Atrophic Corpus Callosum Associated with Altered Functional Asymmetry in Major Depressive Disorder

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Purpose: Impairments in intra- and inter-hemispheric information transfer circuits have been reported in patients with major depressive disorder (MDD). However, the specific anomalous connection (intra- and/or inter-hemispheric) and hemisphere (left and/or right) in which this connection plays a more dominant role in the pathogenic mechanism underlying MDD are still poorly understood.

Patients and Methods: Structural magnetic resonance imaging and resting-state functional magnetic resonance imaging were performed in 33 patients with MDD and 33 healthy controls. The intra- and inter-hemispheric functional connectivity (FC) strength in the default mode network areas and volume of the callosal subregions were computed using independent samples t-tests. The partial correlations between the volumes and FCs were also computed.

Results: The patients with MDD had smaller volumes in the genu of the corpus callosum than the controls. The intrahemispheric FCs of the bilateral posterior cingulate gyrus, left precuneus, left medial superior frontal gyrus, left medial orbitofrontal gyrus, left angular gyrus and left middle temporal gyrus, and interhemispheric FCs of the bilateral posterior cingulate gyrus in the patients with MDD were lower than those in the controls. Moreover, the intrahemispheric FCs of the precuneus and interhemispheric FCs of middle frontal gyrus, orbital middle frontal gyrus, and anterior cingulate gyrus in the patients with MDD showed right-lateralized asymmetry, which were opposite from the asymmetry patterns observed in the controls. The functional asymmetry of the anterior cingulate gyrus was correlated with the volume of the genu of the corpus callosum and disease duration.

Conclusion: These findings provide robust evidence that intra- and inter-hemispheric disconnections are involved in MDD, and that functional disruptions in the left hemisphere may be more relevant to the pathophysiology of MDD. Furthermore, imbalanced interhemispheric exchanges may contribute to the anatomical deficits in the corpus callosum in patients with MDD.

Keywords: major depressive disorder, asymmetry, functional connectivity, corpus callosum

Introduction

Structural and functional asymmetry are fundamental biological traits in the human brain that may be attributed to lateral genetic expression and/or environmental influence. Each cerebral hemisphere has its own distinct strategy for multifarious perceptual and cognitive processing, such as handedness, language, and visuospatial functions.1 Moreover, emotional modulation is also lateralized within the cerebral hemispheres. Several models, such as the valence hypothesis and the...
right hemisphere hypothesis, have been proposed to describe the relationship between emotions and cerebral lateralization, and some researchers believe that the right hemisphere may be more responsible for affective processing, while the left hemisphere may be more dominant for cognitive processing. The specialized functions within the bilateral hemispheres may be conducive to efficient computation and information communication.

Disrupted hemispheric asymmetry occurs in various neuropsychiatric diseases, such as social anxiety disorder, schizophrenia, epilepsy and major depressive disorder (MDD). As a severe mental disease, MDD involves emotional dysregulation that typically presents as excessive sadness, anhedonia and suicidality. Electroencephalography (EEG) studies have consistently verified a right-lateralized activated pattern of frontal alpha band signal in patients with MDD. Our previous work demonstrated that the altered structural asymmetry in patients with MDD was mainly involved in cortical-striatal-pallidal-thalamic circuits. Notably, many resting-state functional MRI (rs-fMRI) studies have focused on the functional connectivity (FC) of the left and right cerebral hemispheres and consistently showed decreased interhemispheric FCs (FC_inter) in MDD. Furthermore, emerging evidence from task-based functional research suggests that the key pathogenic mechanisms underlying MDD may be deficient top-down (cortical-to-limbic) cognitive control and/or enhanced bottom-up (limbic-to-cortical) emotional processing; however, these disrupted intrahemispheric communications in MDD, which can be represented as intrahemispheric FCs (FC_intra) using rs-fMRI techniques, have not been adequately investigated. Whether the biased functional asymmetries were outcomes of FC_inter and/or FC_intra in patients with MDD remains unknown.

The corpus callosum is the largest of the intra- and inter-hemispheric myelinated axonal tracts that connect and integrate neural activity in the human brain. This formation of precise connections is essential for many aspects of higher neural functioning, including the integration of complex sensory information and regulation of cognitive and affective functions such as attention, memory, language, and abstract reasoning. As a physical pathway for information transfer within/between the hemispheres, the corpus callosum plays an important role in the balance of hemispheric activity. Research on split-brain patients has resulted in numerous insights into cerebral asymmetry and the interhemispheric exchange of information. For example, language is one of the most lateralized brain functions, with the left hemisphere being dominant in most people. Linguistic stimuli transmitted to the right hemisphere cannot be diverted to the left hemisphere in patients who undergo corpus callosotomy, and language-related areas located in the right hemisphere cannot process these stimuli properly, giving rise to lingual abnormalities. A thinning corpus callosum has been found in patients with bipolar disorder and disrupted information exchange caused by impaired callosal function may lead to mood dysregulation in patients with bipolar disorder. Bipolar disorder is a mood disorder characterized by mania and hypomania, and depression is its most common clinical feature. Moreover, impaired white matter integrity and reduced volumes in the corpus callosum have been consistently observed in MDD in previous structural studies.

In the current study, we hypothesized that structural impairments in the corpus callosum may be associated with altered functional asymmetry in patients with MDD. Structural magnetic resonance imaging (MRI) and rs-fMRI were implemented to examine the callosal volumetric changes, asymmetric patterns of functional connectivity within default mode network (DMN) areas and the relationships between potential callosal volumetric changes and functional asymmetry in patients with MDD.

Patients and Methods

Subjects

Thirty-three middle-aged patients diagnosed with MDD (21 females and 12 males) were included from the outpatient clinic of the Department of Psychology of our hospital. In an interview presided over by 2 experienced psychologists, the life-chart methodology was used to evaluate depression duration and severity using the 24-item Hamilton Depression Scale (HAM-D_24). The inclusion criteria were as follows: 1) patients aged between 18 and 48 years, 2) patients who met the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) diagnostic criteria for MDD, 3) patients who were newly diagnosed with a depressive episode and were not currently taking antidepressants, and 4) patients with moderate to severe depression (a total HAM-D_24 score > 20). Thirty-three age-, sex- and education-matched healthy controls (HCs) who also received independent evaluations using the HAM-D_24 were recruited for the study.

All subjects were right-handed, with no history of psychiatric or neurological disorders such as schizophrenia, bipolar disorder, Parkinson’s disease, dementia,
stroke, multiple sclerosis, brain tumors, or major medical
diseases such as diabetes mellitus, heart failure, and
anemia.

All subjects engaged in the study provided written
informed consent before the study started. The Medical
Ethics Committee of Southwest Hospital approved the
study protocol and this study was conducted in accordance
with the Declaration of Helsinki.

MRI Acquisition

Imaging data were obtained using a Siemens 3.0-Tesla Trio
Tim MRI scanner (Siemens AG, Erlangen, Germany)
equipped with a standard 12-channel phase-array head coil.
To reduce head movement, sponge pads were placed on both
sides of each participant’s head. High-resolution structural T1-
weighted MR images and rs-fMRI scans were conducted on all
participants. The structural T1WI used magnetization-
prepared rapid gradient echo (MPRAGE) with the following
parameters: TR = 1900 ms, TE = 2.52 ms, FA = 9°, FOV = 256
× 256 mm², slice thickness = 1 mm, number of slices = 176,
and voxel size = 1 × 1 × 1 mm³. The resting functional scans
were acquired using a 240 contiguous echo-planar imaging
(EPI) sequence with the following settings: TR = 2000 ms,
TE = 30 ms, FA = 90°, slice thickness = 3 mm, number of
slices = 36, FOV = 192 × 192 mm², matrix size = 64 × 64 and
voxel size = 3 × 3 × 3 mm³. All subjects were instructed before
the scan to simply rest with their eyes closed and to not think of
anything in particular or fall asleep.

MRI Analysis

Before analyzing the structural images, we examined
whether the images were impacted by head movement.
The qualified structural images were further volume seg-
mented using FreeSurfer software (Massachusetts General
Hospital, Boston, MA, USA, http://surfer.nmr.mgh.har
vard.edu). The automated post-processing streams
have been depicted in detail in previous studies29,30 and
generally as follows: Talairach coordinate system transform,
bias-field correction, signal strength standardization, skull
and soft tissues strip, volume labeling and white matter
segmentation. The corpus callosum, including the genu
(GCC), anterior midbody (aMCC), posterior midbody
(pMCC), isthmus (ICC) and splenium (SCC) (Figure 1),
was segmented based on a previously proposed
classification.31 The volumes of these 5 callosal subre-
regions were then extracted.

The functional images were processed using the tool-
box for Data Processing & Analysis for Brain Imaging
software (DPABI, version 3.0, http://www.rfmri.org/
dpabi), which is based on the Statistical Parametric
Mapping (SPM) program (Wellcome Department of
Cognitive Neurology, University College, London, UK,
http://www.fil.ion.ucl.ac.uk/spm/software/spm12/), and the
Resting-State fMRI Data Analysis Toolkit (REST, http://
www.restfmri.net), implemented in MATLAB R2012a
(The MathWorks Inc., Natick, MA, USA). The details of
the preprocessing procedures have been described in pre-
vious studies5,11,32 and primarily consist of the following
steps. The first 10 volumes were discarded to stabilize the
signal. The remaining 230 volumes were corrected for
acquisition time differences between slices and for motion
effects, and subjects with more than a 2 mm translation
and 2° maximal rotation were removed. The resulting data
were spatially normalized to the Montreal Neurological
Institute (MNI) space and were spatially smoothed with a
6-mm full-width Gaussian kernel at half maximum.
A temporal filter (0.01–0.08 Hz) was applied to reduce the
effect of low-frequency drifts and high-frequency phy-
siological noise. Linear trends were removed via linear
regression analysis. Per previous reports,33,34 28 DMN
areas, including the bilateral medial superior frontal
gyrus (mSFG), medial orbitofrontal gyrus (mOFG), middle
frontal gyrus (MFG), orbital middle frontal gyrus
(oMFG), anterior cingulate gyrus (ACG), posterior cingu-
late gyrus (PCG), hippocampus (HP), parahippocampal
gyrus (PHG), inferior parietal lobule (IPL), supramarginal
gyrus (SMG), angular gyrus (AG), precuneus (PC), middle
temporal gyrus (MTG), and middle temporal pole (MTP),
were selected, and the correlation coefficients between
these areas were calculated based on the region of interest
(ROI)-wise correlation approach for each participant. The
standard ROIs were defined based on the Automated
Anatomical Labeling (AAL) template.32,35 The resultant
correlation coefficients were transformed to Fisher’s

![Figure 1](http://www.rfmri.org/dpabi) Subdivision of the corpus callosum into five subregions.

Abbreviations: GCC, genu of corpus callosum; aMCC, anterior midbody of corpus callosum; pMCC, posterior midbody of corpus callosum; ICC, isthmus of corpus callosum; SCC, splenium of corpus callosum.
z scores to improve distribution normality. The average coefficient (absolute value) of an ROI with other ROIs from the ipsilateral hemisphere was designated the ROI’s FC_{intra}, and that from the contralateral hemisphere was designated the ROI’s FC_{inter}. To quantify the FC differences between the left and right hemispheres, the asymmetry index (AI) was computed for each ROI using the following formula: \[ \text{AI} = \frac{\text{left FC} - \text{right FC}}{\text{left FC} + \text{right FC}} \times 100/100. \] The AI values ranged from −100 (entirely rightward lateralization) to +100 (entirely leftward lateralization).

**Statistical Analysis**

Demographic characteristics and clinical features were compared between patients with MDD and the HCs using the independent sample t-test (age and HAM-D_{24} score), Mann–Whitney U-test (education level) and chi-square test (sex). The independent two-sample t-test was used to assess significant differences in the volumes of the callosal subregions, FC_{intra}, FC_{inter}, and the AIs of FC_{intra} (AI_{intra}) and FC_{inter} (AI_{inter}) between the patients with MDD and the HCs. Partial correlation analysis was performed to explore the relationships between structural and functional parameters with statistically significant differences and the clinical features of patients with MDD. Age, sex, and education level were imported as covariates. Statistical analyses were performed using SPSS 22.0 software (IBM Inc., Armonk, New York, USA). The Bonferroni method or false discovery rate (FDR) correction was applied to the between-group analyses and correlation analyses that involved multiple comparisons.

**Results**

**Participants’ Characteristics**

Table 1 displays the participants’ demographic and clinical information. The MDD and HC groups were matched for age, sex, and education level (p > 0.05). The HAM-D_{24} scores of patients with MDD were significantly higher than those of the HCs (p < 0.05).

**Callosal Volume Analysis**

Compared with HC group, the MDD group showed significantly smaller GCC volumes (Bonferroni-corrected p < 0.05). No significant differences were found in the aMCC, pMCC, ICC or SCC volumes between the MDD and HC groups (Bonferroni-corrected p > 0.05) (Table 2) or in the total corpus callosum volumes between the MDD and HC groups (p > 0.05).

**Table 1** Demographic Features

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MDD (n = 33)</th>
<th>HC (n = 33)</th>
<th>Diagnosis Effect</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>28.76 ± 1.58</td>
<td>31.64 ± 1.29</td>
<td>t = -1.41</td>
<td>0.162</td>
</tr>
<tr>
<td>Sex, female:male</td>
<td>21:12</td>
<td>18:15</td>
<td>( \chi^2 = 0.56 )</td>
<td>0.453</td>
</tr>
<tr>
<td>Education, years</td>
<td>13.79 ± 0.52</td>
<td>13.67 ± 0.69</td>
<td>u = -0.18</td>
<td>0.855</td>
</tr>
<tr>
<td>Duration of disorder, years</td>
<td>1.60 ± 0.26</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HAM-D_{24} score</td>
<td>30.88 ± 0.69</td>
<td>2.61 ± 0.27</td>
<td>t = 38.24</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Notes: Continuous variables are expressed as mean ± SEM. Statistical significance: p value < 0.05.

**Abbreviations:** MDD, major depressive disorder; HC, healthy control; HAM-D_{24}, 24-item Hamilton Depression Scale.

**Table 2** Volumes of Callosal Subregions in the MDD and HC Groups

<table>
<thead>
<tr>
<th>Subregions</th>
<th>Volume (mm³)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCC</td>
<td>821.60 ± 23.20</td>
<td>-2.92</td>
<td>0.005*</td>
</tr>
<tr>
<td>aMCC</td>
<td>537.64 ± 22.99</td>
<td>-0.31</td>
<td>0.755</td>
</tr>
<tr>
<td>pMCC</td>
<td>553.87 ± 22.72</td>
<td>0.34</td>
<td>0.732</td>
</tr>
<tr>
<td>ICC</td>
<td>501.55 ± 16.25</td>
<td>0.82</td>
<td>0.416</td>
</tr>
<tr>
<td>SCC</td>
<td>943.01 ± 26.44</td>
<td>-0.88</td>
<td>0.385</td>
</tr>
</tbody>
</table>

Notes: Continuous variables are expressed as mean ± SEM. *Bonferroni-corrected p = 0.05/5 = 0.01.

**Abbreviations:** MDD, major depressive disorder; HC, healthy control; GCC, genu of the corpus callosum; aMCC, anterior midbody of the corpus callosum; pMCC, posterior midbody of the corpus callosum; ICC, isthmus of the corpus callosum; SCC, splenium of the corpus callosum.

**Functional Connectivity Analysis**

The FC differences between the MDD and HC groups were visualized using the BrainNet Viewer (http://www.nitrc.org/projects/bnv/) (Figure 2). Supplementary Table 1 shows the average FC strength for all ROIs. Compared with the HC group, the MDD group exhibited significantly lower FC_{intra} strength in the left PCG (t = -4.62, FDR-corrected p = 0.0003), right PCG (t = -3.29, FDR-corrected p = 0.03), left mSFG (t = -2.66, FDR-corrected p = 0.03), left mOFG (t = -3.69, FDR-corrected p = 0.003), left AG (t = -2.70, FDR-corrected p = 0.03), left PC (t = -2.95, FDR-corrected p = 0.02) and left MTG (t = -2.55, FDR-corrected p = 0.03) (Figure 2A), and lower FC_{inter} strength in the left PCG (t = -3.26, FDR-corrected p = 0.03) and right PCG (t = -3.77, FDR-corrected p = 0.005) (Figure 2B). No significantly greater FC_{intra} or FC_{inter} strength was observed in the patients with MDD.

Compared with the HCs, the MDD group showed significantly lower AI_{intra} in the PC (t = -3.33, FDR-corrected p = 0.01) and lower AI_{inter} in the MFG (t =
−3.75, FDR-corrected \( p = 0.005 \)), oMFG \( (t = -3.45, \text{FDR-corrected } p = 0.007) \) and ACG \( (t = -3.24, \text{FDR-corrected } p = 0.009) \) (Figure 3). No significantly greater AI\(_{\text{intra}}\) or AI\(_{\text{inter}}\) was observed in the patients with MDD.

**Correlation Analysis**

The partial correlation analysis revealed a significant positive correlation between the GCC volume and AI\(_{\text{inter}}\) of the ACG \( (r = 0.50, p = 0.005) \), a negative correlation between the HAM-D\(_{24}\) scores and AI\(_{\text{inter}}\) of the mOFG \( (r = -0.48, p = 0.008) \), and a negative correlation between the disease duration and AI\(_{\text{inter}}\) of the ACG \( (r = -0.47, p = 0.009) \) in the patients with MDD (Figure 4).

**Discussion**

The DMN is strongly correlated with controlling and processing emotional/cognitive behaviors and self-generated thought,\(^{38}\) and the PCG, mSFG, mOFG, AG and PC are the core hubs of the DMN, allowing information to communicate within the DMN subsystems, including the medial temporal subsystem and the dorsal medial subsystem.\(^{38}\) The FC\(_{\text{intra}}\) strength in the bilateral PCG, and left mSFG, mOFG, AG, and PC was significantly decreased, and the left PCG showed the greatest differences between the groups (Figure 2A); only the PCG showed concurrent decreases in the FC\(_{\text{intra}}\) and FC\(_{\text{inter}}\) strength in both hemispheres (Figure 2), reflecting that functional
Dysconnectivity of the PCG could be a prominent feature of MDD. The PCG plays an important role in internally directed cognition, attention focus, and possibly control of responses prompting environmental changes. The PCG also has a strong connectivity with other intrinsic networks such as the frontoparietal control network and the dorsal attention network, which are involved in cognition processing. Local PCG impairments or dysregulated intrinsic networks may result in inappropriate functional activities in the PCG, which lead to a distraction of internally directed information processing in patients with MDD. The mSFG and mOFG are parts of the media prefrontal gyrus (mPFG), which controls higher-level cognition and socioemotional and executive behaviors and belongs to the frontoparietal control network. To maintain proper behaviors when adapting to specific circumstances, the mPFG is critical for coordinating sustained attention and flexibly restraining improper responses. However, acute or chronic stress can increase the risk of depression by initiating dysregulated processes involving the autonomic nervous system and hypothalamic-pituitary-adrenocortical (HPA) axis, ultimately resulting in damaged performances in spatial working memory, behavioral flexibility, decision-making and planning, which are the primary executive functions of the mPFG. A task-based fMRI study found that mPFG...
and PCG activation is related to rumination during non-
self-relevant tasks in patients with MDD, revealing the
functional basis of persistent immersion in self-focus in
patients with MDD.47

To our knowledge, this is the first study to explore
asymmetric changes in FCs in patients with MDD. Interest-
ingly, more brain areas showed changes in the
FC_{intra} than FC_{inter}, while more brain areas showed changes
in AI_{inter} than AI_{intra}, suggesting that both intra- and inter-
hemispheric activities were significantly disrupted.
Although the MFG, oMFG and ACG in patients with
MDD did not show significant changes in interhemispheric
connectivity, their rightward asymmetric patterns were
significantly reversed from those of the HCs. Therefore, exam-
in ing alterations in the functional asymmetry of depression
may provide subtle pathophysiological information and
potential therapeutic targets. Decreases in the PC AI_{intra}
and the AI_{inter} of the MFG, oMFG and ACG in patients
with MDD occurred mainly because the average FC
strength of the left side of those areas was lower than that
of the right side, which was contrary to that of the HCs
(Supplementary Table 1). Furthermore, with increased
depressive severity (using HAM-D_{24}), the interhemispheric
combination of the MFG in patients with MDD was later-
alized more to the right than the left. Various studies have
demonstrated hypoperfusion in the left hemisphere and
hyperperfusion in the right hemisphere in patients with
MDD.48–50 Since the left hemisphere may be more efficient
in cognitive control, and the right hemisphere may be more
efficient in affective processing,2,3 dysfunction in the left
hemisphere may cause deficits in sufficient cognitive con-
trastivity of emotional processing, while relatively greater func-
tional activity in the right hemisphere may cause excessive
emotional processing. However, our results show that
decreased intrahemispheric connectivity and interhemi-
spheric index within DMN areas in patients with MDD
were concentrated in the left hemisphere, suggesting the
possibility that MDD is more associated with functional
abnormalities in left cerebral areas implicated in the cogni-
tive modulation of affective states. Findings from a
functional study on emotional judgment48 may support
our speculation. These finding show that left prefrontal
cortex activity is negatively associated with negative emo-
tional valence and positively associated with positive emo-
tional valence in patients with MDD. However, the controls
displayed opposite relationships, and the right prefrontal
cortex displayed no correlations with positive/negative
emotional valence in patients with MDD, indicating
a dissociation of the left and right prefrontal cortex depend-
ing on the emotional valence in the MDD. Moreover, uni-
lateral damage to cerebral areas is more likely to contribute
to depression, especially when the lesions are in the left
hemisphere.51

In the current study, the GCC showed volumetric
changes in patients with MDD, which is consistent with
morphological studies involving adults with early-onset
depression,25,27 adolescents with early-onset depression26
and elderly individuals with late-onset depression.28
Volumetric decreases in the anterior corpus callosum also
occurred in etiology-based recombinant mouse models of
depression, which were established by replacing a
homologous mouse DNA sequence with a 6-base DNA
sequence from the human CREB1 promoter, which is
related to development of recurrent, early-onset MDD.52
However, our results differed from those of a previous
study53 which suggested that an increased corpus callo-
sum volume may be confined to patients with familial
MDD. Methodological heterogeneities in imaging fea-
tures, morphometric techniques, patient samples, disease
severity, and illness duration may lead to such inconsist-
tencies. Furthermore, some participants in that study,53 had
a history of antidepressant use, and long-term therapies
with different antidepressants can block or even reverse
neuronal atrophy and cell loss by increasing neurotrophic
factor expressions.54 The present findings of callosal atro-
phy restricted to the GCC may be related to the topo-
graphic arrangement of transcallosal fiber tracts. The
defined boundaries of the corpus callosum are somewhat
arbitrary because the corpus callosum has no morphologi-
cally macroscopic interior borders. Per Hofer and Frahm’s
new scheme of vertical corpus callosum segmentations,31
the GCC is the major white matter commissure connecting
the prefrontal cortex; the aMCC and pMCC comprise
projections connected with motor areas such as the pre-
motor, supplementary motor and primary motor cortex; the
SCC contains fibers projecting into somatosensory cortical
regions; and the ICC contains fibers projecting into the
auditory, visual, and tempo-parietal regions. Although
structural and functional changes in the motor, sensory,
auditory and visual-related cerebral cortex can also man-
ifest in MDD,55,56 deficits in the prefrontal cortex are one
major abnormality in patients with MDD.57,58 Otherwise,
microstructural abnormalities in the GCC, which are
related to the loss of white matter integrity, may be
a common feature in depression.59–61 In addition, cerebral
blood flow and glucose metabolism in depressed
individuals are reduced in the GCC, suggesting that the GCC may play a more important role than other parts of the corpus callosum in MDD pathophysiology. The GCC may also play an important role in functional asymmetry. Most fibers symmetrically interconnect the homotopic anatomical regions of the two hemispheres, but some heterotopic fibers also asymmetrically project to cortical regions with different functions. Moreover, depression has been linked to demyelination processes in the corpus callosum, which may lead to a reduced quantity and speed of information transfer between hemispheres, and antidepressants may function via specific signaling mechanisms, such as glycoprotein kinase, which govern myelination to achieve therapeutic effects. The ACG is especially crucial for affective processing and executive controls given its strong connections with prefrontal, limbic and paralimbic areas and is related to negative emotion-related behaviors such as depression, pain and stress. As the depressive duration increases, the interhemispheric connectivity of the ACG shows a more leftward asymmetry. Thus, we consider this result a compensatory mobilization for a long-term deficient functional ACG activity, which attempts to maintain affective function, since enhanced ACG activation is considered a promising indicator of therapeutic response in patients with MDD. However, the morphological changes observed in depression seem to be chronic alterations of dendrites, axons and synapses, whereas the positive correlation between duration and the functional asymmetry of the ACG suggests that the rightward asymmetry of the ACG had already occurred during the early stages in patients with MDD. Therefore, the positive relationship between the atrophic GCC and interhemispheric asymmetry of the ACG found in this study suggests that structural abnormalities in the corpus callosum might be ascribed to disturbed interhemispheric interactions in patients with MDD.

Several limitations of the present study should be acknowledged. First, this cross-sectional investigation had a relatively small sample size, thus the morphometric and functional findings may be noncategorical, and further longitudinal studies are necessary to detect potential variations in functional asymmetry following different durations of depression. Second, we segmented the corpus callosum into five sections based on cortical projections, and potential morphometric or functional alterations in other refined subregions may have been missed. Third, only DMN areas were selected for the FC analysis. Although these cerebral areas are strongly linked with MDD, other brain regions that may contribute to MDD pathophysiology were unexamined in this study, and these regions may also exist in altered FC asymmetry. In addition, further studies may be needed to explore the relationship between the white matter integrity of the corpus callosum and functional asymmetry in MDD.

Conclusion
Reduced information exchanges were found within intrahemispheric and between interhemispheric DMN in middle-aged patients with MDD, and the dysfunction levels of intra- and inter-hemispheric communications were comparable. This study provides important new evidence for the potential contributions of altered functional asymmetry to MDD, and suggests that functional asymmetry can be a promising biomarker of condition assessment and even treatment surveillance for MDD. Particularly, ACG asymmetry was related to volumetric decreases in the GCC and to disease duration, indicating that aberrant interhemispheric connections may contribute to the anatomical deficits in the corpus callosum in patients with MDD.

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