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# RESEARCH ARTICLE

# Altered cortical morphology in major depression disorder patients with suicidality

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# Abstract

**Background:** Major depressive disorder (MDD) is associated with high risk of suicide, but the biological underpinnings of suicidality in MDD patients are far from conclusive. Previous neuroimaging studies using voxelbased morphometry (VBM) demonstrated that depressed individuals with suicidal thoughts or behaviors exhibit specific cortical structure alterations. To complement VBM findings, surface-based morphometry (SBM) can provide more details into gray matter structure, including the cortical complexity, cortical thickness and sulcal depth for brain images.

**Objective:** This study aims to use SBM to investigate cortical morphology alterations to obtain evidence for neuroanatomical alterations in depressed patients with suicidality.

**Methods:** Here, 3D T1-weighted MR images of brain from 39 healthy controls, 40 depressed patients without suicidality (patient controls), and 39 with suicidality (suicidal groups) were analyzed based on SBM to estimate the fractal dimension, gyrification index, sulcal depth, and cortical thickness using the Computational Anatomy Toolbox. Correlation analyses were performed between clinical data and cortical surface measurements from patients.

**Results:** Surface-based morphometry showed decreased sulcal depth in the parietal, frontal, limbic, occipital and temporal regions and decreased fractal dimension in the frontal regions in depressed patients with suicidality compared to both healthy and patient controls. Additionally, in patients with depression, the sulcal depth of the left caudal anterior cingulate cortex was negatively correlated with Hamilton Depression Rating Scale scores.

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**Conclusions:** Depressed patients with suicidality had abnormal cortical morphology in some brain regions within the default mode network, frontolimbic circuitry and temporal regions. These structural deficits may be associated with the dysfunction of emotional processing and impulsivity control. This study provides insights into the underlying neurobiology of the suicidal brain.

**Key words:** major depressive disorder; suicidality; surface-based morphometry; fractal dimension; sulcal depth; psychoradiology

# Introduction

As one of the leading causes of disability worldwide, major depressive disorder (MDD) affects more than 264 million people and is characterized by negative emotion, hopelessness, and recurrent thoughts about death and suicide (Do, 2011). Patients with MDD have a considerably increased risk of suicide than the general population and patients with other psychiatric disorders (Bostwick and Pankratz, 2000). About 800 000 people die by suicide every year, and the prediction and prevention of suicide has become urgent. Suicidality includes completed suicidal behaviors, suicidal attempts, suicidal plans, and suicidal ideations, which are thought to emerge from sophisticated interactions between neurocognitive and emotional processes. Mood disorders, especially MDD, are important predisposing factors to suicidality (Nock et al., 2008), but this needs further research because of limited knowledge about neurobiological mechanisms.

In recent years, psychoradiology (https://radiopaedi a.org/articles/psychoradiology), which allows noninvasive characterization in the brain of neuropsychiatric patients, has developed as an emerging subject, (Lui et al., 2016; Kressel, 2017; Port 2018; Sun et al., 2017). At a neuroanatomical level, alterations to the suicidal brain including structure and function have been reported in previous neuroimaging studies (Fan et al., 2013; Li et al., 2019; Monkul et al., 2007; Gosnell et al., 2016; Jia et al., 2014; Peng et al., 2014; Jia et al., 2010; Cyprien et al., 2011; Dombrovski et al., 2012; Zhang et al., 2014). The suicidal brain shows structural changes in the prefrontal cortex (Monkul et al., 2007; Gosnell et al. 2016; Jia et al., 2014), temporal cortex (Gosnell et al., 2016; Peng et al., 2014), and limbic regions (Jia et al., 2010; Cyprien et al., 2011; Dombrovski et al., 2012). In addition, functional alterations have been found in the superior temporal and ventral medial frontal gyrus (Fan et al., 2013) between MDD patients with suicidality and patient controls, whereas this is still controversial in MRI findings. We speculate that inconsistent results may be due to the various features of the included samples and distinct ways of analyzing the neuroimaging data. The neurobiological mechanisms of suicidality in MDD may differ from those in other psychiatric disorders (Zhang et al., 2014). Therefore, in the current study, we focus on suicidality only in individuals in a depressed state to avoid the impact of multiple psychiatric disorders and to obtain more accurate results. In addition, distinct methods such as voxel-based morphometry (VBM) and surfacebased morphometry (SBM) may have caused differences

between studies. Most studies used the VBM method to appraise brain imaging data, and VBM focuses on volume and density alteration of gray matter (GM). However, the differences between groups reported in a VBM study may be attributable to cortical folding, cortical thickness (CT), or abnormalities of the cortical area (Andrea et al., 2005) and are susceptible to disease stages, chronic disease, and antipsychiatry treatment (Shah et al., 2017). Previous studies have proved that development of CT and surface area are genetically independent and result from different neurobiological processes, representing distinct features of cortical development and aging (Wierenga et al., 2014; Amlien et al., 2016). Surface area is highly associated with global measures of the brain (for example, intracranial volume, as a proxy for overall brain size) (Im et al., 2008a; Oquendo et al., 2006). In contrast to the surface area, measures including fractal dimension (FD), local gyrification index (GI), sulcal depth (SD), and CT do not scale proportionately with brain size (Im et al., 2008a). A previous study investigated differences in brain surface area and cortical volume between suicidal and non-suicidal patients with MDD (Kang et al., 2020). Nevertheless, other morphometric characteristics (for example, FD, GI, and SD) have never been explored in suicidal patients with MDD. CT has been investigated in some previous suicidal studies (Wagner et al., 2012; Ding et al., 2015; Segreti et al., 2019), but they chose different inclusion criteria and did not focus on patients with depression. Therefore, we choose those local feature measures (FD, GI, SD, and CT) in our present surface-based morphometry analysis that focuses on the relationship between local cortical characteristics in suicidal patients with MDD.

Cortical characteristics are sensitive to cognitive performance (Gautam et al., 2015) and pathological changes of psychosis such as those found in schizophrenia (Wei et al., 2015). CT is defined as the distance between corresponding points on the pial and white matter (WM) boundaries of the neocortex and used to evaluate GM morphological difference in human brain (Seiger et al., 2018). It has been studied in depression (Schmaal et al., 2017), schizophrenia (Fujito et al., 2018), suicide (Wagner et al., 2012), and others. GI is defined as the ratio of the outer surface of the cortex to the exposed part of the surface and used to assess the degree of local cortical folding, which may be related to the developmental integrity of the cortex and subcortical circuits (Zilles et al., 1988). The alteration in cortical folding was reported as an early biomarker for psychiatric disorders such as depression (Peng et al., 2015) and schizophrenia (Nesvåg et al., 2014). FD is considered to be an estimation of cortical folding complexity, which combines SD, cortical folding, and the convolution of gyrus shape (Im et al., 2006). FD has been applied in previous neuroimaging studies (King et al., 2010; Ha et al., 2005). SD is based on the Euclidean distance between the outer and the pial surface and is sensitive to cortical atrophy (Yun et al., 2013). SD is affected by genetic factors, aging, and neurological and psychiatric conditions (Chen et al., 2016). Therefore, it has been applied as an important index of the morphology of cortical folding in brain morphological studies of Alzheimer's disease, schizophrenia, and others (Im et al., 2008a, 2008b; Turetsky et al., 2009).

Therefore, we aimed to systematically investigate and identify more detailed cortical morphology alterations in brain structure and to obtain neuroanatomical alterations of brain structure in MDD patients with suicidality. According to previous studies, we hypothesize that altered local cortical characteristics in depressed patients with suicidality may reflect markers of vulnerability, which may reveal different morphological measurements, such as GI, FD, SD, and CT, compared to those in depressed patients without suicidality.

# **Methods**

## Participants and assessment

This study was authorized by the local ethics committee, completely in accordance with international standards for the ethical use of human participants in research. We included 39 depressed patients with suicidality (24 suicidal attempters and 15 suicidal ideators; SU group), 40 MDD patients without suicidality (patient controls; PC group), and 39 healthy controls (HC group) in this study. All participants were of Han ethnicity, and all were right-handed. Sex and age were matched among the three groups. The patients were recruited from the Department of Psychiatry at the West China Hospital of Sichuan University, Chengdu, China, and were diagnosed based on the Structured Clinical Interview for DSM-IV disorders (SCID-IV) by two experienced psychiatrists. The clinical assessment of suicidal patients was performed on the same day of scanning, and suicidal patients were included who had a history of suicidal behavior or a high intent to die. We recorded the number and methods of suicidal attempts. Suicidal ideation was defined as any thought of killing oneself, and any non-suicidal self-injury was excluded. There had to be evidence of suicidal ideation, such as records in a diary, communication of suicidal ideation with friends or relatives, records from patients' social networks or new media (such as WeChat, Weibo, Instagram, etc.), or more seriously planned suicidal methods or tools prepared for suicide. Detailed information on suicidal patients is listed in Supplemental Table S1. According to previous studies (Alexopoulos et al., 2015; Baeken et al., 2013), the patients were not treated with medication for 2 weeks before scanning to exclude the effect of medication. Participants were excluded who had a history of past and present psychiatric disease and head injury.

Current clinical symptoms were assessed via the 17item Hamilton Depression Rating Scale (HAMD) and Hamilton Anxiety Rating Scale (HAMA) in both groups of patients. Those patients whose suicide item score on HAMD (HAMD-3)  $\leq$ 1 were included in control patients. The Barratt Impulsiveness Scale (BIS) scores were only assessed in the suicidality group.

### MRI data acquisition

Brain imaging data were collected on a three-Tesla MRI system (Siemens, Trio) with an eight-channel phasearray head coil. A magnetization prepared rapid gradient echo (MPRAGE) sequence was used for the T1-weighted acquisition with the following parameters: repetition time = 1900 ms, echo time = 2.26 ms, flip angle =  $90^{\circ}$ , field of view =  $256 \times 256$  mm, slice thickness = 1 mm with no slice gap, and single voxel size = 1 mm<sup>3</sup>. During scanning, participants closed their eyes and relaxed themselves but were asked to not fall asleep and move as little as possible.

## MRI data analysis

We analyzed imaging data using an automated Computational Anatomy Toolbox (CAT12) (http://www.neur o.uni-jena.de/cat12/CAT12-Manual.pdf) within Statistical Parametric Mapping (SPM12) while running MATLAB (R2013b). We performed SBM analysis to estimate GI, FD, SD, and CT in the HC, PC, and SU groups according to standard protocol, applying default settings unless indicated otherwise. The SBM analysis is based on spherical mapping and registration per hemisphere when preprocessing the brain imaging data in CAT12 (Yotter *et al.*, 2011b).

#### Fractal dimension

Cortical fold complexity was estimated by FD, which was analyzed by a recognized method to assess local FD using spherical harmonic reconstructions (Yotter *et al.*, 2011a) as implemented in CAT12. FD was separately calculated for both hemispheres. After that, the resampled FD data was smoothed using a 25-mm full-width at half-maximum (FWHM) Gaussian kernel (Ashburner and Friston, 2005).

#### Gyrification index

We extract GI as implemented in CAT12 and based on absolute mean curvature, which is described by Luders *et al.* (2006). After that, the resampled GI data was smoothed using a 25-mm FWHM Gaussian kernel (Ashburner and Friston, 2005).

Table 1: Demographic and	clinical characteristics	of all participants.
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Characteristics	HC	PC	SU	F/T/X <sup>2</sup>	Р
Case (N)	39	40	39	/	/
Gender (F/M)	22/17	23/17	28/11	2.445	0.295
Age	$30.00\pm8.24$	$27.35\pm10.32$	$31.67\pm10.33$	1.999	0.140
Education duration	$12.05\pm2.21$	$12.33\pm2.90$	$12.49\pm3.87$	0.202	0.818
Medication status (Yes/No)	/	26/14	26/13	0.024	0.876
HAMD	/	$23.64\pm6.12$	$\textbf{30.18} \pm \textbf{9.22}$	- 3.609	0.001
НАМА	/	$22.50\pm9.07$	$25.03\pm11.17$	- 1.075	0.286
BIS	/	/	$\textbf{58.36} \pm \textbf{14.43}$	/	/
Suicidal times	/	/	$\textbf{3.42} \pm \textbf{4.69}$	/	/

Statistical significance between the PC and SU groups was found with only the HAMD (P < 0.05). There were no significant differences found for sex, age, and education duration (chi-square test for sex and one-way ANOVA for age and education duration, all P > 0.05). The medication status and HAMA did not significantly differ between the PC and SU groups (chi-square test and two-sample t-test, respectively, both P > 0.05). Data are the means  $\pm$  SD.

Abbreviations: HC: healthy controls; PC: patient controls; SU: suicidal patients; SD: standard deviation; HAMD: Hamilton Depression Rating Scale; HAMA: Hamilton Anxiety Rating Scale; BIS: Barratt Impulsiveness Scale.

#### Sulcal depth

As implemented in CAT12, sqrt-transformed SD was extracted based on the Euclidean distance between the central surface and its convex hull and then transformed with the sqrt function. After that, the resampled SD data was also smoothed using a 25-mm FWHM Gaussian kernel (Ashburner and Friston, 2005).

#### **Cortical thickness**

As implemented in CAT12, CT was analyzed following the workflow specified in Dahnke *et al.* (2013) Specifically, this algorithm uses tissue segmentation to evaluate the WM distance and also projects the local maxima to other GM voxels. Then, the resampled CT data were smoothed using a 15-mm FWHM Gaussian kernel (Ashburner and Friston, 2005).

#### Statistical analysis

We used one-way analysis of variance (ANOVA) to compare morphometric measures including GI, FD, SD, and CT in the CAT12/SPM12 and then post hoc analysis was conducted to determine which of the three groups differed significantly. Next, we performed a two-sample t-test between suicidal attempters (SA) and suicidal ideators (SI) to compare GI, FD, SD, and CT in the CAT12/SPM12. For all statistical analyses, age, sex and medication status were used as covariates. A false discovery rate (FDR) corrected was applied to multiple comparison correction for the accuracy of results. In addition, we performed a two-sample t-test between the depressed patients with and without suicidality along with age, sex, medication status, and HAMD scores as covariates to exclude the effect of HAMD scores. All results were labeled using the Desikan–Killiany atlas (DK40) (Desikan et al., 2006). In addition, to analyze the relationships between clinical data and cortical surface measures, we used the DK40 atlas to extract mean SD, FD, GI, and CT from distinct regions of interest. We focused on these significantly different brain regions, with a size greater than 1000 vertices (cluster size  $\times$  percentage covered in the specific region) according to previous study (Schmitgen *et al.*, 2019). Then, HAMD, HAMA, BIS scores, and suicide item scores on HAMD (HAMD-3) and cortical surface measures including GI, FD, SD, and CT of all selected regions were used in the Pearson correlation analyses in SPSS software (http://www.spss.com), and the *P* values for the correlation analyses were corrected by FDR correction in MATLAB.

## **Results**

## Clinical and demographic measures

Table 1 shows the clinical and demographic measures of all participants. Sex, age, and education duration showed no significant differences in HC, PC, and SU groups (chi-square test for sex and one-way ANOVA for age and education duration, all P > 0.05). The medication status was matched in the PC and SU groups (chi-square test, P > 0.05). The HAMD scores were significantly higher in the SU group than in the PC group (two-sample t-test, P = 0.001), and HAMA scores indicated no significant difference between the PC and SU groups (two-sample t-test, P = 0.286).

## Cortical surface measures analysis

SD values were different among HC, PC, and SU groups in the parietal, frontal, limbic, temporal, and occipital regions (P < 0.05, FDR-corrected) (Fig. 1 and Table 2). Specifically, the PC group showed higher SD in the left superior frontal, precuneus, anterior cingulate, posterior cingulate (PCC), orbitofrontal, lateral occipital, inferior parietal, and right superior temporal regions than the SU group. The HC group showed higher SD in the bilateral anterior cingulate (ACC), insula, orbitofrontal, precuneus, left superior frontal, PCC, inferior parietal, and right superior temporal regions than the SU group. The HC group showed increased SD in left paracentral gyrus than the PC group. FD values were different among the three groups in the left superior frontal gyrus and



Figure 1: Different SD values comparisons among HC, PC, and SU groups. The overall results indicated altered SD values among the three groups in the frontal, limbic, parietal, temporal, and occipital regions (A). The HC group showed higher SD in the bilateral anterior cingulate, insula, orbitofrontal, and precuneus regions, the left superior frontal, PCC, and inferior parietal regions, and the right superior temporal regions than the SU group (B). The PC group showed higher SD in the left superior frontal, precuneus, anterior cingulate, PCC, orbitofrontal, lateral occipital, and inferior parietal regions and the right superior temporal regions than the SU group (C). The HC group showed higher SD in the left paracentral gyrus than the PC group (D). Statistical inferences were drawn at a threshold of P < 0.05 (FDR-corrected). Abbreviations: HC: healthy controls; PC: patient controls; SU: suicidal patients

Table 2: Brain regions showing significant differences among HC, PC, and SU groups.

		Size (vertices)	Main area of cluster	Comparison (P value of post hoc)		
Hemisphere	P FDR-corrected			PC > SU	HC > PC	HC > SU
Fractal dimension						
Left	0.00014	392	Frontal gyrus	0.00001		
Sulcus depth						
Left	0.00000	17 021	Precuneus/Frontal	0.00000	0.00010	0.00000
			gyrus/Cingulate/			
	0.00004	5111	Insula/Temporal gyrus		0.00056	0.00001
	0.00037	1254	Parietal gyrus	0.00011		0.00136
	0.00029	1091	Occipital/Temporal gyrus	0.00003		
	0.00137	668	Insula/Orbitofrontal gyrus			0.00001
Right	0.00018	1344	Temporal gyrus	0.00016		0.00009
	0.00004	1166	Insula/Temporal gyrus			0.00001
	0.00026	731	Cingulate cortex			0.00006
	0.00007	455	Parietal gyrus			0.00001
	0.00041	316	Orbitofrontal gyrus			0.00001

The region column shows the label according to the DK40 atlas. Abbreviations: FD: fractal dimension; SD: sulcal depth; PC: patient controls; SU: suicidal patients; HC: healthy controls.

medial orbitofrontal gyrus. Specifically, the PC group had increased FD compared to the SU group in these regions at a corrected threshold of FDR-corrected P < 0.05 (Fig. 2 and Table 2). The cluster breakdown of the significantly different brain regions is showed in Supplemental Table S2. However, GI and CT analysis showed there was no difference among the three groups after FDR correction at P < 0.05. Detailed statistical analysis results are shown in Supplemental Table S3 and Fig. S1. Differences between

the SA group and SI group were not found, and the detailed statistical analysis results are shown in Supplemental Table S4 and Fig. S2. We found the HAMD scores showed significant differences between depressed patients with and without suicidality. Therefore, we performed a two-sample t-test between the two groups with HAMD scores as a covariate. The results are shown in Supplemental Fig. S3. As Supplemental Fig. S3 shows, the two-sample t-test results with HAMD scores as a



**Figure 2:** Different FD values comparisons among the HC, PC, and SU groups. FD values were significantly different among the three groups in the left frontal regions (A). The SU group showed significantly decreased FD in the left frontal regions compared with the PC group (B). Statistical inferences were drawn at a threshold of P < 0.05 (FDR-corrected). Abbreviations: HC: healthy controls; PC: patient controls; SU: suicidal patients.

covariate are consistent with the post hoc analysis results without HAMD scores as a covariate in the main area of each cluster between the PC and SU groups.

#### **Correlation analysis**

There were predominantly negative correlations between HAMD scores and cortical SD values in the left caudal ACC (r = -0.356, P = 0.002) in depressed patients (combined PC and SU groups). In addition, negative correlations were found between HAMD-3 scores and cortical SD values of left rostral ACC (r = -0.316, P = 0.006), left caudal ACC (r = -0.302, P = 0.009), and left PCC (r = -0.295, P = 0.011) in depressed patients (combined PC and SU groups). All P values survived after FDR correction (P < 0.05, Fig. 3).

# Discussion

In the current study, we systematically researched surface measures in healthy controls and MDD patients with or without suicidality, including GI, FD, SD, and CT. Furthermore, we investigated the association between these brain surface measures and clinical variables. In the current study, we found two main results: (i) Compared to individuals without suicidality (HC and PC), the patients with suicidality (SU) showed significantly decreased SD in the frontal, limbic, parietal, temporal, and occipital regions and decreased FD in the frontal region. The altered brain regions were situated almost in the frontolimbic circuitry, default mode network (DMN), and temporal regions. (ii) In depresed patients (combined PC and SU groups), we found HAMD scores were negatively correlated with SD values for the left caudal anterior cingulate cortex, and HAMD-3 scores were negatively correlated with SD values of the left rostral ACC, left caudal ACCs, and left PCC.

In our study, we found decreased SD in the precuneus, PCC, and inferior parietal lobule in the SU group compared to both the HC and PC groups. The precuneus and PCC, as parts of the DMN, combine bottom-up attention with information from memory and perception (Buckner et al., 2008). The alteration in these areas suggested a decreased ability to suppress intrusive thoughts in the context of suicidal thoughts (Minzenberg et al., 2015). In addition, the inferior parietal lobule is the posterior hub of the DMN. A previous study found that suicidal ideation in patients with depression was related to decreased metabolic activities in parietal regions, especially the inferior parietal lobule (van Heeringen et al., 2017). The DMN is pivotal for conscious information processing, especially self-awareness (Vogt and Laureys, 2005). High self-awareness may increase the intention to evade from the self, and suicide is known as a way to evade selfawareness, suggesting that people who have high levels of self-awareness may have a high intent to commit suicide (Selimbegovic and Chatard, 2013). When exposed to negative stimuli, the dysfunction of the DMN may cause greater self-referential responses, which have been associated with suicide. Therefore, we speculate that the structural alterations in the DMN may be considered to be markers for suicidal risk in MDD, which is related to high self-awareness in these regions.

In addition, we found decreased SD and FD in the superior frontal gyrus (SFG) and orbitofrontal cortex (OFC) in the SU group. The SFG partly overlaps with the prefrontal cortex (PFC), and the OFC is a part of PFC region. The PFC has been confirmed to associate with many types of emotional and cognitive processing. Early postmortem studies reported reduced serotonin transporter binding sites and increased 5hydroxytryptamine (5-HT) receptor binding in the PFC of the suicidal brain (Oquendo et al., 2006). Increased serotonin levels have been associated with high levels of impulsivity, which is a personality trait associated with suicide (Lopez-Castroman et al., 2014). Abnormal structure in the OFC were reported to be related to aggression and impulsivity. Abnormalities in the OFC make depressed patients more prone to make dangerous choices such as suicide (Jollant et al., 2010). Apart from this, the dysfunction of OFC may lead to decreased selfesteem and negative self-thinking (Rolls, 2013). According to these findings, we assumed that the altered cortical morphology of PFC may be related to amotivation and a bias toward negatively valanced stimuli in depressed patients, and these negative symptoms may



Figure 3: Associations between clinical and cortical surface measures. HAMD scores were negatively correlated with SD value for the left caudal ACC (B) in depressed patients (combined PC and SU groups), HAMD-3 scores were negatively correlated with SD values of left rostral ACC, left caudal ACC and left PCC (C) in depressed patients (combined PC and SU groups). Abbreviations: ACC: anterior cingulate cortex; HAMD: Hamilton Depression Rating Scale; SD: sulcal depth.

lead to a suicidal choice when facing environmental stressors.

Also, we reported decreased SD in ACC in the SU group compared to both the HC and PC groups. As the ACC connects to the emotional limbic system and the cognitive PFC, it play a critical role in the human brain (Stevens et al., 2011). Cingulate cortex structural abnormalities have commonly been found in MDD patients with suicidality compared to those patients without suicidality (van Heeringen et al., 2011). This is consistent with our finding that the SD of cingulate cortex components such as rostral ACC, caudal ACC, and PCC were negatively corrected with suicide item scores on HAMD. Wagner et al. found decreased CT, GMV, and GM density of the ACC in depressed patients at high suicidal risk compared to patients at low suicidal risk (Wagner et al., 2012, 2011). A previous postmortem study on suicide reported that depressed patients who died by suicide had a decreased number and length of dendritic branches in the ACC compared to control patients (Hercher et al., 2010). Vulnerability to suicidality may be concerned with the function of the ACC, including impulsive inhibitory control (Fineberg et al., 2009) and modulation of emotional responses (Etkin et al., 2011). Specifically, an impulsive personality may drive impulsive behaviors, and the ACC may exert impulsive inhibitory control (Wagner et al., 2011). The decreased SD may lead to dysfunction in the ACC and it is more likely to cause impulsive thoughts or behaviors. As the ACC is involved in multiple functions, including emotional and cognitive control, neurobiological mechanisms of the ACC in the suicidality of MDD patients need further study.

In our current study, we found decreased SD of the insular cortex in depressed patients with suicidality compared with HC groups. The insular cortex, as a component of the limbic lobe, receives afferent stimulus from parts of the thalamus and is connected with the amygdala and other limbic regions. A higher density of spindle neurons was found in the right frontal insular cortex, and these neurons participated in cognitive-emotional processes such as empathy and metacognitive emotional feelings (Nieuwenhuys, 2012). The insular cortex has been confirmed to be involved in self-awareness (Craig, 2009). As we discussed above, higher self-awareness in the depressed state may be a factor of vulnerability to suicidal behavior. We speculate that the altered structure in the insular cortex may be associated with the dysfunction of self-awareness.

The SFG, OFC, ACC, and insular cortex are all located in the frontolimbic circuitry. Abnormalities in the frontolimbic circuitry in suicidal patients have been reported in many studies (Monkul et al., 2007; Wagner et al., 2011; Du et al., 2017). Both the prefrontal and cingulate cortices are involved in emotional processing and cognitive function (Allman et al., 2001; Fettes et al., 2017). In comparison with other states, the ACC and OFC may be more related to suicidal vulnerability in depression (Zhang et al., 2014). The interruption of glutamatergic and GABAergic pathways in the ACC and PFC in the suicidal brain have been reported in previous studies (Lutz et al., 2017). Changes in these structures that affect excitability and inhibitory transmission are believed to be the basis for the abnormalities in neuroimaging studies. Thus, according to these findings, we deduced that a vulnerability to

suicidality in patients with MDD is related to disbalance in the frontolimbic network, characterized by dysfunction of emotional processing and cognitive function, which may be caused by structural alteration within this network.

These findings also identified a decreased SD in the bilateral temporal regions, especially the left superior and inferior temporal areas and the right superior and middle temporal areas, in the SU group compared with both the healthy and patient controls. Consistent with our study, Pan *et al.*, (2015) found that the decreased volume of the superior temporal gyrus in adolescents with suicidal behavior, and they suggested this may be related to social-emotional information evaluation abnormalities. However, in our study, whether this alteration of SD in the bilateral temporal was relevant to suicidality in MDD patients remains to be clarified.

Particularly, we found there were no significant differences in GI and CT among the three groups that survived FDR correction in the current study. However, two previous studies reported altered CT in the SU group (Wagner et al., 2012; Ding et al., 2015). This discrepancy may have been related to the inconsistent inclusion criteria. One study included mood disorder patients, including MDD and bipolar disorders (Ding et al., 2015), while another study included high risk for suicide, covering not only SA but also first-degree relatives of succeeded and attempted suicides (Wagner et al., 2012). On the other hand, our study may prove that SD and FD are more sensitive measures than CT in cortical atrophy and development (Im et al., 2008b). Previous studies also reported that although CT changes relatively small, the average SD is greatly increased in normal aging (Kochunov et al., 2008, 2005). We concluded that in suicidal patients with depression, the alterations in SD and FD may not be accompanied by CT changes. Both FD and GI are used to estimate brain cortical folding complexity. Compared to GI, FD may help to reduce data variability because it is independent of the definition of the outer cortex surface boundary and the normalization of the brain (Yotter et al., 2011a). That may explain why there were no significant differences in GI, while FD differed among three groups. It has also been suggested that FD is more sensitive than GI when evaluating cortical folding complexity.

There are some limitations in our study. First, the effect of medication cannot be excluded completely as we included some patients receiving medications. To mitigate the effects of medication, the patients were not treated with medication for two weeks in our current study. Meanwhile, we matched the medication status in the PC and SU groups and used the medication status as a covariate in the statistical analysis of this study. Second, we included both SI and SA in the SU group, which may have increased the heterogeneity of the included sample. Therefore, we performed a sub-analysis between SI and SA and found that there were no significant differences between them. Furthermore, in this study we did not analyze the brain morphological alteration between

patients who planned suicide and those who acted suicide, and the relationship between brain morphological alteration and the lethality of attempt, which is worth further study. Third, the results should be explained with caution because of the modest sample.

## Conclusion

These results indicate that a number of subtle abnormalities in cortical morphology occurred in depressed patients with suicidality. Abnormal cortical morphology of DMN, frontolimbic circuitry, and temporal regions are implicated in depressed patients with suicidality. These structural deficits may be associated with dysfunction in emotional processing and impulsivity control. This study provided insights into the underlying neurobiology of suicidal brain and new evidence for therapeutic targets for depression patients with suicidality. To further elucidate the neurobiological mechanism of the suicidal brain in depression, future studies need to use a larger sample sizes, and more complex network analyses on the suicidal brain should be applied.

## Supplementary materials

Supplementary data are available at Psychoradiology online.

# **Author contributions**

H.L. analyzed and interpretated of data and drafted for the work. H.Z. and L.Y. collected data included imaging and clinical scale data. F.Z., Z.Q., and T.C. revised it critically for important intellectual content. Z.J. and Q.G. contributed to the conception and design of the work, and made final approval for the version to be published.

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## **Conflict of interest**

One of the authors (Q.G.) is also the editor-in-chief of *Psychoradiology*. He was blinded from reviewing or making decisions on the manuscript.

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