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Research report

Possible involvement of rumination in gray matter abnormalities in persistent symptoms of major depression: An exploratory magnetic resonance imaging voxel-based morphometry study



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ABSTRACT

Background: A recent meta-analysis of many magnetic resonance imaging (MRI) studies has identified brain regions with gray matter (GM) abnormalities in patients with major depressive disorder (MDD). A few studies addressing GM abnormalities in patients with treatment-resistant depression (TRD) have yielded inconsistent results. Moreover, although TRD patients tend to exhibit ruminative thoughts, it remains unclear whether rumination is related to GM abnormalities in such patients or not.

Methods: We conducted structural MRI scans and voxel-based morphometry (VBM) to identify GM differences among 29 TRD patients and 29 healthy age-matched and sex-matched controls. A response style questionnaire was used to assess the respective degrees of rumination in TRD patients. Structural correlates of rumination were examined.

Results: TRD patients showed several regions with smaller GM volume than in healthy subjects: the left dorsal anterior cingulate cortex (ACC), right ventral ACC, right superior frontal gyrus, right cerebellum (Crus I), and cerebellar vermis. GM volumes in these regions did not correlate to rumination. However, whole-brain analysis revealed that rumination was positively correlated with the GM volume in the right superior temporal gyrus in TRD patients.

Limitations: Structural correlates of rumination were examined only in TRD patients.

Conclusions: Our data provide additional evidence supporting the hypothesis that TRD patients show GM abnormalities compared with healthy subjects. Furthermore, this report is the first to describe a study identifying brain regions for which the GM volume is correlated with rumination in TRD patients. These results improve our understanding of the anatomical characteristics of TRD.

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1. Introduction

Major depressive disorder (MDD) is a common psychiatric disorder with a high prevalence of approximately 20% (Kessler et al.,

http://dx.doi.org/10.1016/j.jad.2014.06.030 0165-0327/© 2014 Elsevier B.V. All rights reserved. 2005). About 10–30% of patients with MDD are reportedly resistant to antidepressant treatment (Rush et al., 2006). Treatment-resistant depression (TRD) is recognized as a cause of marked disability and financial burden to individuals and to society, which relates to increased rates of suicide attempts and mortality (Culpepper, 2011; Greden, 2001). Considering the lack of effective treatment against TRD, it is important to elucidate brain abnormalities in such patients.

Numerous neuroimaging studies have provided evidence of anatomical abnormalities in patients with MDD. A recent meta-analysis of 23 magnetic resonance imaging (MRI) studies identified brain regions

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in which the gray matter (GM) volume abnormality was observed in MDD patients (n=986) compared with healthy subjects (n=937) (Bora et al., 2012). Regions with smaller GM volumes in MDD patients included the bilateral rostral anterior cingulate cortex (ACC) extending to the subgenual and rostral parts of the dorsal ACC (Brodmann areas (BA) 24 and 32), bilateral dorsomedial frontal cortex (BA6/8/9), right dorsolateral/precentral frontal cortex (BA9), right anterior insula/ inferior frontal cortex, bilateral putamen, and bilateral caudate (Bora et al., 2012). The MDD patients examined in this meta-analysis included patients who were medication-free or undergoing antidepressant treatment and those with TRD (Bora et al., 2012). In contrast, the few studies that have examined GM abnormalities in TRD patients have vielded inconsistent results. Shah et al. (2002) demonstrated that TRD patients (n=20) showed less GM volume in the right putamen, bilateral hippocampus, bilateral superior frontal gyrus, left superior temporal and precentral gyri, left medial temporal gyrus, and rostral ACC, and greater GM volume in the left cuneus, precuneous, and lingual gyrus compared with healthy controls (n=20). Another study revealed that TRD (n=18) showed reduced GM volume in the right middle temporal gyrus and bilateral caudate compared with healthy subjects (n=17) (Ma et al., 2012). More recently, Serra-Blasco et al. (2013) reported, in TRD patients (n=22), less GM volume in the right superior frontal gyrus (BA 8/9), left cingulate gyrus (BA24), bilateral medial frontal gyrus (BA6/8 and BA10 in left or right side respectively), left insula (BA13), left inferior frontal gyrus (BA44), left parahippocampal gyrus (BA35), left transverse temporal gyrus (BA21), and left post-central gyrus (BA40). Considering the inconsistency of the results among these earlier studies, additional studies must be undertaken to elucidate the anatomical abnormalities of TRD.

A growing body of evidence suggests that ruminative thinking is involved in the pathophysiology of MDD, especially TRD. Rumination is defined as repetitive thinking particularly addressing depressive symptoms. It is probably involved in the causes. meanings, and consequences of these symptoms (Nolen-Hoeksema, 1991). Ciesla and Roberts (2002) reported that rumination is associated with poor response to antidepressants in MDD patients. Furthermore, results demonstrated that ruminationfocused cognitive-behavioral therapy, in addition to antidepressant treatment, improved residual symptoms and remission rates in TRD patients. This improvement was accompanied by reduction in the degree of rumination (Watkins et al., 2011). These results of studies implicate rumination in TRD. It is particularly interesting that a recent MRI study revealed that GM volume in the bilateral inferior frontal gyrus, left ACC, and in the bilateral middle cingulate cortex was negatively associated with rumination in healthy subjects (Kuhn et al., 2012). Nevertheless, it remains

Table 1

Demographic and clinical characteristics of participants.

unknown whether such neural correlates of rumination are detectable in TRD patients.

For this study, we conducted VBM analysis using T1-weighted MRI images to examine GM abnormalities in TRD patients (n=29) compared with healthy subjects (n=29). Additionally, we measured rumination traits. Then we examined whether brain regions exist in which rumination is associated with GM volume in TRD patients.

2. Methods

2.1. Participants

Twenty-nine patients were recruited from the Department of Psychiatry and Neurosciences at Hiroshima University Hospital. Inclusion criteria in this study were: (a) outpatients, (b) diagnosis of major depressive disorder for the current episode established by a trained psychiatrist and clinical psychologist using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996), (c) Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960) score of 8 or greater, and (d) patients designated as having treatment-resistant depression (TRD) according to the definition presented by Thase and Rush (1997) with the level of treatment resistance at stage 2 (n=15) and stage 3 (n=14). Exclusion criteria were the following: current or previous diagnosis of a psychotic spectrum disorder, evidence of organic brain disorder, mental retardation, personality disorder, current high risk of suicide, substance abuse, and severe somatic disease. Twenty-nine healthy control participants were recruited from the normal population. These control participants exhibited no symptom of depression and had no history of psychiatric disorder. Physical and clinical information related to patients and healthy controls is presented in Table 1. Information related to medications is shown in Table 2. One patient discontinued the medication because of adverse effects and ineffectiveness at MRI scanning. Seven patients were taking one antidepressant with anxiolytics at MRI scanning. One was taking one antidepressant with mood stabilizers, antipsychotics, and anxiolytics. One was taking one antidepressant with mood stabilizers and anxiolytics. One was taking one antidepressant with mood stabilizers and antipsychotics. One was taking one antidepressant with antipsychotics and anxiolytics. One was taking one antidepressant with antipsychotics. One was taking one antidepressant with methylphenidate and anxiolytics. One was taking antidepressants of two types. Five were taking antidepressants of two types with antipsychotics and anxiolytics. Five were taking antidepressants of

Variables (mean \pm sd [*])	TRD	НС	Hedge g	t	Df	р
N (male/female) Age, year Age at illness onset, year Duration of illness, month Number of episodes, median (range)	$29 (16/13) 39.57 \pm 8.29 34.72 \pm 7.56 52.55 \pm 57.81 2 (1-4) 2 (1-4) 2 (1-2) (10,12) (10,13) (10,1$	29 (16/13) 38.66 ± 8.36	0.11	0.43	56.00	0.672
BDI RSO	13.90 ± 4.33 24.31 ± 8.68 49.14 + 10.01	5.07 ± 4.34	2.77	10.68 ^a	41.19	< 0.001
Total tissue volume Gray matter volume White matter volume Cerebrospinal fluid	$\begin{array}{c} 1466.88 \pm 163.50 \\ 589.23 \pm 63.53 \\ 640.51 \pm 91.92 \\ 237.15 \pm 45.61 \end{array}$	$\begin{array}{c} 1387.85 \pm 102.22 \\ 578.55 \pm 50.66 \\ 600.23 \pm 53.62 \\ 209.07 \pm 31.41 \end{array}$	0.57 0.18 0.53 0.71	2.21 ^a 0.71 ^b 2.04 ^a 2.73 ^b	46.99 56.00 45.08 56.00	0.032 0.482 0.047 < 0.001

TRD, treatment-resistant depression; HC, healthy control; HRSD, Hamilton rating scale for depression; BDI, Beck depression inventory; RSQ, response style questionnaire^{*}, except for Gender and Number of episodes.

^a *p* values were obtained using a Welch corrected *t*-test.

^b *p* values were obtained using a two-sample *t*-test.

Table 2					
Medication	information	of	patients	with	TRD

Medication category	Medication load in all patients (Mean \pm SD)	Individual medications (n)
Antidepressants	1.90 ± 0.77	Imipramine $(n=3)$ Clomipramine $(n=6)$ Trazodone $(n=7)$ Amoxapine $(n=3)$ Paroxetine $(n=6)$ Sertraline $(n=4)$ Nortriptyline $(n=2)$ Amitriptyline $(n=1)$ Fluvoxamine $(n=2)$ Milnacipran $(n=8)$ Mianserin $(n=2)$
Mood stabilizers	0.41 + 0.82	Lithium $(n=6)$
Antipsychotics	0.34 ± 0.48	Quetiapine $(n=3)$ Sulpiride $(n=4)$ Risperidone $(n=1)$ Blonanserin $(n=1)$
Stimulants	0.03 ± 0.19	Methylphenidate $(n=1)$
Anxiolytics	1.35 ± 0.86	Alprazolam $(n=8)$ Other $(n=23)$
Medication load score of all medications	4.21 ± 1.74	

two types with anxiolytics. Two were taking antidepressants of two types with mood stabilizers. One was taking antidepressants of three types with mood stabilizers. One was taking antidepressants of three types with antipsychotics. Three patients had previously received the electroconvulsive therapy. This study protocol was approved by the Ethics Committee of the Hiroshima University Graduate School of Biomedical & Health Sciences. Written informed consent was obtained from all participants.

2.2. Clinical assessments

To evaluate the depressive symptoms, HRSD (Hamilton, 1960; Nakane and Williams, 2003) and the Beck Depression Inventory (BDI) (Beck et al., 1961; Hayashi and Takimoto, 1991) were used. Ruminative thinking was assessed using a response style questionnaire (Nagura and Hashimoto, 1999; Nolen-Hoeksema and Morrow, 1991).

2.3. Magnetic resonance imaging acquisition

Scanning was conducted (Symphony 1.5T; Siemens AG, Munich, Germany). Structural MR images were acquired for VBM analysis using a T1-weighted gradient echo pulse sequence (TR 12 ms, TE 4.5 ms, flip angle 20°, FOV 256 mm, and voxel dimensions of $1 \times 1 \times 1 \text{ mm}^3$).

The VBM analysis was conducted using Matlab (ver. R2011b; the MathWorks Inc., Natick, MA), Statistical Parametric Mapping (SPM8) software (Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm), and VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html) under OS X. The VBM8 toolbox extends the unified model (Ashburner and Friston, 2005). Images were bias-corrected and segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) using the maximum *a-posteriori* spatial probability segmentation approach extended by partial volume estimation. Then iterative highdimensional normalization by the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra method (DARTEL) (Ashburner, 2007) was applied to the segmented images to register them to the space of the Montreal Neurological Institute (MNI). Tissue deformation was used to modulate the individual

2.4. Statistical analysis

We conducted *t*-tests to examine group differences in age, depressive symptoms, and brain volumes including GM, WM, and CSF. We used Welch corrected *t*-tests for this analysis when the variance was heterogeneous. Then, two sample *t*-tests with covariates were used to examine the group difference in GM volume between TRD patients and healthy subjects controlling the effects of age, sex, and total brain volume using SPM8. To examine the relation between brain volume and rumination, the mean signal intensities on regions that showed significant differences in GM volume between TRD patients and healthy controls were extracted using marsbar (http://marsbar.sourceforge.net/). We conducted partial correlation analysis to remove the effects of medication. For calculation of the medication load score (Almeida et al., 2009; Phillips et al., 2008), the medication dose was coded as levels 1, 2, 3 and more using Sackeim (2001) criteria. For each medication, we coded the patients on levels 1 and 2 of the criteria as low (1), and on level 3 or more as high (2). After we coded the dosage of all medications, we calculated the medication load score by summing individual medication codes. Partial correlation analysis was conducted using R ver. 3.0.2 and Ppcor version 1.0 for Mac OS X (R Core Team, 2013). Furthermore, to explore brain regions that were correlated with rumination, we conducted regression analysis of the whole brain using SPM8. During regression analysis, the effects of age, sex, medication load score, and total brain volume were regressed out. To minimize Type 2 errors, we used a threshold of uncorrected p < 0.001 and a cluster size of at least 50 voxels (Kanai et al., 2011), but we mainly discussed areas that exceeded the cluster level threshold of p < 0.05 (corrected) for the whole brain. To correct the multiple comparisons, we conducted a Monte-Carlo simulation using 3dFWHM and AlphaSim in Analysis of Functional NeuroImages (AFNI) software (Cox, 1996). To conduct the AlphaSim simulations, we entered p = 0.001 at the individual voxel threshold. We used 1000 iteration and 10.62, 12.30, and 11.28 mm for smoothness in a two sample t-test and 10.80, 12.43, and 11.50 mm for smoothness in regression analysis (using 3dFWHM). The voxel size was $1.5 \times 1.5 \times 1.5$ mm³. As a results of AlphaSim simulations, the cluster extent to obtain a cluster level threshold of p < 0.05 (corrected) was 557 voxels for a two sample *t*-test and 576 voxels for regression analysis.

3. Results

3.1. Clinical characteristics

Clinical characteristics are presented in Table 1. In TRD patients, 11 patients (37.93%) were experiencing their first depression episode. The mean episode duration was 16.07 ± 11.44 months. HRSD scores in TRD patients were 13.90 ± 4.33 . The TRD patient group showed significantly higher depressive symptoms (BDI score) than controls (Hedges g=2.77, t (41.19)=10.68, p < 0.001). The RSQ score in TRD patients was 49.14 ± 10.01 .

The TRD and control group were well matched for age and sex (Table 1). TRD patients showed a slightly larger total brain volume including GM, WM, and CSF than that of control participants (Table 1). The total volume of GM was not different between groups, although TRD patients showed significantly larger WM and CSF than those of control participants (Table 1). In the following analyses for examining group differences in GM volume and correlation of GM volume with rumination, the effects of total brain volume were controlled as with age and sex.

3.2. Group differences in brain GM volumes

TRD patients showed a significantly smaller GM volume in the left dorsal ACC (BA33), right ventral ACC (BA32), right superior frontal gyrus (BA10), right cerebellum (Crus I), and cerebellar vermis ($p_{uncorrected} < 0.001$, cluster size > 50) (Fig. 1). Of those regions, the left dorsal ACC and right cerebellum (Crus I) survived the cluster level threshold p < 0.05 (corrected) for the whole brain (Table 3). No region with larger GM volume in TRD patients was identified.

3.3. Brain regions associated with rumination in patients with TRD

No region in which the GM volume was smaller in TRD patients than in healthy controls was significantly correlated to rumination (Table 3). However, regression analysis in the whole brain showed positive correlation of GM volume in the right superior temporal gyrus with rumination in patients (Fig. 2, Table 4).

4. Discussion

This study was undertaken to elucidate the anatomical characteristics in the brain of patients with TRD. The total brain volume including GM, WM, and CSF was slightly larger in TRD patients (Table 1). This increase was likely attributable to larger WM and CSF (Table 1); the latter was consistent with a meta-analysis of structural MRI studies in MDD patients (Kempton et al., 2011). In contrast, the total GM volume did not differ between controls and TRD patients (Table 1). We found several regions for which TRD patients showed smaller GM volume: the ACC, superior frontal gyrus, and cerebellum. Furthermore, this report is the first to demonstrate that GM volume in the superior temporal gyrus is related to rumination in TRD patients.

The GM volume in the ventral and dorsal ACC was smaller in TRD patients than in healthy controls (Fig. 1A and B, Table 3), which is partially consistent with results reported for previous studies (Serra-Blasco et al., 2013; Shah et al., 2002). The ACC has been identified using VBM meta-analysis as a region with the most robust reductions in GM volume in MDD patients (Bora et al., 2012). It is particularly interesting that the smaller GM in the ACC was observed in patients with multi-episode patients, but not with first-episode patients (Bora et al., 2012). Considering that most patients in the present study (62.07%) had multiple episodes, it is possible that progressive reduction of GM volume in the ACC develops through recurrent depressive episodes. Future studies should be conducted to examine the manner in which such progressive GM reduction in the ACC, if any, is involved in TRD development.

In addition to the ACC, we found less GM volume in the superior frontal gyrus in patients with TRD (Fig. 1C, Table 3), but the difference did not survive the cluster level threshold p < 0.05



Fig. 1. Reduction of gray matter volume in patients with treatment-resistant depression compared with healthy controls. Gray matter volume reductions in the right ventral anterior cingulate cortex (A), left dorsal anterior cingulate cortex, cerebellar vermis (B), right superior frontal gyrus (C), and cerebellum Crus I (D) are observed ($p_{uncorrected} < 0.001$, cluster size > 50).

Table 3

Brain	regions	showing	gray	matter	volume	reduction	in	patients	with	TRD,	and	correlation	with	rumination.
			0 .											

Brain region	Side	BA	MNI co	MNI coordinates		MNI coordinates		Cluster size	Z value	Partial correlati	on with rumination
			x	у	z			r	р		
Dorsal ACC	Left	33	-3	9	22	580	3.98	0.13	0.51		
Ventral ACC	Right	32	3	34	-8	250	3.48	-0.14	0.49		
Superior frontal gyrus	Right	10	21	44	30	61	3.63	0.11	0.57		
Cerebellum (Crus I)	Right		20	-85	-24	1272	3.95	0.23	0.23		
Cerebellum vermis	-		-4	-52	-24	497	3.68	0.14	0.48		

Brain regions with underlines survived the cluster level threshold p < 0.05 (corrected) for the whole brain. (x y z), coordinates of primary peak locations in the MNI space. The p values were obtained by partial correlation analysis.

ACC, anterior cingulate cortex; BA, Brodmann area; MNI, Montreal Neurological Institute.



Fig. 2. Gray matter volume of the right superior temporal gyrus showed positive correlation with the RSQ score ($p_{uncorrected} < 0.001$, cluster size > 50) (A). Scatter plots portraying the relation between the volume of the right superior temporal gyrus and RSQ score (B).

Table 4

Brain regions showing gray matter volume associated with rumination in patients with TRD.

Brain region	Side	MNI coo	rdinates		Cluster size	Z value	r [95% CI]	р
		x	у	z				
Superior temporal gyrus	Right	44	-4	- 18	53	3.43	0.55 [0.23 0.76]	0.002

 $(x \ y \ z)$, coordinates of primary peak locations in the MNI space. The p value was obtained using regression analysis. MNI, Montreal Neurological Institute.

(corrected). Although the superior frontal gyrus was not identified by the meta-analysis of VBM studies of MDD patients (Bora et al., 2012), our results were supported by those of previous studies (Serra-Blasco et al., 2013; Shah et al., 2002). It is particularly interesting that Serra-Blasco et al. (2013) demonstrated that the GM changes in the superior frontal gyrus were not observed in first-episode patients or in remitted patients, suggesting that progressive reductions in GM volume in this region might be a specific marker for TRD. It is also interesting that a functional MRI study recently demonstrated that the superior frontal gyrus showed lower resting-state brain activity not only in TRD patients but also in patients with treatment-sensitive depression (Guo et al., 2012), suggesting its role as a trait marker for MDD. Further studies must be conducted to ascertain how the superior frontal gyrus is involved in the pathophysiology of MDD from both structural and functional points of view.

In this study, we found significant reduction in GM volume in the cerebellum (vermis and Crus I) in TRD patients compared with healthy control subjects (Fig. 1B and D, Table 3). GM reduction in the cerebellar Crus I survived the cluster level threshold p < 0.05 (corrected) (Table 3). These results are inconsistent with results of previous studies (Ma et al., 2012; Serra-Blasco et al., 2013; Shah et al., 2002). Furthermore, recent meta-analyses have not identified the cerebellum as a region in which the GM volume was changed in MDD patients (Bora et al., 2012; Kempton et al., 2011). However, an earlier report by Frodl et al. (2008) described progressive GM reduction in several subregions of the cerebellum during 3 years in patients with MDD compared with healthy subjects. Moreover, the resting-state activity in the cerebellum was decreased in TRD patients, but not in patients with treatment-sensitive depression (Guo et al., 2012). It is interesting to examine whether structural changes in the cerebellum contribute to decreased resting-state activity in TRD patients or vice versa.

Structural correlates of rumination in TRD patients are not described in any report of the literature, although TRD patients are known to exhibit a tendency for ruminative thinking (Eisendrath et al., 2011). The present study found no correlation between rumination and GM volume in the ACC, superior frontal

gyrus, or cerebellum, where TRD patients showed less GM volume (Table 3). However, regression analysis of the whole brain revealed that rumination was positively correlated with GM volume in the superior temporal gyrus (Fig. 2, Table 4). In contrast, the superior temporal gyrus was previously reported to show no correlation with rumination in healthy subjects (Kuhn et al., 2012). It is noteworthy that the superior temporal gyrus showed stronger activation during rumination versus concrete distraction in MDD patients (Cooney et al., 2010). Considering this result, our result (Fig. 2, Table 4), and that the degrees of rumination in healthy controls are lower than those in MDD patients (Coonev et al., 2010): it is speculated that the superior temporal gyrus shows a larger GM in TRD patients. However, TRD patients showed no significant differences in the GM volume of the right superior temporal gyrus, even at a relaxed threshold (p < 0.005, uncorrected), which is consistent with results of previous studies (Ma et al., 2012; Serra-Blasco et al., 2013; Shah et al., 2002). Future studies must address how structural correlates of rumination observed in the present study are involved in the pathophysiology of TRD.

This study has several important limitations. First, rumination was not assessed in healthy subjects because this study was conducted to address the structural correlates of rumination in TRD patients. However, considering that brain regions correlated to rumination in healthy patients (Kuhn et al., 2012) differed from those in TRD patients (Table 4), the lack of the data in healthy subjects in this study limited the consideration of the structural correlates of rumination. Second, additional studies must be undertaken to confirm our results because no report in the relevant literature has described a study examining the structural correlates of rumination using VBM analysis in TRD patients. Third, the number of participants in this study was not large, although they are more numerous than in many previous studies (Ma et al., 2012; Serra-Blasco et al., 2013; Shah et al., 2002). Last, but not least, the differences in the severity of symptoms and of treatment resistance in TRD patients might be involved in the inconsistency of results between this and some prior studies (Ma et al., 2012; Serra-Blasco et al., 2013; Shah et al., 2002), although it is noteworthy that some results show consistency among these studies. Additionally, it would be interesting to separate firstepisode and recurrent TRD patients. Furthermore, this study did not include a first-depressive episode, drug-naïve patients, or those with treatment-sensitive depression. A large-scale study including all the categories of patients above must be done to elucidate the anatomical characteristics of TRD.

In summary, this study provides evidence of GM abnormalities in TRD patients compared with control subjects. Moreover, this report is the first describing exploratory analysis of brain regions to which rumination was associated with GM changes in TRD patients. These results therefore improve our understanding of the anatomical characteristics of TRD.

Conflict of interest

All authors declare that they have no conflicts of interest.

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