	1.38	–
Pre-tx HDRS-17[c]	21.9 (3.5)	21.0 (4.0)	–	0.76	–
Pre-tx YMRS[c]	1.7(1.7)	1.3 (1.2)	–	0.85	–
Post-tx HDRS-17[c]	16.3 (6.0)	3.4 (2.0)	–	10.05**	–
Post-tx YMRS[c]	1.0 (1.6)	0.5 (0.8)	–	1.42	–
Medication					
Antidepressants (SSRI/SNRI/others, n)	8/9/8	7/7/5	0	–	–
Benzodiazepines (n)	17	12	0	–	–
Acoustic attention task					
Median of reaction time[b]	648.5 (90.6)[&]	568.5 (98.5)	599.3 (79.6)	4.57*	3.77*
Omission[b]	0.4 (0.8)	0.1 (0.3)	0.4 (0.9)	0.98	–
False alarm[b]	0.6 (1.0)	0.2 (0.7)	0.4 (0.8)	1.57	–
Visual attention_Go/No-Go task					
Median of reaction time[b]	501.7 (81.6)[&]	443.3 (63.1)	488.7 (64.1)	3.88*	2.86†
Omission[b]	0.5 (1.0)[&,Φ]	0.1 (0.2)	0.0 (0.0)	4.41*	2.35
False alarm[b]	1.6 (1.7)[Φ]	1.4 (1.6)	0.3 (0.8)	5.36**	4.11*
Verbal memory					
Immediate_Word lists I 1st recalls[b]	5.2 (1.4)[Ψ]	6.1 (1.5)	6.8 (2.0)	3.99*	2.74†
Delayed_Word lists II recalls[b]	7.4 (2.6)[⊛,Ψ]	9.1 (1.6)	9.2 (1.9)	5.70*	3.00†
Facial memory					
Immediate_Face recognition I[b]	34.8 (3.7)	37.0 (4.4)	36.6 (3.5)	2.14	–
Delayed_Face recognition II[b]	33.2 (3.0)[Ψ]	35.0 (3.8)	35.7 (3.0)	3.77*	2.46†
Executive function_WCST					
% Errors[b]	38.0 (19.8)	28.0 (20.2)	27.6 (15.2)	2.46†	0.31
% Conceptual level responses[b]	49.1 (28.2)	64.8 (26.3)	62.6 (22.6)	2.53†	0.48
Categories completed[b]	3.4 (2.4)[⊛,Ψ]	4.7 (2.1)	4.9 (1.9)	3.52*	0.88

MDD, major depressive disorder; NPar, nonparametric test; Pre-tx, pre-treated; Post-tx, post-treated; HDRS-17, 17-item Hamilton Depression Rating Scales; YMRS, Young Mania Rating Scale; SD, standard deviation; WCST, Wisconsin Card Sorting Test; SSRI, specific serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; others including NDRI (norepinephrine dopamine reuptake inhibitor) and NaSSA (Noradrenergic/Specific Serotonergic Agent)

[a]All data are given as the mean (SD) if not otherwise specified; [b]ANOVA, $F(df=2,66)$; Post-hoc: (Non-remitting>Remitting)[&], (Non-remitting>Healthy)[Φ], (Remitting>Healthy)[#], (Non-remitting<Remitting)[⊛], (Non-remitting<Healthy)[Ψ];

[c]Student's t-test; [d]Covariate = age and education.

*$P<0.05$; **$P<.01$; †$P<.10$.

non-remitters had lower scores on immediate and delayed verbal memory (Word lists I and II recall) and delayed facial memory (Face recognition II), the ANCOVA results, controlled for age and education, showed no statistically significance difference between groups ($P<0.10$; Table 1). When compared to healthy subjects, both groups of depressives presented comparable executive performance after controlling for their age and education (i.e., "Categories completed" item, $F(2, 64)=0.88$; $P=0.419$) (Table 1). These findings suggest that non-remitting depressives had worse cognitive function including acoustic and visual attention than did the remitters or healthy subjects. We also found that the remitters had milder visual attention deficits with an increased potential for false alarms to visual stimuli.

Regional gray matter volume (GMV) aberrancy among groups

Compared to controls, the non-remitting MDD patients showed significantly reduced GMV in the left thalamus, dorsolateral prefrontal cortex (DLPFC; Brodmann area, or BA, 9), and precentral frontal gyrus (BA 4), while the remitting patients showed reduced GMV in the right medial/superior frontal gyrus (BA 6), left superior frontal gyrus (BA 6) and medial part of the left postcentral parietal gyrus (BA 3) (Fig. 1

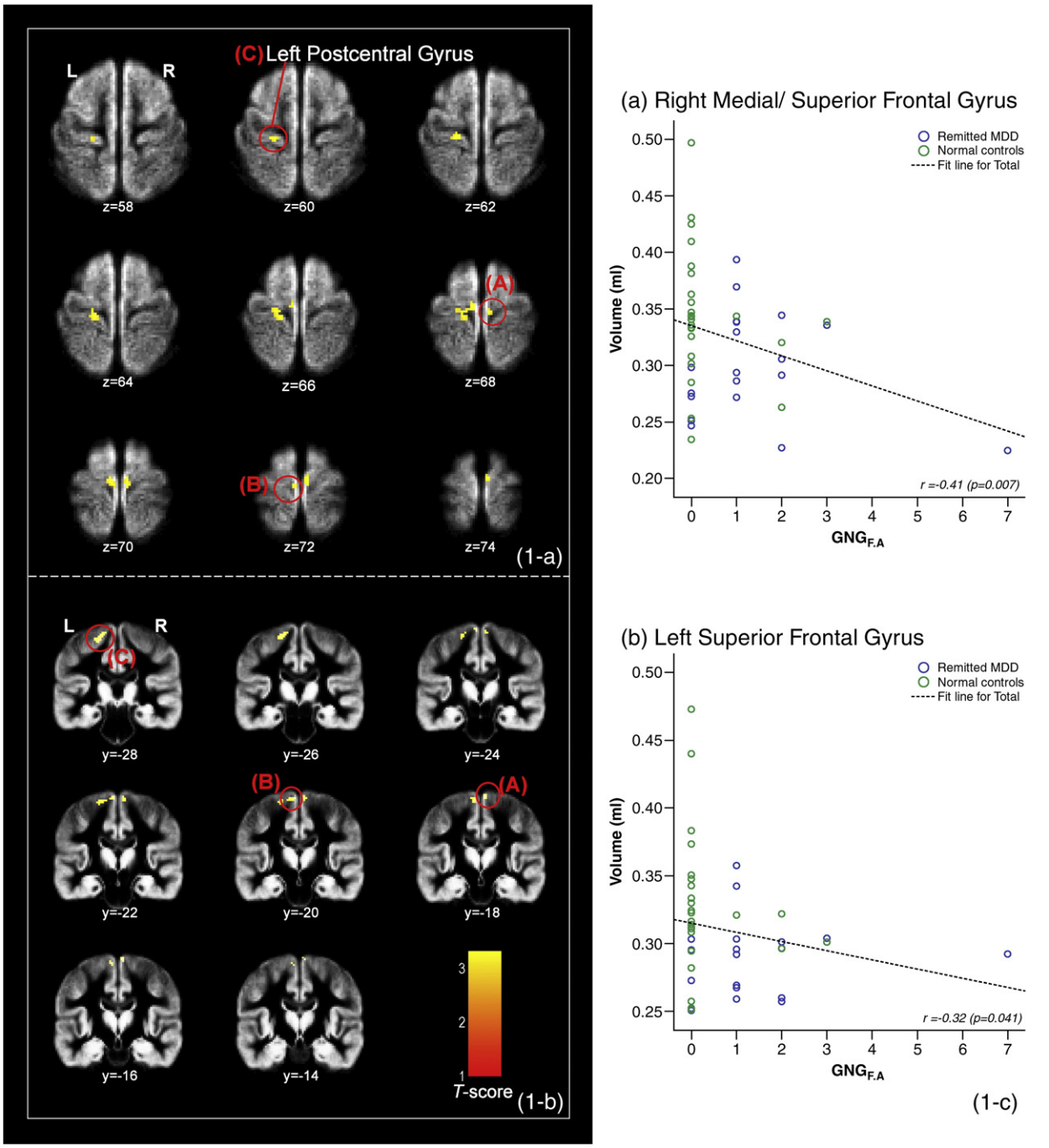


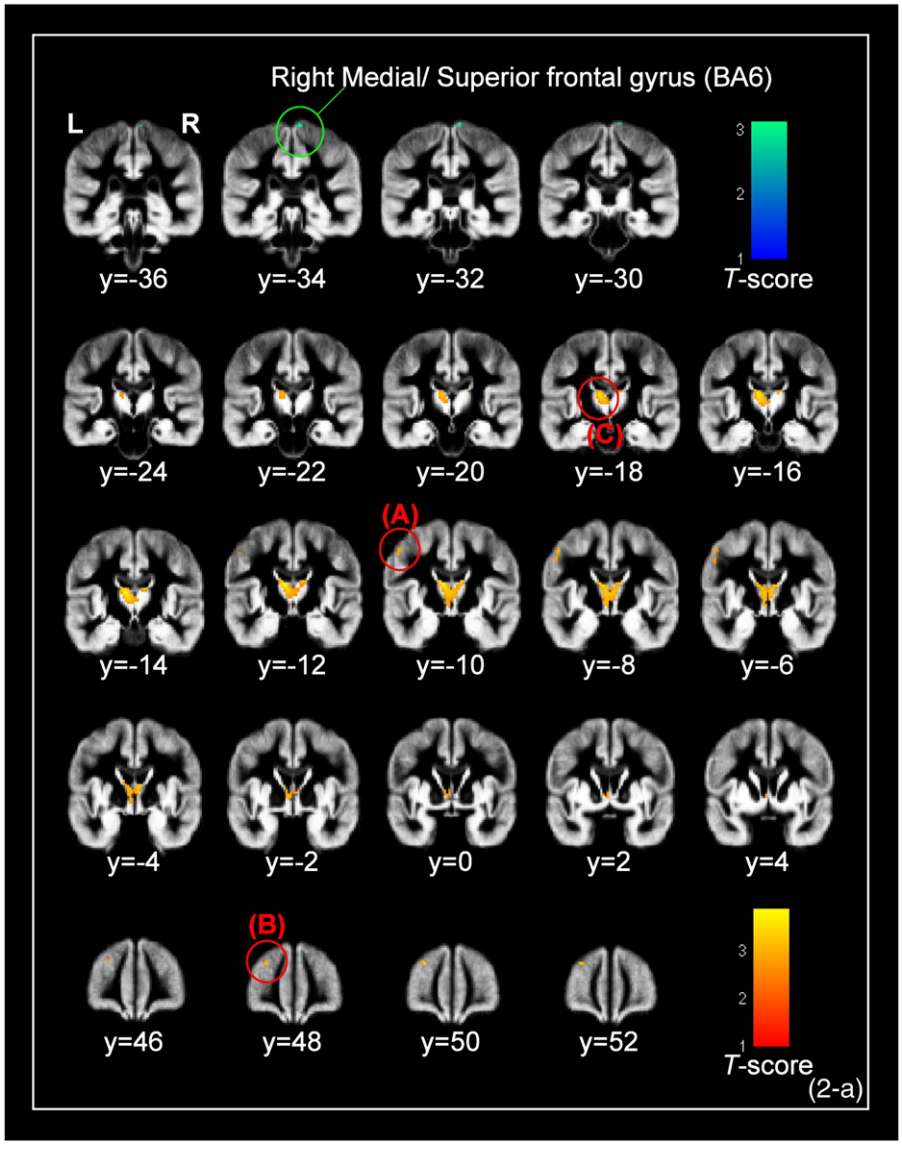
Fig. 1. Reduction of gray matter volumes (GMV) in the patients with remission vs. normal control subjects. *Note.* Left figures (axial view, 1-a; coronal view, 1-b) illustrate the areas of GMV reduction in the remitting patients with major depressive disorders as compared to healthy controls ($p_{uncorrected}<0.005$, cluster size = 20), including the right medial/superior frontal gyrus (A), left superior frontal gyrus (B) and left postcentral gyrus (C). Right figures (scatter plot and curve-fitting, 1-c) show significant correlations between greater GMV reduction and more false alarms on Go/No-Go task ($GNG_{F.A}$), suggesting that patients with depression had poorer attention and smaller GMV over bilateral superior/medial frontal gyrus.

Table 2
Gray matter volume comparison between non-remitting depressives, remitted depressives and normal controls.

Gray matter volume	Anatomical regions	Brodmann area	*x*	*y*	*z*	*Z*[a]
N-R<NC	L Thalamus		-8	-14	12	3.67
	L Dorsolateral prefrontal cortex	9	-28	50	28	3.43
	L Precentral gyrus	4	-50	-8	46	3.03
R<NC	R Medial/superior frontal gyrus	6	6	-18	72	3.18
	L Superior frontal gyrus	6	-8	-16	68	3.03
	L Postcentral gyrus (1)[b]	3	-22	-28	60	3.03
N-R<R	R Occipital lobe, cuneus	19	10	-90	38	3.63
	R Temporal fusiform gyrus	36	40	-44	-26	3.07
	L Dorsolateral prefrontal cortex	9	-28	52	28	3.53
	L Postcentral gyrus (2)[b]	3	-56	-16	52	3.70
R<NR	R Inferior temporal gyrus	20	38	-10	-30	3.37
	R Middle temporal gyrus	21	62	2	-22	3.21
	R Amygdala/parahippocampal gyrus		22	0	-22	2.85
	L Temporal fusiform gyrus	20	-44	-2	-22	3.33
	L Postcentral gyrus (3)[b]	3	-16	-32	62	3.16
	L Inferior temporal gyrus	20	-28	-18	-32	2.92

N-R, Non-Remitting depressives; R, Remitting depressives; NC, Normal Controls; L, Left; R, Right.
[a] Results of post hoc ANCOVA (adjust to age, education and total brain volume); $P<0.05$ small volume corrected.
[b] When several coordinates were located in the same anatomical area, numbers 1, 2 and 3 (in the brackets) were used to differentiate each coordinate.

and Table 2). To test if the brain areas, which had different GMV in the non-remitters compared with the controls, also showed a difference between the remitters and the controls, we lowered the extent threshold to 10 voxels ($P_{\text{uncorrected}}<0.005$). We saw GMV reduction over the right medial/superior frontal gyrus in the non-remitting patients when compared to healthy controls (Fig. 2-a) but no changes



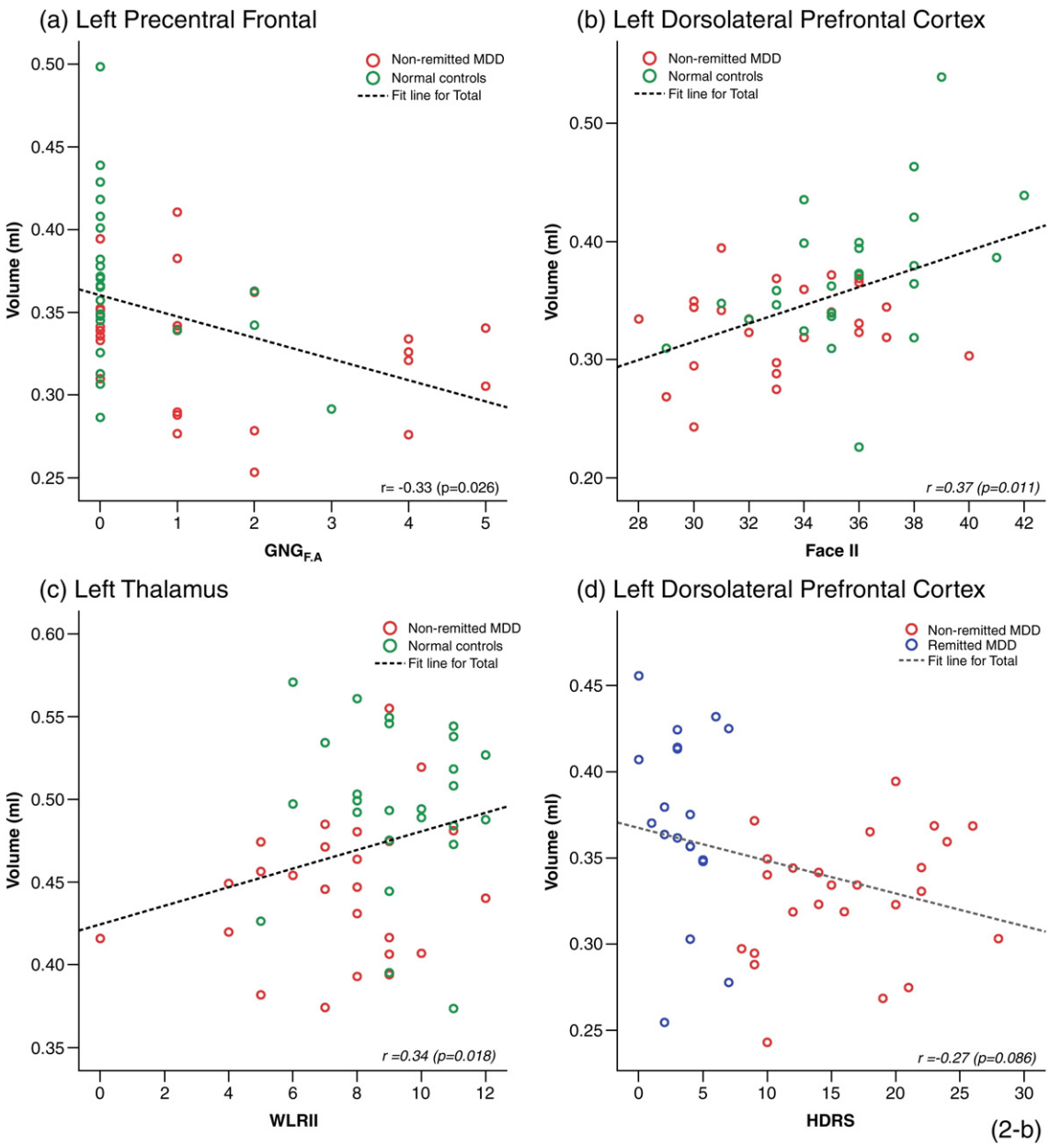


Fig. 2. Reduction of gray matter volumes (GMV) in the non-remitting depressives versus normal subjects. *Note:* Left figure (coronal view, 2-a) illustrates the areas of GMV reduction in the non-remitting patients as compared to healthy controls ($p_{\text{uncorrected}}<0.005$, cluster size = 20), including the left precentral gyrus (A in a red circle), left dorsolateral prefrontal cortex (B) and thalamus (C). A reduction of GMV over right medial/superior frontal gyrus is also observed (in a green circle) under a lower threshold ($p_{\text{uncorrected}}<0.005$, cluster size = 10). Right figures (scatter plot and curve-fitting, 2-b) show significant correlations between more GMV reduction and more false alarms on Go/No-Go task ($GNG_{F.A}$), lower scores on delayed verbal (Word Lists II recalls, WLRII) and facial memory (Face II recognition), as well as higher depressive scores (Hamilton Depression Rating Scales, HDRS).

in the lowered threshold when remitting depressives and healthy controls were compared. This suggested the GMV reduction over the right medial/superior frontal gyrus has no ability to distinguish the non-remitting from the remitting depressives.

Non-remitting MDD patients achieving symptomatic remission had a larger GMV in right BA 19 and 36, left BA 9 and lateral part of BA 3. Furthermore, the non-remitting patients showed a larger GMV in the right amygdala, right BA 21, bilateral BA 20, another medial part of BA 3, and left BA 20, when compared to the remitting subjects (Table 2). We also investigated whether or not an enlarged GMV existed in the depressives when compared to normal subjects; however, no areas survived under the stricter threshold of the FWE-corrected *P*-value<0.05. These results indicated that the gray matter volume in the left DLPFC was significantly smaller in the non-remitted when compared to the remitting patients and healthy controls.

Relationship between depressive symptom rating, cognition, and gray matter volume

Depressive symptom rating vs. gray matter volume

Table 3 shows the significant negative correlations between HDRS-17 scores and the GMV of the left lateral part of BA 3 (r = -0.41), left BA 9 (r = -0.27), right BA 19 (r = -0.33) and right BA 36 (r = -0.41). Significant positive correlations existed between HDRS-17 and the GMV of the right amygdala/parahippocampal gyrus (r = 0.43), left medial part of BA 3 (r = 0.50) and bilateral BA 20 (r = 0.41, right; r = 0.40, left).

Table 3
Correlation (adjusted for age, education and total intracranial volumes) between gray matter abnormalities, depressive symptoms and cognitive variables.

Clinical variables	Anatomical regions	Brodmann area	Correlation (r)	P-value
HDRS				
	R Occipital lobe, cuneus	19	-0.33*	0.035
	R Temporal fusiform gyrus	36	-0.41**	0.007
	R Inferior temporal gyrus	20	0.41**	0.007
	R Amygdala/parahippocampal gyrus		0.43**	0.005
	L Dorsolateral prefrontal cortex	9	-0.27†	0.086
	L Postcentral gyrus (2)	3	-0.41**	0.007
	L Postcentral gyrus (3)	3	0.50**	0.001
	L Temporal fusiform gyrus	20	0.40**	0.009
Acoustic attention				
Median	R Inferior temporal gyrus	20	0.37*	0.016
Median	R Amygdala/parahippocampal gyrus		0.42**	0.006
Median	L Postcentral gyrus (2)	3	-0.35*	0.026
Median	L Inferior temporal gyrus	20	0.44*	0.004
Median/SD	L Temporal fusiform gyrus	20	0.33*/0.31*	0.032/0.05
Go/No-Go test				
F.A	R Medial/superior frontal gyrus	6	-0.41**	0.007
F.A	L Precentral gyrus	4	-0.33*	0.026
F.A	L Postcentral gyrus (1)	3	-0.32*	0.041
F.A	L Superior frontal gyrus	6	-0.32*	0.041
Verbal memory				
WLRII	R Amygdala/parahippocampal gyrus		-0.31*	0.049
WLR1st/WLRII	L Thalamus		0.33*/0.34*	0.026/0.018
WLRII	L Postcentral gyrus (3)	3	-0.39*	0.013
Facial Memory				
Face II	R Occipital lobe, cuneus	19	0.38*	0.015
Face II	L Dorsolateral prefrontal cortex	9	0.37*	0.011

HDRS, 17-item Hamilton Depression Rating Scales; L, Left; R, Right; Median, Median of reaction time; SD, SD of reaction time; F.A, False alarm; WLR1st, Word Lists 1st Recalls; WLR II, Word Lists II Recalls; Face II, Face Recognition II task.
[a]All data given were done by partial correlation, controlling for age, educational level and total intracranial volumes.
*$P<0.05$; **$P<0.01$; †$P<0.10$.

Cognitive function vs. gray matter volume

An increased median reaction time during the acoustic attention test was positively associated with GMV in the right amygdala/parahippocampal gyrus and bilateral BA 20, yet it was negatively correlated with GMV in the left BA 3 ($r=$-0.35). Areas where GMV was smaller in the remitting patients when compared to normal controls, including bilateral BA 6 and left postcentral gyrus (BA 3) (Fig. 1), were associated with increased false alarms during Go/No-Go testing. Impaired, delayed verbal memory was associated with larger GMV in the right amygdala/parahippocampal gyrus, thalamus, and left BA 3 (the more medial part of the left postcentral gyrus). Furthermore, smaller left BA 9 (DLPFC) and right BA 19 (occipital cuneus) GMV correlated with poorer facial memory (Table 3).

Discussion

To the best of our knowledge, the relationships between structural changes and altered cognitive function in remitting and non-remitting adults with MDD have not been well studied. In the first VBM study comparing remitting with non-remitting MDD, the remitting patients were morphologically different from non-remitters and many of the structural deficits were correlated with their depression and worsening cognition. The remitters had only mild visual attentional deficits, which correlated positively with reduced GMV over left postcentral parietal gyrus (BA 3) and bilateral superior/medial frontal gyrus (BA 6). In contrast, the non-remitting patients showed more cognitive problems including poor attention and memory, and they also presented a significant GMV reduction in the left DLPFC (BA 9) when compared to the other two groups.

Consistent with our hypothesis, there were structural differences between remitting and non-remitting patients. In our non-remitting patients, these structural abnormalities included reduced GMV over the left prefrontal and frontal cortex (BA 3, 4 and 9), right temporal fusiform (BA 36), and occipital cuneus. This was consistent with the findings of a recent VBM study in adults with MDD (Vasic et al., 2008), where the authors found that non-remitting patients had gray matter reductions over several temporal and frontal regions, including the left DLPFC. Another VBM study in non-remitting geriatric males with MDD also reported GMV reductions in the bilateral prefrontal cortex when compared to healthy controls (Taki et al., 2005). Structural reductions over the left DLPFC were observed only in our non-remitting patients but not in remitting ones, which means that structural deficits in the left DLPFC might predict poor or delayed antidepressant responses in patients with recurrent MDD. Previous investigations have shown that longer duration and more episodes of depression contribute to reduction in brain structures such as the hippocampus and even in total brain volume (Bell-McGinty et al., 2002; Drevets et al., 2008; Lampe et al., 2003; Sheline et al., 2002, 2003). Whether or not these structural reductions were a result of neuronal degeneration from recurrent depression (Lampe et al., 2003; Rajkowska et al., 2005; Sheline et al., 2003; Stockmeier et al., 2004) requires further study.

Compared to controls, the remitting patients had limited visual attention deficits, which correlated with reduced GMV in left BA 3 and bilateral BA 6. This is consistent with previous findings that neurocognitive deficits were also found during euthymic stages, especially in patients with recurrent episodes of MDD (Gorenstein et al., 2006; Kessing, 1998; Tham et al., 1997). Our structural findings were also consistent with two recent VBM studies. One conducted by Yuan et al. (2008) found that geriatric depressed patients who were in remission from their first episode of depression had reduced GMV in left BA 3, right BA 6 (superior frontal gyrus) and right BA 21 (middle temporal gyrus) in comparison with well-matched healthy controls. Another study conducted in adult female patients with

MDD also found reduced gray matter in the right superior frontal gyrus (Leung et al., 2009). Reduction in left BA 3 of the primary sensorimotor cortex is not a finding frequently reported with MDD, but our VBM results duplicated the findings of previous researchers (Yuan et al., 2008). We also found a significant correlation between smaller left BA 3 and greater psychopathology as well as poorer attention. BA 6 (superior frontal gyrus) is composed of premotor cortex and supplemental motor cortex and functions as a mediator in planning complex movements; it is also associated with attention and working memory (Proverbio, 2002). In our study, the remitting MDD patients showed smaller BA 6 bilaterally, possibly leading to poorer performance in doing a Go/No-Go task that required good visual attention and sensorimotor cooperation.

With regard to the structure–cognition relationship, only a few VBM studies have focused on this point (Leung et al., 2009; Vasic et al., 2008; Yuan et al., 2008). Among these studies, two involved depressed adults (Leung et al., 2009; Vasic et al., 2008), but they had small samples ($N = 15–17$) and included only patients without remission. Because the neuropsychological test batteries used were different across studies and focused only on non-remitting depressed patients, the results of structure–cognition relationships from different studies were not consistent. One (Vasic et al., 2008) found that attention deficits were correlated with the size of right inferior frontal gyrus, while the other (Leung et al., 2009) reported that problems with attention were correlated with reduced gray matter in the right superior frontal, anterior cingulate and fusiform gyri. By expanding the sample size and dividing patients into remitting and non-remitting groups, we found that patients with non-remitting MDD performed significantly worse in both acoustic and visual attention, but not in memory or executive function. The worsening performances of attention were correlated with GMV abnormalities involving bilateral superior frontal gyri, bilateral postcentral gyri, bilateral temporal lobes including fusiform gyri, and right amygdala/parahippocampal gyri. Although the actual cognitive circuit in depression is still unclear, all of the above areas are possibly involved. Notably, the finding of a significantly smaller bilateral medial/superior frontal gyrus (BA 6) in the remitting patients was associated with visual attention deficits and may be part of the circuit.

The volumes of some small areas in the same gyrus such as the postcentral parietal gyrus (BA 3) in this VBM-study (see panels "NR < R" and "R < NR" in Table 2) did not reduce or enlarge in the same direction in all groups. However, the changes correlated well with clinical variables including depressive symptom ratings, acoustic attention, and visual attention (Table 3). The underlying mechanism for increases in GMV is still unknown. It might possibly be due to chronic neuronal damage such as an inflammatory process, or chronic functional hyperactivation leading to increased synaptic connections (Stoll et al., 1998; Wu et al., 2007). This observation highlights the difficulties in using region-of-interest methods to investigate GMV alterations, because the averaged volumes could be influenced by different components of the reduced or enlarged brain clusters. Our findings from a voxel-based approach were of importance because they provided not only evidence of biological differences in depression, but also explained why the results of previous structural studies could be inconsistent. Therefore, the methodology of structural analysis is also an important contributor to the morphological results.

The interpretation of our findings needs to be tempered by five limitations. First, gender differences may influence GMV deficits in depression (Hastings et al., 2004; Lavretsky et al., 2004; Taki et al., 2005). Because of the relatively small sample size and lack of gender differences between groups, we did not do a further analysis. Second, patients recruited were not drug-free but all were treated with antidepressants; however, treatment was necessary in order to see the differences between remitting and non-remitting MDD, and medication should have had a limited impact on structural findings. Third, comorbid psychiatric conditions in the depressives should be taken into consideration when interpreting our results; however, there was no statistically significant difference in comorbid conditions between our depressive groups. Fourth, the patients we recruited were all recurrent MDD patients. Whether or not these results could be duplicated in first episode MDD requires further study. Finally, although all our patients were Chinese and the results might not be generalized to MDD patients worldwide, our findings were consistent with previous studies conducted not only in Chinese populations (Yuan et al., 2008) but also among Caucasians (Taki et al., 2005; Vasic et al., 2008). Therefore, MDD appears to share some common biological characteristics across ethnic groups.

In support of our hypothesis, there were significant structural differences between patients who were able to achieve remission and those who responded poorly to antidepressants. Many of the structural abnormalities were correlated with the severity of depression and cognitive dysfunction. Patients with remission had minimal attention problems with reduced GMV over left BA 3 and bilateral BA 6. In contrast, the non-remitting patients showed more cognitive problems including poor acoustic and visual attention, and they also presented a significant GMV reduction in the left DLPFC (BA 9) when compared with the other two groups. Our results are important because this VBM study indicated that patients with MDD were heterogeneous, and not all MDD patients had the same morphological deficits. Furthermore, it implied that severity of depression and patients' responses to antidepressants should also be taken into consideration when investigating structural alterations in MDD.

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