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Regional cortical thinning in patients with major depressive disorder: A surface-based morphometry study

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ABSTRACT

This study uses surfaced-based morphometry to investigate cortical thinning and its functional correlates in patients with major depressive disorder (MDD). Subjects with MDD ($N=36$) and healthy control subjects ($N=36$) were enrolled in the study. Each subject received T1 structural magnetic resonance imaging (MRI), clinical evaluations, and neuropsychological examinations of executive functions with the Color Trail Test (CTT) and the Wisconsin Card Sorting Test (WCST). This study used an automated surface-based method (FreeSurfer) to measure cortical thickness and to generate the thickness maps for each subject. Statistical comparisons were performed using a general linear model. Compared with healthy controls, subjects with MDD showed the largest area of cortical thinning in the prefrontal cortex. This study also noted smaller areas of cortical thinning in the bilateral inferior parietal cortex, left middle temporal gyrus, left entorhinal cortex, left lingual cortex, and right postcentral gyrus. Regression analysis demonstrated cortical thinning in several frontoparietal regions, predicting worse executive performance measured by CTT 2, though the patterns of cortical thickness/executive performance correlation differed in healthy controls and MDD subjects. In conclusion, the results provide further evidence for the significant role of a prefrontal structural deficit and an aberrant structural/functional relationship in patients with MDD.

1. Introduction

Major depressive disorder (MDD), in addition to its characteristic mood disturbances, is accompanied by substantial cognitive and social functional impairment. Previous imaging studies found structural deficits in cortical or subcortical regions in patients with MDD. Studies using the region of interest (ROI) approach identified several structural deficits in regions critical for emotional processing and stress regulation, including the prefrontal lobe (Kumar et al., 1998), anterior cingulate cortex (Ballmaier et al., 2004; Caetano et al., 2006), orbitofrontal cortex (Ballmaier et al., 2004; Lacerda et al., 2004; Monkul et al., 2007) and hippocampus (Bremner et al., 2000; Caetano et al., 2004; Frodl et al., 2006; Maller et al., 2007). These structural deficits are generally more apparent in patients with a more severe or persistent form of the illness (Lorenzetti et al., 2009). Recent studies using whole-brain approaches with voxel-based morphometry (VBM) (Ashburner and Friston, 2000) avoided the limitation of searching only limited ROIs, and also consistently found decreased gray matter volume (GMV) in MDD patients. The first study (Bell-McGinty et al., 2002), which used VBM in elderly depressed patients, found reduced GMV in the right hippocampus and bilateral middle frontal gyrus. Later studies of MDD showed a reduced GMV in the hippocampus (Egger et al., 2008; Vasic et al., 2008), amygdala (Tang et al., 2007; Egger et al., 2008), anterior cingulate cortex (Tang et al., 2007; Vasic et al., 2008), thalamus (Vasic et al., 2008), medial orbitofrontal cortex (Egger et al., 2008), and right superior frontal gyrus (Yuan et al., 2008). To circumvent the issue that these structural changes might be caused by antidepressant usage, two studies using first-episode drug-naïve patients also found a significant reduction of GMV in the bilateral hippocampus (Zou et al., 2010) and anterior cingulate cortex (Tang et al., 2007), and they provided evidence that structural deficits may have existed prior to using any medication. Studies in subjects at high risk for depression, which included family members of patients with MDD (Amico et al., 2011) or adults reporting childhood emotional maltreatment (van Harmelen et al., 2010), also found significant structural changes, and these findings suggested that the structural changes may be present even before onset of the disease. Until recently, nearly all structural studies of MDD have been volume-based, and studies measuring cortical thickness in MDD have been rare. The only study (Koolschijn et al., 2010) that measured the

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cortical thickness of elderly female MDD patients did not find significant cortical thinning. However, patient selection in the study was limited to depressed elderly females, and the negative finding may not extend to the non-geriatric population. One study (Peterson et al., 2009) found diffused cortical thinning in subjects with a familial risk for MDD. Further studies using cortical thickness may contribute to enhancing understanding of the nature of the structural deficit in patients with MDD.

The functional nature of these structural deficits can be understood by analyzing the association between structural and cognitive functional impairment. Executive dysfunction has been the most replicated cognitive function deficit in MDD, and it has been found to correlate with social disability (Kiosses et al., 2000), poor antidepressant response (Kalayam and Alexopoulos, 1999; Dunkin et al., 2000), and a higher probability of relapse (Alexopoulos et al., 2000). Early studies linked executive dysfunction with prefrontal cortical deficits (Rogers et al., 2004; Vasic et al., 2007; Elderkin-Thompson et al., 2009), though limbic structures were found to produce the same correlations. In an ROI-based study, Frodl et al. (2006) found significantly lower hippocampal volumes in MDD patients, which were correlated with poorer performance in executive function, as measured by the Wisconsin Card Sorting Test (WCST). In another study, Vasic et al. (2008) found that a loss of GMV in the left hippocampus and anterior cingulate in patients with MDD was associated with a poor performance in the WCST. These studies replicated the executive control deficits in MDD and indicated that the structural deficits found in MDD may involve structures or networks critical for executive control.

To further delineate the regional structural deficits of the cortex and their relationship to cognitive dysfunction, this study used surface-based morphometry (SBM) to investigate regional cortical thinning and its association with cognitive performance in patients with MDD. SBM is a non-ROI-based approach used to analyze structural deficits by measuring and comparing the cortical thickness according to vertex. Compared with VBM, cortical thinning is often regionally specific, and has been used to provide crucial information for exploring disease-specific anatomical changes in schizophrenia (Kuperberg et al., 2003; Goldman et al., 2009; Schultz et al., 2010), bipolar disorder (Fornito et al., 2008), and other neuropsychiatric illnesses. Based on previous studies of prefrontal dysfunction in MDD (Rogers et al., 2004; Fitzgerald et al., 2006), we hypothesized that more prominent cortical thinning would be found in the prefrontal areas of MDD patients. Since previous studies provided preliminary evidence of a correlation between structural deficit and executive dysfunction in MDD, executive functions were also measured in these subjects using the WCST and Color Trail-making Test (CTT), and regression analysis for cognitive performance was conducted to further elaborate on the possible functional roles of these structural deficits.

2. Materials and methods

2.1. Participants

Thirty-six first episode ($N=4$) and recurrent ($N=32$) MDD outpatients were recruited at Taipei Veterans General Hospital. The diagnoses were established via structured history taking based on the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV) criteria (American Psychiatric Association, 1994). These patients had been using a variety of antidepressant medications before participating in the experiment, including buproprion ($N=12$), venlafaxin ($N=6$), duloxetine ($N=6$), paroxetine ($N=4$), sertraline ($N=6$), and escitalopram ($N=2$). This study evaluated the severity of symptoms by using the 17-item Hamilton Rating Scale for Depression (HAMD-17) and the Montgomery-Åsberg Depression Rating Scale (MADRS). Participants were screened to exclude substance abuse or dependence within the past 6 months, a history of head injury resulting in a sustained loss of consciousness and/or cognitive sequelae, neurological illnesses, or any comorbidity with schizophrenia, bipolar disorders, other major psychoses, obsessive–compulsive spectrum disorders, post-traumatic stress disorders, or cluster B personality disorders. Comorbidity with anxiety-related disorders was not excluded in this study and the participants were comorbid with several anxiety-related disorders, including panic disorder ($N=12$), general anxiety disorder ($N=8$), and social anxiety disorder ($N=4$). Thirty-six age-, gender-, and handedness-matched healthy controls were also recruited via advertisements. An experienced psychiatrist was in charge of screening these participants by using the Mini International Neuropsychiatric Interview (MINI) to exclude subjects with major psychiatric illnesses. Candidates with a family history of an axis I disorder, including schizophrenia, major depression, or bipolar disorder in first-degree relatives, were also excluded. All procedures were approved by the institutional review board of Taipei Veterans General Hospital. All participants provided written informed consent upon receiving a complete explanation of the experimental procedures.

2.2. Evaluation of cognitive functions

The executive functions were evaluated using the CTT and WCST. The CTT retains the psychometric properties of the standard Trail-Making Test (TMT), though CTT substitutes the use of color for the use of English alphabet letters, rendering it more suitable in cross-cultural and other special-needs contexts. For the Color Trails 1 trial (CTT 1), participants used pencils to rapidly connect circles numbered 1 through 25 sequentially. For the Color Trails 2 trial (CTT 2), participants rapidly connected numbered circles sequentially, though alternating between pink and yellow colors. The examiner used a stopwatch to record the amount of time required to complete the task, which then served as a measurement of performance. The WCST utilized the 128-card procedure (Heaton et al., 1993). The number of perseverative and non-perseverative errors and the number of categories completed were used to measure performance.

2.3. Magnetic resonance imaging

2.3.1. Image acquisition

All MRI scans were performed using a 1.5-T MRI system (Excite II; GE Medical Systems, Milwaukee, WI, USA). T1-weighted images (T1 images) were acquired parallel to the anterior commissure–posterior commissure line by using a 3D 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 thicknesses of 1.5 mm.

2.3.2. Surface-based morphometric analysis

All the structural T1 images were analyzed using FreeSurfer (version 4.0.5, www.nmr.mgh.harvard.edu/martinos) to create anatomical surface models and to perform statistical analyses (Dale et al., 1999; Fischl et al., 1999a). For each subject, the processing stream included the removal of non-brain tissue, transformation to Talairach space, and segmentation of gray-white matter tissue. The thickness measurements across the cortex were computed by finding the point on the gray matter–white matter boundary surface that was closest to a given point on the

Table 1
Means, standard deviations, and group comparisons of demographic data, rating scale scores and neuropsychological performance for healthy and patients.

Subject characteristics	MDD patients ($n=36$)	Healthy controls ($n=36$)	t	p
Age (years)	41.64 ± 12.04	41.81 ± 10.70	−0.06	0.951
Sex	12M/24F	14M/22F	$\chi^2=0.06$	0.806
Education level	13.67 ± 2.78	14.94 ± 2.72	−1.97	0.053
Handedness	35R/1L	36R/0L	$\chi^2=0.06$	1.000
Age at onset	31.78 ± 12.02 (15 61)[a]			
Length of illness (years)	9.64 ± 7.23 (1 26)			
Numbers of episodes	4.64 ± 3.30 (1 10)			
HAMD-17	13.25 ± 9.2			
MADRS	16.31 ± 11.68			
Medications				
Antidepressant	$N=36$			
Antipsychotics	$N=4$			
Anticonvulsant	$N=3$			
Lithium	$N=0$			
Neuropsychological test				
Color Trail Test(CTT)				
Trail 1 time	52.9 ± 15.8	46.63 ± 13.69	1.80	0.076
Trail 2 time	102.8 ± 32.38	78.32 ± 16	4.06	0.0001**
WCST				
Perseverative errors	15.53 ± 12.99	13.47 ± 10.43	0.74	0.462
Non-perseverative errors	18.56 ± 16.16	18.72 ± 17.78	−0.04	0.967
Category finished	4.53 ± 2.1	4.75 ± 2.08	−0.45	0.653

HAMD-17 = 17-item Hamilton Scale for Depression; MADRS = Montgomery-Åsberg Depression Rating Scale; CTT = Color Trail Test; WCST = Wisconsin Card Sorting Test.
[a] : ranges of demographic information.
** $P<0.01$.

estimated pial surface (and vice versa), and averaging these two values (Fischl and Dale, 2000). The accuracy of the thickness measurements derived by this technique has been validated by histological (Rosas et al., 2002) and manual measurements (Kuperberg et al., 2003). To map each subject to a common space, the surface representing the gray matter–white matter border was registered to an average cortical surface atlas using a nonlinear procedure that optimally aligned sulcal and gyral features across subjects (Fischl et al., 1999a). For the vertex-by-vertex cluster analysis, the thickness maps for all subjects in both groups were converted to the common atlas space (Fischl et al., 1999a; Fischl et al., 1999b). The data were smoothed by applying a 2D Gaussian-smoothing kernel of 10 mm.

2.4. Statistical analysis

A general linear model (GLM) was used to test for cortical thickness differences between the two groups, using age and education years as covariates of no interest. This study used an uncorrected threshold of $P<0.01$ for initial vertex-wise comparisons. To correct for multiple comparisons, a Monte Carlo simulation with 10,000 times was performed. Only the cluster with a continuous extent of 100 vertices and a significance threshold of $P<0.05$ in the cluster level were reported.

2.4.1. Correlation of cortical thickness with cognitive performance

The mean cortical thickness values were extracted from the significant clusters of all subjects. The association between cortical thickness and cognitive performance was investigated using multiple regression analyses after adjusting both variables for age. For these analyses, cortical thickness was the dependent variable, and cognitive performance and age were covariates. An interaction term (performance by group) was included in the model to test whether the slope of the relationship differed by group. The measurement of cognitive performance was the covariate of interest. Age was regarded as a potential confounder due to its documented effect on cortical thickness and cognitive function. If a significant correlation in the combined group was found, regressions were computed for each group separately. The correlative relationship was considered significant at $P<0.05$.

3. Results

3.1. Clinical characteristics and cognitive performance

No significant differences were present in age, gender, or education level between healthy controls and the MDD patients (Table 1). Concerning executive function, the MDD patients did not show significant performance impairment in the WCST or CTT 1 (all $P>0.05$). However, the MDD patients took a significantly longer amount of time to finish the CTT 2.

3.2. Cortical thinning in MDD

MDD patients showed significant cortical thinning in different cerebral lobules, with the largest areas of thinning in the prefrontal region (Table 2, Fig. 1), including bilateral superior and middle frontal gyrus, right precentral gyrus, and right orbitofrontal gyrus. Smaller clusters of cortical thinning were also noted in the parietal lobe (bilateral inferior parietal regions and left postcentral gyrus), temporal lobe (left entorhinal and middle temporal cortex), and occipital lobe (left lateral occipital and lingual gyrus). The only regions showing significantly higher thicknesses in MDD patients were the left anterior insula and lateral orbitofrontal gyrus.

Since previous works (Frodl et al., 2003; Kronmüller et al., 2009) suggested that patients with multiple episodes are worse off compared with first-episode patients, further analysis was conducted to analyze the effect of the numbers of past depressive episodes on

Table 2
Cortical regions showing significant different cortical thickness in MDD.

Cluster no	Structures	Max -logP	Size(mm^2)	TalX	TalY	TalZ	Clusterwise *P*	NVtxs
MDD<HC								
LH								
Frontal								
1	Superior frontal	−4.6	1383.58	−8	55	26	0.0001	2392
2	Precentral	−3.5	98.33	−25	−11	52	0.0012	212
3	Rostral middle frontal	−3.3	556.37	−24	48	−4	0.0001	761
4	Superior frontal	−2.5	65.97	−10	−7	63	0.0014	182
5	Caudal middle frontal	−2.4	93.09	−42	5	41	0.0012	188
6	Superior frontal	−2.3	55.55	−10	1	45	0.0014	138
Temporal								
7	Entorhinal	−3.0	94.25	−29	−2	−31	0.0012	191
8	Middle temporal	−2.6	185.56	−56	−24	−11	0.0004	304
Parietal								
9	Inferior parietal	−2.5	45.15	−50	−53	25	0.0014	101
10	Inferior parietal	−2.3	100.56	−31	−70	22	0.0012	151
Occipital								
11	Lateral occipital	−3.0	96.87	−24	−94	−9	0.0012	133
12	Lingual	−2.7	185.23	−13	−70	−2	0.0004	242
RH								
Frontal								
1	Precentral	−5.1	338.69	52	8	27	0.0001	656
2	Rostral middle frontal	−4.5	464.2	21	58	11	0.0001	573
3	Superior frontal	−4.3	1197.75	16	49	25	0.0001	2025
4	Rostral middle frontal	−3.8	82.61	29	34	20	0.0011	154
5	Caudal middle frontal	−3.7	342.02	38	23	38	0.0001	585
6	Lateral orbitofrontal	−3.1	168.85	24	44	−11	0.0008	269
7	Pars opercularis	−3.1	94	36	18	20	0.0011	219
8	Superior frontal	−2.7	122.61	9	3	51	0.001	250
Parietal								
9	Postcentral	−2.9	33.05	23	−27	50	0.0011	100
10	Supramarginal	−2.7	123.09	42	−35	37	0.001	348
11	Inferior parietal	−2.7	99.94	54	−45	30	0.0011	196
MDD>HC								
LH								
1	Lateral orbitofrontal	2.9	63.7	−25	16	−14	0.0014	153
2	Insula	2.7	108.6	−34	7	0	0.0012	230
RH								

LH = left hemisphere, RH = right hemisphere, TalX = X coordinate in Talaraich space, TalY = Y coordinate in Talaraich space, TalZ = Z coordinate in Talaraich space. NVtxs = numbers of vertex.

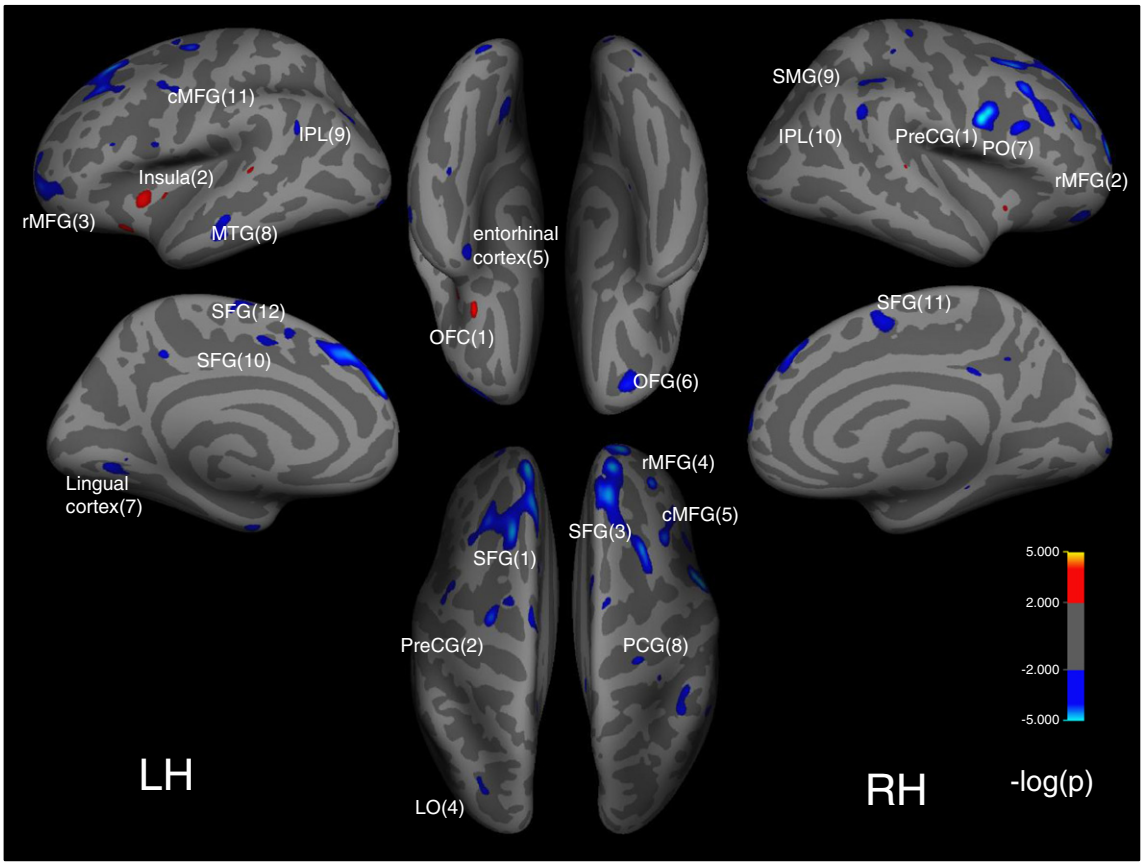

Fig. 1. Regions showing significant between-group differences in cortical thicknesses on the lateral and medial inflated cortical surfaces. The clusters of MDD<HC were rendered in blue and MDD>HC in red. The number enclosed in parentheses for each structural description represents the cluster no. in Table 2. LH = left hemisphere; RH = right hemisphere. cMFG = caudal middle frontal gyrus; IPL = inferior parietal lobe; MTG = middle temporal gyrus; OFG = orbitofrontal gyrus; PO = pars opercularis; PreCG = precentral gyrus; LO = lateral occipital area; rMFG = rostral middle frontal gyrus; SFG = superior frontal gyrus; SMG = supramarginal gyrus.

cortical thickness within the MDD group. The MDD patients were split into two groups based on the median number ($N=3$) of past depressive episodes: Group 1 had a number of past depressive episodes equal to or higher than four ($N=17$), and Group 2 had a number of past depressive episodes lower than four ($N=19$) (see supplementary Table 1 for detailed demographic data of these two groups). The age was used as a covariate in the analysis. The results showed that the MDD patients with more past depressive episodes (Group 1) showed significant cortical thinning in the left prefrontal lobe, including left lateral orbitofrontal, par opercularis, and caudal and rostral middle frontal gyrus (Supplementary Table 2). To a lesser extent, cortical thinning also occurred in the right caudal middle frontal, right inferior parietal lobe, and right cuneus areas. Conversely, the areas of increased cortical thickness involved bilateral superior parietal areas.

3.3. Functional correlate of cortical thinning by regression analysis

The clusters showing the cortical differences between MDD patients and healthy controls were used to define the ROIs for behavioral correlations. The cortical thickness values were averaged across all vertices within the significant clusters. Regression analysis showed that the cortical thickness in several clusters of the bilateral frontal and parietal regions (Table 3) was inversely correlated with the time required to complete the CTT 2 in the combined group. For these correlations, cortical thinning predicted worse executive performance. The regression analysis was also conducted within each group (Table 3). The results showed that the cortical thickness of the right rostral middle frontal gyrus, superior frontal gyrus, caudal middle frontal gyrus, and supramarginal gyrus had a significant correlation with CTT 2 performance only in healthy controls (Fig. 2). Conversely, the cortical thickness of the left superior frontal gyrus showed a significant correlation only in MDD patients.

This study also performed regression analysis of the correlation between cortical thickness and clinical variables in the MDD group, with age as a covariate. The results did not reveal any significant correlation between the duration of illness, symptom severity (as measured by the HAMD-17 and MADRS), and cortical thickness of the ROIs in MDD patients ($P>0.05$).

Table 3
Regression analyses of cortical thickness on finishing time of CTT 2 with the interaction term of time by group, and within group regressions.

ROI	Time		Time by group		Within group			
					Controls		Patients	
	t	*p*	*t*	*p*	*t*	*p*	*t*	*p*
Left SFG(1)	−2.00	0.048*	0.70	0.48	−1.89	0.06	−2.28	0.029*
Left IPL(9)	−2.27	0.026*	1.62	0.108	−1.75	0.18	−1.37	0.08
Right rMFG(2)	−2.64	0.010*	2.06	0.040*	−2.67	0.01*	−0.59	0.55
Right SFG(3)	−3.37	0.001**	2.32	0.020*	−3.30	0.002**	−1.62	0.11
Right cMFG(5)	−2.84	0.005**	1.83	0.079	−3.09	0.004**	−1.25	0.21
Right SMG(10)	−2.98	0.003**	2.29	0.024*	−3.19	0.003**	−0.71	0.47

SFG = superior frontal gyrus; rMFG = rostral middle frontal gyrus; cMFG = caudal middle frontal gyrus; SMG = supramarginal gyrus.
* $P<0.05$.
** $P<0.01$.

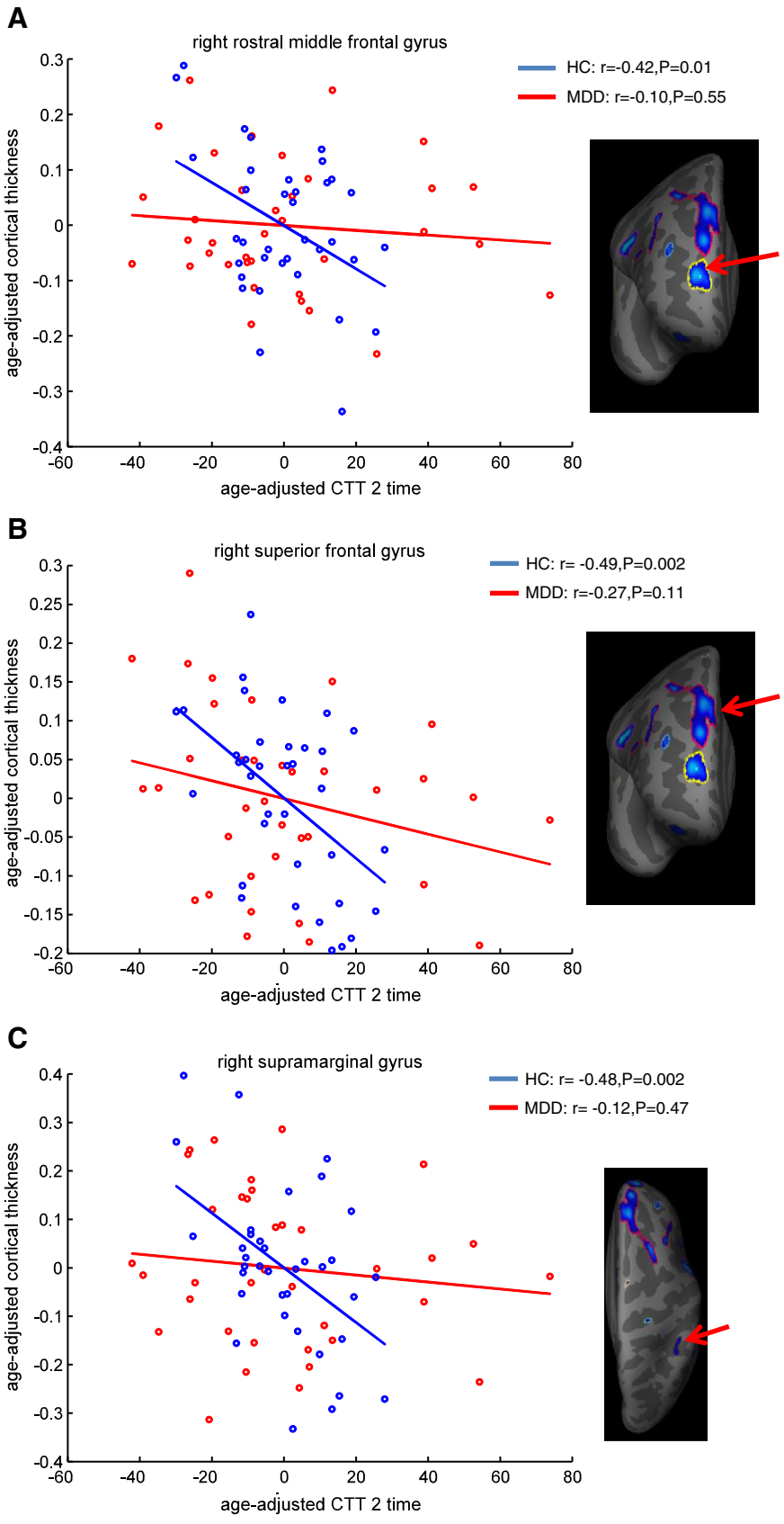

Fig. 2. Scatter plots of the age-corrected regressions of regional cortical thickness and finishing time of CTT 2 in the 3 regions that showed significant between-group differences in thickness/executive performance relationships: (A) right rostral middle frontal gyrus, right superior frontal gyrus and (C) right supramarginal gyrus. Separate regression lines are given for controls and patients. Cortical thickness is related to CTT 2 performance only in controls, but not in MDD.

4. Discussion

The objective of this study is to use SBM to measure cortical thinning and its association with cognitive deficits in MDD patients. Consistent with the hypothesis of this study, the largest areas of thinning were in the prefrontal cortex of MDD patients, especially in the bilateral superior frontal gyrus. To a lesser extent, cortical thinning was present in the parietal, temporal, and occipital lobes. Cortical thinning in the prefrontal cortex was also modulated by the numbers of past depressive episodes, indicating that the patients with more depressive episodes had significantly more cortical thinning in the prefrontal cortex, especially in the left side. Cortical thickness in several clusters showing significant cortical thinning in MDD patients predicted executive function performance, as measured by the CTT 2. Further, within-group analysis demonstrated a different pattern of cortical thickness/executive performance correlation in MDD patients and healthy controls, suggesting an aberrant structure–function relationship in MDD patients.

The prefrontal lobe is significant for the cortical-limbic dysregulation model of depression (Mayberg, 1997). Additionally, the structural abnormalities in the prefrontal lobe were found to correlate with poor clinical response (Salvadore et al., 2011). This study demonstrated that the largest areas of cortical thinning occur in the prefrontal lobe, including the bilateral superior frontal gyrus and the rostral and caudal middle frontal gyruses. Bilateral cortical thinning in the superior frontal gyrus was also reported in a previous SBM study in subjects at a risk for depression (Mollica et al., 2009) and in VBM studies of MDD patients (Yuan et al., 2008; Li et al., 2010). Decreased metabolism in the superior frontal gyrus was also reported in previous positron emission tomography (PET) studies (Bonte et al., 2001). Cortical thinning in the rostral and caudal middle frontal areas is located in Brodmann area 9, which is located near the traditionally named dorsolateral prefrontal cortex (DLPFC). Functional impairment in the DLPFC was consistently found in previous PET studies (Bench et al., 1992; Bonte et al., 2001; Oda et al., 2003) and functional MRI (fMRI) (Elliott et al., 2002; Oda et al., 2003; Lawrence et al., 2004), and also serves as a target for repetitive transcranial magnetic stimulation (rTMS) treatment (Fitzgerald et al., 2006). The findings of this study provide further evidence for prefrontal pathology in MDD, and also localize the deficit to more detailed prefrontal subregions. The cortical thinning deficit in the prefrontal lobe was found to be bilateral in this study, though the MDD patients with more past depressive episodes showed significantly more cortical thinning in the left prefrontal cortex compared to those with the number of past depressive episodes lower than four. This is consistent with the previous finding of more significant left prefrontal pathology suggested in a previous imaging study (Kiosses et al., 2000) and meta-analysis (Koolschijn et al., 2009).

In addition to the prefrontal cortex, this study also noted cortical thinning in the temporal, parietal, and occipital lobe in the MDD patients. Regarding the structures in the temporal lobe, significant cortical thinning was present in the left entorhinal cortex. The entorhinal cortex and hippocampus constitute structures critical for episodic memory and emotional regulation. Previous MRI studies also found reduced volumes of the entorhinal cortex in refractory MDD patients (Furtado et al., 2008). Cortical thinning was also present in the primary sensory areas, including the right post-central gyrus (primary somatosensory) and the left lingual cortex (primary visual). Although they were not the focus of discussion in previous studies, structural or functional deficits in these primary sensory areas are consistent in MDD patients. The post-central gyrus, which constitutes the primary sensorimotor cortex, was found to have volumetric deficits in previous VBM studies of MDD patients (Yuan et al., 2008; Li et al., 2010) and in an SBM study of subjects at risk for depression (Mollica et al., 2009). Cortical thinning in the post-central gyrus was also demonstrated in patients with bipolar disorder (Lyoo et al., 2006) and in first-episode schizophrenia patients (Schultz et al., 2010). Concerning the lingual cortex, deficits in visual processing and fMRI activation were reported in previous functional studies (Desseilles et al., 2009). Furthermore, a recent whole-brain functional connectivity study (Veer et al., 2010) showed a significant reduction in the functional connectivity of a lingual-inferior temporal network in MDD patients. The findings of cortical thinning in these two primary sensory areas provide further evidence that structural deficits exist in primary visual and somatosensory areas in MDD patients. This finding suggests a possible role of the primary sensorimotor cortex in the modulation of depression and mood (Canbeyli, 2010).

The largest region with a significant increase in cortical thickness in MDD patients is the left anterior insula. The anterior insula contains the key nodes in visceral-autonomic/social-emotional networks, and is critical for emotional regulation, regardless of valence (Dolan, 2002; Phan et al., 2002). Increased activations of anterior insula during emotion processing is a consistent finding in previous fMRI or PET studies of MDD patients, and these patterns of hyper-activations were attenuated after antidepressant treatments (Arce et al., 2008; Delaveau et al., 2010). Increased left insular volume was reported in a VBM study of bipolar disorder (Lochhead et al., 2004) and of subjects with a familial predisposition to bipolar disorder (Kempton et al., 2009), though this has not been reported in previous morphometric studies of MDD patients. The findings call for replication because previous imaging studies have generally shown gray matter volume loss (Soriano-Mas et al., 2011) or decreased functional connectivity (Veer et al., 2010) in MDD patients.

A regression analysis was conducted between cortical thickness and executive performance because previous studies on aged groups (Burggren et al., 2011) and schizophrenia (Hartberg et al., 2010; Ehrlich et al., 2011) provided evidence that the significant relationships between cortical thickness and neurocognitive performances were localized in brain areas known to be involved in cognition. In this regression analysis, cortical thickness in several frontoparietal regions correlated with the performance of executive function identified by the CTT 2, implicating that the structural deficit in MDD may involve the cortical network, which is significant for executive controls. Compared to the CTT 1, the CTT 2 specifically requires the mental flexibility and cognitive-shifting aspects of the executive function, and also necessitates the subjects to shift to different thoughts in response to changing situations. The CTT, which retains the psychometric properties of the standard TMT, was used in this study because of the cultural backgrounds of the participants. A significant slowing of the TMT has also been noted in previous behavioral studies of MDD patients (Austin et al., 1999; Channon and Green, 1999; Moritz et al., 2001). Another VBM study (Yuan et al., 2009) found prominent TMT deficits in MDD patients, and these deficits were associated with large white matter volumes in the right inferior frontal lobe. These results provide additional support for the executive dysfunction measured by the CTT in MDD patients, and prefrontal regions are significant in executive control. These results also provide preliminary evidence for an aberrant cortical structure/functional relationship in MDD patients, indicating that the left prefrontal cortex is significant for determining the executive performance in MDD, while the right frontoparietal regions were predominant in healthy controls.

An imperative caveat of this study is that all the MDD participants were medicated with various antidepressants, anticonvulsants, or antipsychotics. Although the effects of antidepressants on cortical thickness are unclear, antidepressants were found to have a neurotrophic effect on the hippocampus in previous animal studies (Banasr et al., 2004). Longitudinal studies are required to identify changes in cerebral surface anatomy during the course of MDD and in the effects of different antidepressant treatments.

In conclusion, the results of this study support the hypothesis that MDD patients experience cortical thinning mostly in the prefrontal lobe, while also demonstrating thinning to a lesser extent in the parietal, temporal, and occipital regions. The patients with more past

depressive episodes showed more significant cortical thinning in the prefrontal cortex, especially in the left side. Different patterns of cortical thickness/executive performance in healthy controls were also observed, suggesting that the structure–function relationship is aberrant in the disease process.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.pscychresns.2011.07.011.

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