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Age-related atrophy of cortical thickness and genetic effect of ANK3 gene in first episode MDD patients

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ABSTRACT

Brain ageing is thought to be related to geriatric depression, but the relationship between ageing and depression among middle aged individuals is unknown. The present study aimed to evaluate whether the age-related reduction of brain cortical thickness (CT) can be found in adult first-episode MDD patients, as well as to identify the possible genetic effect of the ANK3 gene polymorphism age-relates CT reduction. This study recruited 153 first-episode MDD patients with a disease duration < 2 years and 276 healthy controls (HC), and the CT of 68 whole brain regions and two ANK3 SNPs (rs1994336 and rs10994359) were analyzed. The results showed that although the CT of both groups was negative correlated with age, the MDD group had significant greater age-related decrease in CT than the HC group (-9.35×10^{-3} mm/year for MDD vs. -1.23×10^{-3} mm/year for HC in the left lateral orbitofrontal lobe). The multivariate analysis of covariance (MANCOVA) results yielded significant interactions of diagnosis × age, genotype × age and diagnosis × genotype interaction for rs10994359. In HC, the C allele showed a protective effect on age-related CT reduction. The reduction in CT with age was several times as greater in non-C carriers as in C carriers (-3.54×10^{-3} vs.-0.15×10^{-3} mm/year in left supramarginal gyrus) for HC. However, this protective effect disappeared in patients with MDD. We did not find a clear effect of rs1994336 on the age-related CT reduction. The findings indicate that the widespread accelerated brain ageing occurs early in adult-onset depression and this ageing may be a pathological mechanisms of depression rather than an outcome of the disease. The ANK3 rs10994359 polymorphism may partially affect regional cortical ageing in MDD.

1. Introduction

Major depressive disorder (MDD) is associated with increased risks of ageing-related diseases such as heart disease, obesity and diabetes (Ferrari et al., 2013). Recently, increasing evidence suggests that accelerated biological ageing is a characteristic of MDD, as indicated by accelerated brain ageing among patients with MDD (Alves et al., 2014). Compared with control subjects, MDD patients exhibited higher epigenetic ageing in brain tissue, suggesting that they are biologically older than their corresponding chronological age (Han et al., 2018). Usually, neurobiological ageing is associated with a reduction in brain structure (such as grey matter volume) (Ge et al., 2002). Focal age-related volumetric decreases, such as decrease in putamen, are reported to be greater in individuals with MDD than in controls (Sacchet et al., 2017). Other studies have shown that the grey matter of depressed people has a diffuse volume reduction, characterized by accelerated ageing of total grey matter volume (Frodl et al., 2008). It is unclear whether brain ageing in MDD is a cause or outcome of the disease. A 7-year longitudinal study confirmed age-related grey matter abnormalities in melancholic MDD patients (Soriano-Mas et al., 2011), and the number of relapses between scans was associated with a decrease in grey matter volume, indicating that a reduction in brain volume may

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advance as the disease progresses. Moreover, our previous study confirmed a significant reduction in grey matter volume in patients with first-episode MDD, implying that a decrease in brain volume begins in the early stage of disease (Cheng et al., 2010). Therefore, it is important to realize that the ageing of the brain in depression is emerging in the early stages of the disease, because it raises the significance of early identification and intervention as early as possible to prevent the acceleration of brain ageing.

Cortical grey matter volume is a nonspecific indicator of brain morphology because it is a combination of the other two features (surface area and thickness). Thus, a reduction in cortical volume may suggest a reduction in thickness and/or area. The two characteristic components of grey matter result from independent well-differentiated corticogenesis stage during development (Geschwind and Rakic, 2013; Rakic, 1988) and uncorrelated genetic control (Dale and Sereno, 1993; Winkler et al., 2010) under distinct genes (Chen et al., 2015). Regional differences in thickness may reflect potential regional cellular structural differences. Therefore, for imaging genetic studies, cortical thickness can be prioritized as a separate feature of interest rather than grey matter volume (Winkler et al., 2010). A recent study on normal healthy ageing suggested that age is negatively correlated with cortical thickness, indicating that cortical thickness may be a reliable biomarker for normal ageing (Bajaj et al., 2017).

To date, the underground physiology of brain ageing in depression has been unclear. The ageing of brain structures of patients with MDD seems to be influenced by their genetic background. The CACNA1C A allele affects the medial prefrontal cortex (mPFC) in mood disorder, and shows age-related cortical thinning in the anterior cingulate cortex (cACC) (Soeiro-de-Souza et al., 2017). Recent genome-wide association studies (GWAS) of patient populations and genetic linkage studies have demonstrated that the ankyrin-G (AnkG) gene is involved in neuropsychiatric disorders, including mood disorder (Ferreira et al., 2008; Schulze et al., 2009; Scott et al., 2009). The *ANK3* gene is the first gene to achieve genome-wide significance and is strongly related to the occurrence of mood disorders (Ferreira et al., 2008) and psychotic experience (Legge et al., 2019). To date, *ANK3* rs10994336, has been the most widely studied polymorphism, and most association studies based on mood disorders examined this polymorphism. *ANK3* is suspected to participate in the stabilization and localization of ion channels and cell adhesion molecules to nodes of Ranvier and axonal initial segments (Hedstrom et al., 2008; Kordeli et al., 1995) and play a role in the developing cortex (Durak et al., 2015), the onset of myelination (Ching et al., 1999), and neurogenesis in adults (Paez-Gonzalez et al., 2011). Alterations in AnkG sequence or intracellular levels could disrupt these mechanisms and affect the function of neural circuits involved in mood and cognition (Leussis et al., 2013). AnkG hemozygous mice present cognitive impairment and elevated anxiety/depressive-like traits (Liu et al., 2017). The risk alleles of mood disorder have been associated with reduced neuronal *ANK3* expression in multiple brain regions (Roussos et al., 2012; Rueckert et al., 2013). Clifford et al. found that the G allele rs1938526 of *ANK3* was associated with general cognitive impairment and widespread cortical thinning in patients with first-episode psychosis patients (Cassidy et al., 2014). A recent systematic review found that the *ANK3* gene has an impact on white matter integrity, which contains genome-wide supported risk variants for mood disorder (Gurung and Prata, 2015). These studies indicate that *ANK3* may be associated with the development of structural brain abnormalities implicated in mood disorder.

To our knowledge, no study has yet examined accelerated ageing of the whole brain or the relationship between *ANK3* gene and brain ageing among adults with MDD. The first aim of the present study was to identify the pattern of cortical ageing in first-episode adult-onset MDD. We also wanted to determine whether *ANK3* had an effect on brain ageing as indicated by cortical thickness atrophy.

2. Methods and materials

2.1. Participants

This research was approved by the Institutional Review Board of Kunming Medical University (NCT00703742. https://clinicaltrials.gov/). Each participant was required to sign a written informed consent form after receiving a complete description of the study. The diagnosis of MDD was independently made by two experienced psychiatrists in accordance with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV, American Psychiatric Association, 1994). A total of 153 right-handed MDD patients were recruited from the out/inpatients clinics of the Department of Psychiatry, First Affiliated Hospital of Kunming Medical University. These MDD patients were Han Chinese people between 18 and 60 years old who had scores of 17 or greater on the 17-item Hamilton Depression Rating Scale (HDRS), were untreated and were in their first episodes. Clinical data on age, age of onset, duration of disease, sex and years of education were collected. The duration of disease, defined as the period between the initial manifestation clearly attributable to MDD and the day that the patients underwent magnetic resonance imaging (MRI), was < 2 years. The exclusion criteria were as follow: (1) another diagnosed axis I psychiatric disorder; (2) organic brain disorders or neurological disorders; (3) obvious psychiatric symptoms, such as delusions or hallucinations; (4) any physical illness as assessed by personal history; (5) clinical conditions that could cause cerebral atrophy (such as a history of arterial hypertension, diabetes mellitus, stroke); and (6) inability to undergo an MRI scan, including subjects with metal implants. Of the MDD patients who participated in clinical screening, none of them met the exclusion criteria and thus they all underwent MRI scans. We recruited 276 right-handed Han Chinese healthy controls (HC) matched by sex, age and years of education with the MDD patients in the local community. All of the HCs had no history of psychiatric, neurological or organic diseases according to the exclusion criteria and were without known histories of any psychiatric illnesses in first-degree relatives. The depressive symptoms and anxiety of all of the participants were assessed by two experienced psychiatrists using the 17-item Hamilton Depression Rating Scale (HDRS, Hamilton 1960) and the 14-item Hamilton Anxiety Scale (HAMA).

2.2. DNA extraction and ANK3 genotyping

For each participant, peripheral venous blood samples were obtained and DNA was extracted by AxyPrepTM Blood Genomic DNA small Kit (AxyGen, U.S.). DNA samples from the finished product were placed in a -80° cryogenic refrigerator. *ANK3* rs10994336 and rs10994359 were examined by the TaqMan allelic discrimination assay (Applied Biosystems, ABI Assay ID: rs10994336: C_31344821_10; rs10994359: C_31344870_10). We used a 7500 Real-Time PCR system and the SDS v2.3 software (Thermo Fisher Scientific Co.) to analyse the genotypes (supplementary Fig. 1). All genetic statistical analyses were performed using the SHEsis online software (http://analysis.bio-x.cn) to test whether the data were in accordance with the Hardy-Weinberg equilibrium (HWE) and to analyse differences in the allele frequencies and genotypes between the two groups.

2.3. MRI data acquisition

MRI scanning was carried out at a Philips Achieva 3.0-T MRI scanner (Philips, The Netherlands) and by a skilled radiological technician in a standard scanning head coil. The cushions were used for each participant to minimize head movement. T1 and T2 weighted scans were performed to rule out the obvious structural abnormalities. Then three-dimensional structural data were obtained by fast spoiled gradient recalled acquisition (FSPGR) for each participant. The parameters were as follows: TR = 7.38 ms, TE = 3.4, ms = 1.2 mm,

FOV = 250 × 250 mm, MARTIX = 256 × 256, no interval, inspire angle = 8°, slice number = 230, scanning time = 6 min 53 sec. All of the sections were acquired parallel to the anterior-posterior commissure line. We obtained MRI data from 153 MDD patients and 274 controls from the same samples used for genotyping.

2.4. Calculations of cortical thickness

We used the FreeSurfer package 5.1.0 (http://surfer.nmr.mgh.harvard.edu) for cortical surface reconstruction and thickness measurement. On the Ubuntu (version 12. 04) platform, we used the FreeSurfer package for surface-based morphometry (SBM) analysis. The general process included removing non-brain structures such as skulls, performing Talairach transformations, dividing grey matter tissue, and reconstructing the whole brain surface using a triangular mesh. Finally, the reconstructed images of each individual were mapped to a common spherical coordinate system using a spherical transformation for comparative analysis. Data were smoothed with the full width at half maximum (FWHM) value of 10 mm Gaussian kernel. The software automatically divides each hemisphere cortex into 34 anatomical brain regions based on the native Desikan-Kiliany brain map (Desikan et al., 2006), and extracts the cortical thickness of each brain region. All results of cortical parcellations were qualified by the FreeSurfer QA Tools (available from http://www.freesurfer.net/fswiki/QATools).

2.5. Statistical analysis

Statistical analyses were performed using SPSS 22.0, (IBM Corporation. USA). Normally distributed continuous data are showed as mean ± s.d. We first compared the difference in CT between groups. The regions with differences between groups were chosen for the next regression analysis. In the primary analysis, the test level was set to $\alpha = 0.05$, two-sided. Areas with statistically significant differences in the above ANCOVA were further compared. To correct for multiple comparisons, we applied false discovery rate (FDR) correction (Benjamini et al., 2001) to the main effect of diagnosis, age, and the diagnosis-by-genotype interaction using $q < 0.05$. Because we compared two hemisphere separately, the numbers of comparisons in the main analyses were set as 34 (34 cortical regions with the Desikan-Kiliany atlas of brain map) for cerebral cortical regions, and a significance level of $p < 0.0015$ ($p < 0.05/34$) was used for the analysis (Han et al., 2017). FDR correction was applied to each analysis of the diagnostic effect, genotypic effect, and interaction effectsof the structural cortical thickness outcome in the main analyses. To analyse group differences due to demographic and clinical characteristics, age, education level and HDRS scores were analysed using t-tests, and the differences in the distributions of genotypes across genders were analysed using chi-squared tests.

Then, we performed statistical analysis consisting of a multiple linear regression among the HC and MDD groups separately, in which, cortical thickness was the dependent variable and, whereas age was the main explanatory variable (adjusted for gender and education). We further assessed the age × group interaction in a specific region by comparing the between-group difference of slopes of the lines best fitting for each group. To assess the effect of the group × age × genotype interaction on cortical thickness, we then performed a multivariate analysis of covariance (MANCOVA) to assess group (MDD, control) × age × genotype (C carrier and non-C carrier for rs10994359) interactions associated with cortical thickness. We performed this analysis with sex and education as covariates (between-subjects model: Design: + edu + sex + diagnosis + genotype + age + diagnosis × genotype + diagnosis × age + genotype × age + diagnosis × genotype × age) according to the statistical methods used in previous imaging genetic studies (Fani et al., 2013). Few studies have reported the effect of *ANK3* SNP polymorphism on brain morphological changes. The *ANK3* rs10994359 allele has shown a weak risk for disease in previous research. In this exploratory analysis, the P value was set at 0.01 for the "diagnosis" effect, while for the main effect of "genotype", "age", and the interaction effect of "diagnosis" by "genotype" and "age", the P value was set to 0.05, as we expected the effect of "genotype" and "age" to be more subtle. The results were considered significant after correction for multiple comparisons across the whole brain at $P < 0.05$ (Han et al., 2017; Zhang et al., 2013).

To further identify the genotype effect on age and cortical thickness, we executed linear regression separately in two groups: C carriers (C/T and C/C) and non-C carriers (T/T) of allele *ANK3* rs10994359. We chose loci rs10994359 because our results revealed that the rs10994359 allele C showed a deferent distribution between the HC and MDD groups and could affect cortical thickness. We also compared the slopes of age and cortical thickness with age in brain regions of Ccarriers and non-C carriers. The difference in the effects of rs10994359 on cortical thickness between the HC and MDD groups were analysed by ANCOVA with age and education as covariates.

3. Results

3.1. ANK3 gene rs10994336 and rs10994359 polymorphisms in the MDD and HC groups

We successfully genotyped two SNPs in 153 depressive patients and 274 normal controls. The demographic and clinical characteristics of the MDD and control groups are presented in Table 1. As expected, the MDD group reported greater severity of depression as measured by the HAMD than the control group.

The success rates of rs10994336 and rs10994359 genotyping in the HC group were 99.28% (274/276). In the MDD group, the success rate for rs10994359 genotyping was 100% (153/153), and for rs10994336 genotyping, it was 99.35% (152/153). The distribution of the rs10994359 polymorphisms met the HWE requirements in the two groups of subjects considered in this analysis ($p > 0.05$).

As shown in Table 1, we did not find any statistically significant differences in rs10994336 and rs10994359 when the analysing the allele frequency and the genotype frequency between the HC and MDD groups ($p > 0.05$).

3.2. Abnormal cortical thickness in MDD

We measured cortical thickness of 68 brain regions among 153 patients and 274 controls and then compared the difference between MDD patients and HCs. Compared with HCs, MDD patients showed significant abnormalities in cortical thickness of multiple areas, after

Table 1
Demographic data and genotypes of MDD and HC.

	HC (n = 276)	MDD (n = 153)	X^2/t	P
Gender (male/female)	102/174	48/105	1.455	0.249
Age	35.04 ± 12.56	33.57 ± 10.23	1.060	0.290
Education (year)	15.00 ± 4.07	11.75 ± 4.35	7.873	< 0.0001
HAMD score	0.4522 ± 0.6747	24.29 ± 4.84	−79.954	< 0.0001
HAMA score	0.6765 ± 0.7576	22.24 ± 5.53	−63.273	< 0.0001
rs10994359	n = 274	n = 153		
CC	40(0.146)	14(0.092)		
CT	119(0.434)	58(0.379)	5.01	0.061
TT	115(0.420)	81(0.529)		
C	199(0.322)	86(0.281)	1.610	0.205
T	419(0.678)	220(0.719)		
rs10994336	n = 274	n = 152		
CC	157(0.649)	95(0.575)		
CT	102(0.303)	49(0.369)	1.136	0.567
TT	14(0.048)	8(0.056)		
C	416(0.762)	239(0.786)	0.651	0.420
T	130(0.238)	65(0.214)		

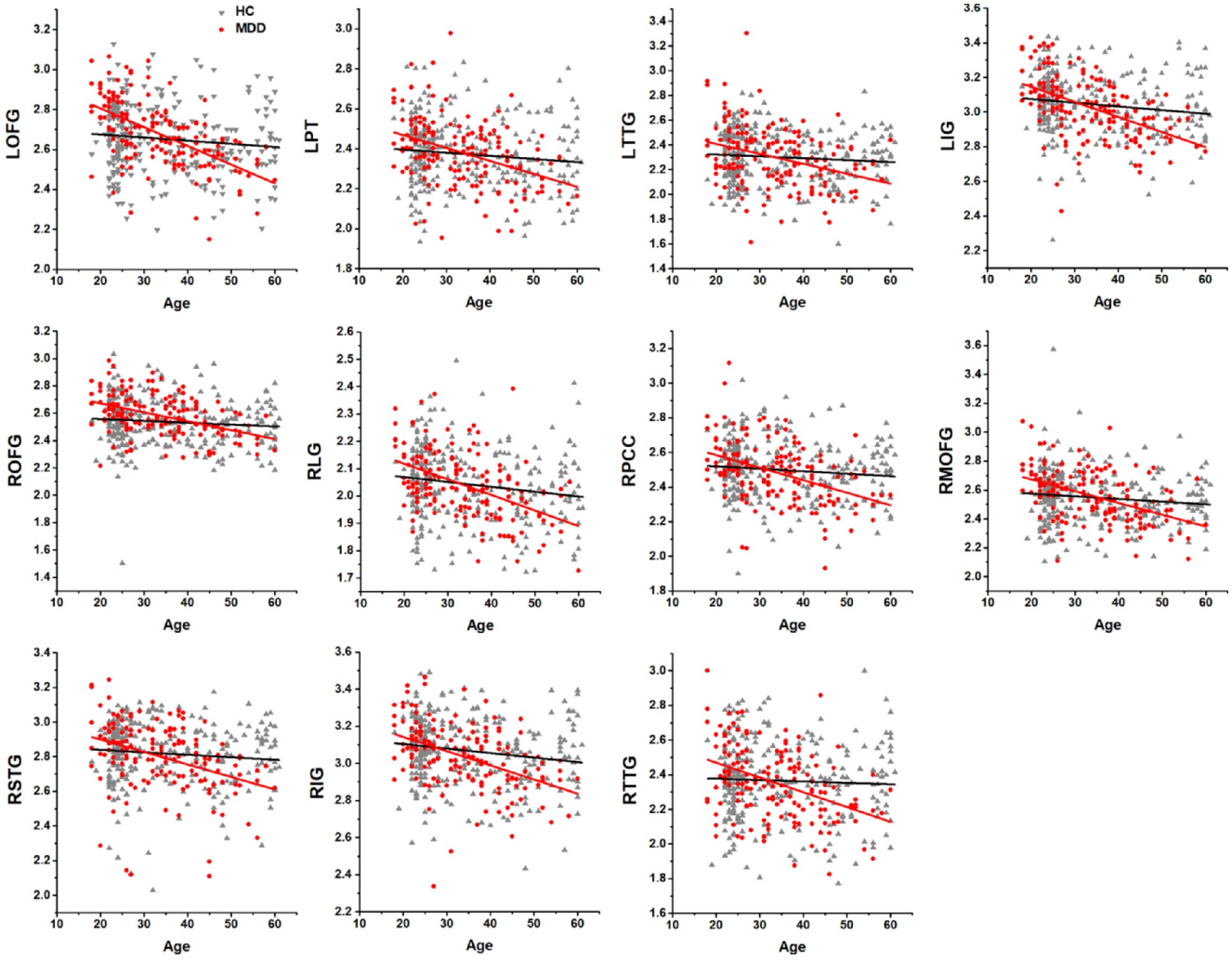

Fig. 1. Significant reduction of slope for cortical thickness with age in MDD. In most regions, the cortical thickness declined with age among both HC and MDD patients. However, the reduction was more accelerated among MDD patients than among HC. The figures showed that there was significant difference ($P < 0.001$) in the reduction of cortical thickness with age between MDD patients than HC. HC, health control; MDD, major depressive disorder; LOFG, left lateral orbitofrontal gyrus; LPT, left parstriangularis; LTTG, left transverse temporal gyrus; LIG, left insula lobe; ROFG, left lateral orbitofrontal gyrus; RLG, right lingual gyrus; RPCC, right posterior cingulate gyrus; RMOFG, right medial orbitofrontal gyrus (RMOFG); RSTG, right superior temporal gyrus; RIG, right insula lobe; RTTG, right transverse temporal gyrus.

Table 2
Interaction of age, genotype and diagnosis on cortical thickness.

	rs10994336		rs10994359	
	F	P	F	P
Diagnosis	2.400	0.005	2.581	0.003
Genotype	0.915	0.531	1.527	0.112
Age	2.418	0.0001	2.378	< 0.0001
Diagnosis × age	1.415	0.054	1.456	0.041
Diagnosis × genotype	1.681	0.069	2.159	0.013
Genotype × age	1.175	0.222	1.511	0.028
Diagnosis × age × genotype	1.206	0.190	0.875	0.682

adjusting the analysis for age, education and sex (Supplementary table 1).

3.3. Significant age-related reduction in cortical thickness in MDD patients than compared with HCs

Both groups showed negative correlation between a cortical thickness and age. The older of the age, the thinner of the CT. However, the slope of CT reduction with age of MDD group was significantly greater than that of the HC group in multiple brain regions (Supplementary table 2, Fig. 1), especially in the orbitofrontal lobe, insula and posterior cingulate ($p < 0.0001$). For example, the reduction in cortical thickness with age for MDD vs. HC were -9.35×10^{-3} vs. -1.23×10^{-3} mm/year in left lateral orbitofrontal lobe.

3.4. Interactions of age, diagnose and ANK3 polymorphism on cortical thickness

We found that for the rs10994336 locus, there was no significant effect of diagnosis or genotype on cortical thickness, or the interaction between diagnosis, genotype and age on cortical thickness. Only a slight trend of diagnosis × age on cortical thickness was found (Table 2). However, for loci rs10994359, the MANCOVA revealed significant multivariate effects of age ($F = 2.378$, $p = 0.112$), and diagnosis ($F = 2.581$, $p = 0.003$) on cortical thickness. The genotype alone did not affect the cortical thickness ($F = 1.527$, $p < 0.001$). In total, these effects were qualified by a significant diagnosis × age interaction ($F = 1.456$, $p = 0.041$), a diagnosis × genotype interaction ($F = 2.159$, $p = 0.013$), and a genotype × age interaction ($F = 1.511$,

Table 3
Effect of age, diagnosis and rs10994359 genotype interactions on cortical thickness of different regions.

	Hemisphere	Regions	F	P
Diagnosis	Left	Caudal middle frontal gyrus	8.909	0.003
	Left	Parsopercularis gyrus	10.082	0.002
	Left	Superior frontal gyrus	9.342	0.002
	Right	Supramarginal gyrus	8.354	0.004
Genotype	Left	Paracentral gyrus	4.526	0.034
Age	Left	Caudal middle frontal gyrus	3.969	0.008
	Left	Parsopercularis gyrus	4.672	0.000
	Left	Pericalcarine gyrus	4.232	0.000
	Left	Rostral anterior cingulate gyrus	4.987	0.002
	Left	Superior frontal gyrus	3.554	0.014
	Right	Inferior temporal gyrus	4.003	0.008
	Right	Lateral orbito-frontal gyrus	8.825	0.000
	Right	Pericalcarine gyrus	13.125	0.000
	Right	Supramarginal gyrus	5.290	0.001
Diagnosis × age	Right	Lateral orbito frontal gyrus	2.667	0.047
Diagnosis × genotype	Left	Paracentral gyrus	7.064	0.008
	Left	Rostral anterior cingulate gyrus	4.310	0.039
	Left	Superior frontal gyrus	4.515	0.034
	Right	Precentral gyrus	7.825	0.005
Age × genotype	Right	Precentral gyrus	2.751	0.042

p = 0.028).

We further observed the multivariate effects of age, group and genotype on cortical thickness in different regions. The results showed that the effect of the diagnosis × age interaction was most significant in the right lateral orbitofrontal gyrus, the effect of the age × genotype interaction was most significant in right precentral lobe, and the effect of the diagnosis × genotype interaction was most significant in the left paracentral lobe, rostral anterior cingulate gyrus, superior frontal lobe and right precentral lobe (Table 3, multiple comparisons corrected).

3.5. Different genotype effect on cortical thickness in MDD patients and HC

The main effect of rs10994359 on cortical thickness differed between groups in some regions, including the left paracentral gyrus, rostral anterior cingulate gyrus, superior frontal gyrus and right precentral gyrus (Table 3).

We then analysed the effect of genotype on age-related reductions in cortical thickness. In HC, the cortical thickness was higher in several regions among C carrier than among individuals who were TT homozygous (Supplementary table 3). We found only a few regions with weak negative correlations between age and cortical thickness among C carriers, while many regions showed negative correlations between age and cortical thickness in TT homozygous (Supplementary table 4). The slope of cortical thickness with age among TT homozygous was significant greater than that among C carriers, especially in the left inferior parietal gyrus (3.32×10^{-3} vs. -0.47×10^{-3} mm/year), left supramarginal gyrus (3.54×10^{-3} vs. -0.15×10^{-3} mm/year), left pars orbitalis gyrus, lingual gyrus, and isthmus cingulate gyrus (Table 4). There was a significant difference of the slopes for cortical thickness with age between TT genotype and C-carrier (Table 4, Fig. 2).

However, in MDD patients, the protective effect of C carrier on cortical thickness against age disappeared. Unlike in HC, the cortical thickness in several regions were lower among C carrier than among TT homozygous individuals (Supplementary table 5) with MDD, and most of the brain regions showed significant negative correlations between age and cortical thickness in both C allele carriers and non-C carriers (Supplementary table 6). There was no significant difference in the slopes between the TT homozygous individuals and C-carrier in any regions.

4. Discussion

Our results revealed obvious age-related grey matter atrophy in multiple regions in adult MDD patients. Although age-related cortical thinning might also occur in healthy individuals, this trend seemed to become more obvious in MDD, especially in the OFC, insula and post cingulate gyrus, which are core regions that affect mood regulation. Because the duration of depression in our patients was < 24 months, these results indicated the presence of widespread ageing in MDD patients, even at the very early stage. Cortical thinning is a major manifestation of age-related abnormalities in brain morphology and has been consistently described in both postmortem and MRI studies. These changes include a reduction in total brain weight and cortical thickness, as well as cortical atrophy (Kemper, 1994). Moreover, these morphological alterations may occur faster in particular areas of the cortex such as the PFC (Salat et al., 2004). Cortical thickness can be modulated by numerous factors, including the number, size and myelination of neurons in the cortical columns (Panizzon et al., 2009). Neuronal survival and dendritic volume could be promoted in the adult brain by glutamatergic signaling via N-methyl-D-aspartate receptors (Burgoyne et al., 1993), which have been reported to be altered in MDD patients. A recent study found robust age-related upregulation of genes that are highly expressed in oligodendrocytes and astrocytes, while genes highly expressed in layer 2/3 glutamatergic neurons were downregulated across age (French et al., 2017). Previous research has found evidence of accelerated biological ageing of the putamen volume of individuals with mood disorders (Sacchet et al., 2017). Other studies have reported that individuals with bipolar disorder exhibit accelerated grey matter reduction with age (Brambilla et al., 2001). Treatments against reductions in brain ageing may improve symptoms and prognoses for people with MDD. Evidence also showed that depression itself could become a risk factor for ageing. As our previous study revealed, structural abnormalities are more serious 12 months after the onset of depression, even in first-episode patients (Cheng et al., 2010). These results suggest the importance of intervening in depression as early as possible.

In this study, we identified slight contributions of the *ANK3* locus rs10994359 polymorphism to cortical thickness reduction with age, specifically in mood regulation regions like such as the PCC, precuneus and frontal lobe, without the effect of medications and prolonged duration. It seemed that the C allele had a protective effect on age-

Table 4
Slope difference for cortical thickness with age of different genotypes in HC.

Hemisphere	Regions	Slope		F	p
		HC-C (n = 159)	HC-TT (n = 115)		
Left	Inferior parietal gyrus (LIPG)	0.00047	−0.00332	4.052	0.045
Left	Isthmus cingulate gyrus (LCG)	0.00079	−0.00339	4.666	0.032
Left	Lingual gyrus (LLG)	−0.00069	−0.00340	5.020	0.026
Left	Pars orbitalis gyrus (LOG)	−0.00096	−0.00563	4.333	0.038
Left	Supramarginal gyrus (LSMG)	0.00015	−0.00354	5.869	0.016

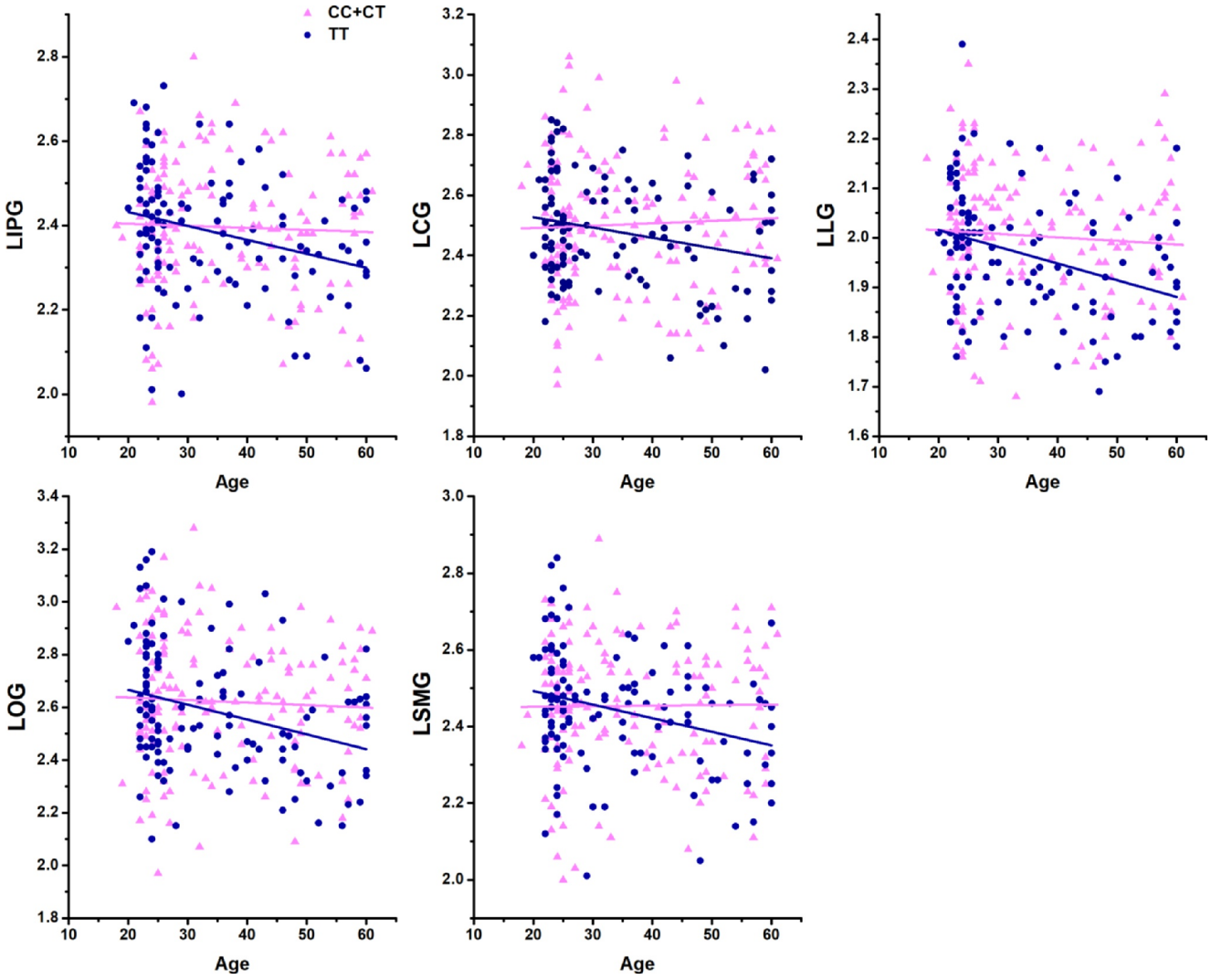

Fig. 2. Correlation between cortical thickness with age of different genotype in HC. The reduction slope of cortical thickness with age among TT homozygous was significant greater than that among C carriers, especially in the left inferior parietal gyrus (LIPG), left supramarginal gyrus (LSMG), left pars orbitalis gyrus (LOG), lingual gyrus (LLG), and isthmus cingulate gyrus (LCG)

related cortical thickness reduction against age among HC in mood regulation regions such as the isthmus cingulate gyrus, inferior parietal gyrus and precuneus. However, this effect disappeared in MDD patients, while there was no significant difference in the slopes between TT homozygous individuals and C carriers. Our results also suggested different modulations of rs10994359 on the cortical thickness of different brain regions. There was a slightly lower but not significant trend of the CC genotype in MDD patients. We believe these results might be due to the samples used in the present study. Actually, most studies of rs10994359 reported the C allele as a risk factor for mood disorder. However, many studies targeted on ANK3 have failed to detect a significant association between this polymorphism and a disease after multiple test corrections (Leussis et al., 2012). The genome-wide significant SNPs identified to date have only very small effects on disease, with odds ratios below 1.2 on average (Psychiatric, 2011), indicating a slightly increased risk of disease for carriers of the risk allele. It is possible that the contribution of this polymorphism to variation in brain processes underlying disease is much larger than its contribution to disease risk per se. The mechanism of the differential effects of rs10994359 on cortical thickness in HC and MDD patients is not clear. The inverted gene effects of patients and controls have been observed for other genes. For example, an inverted U-shape effect of the norepinephrine transporter (NET) gene SNPs was found in patients with attention deficit hyperactivity disorder (ADHD), with the T allele carrier having lower attention problem scores compared to patients with the AA genotype, whereas T allele carriers in the community sample had more attention problem (Nemoda et al., 2018). A similar U-shaped genetic effect is observed in the COMT gene in Parkinson's disease (Fallon et al., 2013), during attentional formation processing, Val homozygotes showed higher dorsolateral prefrontal cortex activity than Met carriers, while an opposite pattern was observed in healthy older individuals. Another study on MDD found a nonlinear modulation effect of COMT on global functional connectivity density (Gong et al., 2017). In the control system, the prefrontal cortex showed inverted U-shaped modulation, but in the processing system, the hippocampus and occipital cortex showed U-shaped modulation. Thus, the findings of the nonlinear inverted modulation might reflect DA signalling in the brain in MDD patients. A potential explanation of the inverted modulation in patients is the balance mechanism of the brain (Tian et al., 2013) and the anticorrelated relationship between the control and processing systems in the human brain. However, the inverted modulation of ANK3 rs10994359 might imply an imbalanced regulation or compensatory role of genetic effects on different regions or circuits in MDD. From this study, the *ANK3* rs10994359 polymorphism only partially contributed to the age-dependent reduction of CT in MDD. These results might imply that the genetic background of CT might be related to

multiple genes. Future studies of multiple genetic contributions or interactions might be better to elucidate the association of genes with age-related CT reduction.

The mechanism by which the C allele of rs10994359 influences brain morphology is not fully elucidated, but some data indicate that this may occur through direct regulation of maintenance of the neural membrane. The protein AnkG is required in the clustering of sodium voltage gated channels in nodes of Ranvier and axonal segments and is involved in the maintenance of membrane domains. This modular protein is an essential factor for enabling the propagation of action potentials in myelinated neurons (Kretschmer et al., 2002). A recent study suggests that AnkG plays an essential role in the maturation and long-term stabilization of the newly assembled nodal complex (Saifetiarova et al., 2017). In addition to maintaining the normal function of neurons, AnkG regulates neurogenesis and Wnt signaling by altering the subcellular localization of β-catenin (Durak et al., 2015). *ANK3* gene mutations and abnormal expression mediate the neurodevelopmental abnormalities (Roussos et al., 2012). GABA-A-receptor-based interneuron circuitry is essential for higher order function of the human nervous system and is implicated in schizophrenia, depression, and autism. The results support that AnkG promotes the stability of somatodendritic GABAergic synapses in vitro and in vivo (Tseng et al., 2015). Rangaraju et al. reported significantly lower levels of *ANK3* expression in chronologically younger individuals than in middle aged individuals, who presumably have been exposed to more severe and acute negative mood and stress (Rangaraju et al., 2016). Of note, *ANK3* was previously reported to overexpress in fibroblasts from patients with Hutchinson-Gilford progeria syndrome, which is a form of accelerated ageing. Taken together, these studies uncover *ANK3* genes as biological links between mood, stress and ageing, that may be biomarkers as well as targets for preventive or therapeutic interventions(Rangaraju et al., 2016). Moreover, a role of AnkG protein in regulating the postsynaptic compartment organization and function has recently emerged. Neuronal activity promotes AnkG accumulation in distinct spine subdomains, where it differentially regulates NMDA receptor-dependent plasticity (Smith et al., 2014). Luonia et al. reported an interaction between functional variation in the *ANK3* gene and obstetric complications on working memory in healthy adult subjects (Luoni et al., 2016). These results suggest the potential of AnkG for mediating the effects of stress exposure to neurodysfunctions associated with depression (Duman and Aghajanian, 2012).

Some limitations of this study should be noted. First, as a cross-sectional study, we can only find a correlation between age and cortical thickness. Future longitudinal prospective studies are necessary to observe the development of cortical thickness with age in patients with MDD. Second, although we calculated all 68 regions of the whole brain according to the template, it is possible that age-related abnormal morphology may occur cross-regionally. A voxelwise strategy would be better to find extensive changes in the brain.

In summary, the present findings support prominent ageing in first-episode MDD with a short duration, suggesting the importance of early intervention to prevent the accelerated degeneration in depression. The results also suggested a role of the *ANK3* gene polymorphism rs10994359 C allele in the modulation of age-related cortical thinning in MDD. Further studies investigating the time point of the ageing and link between the *ANK3* rs10994359 genotype and the brain-morphological phenotype in MDD are also necessary.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2020.102384.

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