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The reductions in the subcallosal region cortical volume and surface area in major depressive disorder across the adult life span

Dongtao Wei[1,2], Kangcheng Wang[1,2], Jie Meng[1,2], Kaixiang Zhuang[1,2], Qunlin Chen[1,2], Wenjing Yan[1,2], Peng Xie[3–5], and Jiang Qiu[1,2]

[1]Key Laboratory of Cognition and Personality (Ministry of Education), Chongqing 400715, China; [2]School of Psychology, Southwest University, Chongqing 400715, China; [3]Institute of Neuroscience, Chongqing Medical University, Chongqing, China; [4]Chongqing Key Laboratory of Neurobiology, Chongqing, China and [5]Department of Neurology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China

Original Article

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Author for correspondence:
Peng Xie, E-mail: xiepeng@cqmu.edu.cn; Jiang Qiu, E-mail: qiuj318@swu.edu.cn

Abstract

Background. Imaging studies have shown that the subcallosal region (SCR) volume was decreased in patients with major depressive disorder (MDD). However, whether the volumetric reductions in the SCR are due to thinning of the cortex or a loss of surface area (SA) remains unclear. In addition, the relationship between cortical measurements of the SCR and age through the adult life span in MDD remains unclear.

Methods. We used a cross-sectional design from 114 individuals with MDD and 112 matched healthy control (HC) individuals across the adult life span (range: 18–74 years). The mean cortical volume (CV), SA and cortical thickness (CT) of the SCR were computed using cortical parcellation based on FreeSurfer software. Multivariate analyses of covariance models were performed to compare differences between the MDD and HC groups on cortical measurements of the SCR. Multiple linear regression models were used to test age-by-group interaction effects on these cortical measurements of the SCR.

Results. The MDD had significant reductions in the CV and SA of the left SCR compared with HC individuals after controlling of other variables. The left SCR CV and SA reductions compared with matched controls were observed only in early adulthood patients. We also found a significant age-related CT reduction in the SCR both in the MDD and HC participants.

Conclusions. The SCR volume reduction was mainly driven by SA in MDD. The different trajectories between the CT and SA of the SCR with age may provide valuable information to distinguish pathological processes and normal ageing in MDD.

Introduction

The subcallosal region (SCR) mainly includes the subcallosal area (BA25 and prelimbic BA32) and the perigenual ventromedial prefrontal cortex (vmPFC) (BA10m) (Hamani *et al.*, 2009, 2011) and is an extensively connected component of the limbic system, including the subcortical cortex, amygdala and hippocampus, and is involved in autonomic regulation (Gianaros *et al.*, 2004), emotion regulation (Wager *et al.*, 2008), autobiographical memory (Addis *et al.*, 2009; van der Meer *et al.*, 2010), and reward-based learning (Valentin *et al.*, 2007). Growing evidence from structural imaging studies has suggested that there are volume reductions in the SCR in major depressive disorder (MDD) (Kempton *et al.*, 2011; Du *et al.*, 2012; Bijanki *et al.*, 2014; Rodriguez-Cano *et al.*, 2014; Jaworska *et al.*, 2016). A recent, large meta-analysis of cortical abnormalities from the ENIGMA MDD working group confirmed thinning of the bilateral medial PFC of depressed adult patients and a reduction in the left medial PFC surface area (SA) in depressed adolescent patients (Schmaal *et al.*, 2017). In addition, the SCR is an important target for deep brain stimulation (DBS) treatment for treatment-resistant depression (Lozano *et al.*, 2008; Hamani *et al.*, 2011, Holtzheimer *et al.*, 2012, Riva-Posse *et al.*, 2018). Taken together, these results strongly suggested that the SCR plays a key role in the pathophysiology of depression and in treatment effects (Riva-Posse *et al.*, 2018).

Previous structural imaging studies examining the effects of depression on the SCR have largely been based on measures of cortical volume (CV). For example, left subgenual PFC volume reductions were found in young women with adolescent-onset MDD (Botteron *et al.*, 2002) and in patients with a family history of depression (Bijanki *et al.*, 2014). Depressed participants with comorbid anxiety also had smaller subgenual PFC volumes than those without anxiety (Jaworska *et al.*, 2016). Thus, decreased subgenual PFC volumes may suggest delayed or altered neurodevelopment in a key emotion regulation region (Jaworska *et al.*, 2016). In

addition, CV is a product of cortical thickness (CT) and SA (Panizzon *et al.*, 2009), and some neuroimaging studies have found that CT and SA differentially contributed to volume loss in neuropsychiatric disorders (Dickerson *et al.*, 2009; Rimol *et al.*, 2012; Ecker *et al.*, 2013). For example, widespread reduction in CV in frontal, temporal, occipital, and parietal regions in schizophrenia was mainly driven by cortical thinning (Rimol *et al.*, 2012). In contrast, the abnormal volumes in autism spectrum disorder were driven by SA rather than CT (Ecker *et al.*, 2013). Thinning of the medial temporal lobe (MTL) contributed to small volumes of the MTL in Alzheimer's disease (Dickerson *et al.*, 2009). In contrast, the small volume of the MTL was associated with diminished MTL SA in normal ageing (Dickerson *et al.*, 2009). It is possible that SA and CT have distinct developmental pathways that are modulated by different neurobiological mechanisms (Ecker *et al.*, 2013). Thus, it is not clear whether volumetric reductions in the SCR in MDD patients are due to thinning, loss of SA, or both.

CT and SA represent distinct genetic aetiologies (Panizzon *et al.*, 2009) and cellular processes (Chenn and Walsh, 2002) and show unique developmental trajectories in children and adolescents (Wierenga *et al.*, 2014) across the adult life span (Hogstrom *et al.*, 2013; Storsve *et al.*, 2014). For instance, the CT was reduced and negatively correlated with increasing age during late childhood and across the adult life span (Storsve *et al.*, 2014). The SA was positively correlated with age until late childhood, and then smaller, steady decreases were observed with increasing age (Amlien *et al.*, 2016). The dominant contributor to CV reductions during adolescence (Tamnes *et al.*, 2017) and with ageing (Storsve *et al.*, 2014) was cortical thinning. In addition, individuals with depression had significant differences in CV that may be differentially affected by depression at various stages of life (Schmaal *et al.*, 2017). For example, a reduction in the left medial PFC SA was found in depressed adolescent (⩽21 years) patients compared with controls (Schmaal *et al.*, 2017). A meta-analysis showed grey matter volume reductions in the bilateral medial PFC in late-life depression (Du *et al.*, 2014). Thus, whether the alterations in SA or CT of the SCR in MDD were associated with age through the adult life span remain unclear.

The aim of the current study was to identify SCR differences in the CT, SA, and CV across the adult lifespan in a large sample of patients with depressive disorders (age range: 18–74 years) and healthy control (HC) subjects (age range: 19–72 years). We used an automated method of regional parcellation (FreeSurfer, Destrieux atlas) to measure the CT, SA, and CV of the bilateral SCR region; specifically, the SCR was region 32 in the Destrieux atlas (Destrieux *et al.*, 2010). Based on neurobiological knowledge as well as previous work, CT and SA are known to represent distinct morphometric features of the cortex that may be differentially affected by depression at various stages of life. We hypothesised that reductions in SCR volume and SA would be observed in patients with depressive disorders compared with HC subjects, while SCR thinning would be associated with ageing.

Materials and methods

Samples

Initially, 383 consecutively recruited MDD outpatients and 260 HC participants were included and underwent a resting-state functional and structural magnetic resonance imaging (MRI) scan as part of a project investigating human neuroimaging markers of MDD (Cheng *et al.*, 2016). They underwent a diagnostic interview by experienced doctors using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, for Axis I Disorders. For this study, the final sample included 114 individuals with MDD (41 males, 73 female) and 112 matched control individuals (40 males, 72 females). The main exclusion criteria were as follows: (1) participants were excluded if they had not completed the personality test (Eysenck Personality Questionnaire, EPQ), resulting in 214 MDDs and 150 HCs remaining; (2) 16 patients with bipolar disorders were excluded, resulting in 198 MDDs and 150 HCs remaining; (3) 32 participants with hypertension, diabetes and cardiovascular disorders were excluded, resulting in 185 MDDs and 131 HCs remaining; (4) participants aged younger than 18 years and older than 75 years were excluded, resulting in 165 MDDs and 126 HCs remaining; (5) 63 participants who had not completed the Short Ruminative Responses Scale test were excluded, resulting in 116 MDDs and 112 HCs remaining; and (6) participants with bad imaging data and bad segments (by visual inspection) were excluded, resulting in the final sample of 114 MDDs and 112 HCs (see Fig. 1). Neuroticism and rumination have important implications for understanding the development and maintenance of depressive episodes. A previous study indicated that ruminative self-focus was associated with enhanced activity of the subgenual anterior cingulate cortex in depression (Mandell *et al.*, 2014). We also wanted to test whether alterations in the structure of the SCR were associated with neuroticism or rumination in depressive disorders. In the end, 112 matched control individuals and 114 individuals with MDD were retained. Of the 114 MDD patients included, 95 were first episode and 19 were recurrence; 29 of the patients had depression with anxiety, and 50 of the patients were medicated for MDD (see Table 1). In the current study, the mean age of the patients with depression was 37.12 years (s.d. = 13.27, range = 18–74), and the mean age of the HC subjects was 39.07 years (s.d. = 12.79, range = 19–72). Depression severity was rated using the 17-item Hamilton Depression Rating Scale (HDRS-17) by interview, as well as the self-report scales in the Beck Depression Inventory-II (BDI-II). Participants provided written informed consent to participate. The study was approved by the Institutional Review Board of Chongqing Medical University for the protection of human subjects and was performed in accordance with the Declaration of Helsinki.

MRI data acquisition

High-resolution T1-weighted structural images were acquired on a 3.0-T Siemens Trio MRI scanner using a 12-channel whole-brain coil (Siemens Medical, Erlangen, Germany) using magnetisation-prepared rapid acquisition gradient-echo sequence (MPRAGE) (echo time = 2.52 ms; repetition time = 1900 ms; inversion time = 900 ms; flip angle = 9°; slices = 176; field of view = 256 × 256; voxel size = 1 × 1 × 1 mm^3).

Cortical surface reconstruction and measures

All cortical parcellations and surface-based cortical reconstruction were performed by using FreeSurfer software (Version 5.3, https://surfer.nmr.mgh.harvard.edu). In brief, T1-weighted images first underwent a series of preprocessing steps that involved intensity non-uniformities, skull stripping, tissue classification, and surface extraction. In each hemisphere, the white matter was segmented,

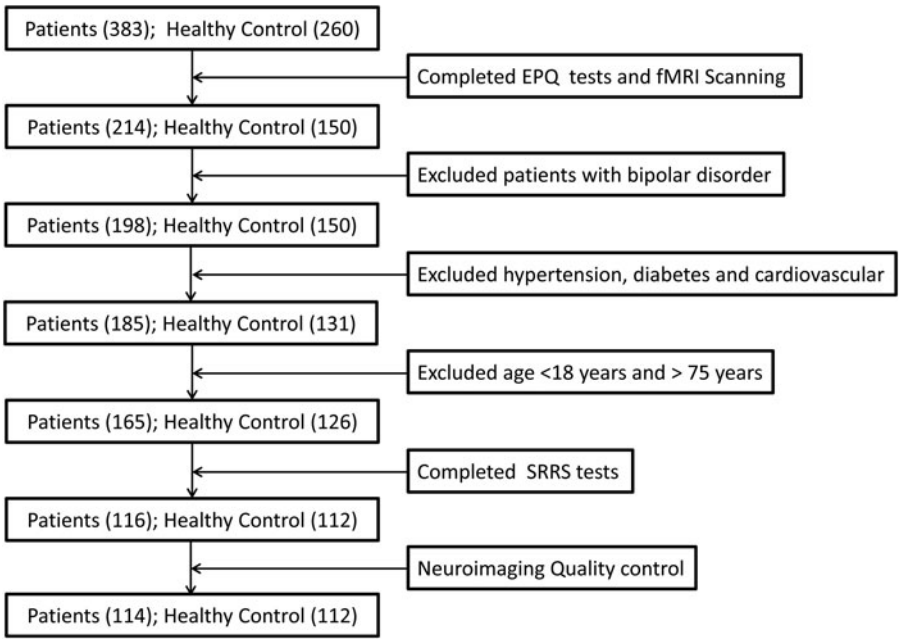

Fig. 1. The pipeline of selecting the sample.

Table 1. Demographic and clinical characteristics of major depression disorders and healthy comparison subjects

	MDDs ($N = 114$)								HCs ($N = 112$)	
	First episode ($n = 95$)		Recurrent ($n = 19$)		Depression with anxiety ($n = 29$)		Medicated MDD ($n = 50$)			
Characteristic	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Age (years)	39.6	12.7	36.8	13.2	37.6	11.9	38.9	11.6	37.1	13.2
Education (years)	11.8	3.5	12.7	3.9	12.1	3.5	11.7	3.1	13.5	4.2
Disease duration (months)	41.9	59.9	98.5	57.2	51.2	55.8	77.4	72.2	–	–
HDRS-17	8.91	4.5	9.3	4.7	8.48	4.8	8.3	4.7	–	–
BDI-II scores	12.8	7.6	12.5	4.7	12.34	7.7	11.4	6.7	–	–
Neuroticism	15.05	5.3	18.0	4.1	16.2	4.8	17	5	13.2	3.7
Extroversion	9.03	4.7	8.3	4.5	9.4	4.7	7.62	4.48	8.2	4.7
Rumination	11.4	2.9	12.7	3.6	11.03	3.3	11.86	3.4	–	–
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Gender										
Female	62	65.3	11	58.6	17	56.7	32	64	72	64.3
Male	33	34.7	8	41.4	12	43.3	18	36	40	35.7

and the surface was generated by tessellation. After correcting for topological defects, the pial surface was produced by nudging the white surface outwards. During the reconstruction, several check points (skull strip, white matter segments and pial surface) were visually inspected, and segmentation errors were corrected. CT was measured by calculating the shortest distance from the grey/white boundary to the grey/cerebrospinal fluid (CSF) boundary at each vertex. Next, the surface was divided into separate cortical regions using an automated labelling approach. Finally, the mean CV (in mm^3), SA (in mm^2), and CT (in mm) were extracted for each of the 148 regions (74 per hemisphere) in the parcellation scheme (i.e. Destrieux atlas) (Destrieux *et al.*, 2010).

In the current study, we computed the CV, SA, and CT of the SCR using the cortical parcellation based on the Destrieux atlas. Specifically, the SCR/gyrus was region 32 in the Destrieux atlas (see Fig. 2) (Destrieux *et al.*, 2010). In addition, the intracranial volume (ICV) was also obtained for each participant.

Statistics

We examined group differences in CV, CT and SA between the MDDs and HCs. To control the type-1 error rate, first, two separate multivariate analyses of covariance (MANCOVA) models were tested on the left and right SCR (CT, SA and CV), with

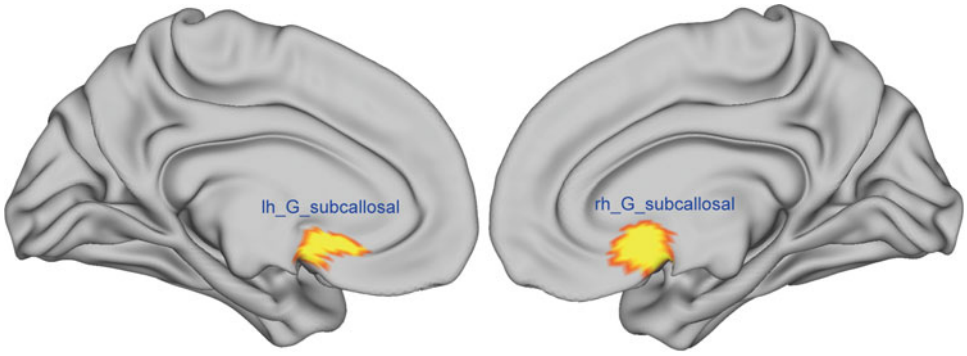

Fig. 2. The left and right SCR/gyrus was region 32 in the Destrieux atlas. The mean CV, SA and CT of this region were computed using cortical parcellation based on FreeSurfer software.

group (MDD = 1, HC = 0) as the between-subject factor while controlling for age, sex, and total ICV. Subsequent univariate analyses were performed for each variable (CT, SA and CV). *p* values were adjusted for the number of variables measured (i.e. corrected for three measures in total). Furthermore, we examined associations between symptom severity and different measurement indices of the SCR (CV, CT and SA) within the MDD patient group.

To investigate the effects of age on the SCR in the MDDs and HCs, we used multiple linear regression models to test age-by-group interaction effects while controlling for sex and total ICV. In addition, a generalised additive model (GAM) was also employed to assess the association between left SCR (CT, SA and CV) and age in the MDDs and HCs. GAM was proposed by Hastie and Tibshirani (1995) as an effective method to tackle the problem of rapidly increasing variance in estimates when there is a large number of variables to model. Given that brain development is known to be a non-linear process, we modelled both linear and non-linear age effects using a GAM (Wood, 2004, 2006). The GAM was implemented to assess a penalty on non-linearity using restricted maximum likelihood to avoid overfitting and thus captures both linear and non-linear effects in a data-driven fashion. In addition, GAM provides accurate delineations of developmental trajectories, as it avoids some of the inherent weaknesses of global polynomial models, e.g. quadratic and cubic models, where the timing of peaks and the end points of the trajectories may be substantially affected by irrelevant factors, such as the age range of the samples (Fjell *et al.*, 2010). Furthermore, to detect potentially different effects of major depression with age, the participants were separated into three groups: early adulthood (18–30 years old; MDD = 35, HC = 50), middle adulthood (31–49 years old; MDD = 55, HC = 38) and later adulthood (50–75 years old; MDD = 24, HC = 24). We set the age cut-off for early adulthood MDD at ⩽30 based on (1) the first phase of early adulthood comes to a close at approximately 28–33 years or at the age 30 transition (Levinson, 1986) and (2) some neuroimaging studies have indicated that in several brain regions, structural growth curves and maturation had not plateaued even by the age of 30 (Amlien *et al.*, 2016; Somerville, 2016). Two-factor covariance analysis was performed, using the CT, SA and CV of the SCR as the dependent variables and group (MDD, HC) and age group as the independent variables, while controlling for age, sex, and total ICV; post hoc multiple comparison tests were performed to determine which means differed among these groups. *p* values were adjusted for the number of variables measured (i.e. corrected for three measures in total).

Statistical analyses were conducted using statistical software (R, Statistical Package version 3.3.2; R Foundation for Statistical Computing; www.R-project.org). The mgcv packages were used to apply the GAM function.

Results

Demographic and clinical measures

A total of 228 participants entered the study. The demographic, clinical, symptom severity and personality data of the MDDs and HCs are presented in Table 1. No significant differences between groups were observed in the demographic characteristics. There were no significant differences in the scores from the HDRS-17 and BDI-II between unmedicated and medicated depression patients. Compared with the recurrent patients, the first-episode patients showed no significant difference in either the HDRS-17 and BDI-II scores.

Multivariate analysis of covariance (MANCOVA)

A significant main effect of group (MDD *v.* HC) was found with the left SCR [$F_{(3,\ 223)} = 2.85$, $p = 0.03$]. Subsequent univariate analyses showed that patients with depression had a smaller CV [$F_{(1,\ 225)} = 6.24$, $p = 0.013$; Fig. 3] and SA [$F_{(1,\ 225)} = 8.09$, $p = 0.005$; Fig. 3] of the left SCR than the HC subjects. There was no main effect of group on CT, SA or CV in the right SCR [$F_{(3,\ 223)} = 1.01$, $p = 0.39$].

We also tested the effects of age on the left SCR in MDDs and HCs. There was no significant interaction effect of age-by-diagnosis on the left/right subcallosal SA, CV and CT. In addition, using the GAMs, we found a significant main effect of age on the left subcallosal CT (see Table 2, Fig. 3) in each group (MDDs and HCs) after controlling for sex and ICV.

To detect potentially different effects of major depression with age, the participants were separated into three groups: early adulthood (18–30 years old; MDD = 35, HC = 50), middle adulthood (31–49 years old; MDD = 55, HC = 38) and later adulthood (50–75 years old; MDD = 24, HC = 24). Two-factor covariance analysis was performed, and there was a significant interaction effect between age group (early, middle, and later adulthood) and group (MDD and HC) for CV ($F = 2.51$, $p = 0.03$) and SA ($F = 3.08$, $p = 0.01$) of the left SCR. Then, post hoc multiple comparisons showed that the reductions in the CV ($t = -2.9$, $p = 0.004$) and SA ($t = -3.2$, $p = 0.002$) of the SCR were observed only in the patients with an adult age of illness onset compared

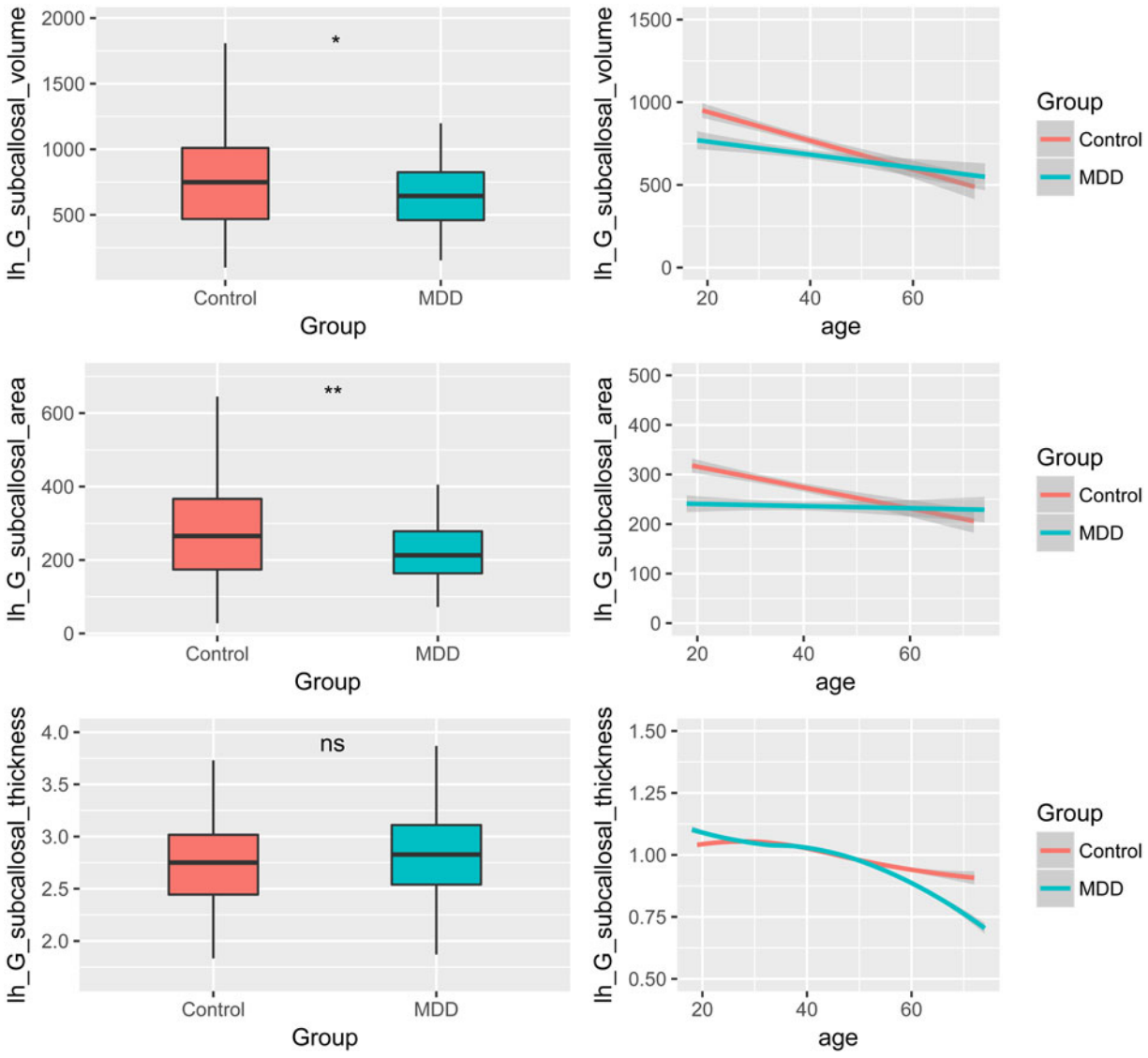

Fig. 3. Left column: The reductions in left SCR volume (top), SA (middle), and thickness (bottom) in the MDD group compared with the HC group after controlling for age, sex and total ICV. Right column: The age-related changes in left SCR volume (top), SA (middle), and thickness (bottom) both in the MDD and HC groups across the adult life span after controlling for sex and total ICV.

with the early adulthood controls (see Fig. 4). We did not detect significant differences in CV ($t = 0.22$, $p = 0.82$) and SA ($t = -0.15$, $p = 0.88$) of SCR in middle adulthood patients compared with age-matched controls or in later adulthood patients compared with their age-matched controls (CV: $t = -1.27$, $p = 0.22$; SA: $t = -1.39$, $p = 0.17$).

Recurrence, medication, duration of illness, neuroticism, rumination and symptom severity

The CV, SA and CT of the SCR were not correlated with symptom severity using the HDRS-17 and BDI-II questionnaires. There are no significant differences on the cortical measurement of left SCG between unmedicated depression patients and medicated depression patients ($F = 0.21$, $p = 0.97$), and between first and recurrent episode patients ($F = 1.36$, $p = 0.26$). Two MANCOVA models were performed on the left and right SCRs (the dependent variables were CT, SA and CV), with diagnostic group (depression patients and depression patients with anxiety) as the between-subject factor while controlling for age, sex, and total ICV. There were no significant differences between depressed patients and depressed patients with anxiety [right: $F_{(1,\ 109)} = 0.21$, $p > 0.05$; left: $F_{(1,\ 109)} = 0.22$, $p > 0.05$]. In addition, our correlation analysis revealed no relationship between neuroticism, rumination and the structural brain measures of SCR within the MDD group.

Discussion

This study examined differences in the CV, CT and SA in the SCR across the adult life span in patients with depressive disorder relative to HC subjects. We also tested the effects of age on the CV, CT and SA of the SCR across the adult life span. We found that patients with depressive disorder had significant differences in the CV and SA of the SCR (Fig. 1) after controlling for the effects of brain size, age and sex. Furthermore, the reductions in

Table 2. Results of nonparametric regression models

Parameter	Dependent variable (SCR)	Group	Estimated degrees of freedom[a,b]	Estimated value of parametric coefficients[a]	Standard error[a]	*p* value[a]
Gender	Volume	–	–	0.199	0.114	0.2
	SA		–	0.247	0.159	0.17
	Thickness		–	0.183	0.161	0.25
ICV	Volume		–	0.488	0.078	<0.001***
	SA		–	0.457	0.081	<0.001***
	Thickness		–	0.128	0.082	0.12
Age	Volume	MDD	1.07	–	–	0.93
		HC	1.58	–	–	0.27
	SA	MDD	1.0	–	–	0.28
		HC	1.68	–	–	0.47
	Thickness	MDD	3.37	–	–	<0.001***
		HC	3.35	–	–	0.04*

[a]Data were calculated using the GAMs.
[b]Degrees of freedom refers to the curvature of the fitted GAM line relative to a simple straight line. Some variables were automatically forced to a linear relationship (df = 1).

the CV and SA of the left SCR were observed only in early adulthood patients (18–30 years) with depressive disorders compared with early adulthood HC groups. However, we found a significant age-related CT reduction in the SCR in both the group with depressive disorders and the HC group (see Fig. 2).

Consistent with our prediction and with prior voxel-based morphometry research (, Botteron *et al.*, 2002, Du *et al.*, 2012, Bijanki *et al.*, 2014; Jaworska *et al.*, 2016), we observed left SCR CV reductions in patients with depressive disorders relative to HC subjects. The SCR has extensive connections with the PFC, nucleus accumbens, hypothalamus and brainstem and has been implicated in the pathophysiology of MDD (Lozano *et al.*, 2008, Hamani *et al.*, 2011). Interestingly, the SCR CV reduction was mainly driven by its SA rather than CT in the current study. In terms of phylogeny, the size of the SA is related to the number of ontogenetic columns, whereas CT is contributed by the number of cells within a column (Rakic, 1988). Previous studies indicated that cortical area expansion might be more efficient to facilitate brain connectivity and functional development (Ruppin *et al.*, 1993; Murre and Sturdy, 1995; Hogstrom *et al.*, 2013). The current results suggest that the reductions in the SA of the SCR may influence abnormal structural and functional connectivity between the SCR and cortical/subcortical areas in MDD. In addition, the SA and CT have distinct developmental pathways that are modulated by different neurobiological mechanisms and at different stages of life (Ecker *et al.*, 2013; Wierenga *et al.*, 2014). For example, the CT decreased non-linearly across ages 4 to 87 (Storsve *et al.*, 2014; Tamnes *et al.*, 2017). In contrast, the SA expanded until approximately 12 years of age, followed by a relatively stable size and then a steady decrease with increasing age (Amlien *et al.*, 2016). Recently, the ENIGMA MDD group found cortical thinning of the bilateral medial PFC of depressed adult patients (>21 years) and a reduction in the left medial PFC SA in depressed adolescent (⩽21 years) patients (Schmaal *et al.*, 2017). Their results indicated that cortical development may be dynamically impacted by depression at different stages of life. In addition, the reduced cortical area may be associated with a disturbance of neurodevelopment in schizophrenia (Rimol *et al.*, 2012) and a delay in cortical maturation in adolescent MDD (Schmaal *et al.*, 2017). In our study, we found the reductions in the CV and SA of the left SCR only in early adulthood patients with depressive disorders (18–30 years) compared with the early adulthood HC group (see Figs 4 and 5). The SA of the SCR did not show a significant age-related decline across the adult life span (see Fig. 3). Thus, the alteration of functional/structural connections between the SCR and the PFC, nucleus accumbens, hypothalamus and brainstem may be influenced by delayed maturation through decreases in growth and branching of dendritic trees and the number of synapses associated with grey matter volume (Anderson, 2011), which may persist in adult MDD patients with an early age of onset of depression.

It has been suggested that SCR dysfunction may disturb stress-autonomic and neuroendocrine responses and reward-related mesolimbic dopamine function (Drevets *et al.*, 1998; Myers-Schulz and Koenigs, 2012). Anxious/depressed scores were negatively associated with vmPFC CT at healthy younger ages (<9 years) (Ducharme *et al.*, 2014). Childhood experiences of maltreatment were associated with lower subgenual anterior cingulate cortex-hippocampus connectivity in adolescence (Herringa *et al.*, 2013). Moreover, early life stress and symptoms of anxiety/depression in childhood and adolescence were involved in the pathogenesis of early-onset MDD (Herringa *et al.*, 2013; Ducharme *et al.*, 2014). In the current study, laterality of the SCR reduction was found, which is consistent with left-lateralised changes reported in the PFC in MDD. For example, a recent meta-analysis showed a reduction in the left medial PFC SA in depressed adolescent (⩽21 years) patients (Schmaal *et al.*, 2017), decreased CT in the left medial PFC associated with an increased number of episodes in MDD (Treadway *et al.*, 2015), and reduced volume in the left subgenual PFC in young patients with early-onset MDD in comparison to control subjects (Botteron *et al.*, 2002). Furthermore, we did not find that the CV, CT, and SA of the SCR were associated with depressive symptoms within the MDD groups, possibly due to depression being a heterogeneous clinical syndrome, and the alterations in SCR structure may be associated

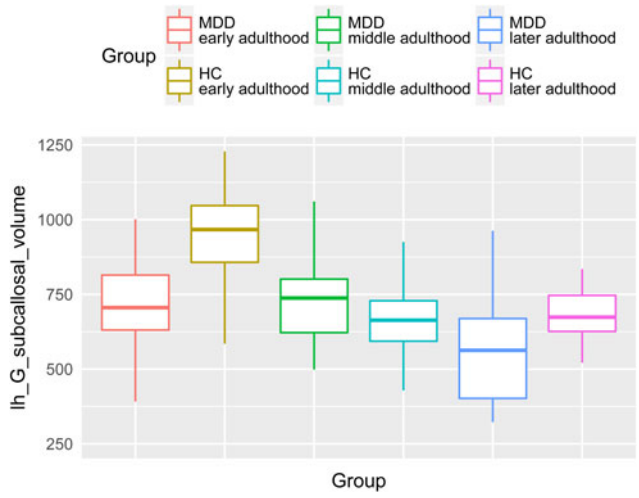

Fig. 4. Post hoc multiple comparisons showed that the reduction in SCR volume ($t = -2.9$, $p = 0.004$) was observed only in patients in the early adult age range (18 years ⩽ age ⩽ 30 years, $N = 35$) compared with early adulthood controls (18 years ⩽ age ⩽ 30 years, $N = 50$).

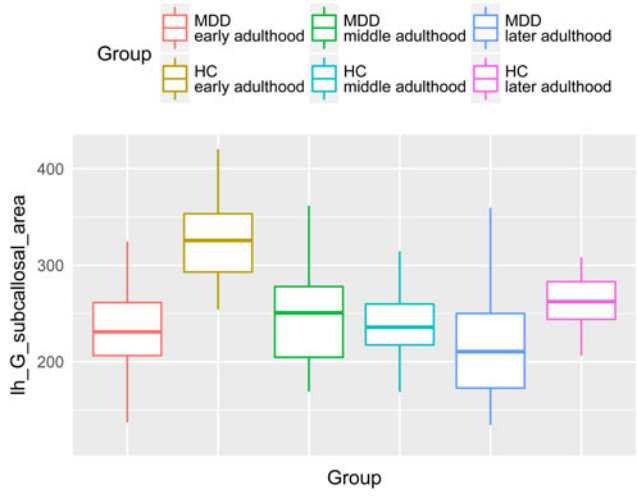

Fig. 5. Post hoc multiple comparisons showed that the reduction in subcallosal SA ($t = -3.2$, $p = 0.002$) was observed only in patients in the early adult age range (18 years ⩽ age ⩽ 30 years, $N = 35$) compared with early adulthood controls (18 years ⩽ age ⩽ 30 years, $N = 50$).

with specific depressive symptoms. The SCR is an important hub in a network that includes cortical structures, the limbic system, the thalamus, the hypothalamus, and brainstem nuclei, and dysfunction in the SCR-subcortical pathways may influence the observed depressive symptoms. Recently, a study indicated that the functional connectivity of SCR was significantly correlated with patient's percent change in the HDRS by treatment (Dunlop *et al.*, 2017). Further studies are required to clarify the relationship between the structural/functional connectivity of SCR and clinical symptoms of depression.

Interestingly, the CT of the SCR showed significant non-linear atrophy with ageing both in the MDD and HC groups. Previous studies indicated that CT changes showed a marked age-related reduction in extensive regions of brain compared with the SA changes across the adult life span (Lemaitre *et al.*, 2012), and SA showed a relatively subtle decrease with age from late childhood to early adulthood (Tamnes *et al.*, 2017). CT might be a more sensitive indicator of morphological ageing than SA in the subgenual PFC. The different trajectories between the CT and SA of the SCR with age may provide valuable information to distinguish pathological processes and normal ageing in MDD.

The current study has some limitations. The first limitation of our study is inherent in its cross-sectional design. In such studies, age-related changes in brain structure may be affected by potential cohort effects. The cross-sectional design of the study limits our ability to test the direction of causality, whether differences in the SCR SA or CV precede and confer vulnerability to or are the consequence of MDD. Second, alterations in the SCR structure are not specific to MDD, as these changes have been observed in other psychiatric disorders, such as post-traumatic stress disorder (Keding and Herringa, 2015), first-episode psychosis (Hirayasu *et al.*, 1999) and first-episode schizophrenia (Koo *et al.*, 2008). Thus, a future study design comparing patients with these disorders is clearly needed to resolve this issue. Third, in the current study, the assessment of the effects of recurrent episodes was based on patients' subjective reports (yes/no). We have not collected data on the number of episodes, the duration of episodes, and the total time spent depressed. This study did not allow an investigation of antidepressant medication effects and the number of episodes on brain structure across the life span because of a lack of detailed information on the number of episodes, duration of episodes and type of antidepressant treatment. Fourth, our MDD samples were adults, and we do not know for certain whether and to what extent there was cortical maturation delay in MDD from early adolescence to adulthood. Future research is needed to investigate the CT and SA changes in depressive disorders in early adolescence, and longitudinal studies are required to understand the relationship between the depressive illness and neural development. In addition, the general intelligence and socioeconomic status of the participants were not collected in our study, and future research is needed to take into account these factors. Finally, we specifically focused on the SCR, which is an important target for DBS treatment for treatment-resistant depression and has extensive connections with the subcortical structures implicated in the pathophysiology of MDD. Therefore, the study did not evaluate the abnormal SA and CT of other brain structures.

Taken together, the left SCR CV reduction was mainly driven by SA rather than CT in early adulthood MDD. The SCR CT might be a more sensitive indicator of morphological ageing than SA both in MDD patients and HCs. The different trajectories between the CT and SA of the SCR with age may provide valuable information to distinguish pathological processes and normal ageing in MDD. Future studies are needed to examine the functional and structural connectivity of the SCR with other brain regions and to relate such connectivity to different dimensions of depressive symptoms and treatment response in MDD.

Author ORCIDs. Dongtao Wei, 0000-0003-2544-8015

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