INTRODUCTION

Major depressive disorder (MDD) is one of the most common psychiatric disorders, and lifetime prevalence reaches up to 16%, and 12-months prevalence is about 6.6%. MDD present various symptoms such as the dysregulation of mood, cognition, and behavior. In spite of high clinical prevalence of the disease, its pathogenesis has not been fully elucidated due to the diversity of clinical features and pathogenesis [1-3]. The relations between the low emotional regulation which is the major feature of major depression and the structural changes such as the medial prefrontal cortex, amygdala, hippocampus, the striatum, and thalamus of MDD's brain have been proposed [4-8].

A number of magnetic resonance imaging (MRI) studies have attempted to investigate the structural brain changes of MDD. In particular, voxel-based morphometry (VBM) has been utilized to investigate morphological changes in the whole brain of MDD. VBM is a automated MRI analysis method to process morphological brain MRI data, and it minimizes operational bias, and objectively analyzes changes in the regional volume of brain tissues [8]. Many neuroimaging studies have been extracted various morphological features of human brain such as curvature [9, 10], fractal dimension [11, 12], thickness [13], and gyrification index [14]. Particularly, sulcal depth has been studied as an important neuroimaging biomarker for brain diseases and has been widely

Reduced Sulcal Depth in Central Sulcus of Major Depressive Disorder

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used to study the morphological characteristics of the cerebral folding [9, 15]. But, we could not find the sulcal depth related neuroimaging study in MDD. FreeSurfer (https://surfer.nmr.mgh.harvard.edu) is the most popular neuroimaging analysis software for MRI analysis; however, FreeSurfer did not provide sulcal depth analysis. CAT12 (https://neuro-jena.github.io/cat) is a useful neuroimaging software that provides structural MRI analysis, and has recently been added to the sulcal depth analysis pipeline. Therefore, this could be one of the reasons that sulcal depth studies have rarely been conducted in MDD.

Cortical gyrification is a complex process that occurs throughout life. It has been known that cortical regions are involved in the processes of brain development, aging, and brain disease-related degeneration. Sulcal depth is an important biomarker for brain morphology in neuroscience and neuropsychological diseases. The structural folding and deepening process of sulci are related to functional areas and occur during brain development, including early radial and later tangential growth. The deep sulcal areas are thought to be the first cortical folds in the early stages of brain development, and the formation of cortical folds could be related to genetic control and cytoarchitectonic areas [16]. The sulcal depth is sensitive to cerebral atrophy, thought to be related to reduced cortical thickness, gyral white matter volume, or tension of the cortico–cortical connections in the subcortical white matter could be secondary deformation due to disease progression. Several studies have analyzed brain morphological changes using sulcal depth, such as in schizophrenia or Alzheimer’s disease (AD) [17, 18]. These studies reported that generally reduced sulcal depths are related to cortical atrophy, and atrophy of the pial surface decreases the sulcal depth. Cortical structures, including the gyri and sulci, can be affected by genetic factors, neuropsychiatric diseases, and aging.

Previously, we performed various MRI study including volumetric MRI, VBM, surface-based vertex analysis, cortical thickness analysis based on old MDD cohort with Magnetom Trio 3T MRI [12-14]. In this study, new MRI data of MDD cohort collected using MAGNETOM Prisma 3T MRI which provides very high gradient performance with maximum gradient amplitude of 80 mT/m and a slew rate of 200. For the benefit of our new MRI scanner, high resolution T1 MRI (isotropic 1 mm) with high signal to noise ratio could be scanned in all subjects, and highly qualified T1 MRI is the most important factor to calculated sulcal depth in cerebral cortices.

In the present study, we hypothesized that there might be significant morphometric changes in the cerebral cortices between depressed patients and healthy controls (NMLs). To test this hypothesis, we investigated the morphometric differences between MDD patients and age and sex-matched NMLs using VBM and sulcal depth analyses.

MATERIALS AND METHODS

Participants

We recruited 69 patients diagnosed with MDD from the outpatient Psychiatry Clinic at the Korea University Anam Hospital in Seoul, Republic of Korea between May 2018 and December 2021. The sample was confirmed as MDD by board certified psychiatrists (Ham B-JH, Han KM) using the Structured Clinical Interview from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Axis I disorders. Basic demographic information, including age, sex, and education level, as well as clinical information, were collected. The patients were aged between 19 and 65 years and had been diagnosed with MDD by board-certified psychiatrists using a structured clinical interview from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Axis I disorders. The exclusion criteria were as follows: (i) any other major psychiatric comorbidity, including personality or substance use disorders; (ii) current psychotic features (e.g., delusions or hallucinations); (iii) history of serious and unstable medical illness; (iv) primary neurological illness, including head trauma with residual effects; and (v) any contraindication to magnetic resonance imaging (MRI) scan, such as metal implants or claustrophobia. Illness duration was also assessed in patients with MDD using the life-chart methodology, psychotropic medication history, and their current status. Illness duration was defined as the elapsed time since the patient had experienced their first mood episode, regardless of inter-episodic periods. We also recruited 23 age-matched normal controls (NML) via community advertisements. Controls were screened for major psychiatric histories and none had a psychiatric disorder. This study was approved by the Institutional Review Board of Korea University Anam Hospital (IRB No: 2018AN0118) and adhered to the principles of the Declaration of Helsinki.

MRI acquisition

All the subjects were scanned with a 3.0 Tesla Siemens MR scanner (Magnetom Prisma, Siemens Medical Solutions, Erlangen, Germany). coronal 3D T1-weighted magnetization prepared rapid gradient echo (MPRAGE) was obtained with the following parameters: ST=1.0 mm, no gap, number of slices=384 slices, TR/TE=2,300/2.26 milliseconds, number of signal averages=1, matrix=256×256, and FOV=256 mm×256 mm. Coronal MRI images were obtained perpendicular to the long axis of the anterior com-
missure to the posterior commissure in the midsagittal pilot.

**Voxel based morphometry and sulcal depth processing**

The MRIs were processed using the Computational Anatomy Toolbox (CAT12, http://www.neuro.uni-jena.de/cat12) for voxel-based morphometry (VBM) and sulcal depth analysis. For VBM, MRIs of all subjects were bias-corrected and spatially normalized to the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) template. Normalized MRI images were partitioned into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). The voxel values of the GM partitions were modulated to preserve the actual GM values. Modulated and unmodulated GM were smoothed using an 8-mm full width at half maximum (FWHM) isotropic gaussian kernel (IGK). The values of individual total intracranial cavity volume (ICV) were automatically calculated from the GM, WM, and cerebrospinal fluid.

For sulcal depth, the CAT12 toolbox included the calculation of the central surface of the bilateral hemisphere based on projection-based thickness. The pipeline of surface analysis included topological correction, spherical mapping, spherical registration. The estimated GM and WM boundaries were constructed by classifying all WM voxels in the MRI. After computing the curvature of the surface, the surface representation was reconstructed to obtain the finest scale of the local surface curvature. The sulcal depth of individuals was calculated based on the Euclidean distance between the central surface and its convex hull. Mean values of sulcal depth were extracted Destrieux (aparc a2009s) atlas using the surface extract additional surface parameters function.

**Statistical analyses**

Statistical analyses were performed with SPSS 24 (SPSS Inc. USA). The differences in age, HDRS, years of education, and Intracranial volume between the normal controls and MDD patients were tested using the independent t-test. Group difference in sex was tested using chi-square. All tests were two-tailed, and the level of significance was p<0.05.

Analysis of covariance (ANCOVA), controlled for age, sex, and ICV, was applied to analyze regional volume changes of GM, and ANCOVA with the confounders of age and sex was applied to analyze regional concentration changes of GM. The correlation between the GM volume or concentration and disease duration, onset, education level, or HRSD scores was tested by partial correlation analysis with the confounders of age, sex, and ICV (for modulated VBM). The statistical threshold level was set to FDR-corrected p<0.05, and the extent threshold was set to kE >200 voxels (676 mm$^3$; 1 voxel=3.375 mm$^3$).

| Table 1. Demographic and clinical data for patients with major depressive disorder and healthy controls |
|---------------------------------------------------------------|
| **MDD (n=46)** | **NML (n=23)** | **t or $\chi^2$** | **p** |
| Age, years | 36.07 (14.34) | 36.78 (14.42) | 0.196 | 0.942 |
| Sex (male/female) | 13/33 | 5/18 | 0.772 |
| Educational (years) | 13.87 (2.90) | 16.09 (1.80) | 3.874 | <0.001 |
| HRSD scores | 15.98 (5.35) | 1.26 (2.12) | -16.299 | <0.001 |
| ICV | 1,406.95 (120.14) | 1,467.89 (143.68) | 1.859 | 0.067 |
| Duration of illness (months) | 109.09 (100.03) | 146.79 (143.68) | 1.859 | 0.067 |
| Family History of mood disorder | 3 (14.2) | 3 (14.2) | 0.196 | 0.942 |
| Past mood episodes (times) | 3.1 (2.1) | 3.1 (2.1) | 0.196 | 0.942 |
| **Medication** | | | |
| SSRI | 8 | n/a | |
| SNRI | 0 | n/a | |
| NDRI | 2 | n/a | |
| NaSSA | 2 | n/a | |
| SSRE | 1 | n/a | |
| Combination of AD | 28 | n/a | |
| Lithium | 0 | n/a | |
| AED | 5 | n/a | |
| Lithium+AED | 0 | n/a | |
| AED+AED | 0 | n/a | |
| AP | 7 | n/a | |
| Combination of AP | 4 | n/a | |

All data are represented as mean (SD) or number (%). MDD: patients with major depressive disorder, NML: healthy controls, HRSD: Hamilton Rating Scale for Depression, ICV: Intracranial volume. *p<0.05. Medication: AD, antidepressants; AED, Anti-epileptic drugs; AP, Antipsychotics; Combination of AD, Combination of two or more types of antidepressants; NaSSA, Noradrenergic and Specific Serotonergic Antidepressant; NDRI, Norepinephrine- Dopamine Reuptake Inhibitor; SNRI, Serotonin and Norepinephrine Reuptake Inhibitor; SSRI, Selective Serotonin Reuptake Inhibitor.
RESULTS AND DISCUSSION

Characteristics of the participants

The Demographic characteristics of each participant, including age, sex, years of education, and Intracranial volume are summarized in Table 1. There were no significant differences in age or sex among the two groups. In the present dataset, for the MDD group, the mean age was 36.07, the mean percentage of females was 71.73%. For the NML group, the mean age was 36.78, and the mean percentage of females was 78.26%.

Voxel based morphometry and sulcal depth

There were no statistically significant differences in the ICV between the patients with MDD and the NML (NML vs. MDD: 1,467.9±143.68 cm$^3$ vs. 1,407.0±120.14 cm$^3$, p=0.067), GM (NML vs. MDD: 662.0±57.23 cm$^3$ vs. 641.3±64.22 cm$^3$, p=0.708), and WM (NML vs. MDD: 526.6±57.06 cm$^3$ vs. 504.7±52.33 cm$^3$, p=0.865) also not different between the two groups In sulcal depth analysis, depressed patients showed reduced sulcal depth in the areas of left posterior ramus of the lateral sulcus, superior frontal sulcus, supramarginal gyrus, central sulcus (Rolando’s fissure), and Heschl’s gyrus. The right posterior ramus of the lateral sulcus, temporal plane of the superior temporal gyrus, anterior transverse collateral sulcus, and central sulcus (Rolando fissure) were also reduced (Fig. 1, 2 and Table 2).

Sulcal depth was negatively correlated with HRSD scores by partial correlation analysis with age and sex. The results showed a negative correlation between sulcal depth and HRSD score in the right parahippocampal gyrus, parahippocampal part of the medial occipitotemporal gyrus, medial orbital sulcus (olfactory sulcus), medial occipitotemporal sulcus (collateral sulcus), and lingual sulcus (Fig. 3). However, there was no relationship between sulcal depth and disease duration, onset, or education level.

In VBM analyses, there were no significant differences between the two groups in the modulated (volume change) or unmodulated (concentration change) gray matter analyses and showed no relationship with disease duration, onset, or HRSD scores.

In this study, not only the central sulci, but also Heschl’s gyrus, posterior ramus of the lateral sulcus, superior frontal sulcus, and supramarginal gyrus of patients with MDD showed reduced sulcal depth compared to NML. As far as our knowledge, these findings are new in MDD. Recent, ENIGMA (Enhancing Neuro Imaging Genetics through Meta-Analysis) with MDD’s big MRI cohort (2148 MDD patients and 7957 healthy controls MRIs) reported reduced regional surface in the pericentral areas, and the study supports our findings [19]. During the developmental process gyrencephalic brain, the cerebral cortices show a predictable fold-

Fig. 1. Reduced sulcal depth in MDD patients. Sulcal depths of MDD were reduced compared to the normal controls in the left hemisphere of posterior ramus of the lateral sulcus (Lat_Fis-post), superior frontal sulcus (S_front_sup), supramarginal gyrus (G_pariet_inf-Supramar), central sulcus (S_central), Heschl’s gyrus (G_temp_sup-G_T_transv), and in the right hemisphere of Lat_Fis-post, temporal plane of the superior temporal gyrus (G_temp_sup-Plan_tempo), anterior transverse collateral sulcus (S_collat_transv_ant), and Heschl’s gyrus. The statistical result was displayed in aparc a2009s atlas (A) and template brain was inflated to show the areas of sulcal depth in detail (B). The statistical levels were set to a Holm-Bonferroni corrected p<0.05 level.
Reduced Sulcal Depth in MDD

The pathological relation between depression and reduced sulcal depth in central sulci is not unclear. But, depressed patients usually suffer anhedonia which is the core feature of depression as well as other mental health disorders. Anhedonia is a severe condition that describes the absence of interest, enjoyment, and motivation. We recently reported higher cortical volume and fractal...
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In the correlation analysis between the sulcal depth and the HRSD score of MDD group, the negative correlation between HRSD score and the sulcal depth in areas including right parahippocampal gyrus, parahippocampal part of the medial occipito-temporal gyrus, medial orbital sulcus (olfactory sulcus), and medial occipito-temporal sulcus (collateral sulcus) and lingual sulcus (Fig. 2) was identified. Zamoscik et al. [21] reported that remitted depressed patients showed stronger functional connectivity than healthy controls between the parahippocampal gyri and the posterior cingulate cortex. Similarly, Couvy-Duchesne et al. [22] observed reduced surface area in the right lingual, fusiform and parahippocampal gyri in patients with anxiety-depression. Significantly shallower olfactory sulci in current and remitted MDD patients was also reported by Takahashi et al. These previous studies support of findings and the results indicate that the negatively correlated areas with HRSD in this study could be an important brain loci related to the clinical symptoms of MDD.

The limitation of this study is the difference of education levels between NML and MDD group. Patients with depression have been considered to have the tendency of lower education level [21, 22], and the MDD patients of this study also showed lower education level compared to NML. To figure it out the effect of education level on sulcal depth, we correlated these two variables by simple or partial correlation with confounder of age, sex, but we could not find any relations between the two variables. This result supports our previous study about hippocampal subfield volume of MDD witch did not correlated with education level [23], and other studies reported, the education years and the gray hippocampal volume of healthy elders was not related [24, 25], and the educational levels and gray matter volume of subcortical structures also did not demonstrate significant correlations [26, 27]. But, one study reported when only including healthy subjects older than 35 years old, the higher education group showed greater hippocampal volume compared to the lower education group. But, However, they could not find any significant difference when young subjects

### Table 2. Reduced sulcal depth in patients with depression

| Label                              | Hemisphere | Corrected p-value | T-value | Ze-value |
|------------------------------------|------------|-------------------|---------|----------|
| Posterior ramus of the lateral sulcus | Left       | 0.004             | 4.189   | 3.927    |
| Superior frontal sulcus            | Left       | 0.021             | 3.766   | 3.569    |
| Supramarginal gyrus                | Left       | 0.021             | 3.384   | 3.236    |
| Central sulcus (Rolando's fissure) | Left       | 0.006             | 3.140   | 3.018    |
| Heschl's gyrus                     | Left       | 0.040             | 1.777   | 1.750    |
| Posterior ramus of the lateral sulcus | Right     | 0.008             | 3.388   | 3.239    |
| Temporal plane of the superior temporal gyrus | Right | 0.013             | 3.385   | 3.237    |
| Anterior transverse collateral sulcus | Right   | 0.026             | 3.358   | 3.212    |
| Central sulcus (Rolando's fissure) | Right     | 0.015             | 2.970   | 2.865    |

p<0.05, Holm-Bonferroni corrected.

In the correlation analysis between the sulcal depth and the HRSD score for Depression (HRSD) scale. Sulcal depths of MDD were negatively correlated with HRSD score in the areas of right parahippocampal gyrus, parahippocampal part of the medial occipito-temporal gyrus, medial orbital sulcus (olfactory sulcus), and medial occipito-temporal sulcus (collateral sulcus) and lingual sulcus. The statistical result was displayed in aparc a2009s atlas, and inflated to show the areas of sulcal depth in detail. The statistical levels were set to a Holm-Bonferroni corrected p<0.05 level.

Fig. 3. The correlation between the sulcal depth and Hamilton Rating Scale for Depression (HRSD) score. Sulcal depths of MDD were negatively correlated with HRSD score in the areas of right parahippocampal gyrus, parahippocampal part of the medial occipito-temporal gyrus, medial orbital sulcus (olfactory sulcus), and medial occipito-temporal sulcus (collateral sulcus) and lingual sulcus. The statistical result was displayed in aparc a2009s atlas, and inflated to show the areas of sulcal depth in detail. The statistical levels were set to a Holm-Bonferroni corrected p<0.05 level.

The dimension in both the pre- and post-central gyri of professional basketball players on a college basketball team [11]. The higher volume or fractal dimension of elite basket players could suggest maturation of the primary motor and somatosensory cortices due to physical exercise. However, depressed individuals with anhedonia experience a loss of social or physical activities. Patients with MDD in this study showed moderate to severe HRSD scores and a mean disease duration of almost nine years. Therefore, the authors cautiously assume that the depressed patients in this study may have had less sensory or physical activity for a long time. So, the authors very carefully interpret the reduced sulcal depth in MDD could be the result of social and physical anhedonia related cerebral degenerations. To confirm this hypothesis, further controlled investigation would be needed.
Reduced Sulcal Depth in MDD

(younger than 35 years) did not show any significant difference [28, 29]. Further studies are necessary to make a consensus on this issue in future.

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REFERENCES

1. Fava M, Kendler KS (2000) Major depressive disorder. Neuron 28:335-341.
2. Hasin DS, Sarvet AL, Meyers JL, Saha TD, Ruan WJ, Stohl M, Grant BF (2018) Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. JAMA Psychiatry 75:336-346.
3. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wolkowitz OM, Yatham LN, Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wolkowitz OM, Yatham LN (2003) Anatomic evaluation of the orbitofrontal cortex in major depressive disorder: results from the National Comorbidity Survey Replication. JAMA 289:3095-3105.
4. Botteron KN, Raichle ME, Drevets WC, Heath AC, Todd RD (2002) Volumetric reduction in left subgenual prefrontal cortex in early onset depression. Biol Psychiatry 51:342-344.
5. Campbell S, MacQueen G (2006) An update on regional brain volume differences associated with mood disorders. Curr Opin Psychiatry 19:25-33.
6. Lacerda AL, Keshavan MS, Hardan AY, Yorbik O, Brambilla P, Sassi RB, Nicoletti M, Mallinger AG, Frank E, Kupfer DJ, Soares JC (2004) Anatomic evaluation of the orbitofrontal cortex in major depressive disorder. Biol Psychiatry 55:353-358.
7. Neumeister A, Charney DS, Drevets WC (2005) Hippocampus, Volume 1: Depression and the Hippocampus. Am J Psychiatry 162:1057.
8. Mak AK, Wong MM, Han SH, Lee TM (2009) Gray matter reduction associated with emotion regulation in female outpatients with major depressive disorder: a voxel-based morphometry study. Prog Neuropsychopharmacol Biol Psychiatry 33:1184-1190.
9. Im K, Lee JM, Seo SW, Hyung Kim S, Kim SL, Na DL (2008) Sulcal morphology changes and their relationship with cortical thickness and gyral white matter volume in mild cognitive impairment and Alzheimer’s disease. Neuroimage 43:103-113.
10. White T, Andreasen NC, Nopoulos P, Magnotta V (2003) Gyration abnormalities in childhood- and adolescent-onset schizophrenia. Biol Psychiatry 54:418-426.
11. Kim JH, Park JW, Tae WS, Ryhu J (2022) Cerebral cortex changes in basketball players. J Korean Med Sci 37:e86.
12. Choi JH, Park DW, Ahn DH, Tae WS, Moon JH (2022) Decreased brain surface complexity in children with attention deficit hyperactivity disorder. J Clin Neurol 18:123-125.
13. Han KM, Tae WS, Kim A, Kang Y, Kang W, Kang J, Kim YK, Kim B, Seong JY, Ham BJ (2020) Serum FAM19A5 levels: a novel biomarker for neuroinflammation and neurodegeneration in major depressive disorder. Brain Behav Immun 87:852-859.
14. Choi KW, Han KM, Kim A, Kang W, Kang Y, Tae WS, Ham BJ (2022) Decreased cortical gyration in patients with bipolar disorder. Psychol Med 52:2232-2244.
15. Yun HJ, Im K, Yang JJ, Yoon U, Lee JM (2013) Automated sulcal depth measurement on cortical surface reflecting geometrical properties of sulci. PLoS One 8:e55977.
16. McKay DR, Kochunov P, Cykowski MD, Kent JW Jr, Laird AR, Lancaster JL, Blangero J, Ghahremani GD, Fox PT (2013) Sulcal depth-position profile is a genetically mediated neuroscientific trait: description and characterization in the central sulcus. J Neurosci 33:15618-15625.
17. Turetsky BI, Crutchley P, Walker J, Gur RE, Moberg PJ (2009) Depth of the olfactory sulcus: a marker of early embryonic disruption in schizophrenia? Schizophr Res 115:8-11.
18. Van Essen DC, Dierker D, Snyder AZ, Raichle ME, Reiss AL, Korenberg J (2006) Symmetry of cortical folding abnormalities in Williams syndrome revealed by surface-based analyses. J Neurosci 26:5470-5483.
19. Schmaa L, Hibrar DP, Sämang PN, Hall GB, Baune BT, Jahnshad N, Cheung JW, van Erp TGM, Bos D, Ikram MA, Vernooij MW, Niessen WJ, Tieleman H, Hofman A, Wittfeld K, Grabe HJ, Janowicz D, Bülow R, Selonke M, Volzke H, Grotegerd D, Dannlowski U, Arolt V, Opel N, Heindel K, Wulf H, Hoehn D, Czisch M, Couvy-Duchesne B, Renteria ME, Strike LT, Wright MJ, Mills NT, de Zubicaray GI, McMahon KL, Medland SE, Martin NG, Gillespie NA, Goya-Maldonado R, Gruber O, Krämer B, Hatton SN, Lagopoulos J, Hickie IB, Frodl T, Carballedo A, Frew EM, van Velzen LS, Penninx BWJH, van Tol MJ, van der Wee NJ, Davey CG, Harrison BJ, Mwangi B, Cao B, Soares JC, Veer IM, Walter H, Schoepf D, Zuroski B, Konrad C, Schramm E, Normann C, Schnell K, Sacchet MD, Gotlib IH, MacQueen GM, Godlewska BR,

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Nickson T, McIntosh AM, Papmeyer M, Whalley HC, Hall J, Sussmann JEF, Li M, Walter M, Aftanas L, Brack I, Bokhan NA, Thompson PM, Veltman DJ (2017) Cortical abnormalities in adults and adolescents with major depression based on brain scans from 20 cohorts worldwide in the ENIGMA Major Depressive Disorder Working Group. Mol Psychiatry 22:900-909.

20. Horsley VAH, Schäfer EA (1888) I. A record of experiments upon the functions of the cerebral cortex. Phil Trans R Soc Lond B 179:1-45.

21. Zamoscik V, Huffziger S, Ebner-Priemer U, Kuehner C, Kirsch P (2014) Increased involvement of the parahippocampal gyri in a sad mood predicts future depressive symptoms. Soc Cogn Affect Neurosci 9:2034-2040.

22. Couvy-Duchesne B, Strike LT, de Zubicaray GI, McMahon KL, Thompson PM, Hickie IB, Martin NG, Wright MJ (2018) Lingual gyrus surface area is associated with anxiety-depression severity in young adults: a genetic clustering approach. eNeuro 5:ENEURO.0153-17.2017.

23. Takahashi T, Nishikawa Y, Yücel M, Whittle S, Lorenzetti V, Walterfang M, Sasabayashi D, Suzuki M, Pantelis C, Allen NB (2016) Olfactory sulcus morphology in patients with current and past major depression. Psychiatry Res Neuroimaging 255:60-65.

24. Bromet E, Andrade LH, Hwang I, Sampson NA, Alonso J, de Girolamo G, de Graaf R, Demyttenaere K, Hu C, Iwata N, Karam AN, Kaur J, Kostychenko S, Lépine JP, Levinson D, Matschinger H, Mora ME, Browne MO, Posada-Villa J, Viana MC, Williams DR, Kessler RC (2011) Cross-national epidemiology of DSM-IV major depressive episode. BMC Med 9:90.

25. Torikka A, Kaltiala-Heino R, Rimpelä A, Marttunen M, Luukkaala T, Rimpelä M (2014) Self-reported depression is increasing among socio-economically disadvantaged adolescents - repeated cross-sectional surveys from Finland from 2000 to 2011. BMC Public Health 14:408.

26. Han KM, Won E, Sim Y, Tae WS (2016) Hippocampal subfield analysis in medication-naïve female patients with major depressive disorder. J Affect Disord 194:21-29.

27. Arenaza-Urquijo EM, Landeau B, La Joie R, Mevel K, Mézenge F, Perrotin A, Desgranges B, Bartrés-Faz D, Eustache F, Chételat G (2013) Relationships between years of education and gray matter volume, metabolism and functional connectivity in healthy elders. Neuroimage 83:450-457.

28. Piras F, Cherubini A, Caltagirone C, Spalletta G (2011) Education mediates microstructural changes in bilateral hippocampus. Hum Brain Mapp 32:282-289.

29. Noble KG, Grieve SM, Korgaonkar MS, Engelhardt LE, Griffith EY, Williams LM, Brickman AM (2012) Hippocampal volume varies with educational attainment across the life-span. Front Hum Neurosci 6:307.