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ORIGINAL PAPER

Morphometry of the Hippocampus Across the Adult Life-Span in Patients with Depressive Disorders: Association with Neuroticism

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Abstract

Neuroticism is one of the main endophenotypes of major depressive disorder (MDD) and is closely related to the negative effect systems of Research Domain Criteria (RDoC) domains. The relationship between neuroticism and aging is dynamic and complex. Moreover, reduced hippocampal volumes are probably the most frequently reported structural neuroimaging finding associated with MDD. However, it remains unclear to what extent hippocampal abnormalities are linked with age and neuroticism changes in people with depression through the adult life span. This study aimed to examine the interplay between aging and neuroticism on hippocampal morphometric across the adult life-span in a relative large sample of patients with depressive disorders (114 patients, 73 females, age range: 18–74 years) and healthy control (HC) subjects (112 healthy controls, 72 females, age range: 19–72 years). MDD patients showed reduced bilateral hippocampal volumes. The effect of aging on the left hippocampal showed linear and the right hippocampal volume non-linear trajectories throughout the adult life span in healthy groups and MDD groups respectively. The hippocampal atrophy was dynamically impacted by depression at the early stages of adult life. Furthermore, we observed that right hippocampal volume reduction was associated with higher neuroticism in depressive patients younger than 30.65 years old. Our results suggest that the age-related atrophy in the right hippocampal volume was more affected by individual differences in neuroticism among younger depressive patients. Hippocampal volume reduction as a vulnerability factor for early-onset and major geriatric depression may have a distinct endophenotype.

Keywords Depression · Hippocampal volume · Neuroticism · Aging

Introduction

Neuroticism reflects a tendency to experience frequent, intense negative emotions when facing uncontrollable challenges and stressors (Barlow et al. 2013; Eysenck 1998). Neuroticism is a vulnerability marker for depression and correlates with a strong gene with depressive symptoms in non-clinical population samples (Docherty et al. 2016; Genetics of Personality et al.2015; Luciano et al. 2018; Okbay et al. 2016; Smith et al. 2016). Furthermore, neuroticism is one of the main endophenotypes of depression (Goldstein and Klein 2014) and closely related to the negative affectivity of the DSM-5 Section III dimensional trait model (Kotov et al. 2017; Lengel, Helle, DeShong, Meyer, and Mullins-Sweatt 2016; Watson, Ellickson-Larew, Stanton, and Levin-Aspenson 2016) and negative valence systems of Research Domain Criteria (RDoC) domains (Webb et al. 2016). Moreover, clinical research found that individual differences

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in neuroticism may affect the treatment resistance and outcomes in major depressive disorders (Mulder 2002; Webb et al. 2018)

Hippocampal volume reduction in major depressive disorders is the most replicated psychiatric neuroimaging findings (Dillon & Pizzagalli 2018; MacQueen and Frodl 2011; Otte et al. 2016a). The ENIGMA MDD working group recently found that the hippocampal volume reductions were mainly present in recurrent and early-onset (≤ 21 years) MDD (Lianne Schmaal et al. 2016a, b). In addition, a recent meta-analysis also found that late-life depression (mean age ≥ 55) was significantly associated with smaller hippocampal volume (Geerlings and Gerritsen 2017). Moreover, the magnitude of hippocampal volume reduction in MDD was modulated by clinical and demographical variables such as gender, early life stress, recurrence, and illness duration (Arnone et al. 2013; Kempton et al. 2011; L. Schmaal et al. 2016a, b; M. T. Treadway et al. 2015a, b). Previous studies indicated that neuroticism is associated with a negative bias, stress-sensitive, illness course, treatment outcomes, and cognitive decline in MDD. However, to the best of our knowledge, no study has yet examined the relationship between individual differences in neuroticism and reduced hippocampal volume in MDD. Also, the hippocampus is not a homogeneous structure and consists of several subfields with distinct morphology: the subiculum, the three cornu ammonis sectors (CA1-3), the dentate gyrus (DG), the fimbria and presubiculum (Marizzoni et al. 2015; Strange, Witter, Lein, and Moser 2014). Chronic stress, cognitive aging, and psychiatric disease have a different effect on distinct subfields of the hippocampus (Small, Schobel, Buxton, Witter, and Barnes, 2011; Treadway et al. 2015a, b). Therefore, it is necessary to investigate to which hippocampal subfield volumes are associated with neuroticism in MDD.

Neuroticism is a partly heritable personality component and shows a gradual pattern of normative change across the life course (Jorm, 2000; Roberts et al., 2017; ; Roberts, Walton, and Viechtbauer 2006), especially in young adulthood. Moreover, the relationship between neuroticism and psychopathology may also differ across age groups and shift across development. For example, early-onset major depression disorder (EOD) has higher levels of neuroticism than late-onset major depression disorder (LOD), which likely means they had differed etiologically (Brodaty et al. 2001b; Sneed, Kasen, and Cohen 2007; Van den Berg et al. 2001). Furthermore, hippocampal volume reduction was associated with childhood maltreatment or low socioeconomic status (Hanson et al. 2015; Riem, Alink, Out, Van Ijzendoorn, and Bakermans-Kranenburg 2015), maybe a significant risk factor for the development of behavioral problems and psychopathology in adolescent and young adult. Hippocampal volume atrophy involved with memory deficits and cognitive decline in older major depression disorder may be associated with an increased risk for Alzheimer's disease (Steffens, McQuoid, Payne, and Potter 2011). Thus, it remains unclear to what extent hippocampal abnormalities are also linked with age and neuroticism changes in people with depression through the adult life span.

Therefore, the present study aimed to investigate the difference in hippocampal volume across the adult life-span in a relatively large sample of patients with depressive disorders (age range: 18–74 years) and healthy control (HC) subjects (age range: 19–72 years). We also examined the association between neuroticism and hippocampal volume and the age growth within major depressive disorders. An automated algorithm from FreeSurfer was used to segment the hippocampal structure and hippocampal subfields. We hypothesized that reductions in hippocampal and hippocampal subfields volume would be observed in patients with depressive disorders compared to HC subjects. Secondly, the effect of age on hippocampal volume would not be linear in depressive patients, with more pronounced reductions in early adult and elder adulthood resulting in non-linear age trajectories. Finally, hippocampal volume reduction may be associated with neuroticism changes in the subgroup of young depressive patients but not in mid-life and elder depressive patients.

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 females) 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 (SRRS) test were excluded, resulting in 116 MDDs and 112 HCs remaining; and (6) participants with terrible imaging data and bad segments (by visual inspection) were excluded, resulting in the final sample of 114 MDDs and 112 HCs. Of the 114 MDD patients included, 95 were the first episode, and 19 were recurrence; 29 of the patients had depression with anxiety, and 50 of the patients were medicated for MDD (see Fig. 1). In the present study, the mean age of the patients with depression was 37.12 years (SD = 13.27, range = 18–74), and the mean age of the HC subjects was 39.07 years (SD = 12.79, range = 19–72). Depression severity was rated using the 17-item Hamilton Depression Rating Scale (HDRS-17) by interview and 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 to protect 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 magnetization-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).

Image Processing

All volumetric segmentation and surface-based cortical reconstruction were performed 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, 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 checkpoints (skull strip, white matter segments, and pial surface) were visually inspected, and segmentation errors were corrected. The subcortical volumes (the bilateral hippocampus, caudate, putamen, nucleus accumbens, pallidum, thalamus, and amygdala) were obtained in FreeSurfer software ver.5.3 from an automated procedure for volumetric measures of brain structures using 3D T1-weighted images (Fischl et al. 2002). The left and right hippocampus were segmented into seven subfields: CA1, CA2-3, CA4-dentate gyrus (DG), subiculum, presubiculum, fimbria, and hippocampal fissure (Van Leemput et al. 2009). This hippocampal subfields segmentation technique based on a prior probabilistic atlas, and the Bayesian modeling approach is

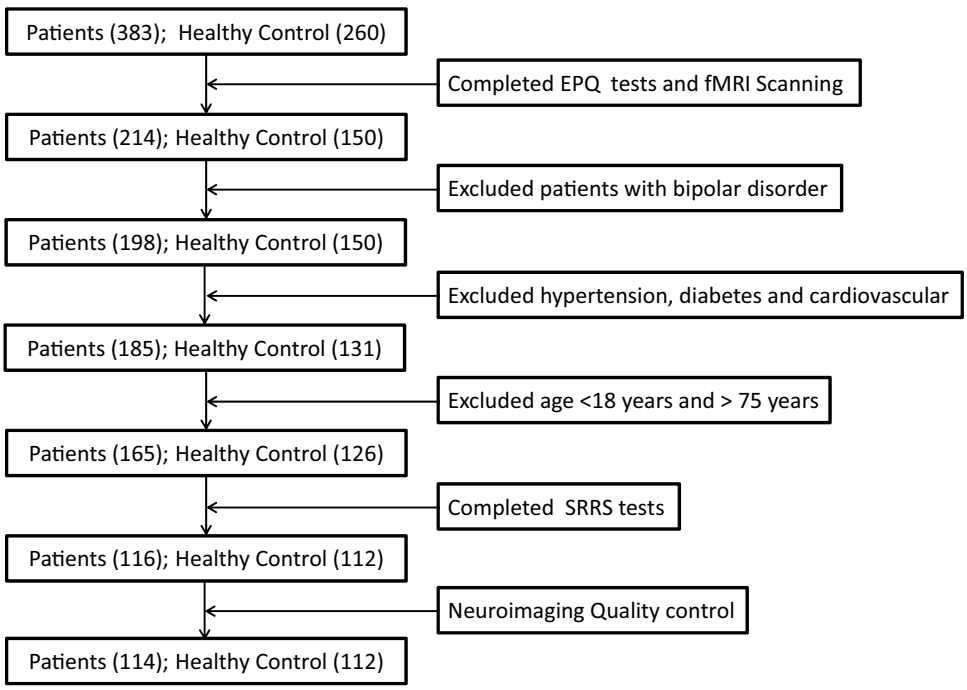

Fig. 1 The pipeline for the sample selection

fully automatic and can be found online (www.freesurfer.net/fswiki/HippocampalSubfieldSegmentation).

Statistics

We examined group differences in left and right hippocampal volumes between the MDDs and HCs. First, two separate covariance analysis models (ANCOVA) were tested on the left and right hippocampal volumes, with diagnosis (MDD = 1, HC = 0) as the between-subject factor while controlling for age, sex, and total intracranial volume (ICV). To examine potentially confounding effects of exposure to medication and recurrence of depression on hippocampal volume, we performed the ANCOVA within the MDD group, with medication or recurrence as the between-subject factor while controlling for age, sex, and total ICV.

To examine the age-related difference in hippocampal volume between MDD and HC, we modeled both linear and non-linear age effects using a generalized additive model (GAM) (Wood, 2004, 2006). The GAM was implemented to assess a penalty on non-linearity using restricted maximum likelihood (REML) to avoid over-fitting 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 endpoints of the trajectories may be substantially affected by irrelevant factors, such as the age range of the samples (Fjell et al. 2010). Smooth terms are specified in a gam formula using *s*, *te*, *ti,* and *t2* terms. Functions (*ti*) define tensor product smooths and interactions within gam model formulae (Wood, 2017). To build a GAM, the factor with the strongest ability to reduce the model residual is age, which should be input into link function *s*(*Age*) preferentially. We identified the second factor diagnosis (MDD = 1, HC = 0) for function *s*(*Group*). The interaction effect was performed using factor-smooth interactions for function *ti*(*Age, Group*) while controlling for gender and total ICV. After defining the sort-order of factors, the GAM can be given as:

g(v) ~ β0 + s(Age, bs = "tp") + s(Group, bs = "fs") + ti(Age, Group, bs = c("tp", "fs")) +Gender + ICV + δ $g(v)$ is a dependent variable that represents the effects of variables on hippocampal volume, β_0 is a constant, *s*() is a smoothing function that describes the relationships between $g(v)$ and the independent variable, and δ is the model residual. The outcomes of GAM include accumulation of explained deviance (ADE), Akaike information criterion (AIC), *F value*, the *p* value of each factor, and generalized cross-validation (GCV) statistics.

To further detect potentially different effects of major depression with age, the participants were separated into three groups: early adulthood (18 to 30 years old; MDD = 34, HC = 50), middle adulthood (31 to 49 years old; MDD = 56, HC = 38) and later adulthood (50 to 75 years old; MDD = 24, HC = 24). We set the age cut-off for early adulthood at ≤ 30 based on (1) the first phase of early adulthood comes to a close at approximately 28–33 years, or 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 separate ANCOVA was performed to study the effects of age-groups×diagnosis interaction on bilateral hippocampal volume while controlling for sex, education, and total ICV. Post hoc multiple comparison tests were performed to determine which means differed among these groups if necessary. *P* values were adjusted for the number of variables measured (i.e., corrected for the bilateral measure).

To examine the effects of age on the relationship between neuroticism and hippocampal volume among MDD and HC groups throughout the adult life span, three-way interactions (age×neuroticism×Group) were performed using a linear regression model in R. The simple slopes analysis was then performed with the Johnson-Neyman technique (Johnson & Fay, 1950; Bauer & Curran, 2005). This method provided us all the moderator's values for which the slope of the predictor was statistically significant.

The ANCOVA, GLM, and moderated analysis were run with the R statistical software package (R, Statistical Package version 4.0.4; R Foundation for Statistical Computing; www. R-project.org). The mgcv packages were used to apply the GAM function.

Results

Participant Characteristics

The demographic, clinical, symptom severity and personality trait data of the MDDs and HCs are presented in Table 1. There was a significant difference between MDD and HC groups in education ($t = -2.91$, $p = 0.004$), with MDD participants reporting lower education than HC participants; neuroticism ($t = 12.39$, $p < 0.001$), with MDD participants reporting higher neuroticism scores than HC participants; extroversion ($t = -7.69$, $p < 0.001$), with MDD participants reporting lower extraversion scores than HC participants.

Table 1 Socio-demographic participant characteristics

Characteristic	MDD (N = 114)	HC (N = 112)	Statistic	*p*
Sex (F:M)	73:41	72:40	1.39×10^{-30}	= 0.99[a]
Age (M, SD)	39.07 (12.8)	37.12 (13.27)	1.13	= 0.26[b]
Education (M, SD)	11.98 (3.55)	13.48 (4.18)	− 2.91	= 0.004[b]
Disease duration (months)	50.10 (61.74)	–	–	–
HDRS-17	20.72 (4.92)	–	–	–
BDI-II Scores	19.83 (7.33)	–	–	–
Neuroticism	16.31 (5.19)	8.19 (4.65)	12.39	< 0.001[b]
Extroversion	8.89 (4.67)	13.17 (3.66)	− 7.69	< 0.001[b]
Rumination (sensitive & assessment)	23.08 (5.70)	–	–	–
First-episode: Recurrence (N)	95:19	–	–	–
Depression with anxiety (N)	29	–	–	–
Antidepressant (N)	50	–	–	–

Diagnoses: *HC* healthy control, *MDD* major depression disorder, *M* mean, *SD* standard deviation, *F* female, *M* male, *N* number

[a]report χ^2 statistic

[b]report *T* value

Hippocampal Volume

Smaller right hippocampal volume ($F(1225) = 8.72$, $p_{correct} = 0.007$) and left hippocampal volume ($F(1225) = 7.06$, $p_{correct} = 0.017$) were found in MDD groups compared with HC groups while controlling for age, sex and total ICV (Fig. 2). Hippocampal subfield volumes differences were also examined between MDD and HC groups, and no region survived after the correction (Supplementary Table 1).

We also tested the effects of age on the bilateral hippocampal volume in MDD and HC groups using GAM. When controlling for sex, ICV and education, we found that a significant interaction effect of age-by-diagnosis on the hippocampal volume (left: $F = 1.38$, $p_{correct} = 0.023$; right: $F = 1.25$, $p_{correct} = 0.028$). However, by following the same analysis procedure, neuroticism-by-diagnosis effect was not detected on the bilateral hippocampal volume (left: $F < 0.001$, $p_{correct} = 1$; right: $F < 0.001$, $p_{correct} = 1$). Further analysis found that the effect of aging on the right hippocampal volume showed a non-linear trajectory in MDD groups (right: EDF = 3, F = 4.55, $p_{correct} = 0.006$; left: EDF = 2.63, F = 2.91, $p_{correct} = 0.06$), with a linear trajectory in HC groups on the left hippocampal volume (right: EDF = 1, F = 3.52, $p_{correct} = 0.13$; left: EDF = 1, F = 9.35, $p_{correct} = 0.006$) (Fig. 2b). Estimated degrees of freedom (EDF) refers to the curvature of the fitted GAM line relative to a simple straight line. Some variables were automatically forced to a linear relationship (EDF = 1). The quadratic effect of age was also performed to examine whether age-related hippocampal volume differences follow a non-linear pattern in MDD and HC groups. As age and age^2 are highly correlated, we used the poly() function in R for these two predictors, which created a pair of uncorrelated variables to model age effects, where one variable was linear and one non-linear. The model with a quadratic relationship provided the best explanation of the relationship between age and the right hippocampal volume than the linear model in MDD groups (ANOVA for model comparison: left Hippocampus $F = 4.60$, $p_{correct} = 0.07$; right Hippocampus $F = 10.03$, $p_{correct} = 0.004$). However, in HC groups, the quadratic model was not significantly better than the linear model (ANOVA for model comparison: left Hippocampus $F = 1.06$, $p_{correct} = 0.61$; right Hippocampus $F = 0.01$, $p_{correct} = 1$). However, no interaction effect (age-groups×diagnosis) was found on the bilateral hippocampal volume (right hippocampal volume: F = 2.56, $p_{correct} = 0.16$; left hippocampal volume: F = 1.30, $p_{correct} = 0.55$).

Neuroticism, Age and Hippocampal Volume Among MDD and HC Groups

There was a marginal three-way interaction between neuroticism, age and groups on the right hippocampal volume (Est. = 1.51, SE = 0.69, t = 2.17, $p_{correct} = 0.06$) while controlling for education, gender, and total ICV. Further simple slopes analysis showed that higher neuroticism was associated with smaller right hippocampal volumes only for early adulthood depressive patients (1 SD below the mean age, see Fig. 3a). Besides, the left hippocampal fissure of subfield was also found statistically significant (Supplementary Table 2). Using the Johnson-Neyman technique, we further found that neuroticism's slope was statistically significant for depressive patients with ages below 30.65 and beyond 70.11 years old. (thirty-three patients and four patients, respectively) (Fig. 3b).

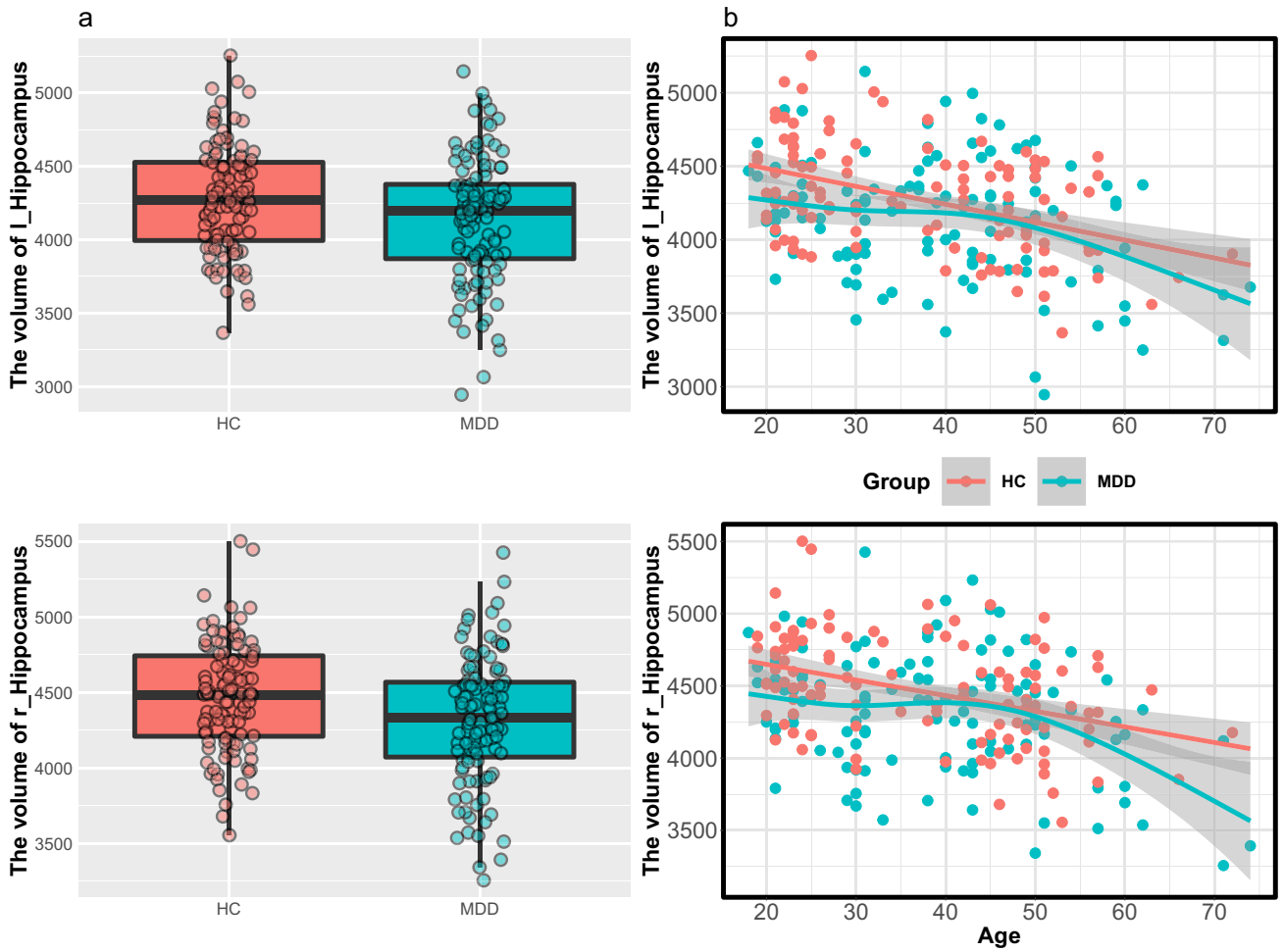

Fig. 2 **a** Hippocampal volume differences were examined between MDD and HC groups. **b** The effects of age on the hippocampal volume in MDD and HC groups using GAM, after controlling age, gender, and total intracranial volume

Recurrence, Symptom Severity, and Hippocampal Volume Within MDD Groups

The hippocampal volume was not correlated with severity using the HDRS-17 and BDI-II questionnaires. Even if we split the MDD group by the inventory cut-off, the significant effect still was not found (Supplementary Table 3). There were no significant differences on the left and right hippocampal volume between first and recurrent episode patients ($F = 0.098$, $p_{correct} = 1$; $F = 0.018$, $p_{correct} = 1$). Furthermore, only significant effects were found on the bilateral volume between the first-episode patient and HC (right: $F = 7.84$, $p_{correct} = 0.011$; left: $F = 6.97$, $p_{correct} = 0.018$). There was no effect on the bilateral volume between the recurrent episode patient and HC (right: $F = 2.81$, $p_{correct} = 0.19$; left: $F = 1.12$, $p_{correct} = 0.55$). Besides, there were significant differences on the left and right hippocampal volume between depression patients and depression patients with anxiety ($F = 5.39$, $p_{correct} = 0.044$; $F = 6.6$, $p_{correct} = 0.023$). Also, the medication effect is not significant on the bilateral hippocampal volume (left: $F = 1.51$, $p_{correct} = 0.45$; right: $F = 1.59$, $p_{correct} = 0.42$).

Discussion

In the present study, we showed that patients with the major depressive disorder had reduced bilateral hippocampus volumes across the adult life span than matched healthy controls. Specifically, the reductions in the bilateral hippocampal volumes were observed in early adulthood, but not in middle adulthood and elder depressive patients. The effect of aging on the bilateral hippocampal volume showed linear and non-linear trajectories throughout the adult life span in healthy groups and MDD groups, respectively. Furthermore, we observed that right hippocampal volume reduction were associated with higher neuroticism in depressive patients younger than 30.65 years old. Thus, this study provides

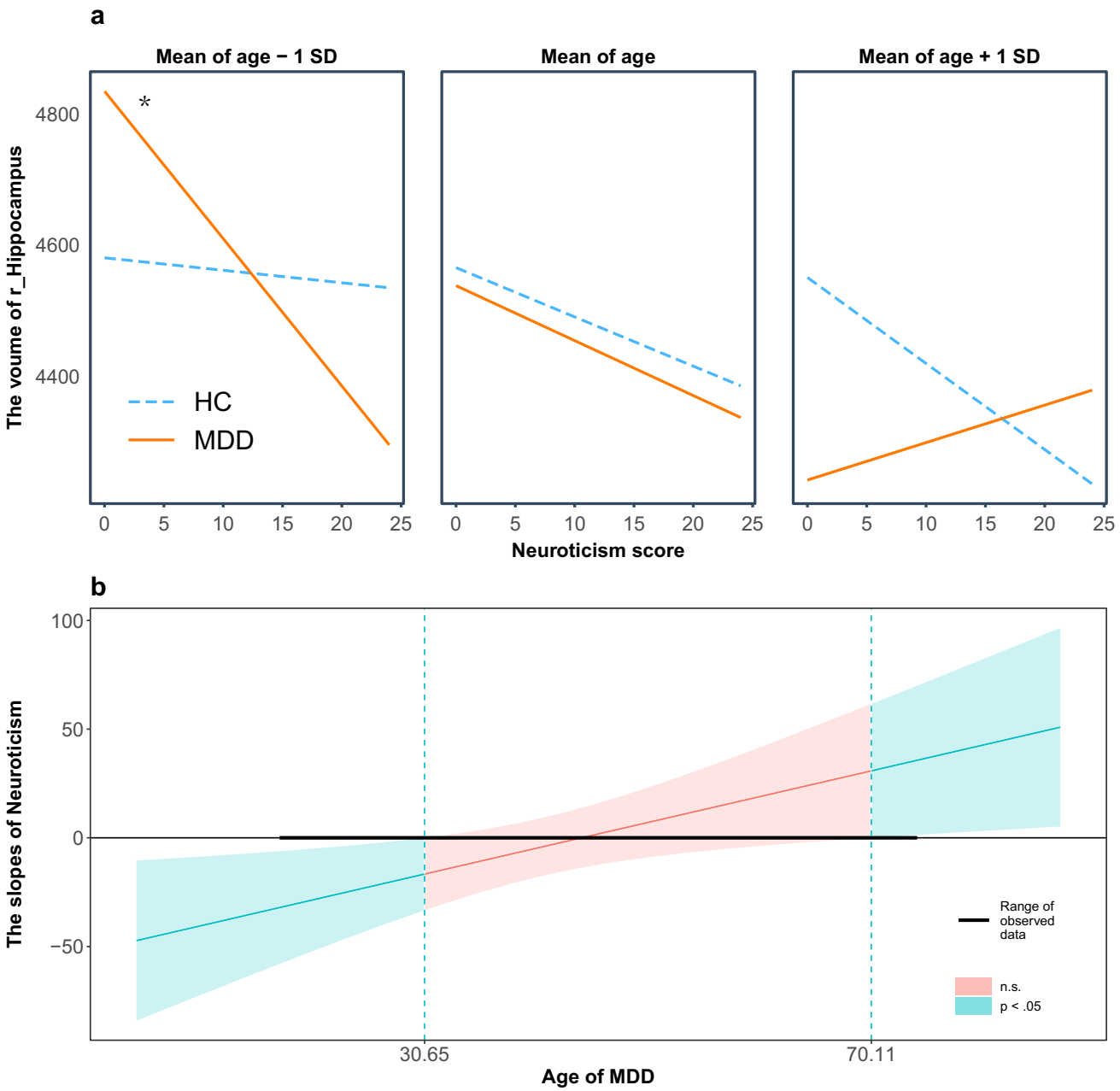

Fig. 3 A marginal three-way interaction between neuroticism, age and groups on right hippocampal volume (Est. = 1.51, SE = 0.69, t = 2.17, $p_{corrected}$ = 0.06) while controlling for education, gender, and total ICV. **a** The simple slopes analysis showed that higher neuroticism was associated with smaller right hippocampal volumes only for early adulthood depressive patients (1 SD below the mean age). **b** Using the Johnson-Neyman technique, the slope of neuroticism was statistically significant for depressive patients with ages younger than 30.65 years old and beyond 70.11 years old

evidence the age-related atrophy in the right hippocampal volumes was more affected by individual differences in neuroticism in young and elder depressive patients.

Consistent with our prediction and prior neuroimaging meta-analyses studies (Otte et al. 2016a; Schmaal et al. 2016a, b; Videbech and Ravnkilde 2004), we observed the bilateral hippocampal volumes reductions in patients with MDD relative to HC subjects. The smaller hippocampal volume in MDD is often linked to the pre-existing vulnerability factors of mood disorders, such as levels of brain-derived neurotrophic (BNDF) decline (Duman and Monteggia 2006; Erickson et al. 2010; Gatt et al. 2009), family history of mental illness (MacMaster et al. 2008) and early-life stress (Saleh et al. 2017; Vythilingam et al. 2002). Previous imaging studies in humans showed that the smaller hippocampal volume was associated with the age of onset,

recurrence, and disease severity of MDD (Belleau, Treadway, and Pizzagalli 2018; Schmaal et al., 2016a, b; Treadway et al., 2015a, b). In the present study, the bilateral hippocampal volume reduction trend was mainly contributed by the early adulthood, and elderly depressive patients also confirmed previous research (Fig. 2b). Some researchers suggested that early-onset and geriatric depression may be similar phenotypically but differ etiologically (Brodaty et al. 2001a). Earlier onset was associated with increased risk in first-degree relatives, early-life stress, and higher heritability (Brodaty et al. 2001a; Korten, Comijs, Lamers, and Penninx 2012; Thapar, Collishaw, Pine, and Thapar 2012). Geriatric major depression was linked to organ disease severity, memory loss, and cognitive decline (Ballmaier et al., 2008; Fiske, Wetherell, & Gatz, 2009). Because our study does not have detailed information on depression history, it is possible that much geriatric major depression has an early onset and has been experienced chronic depression. Interestingly, different from healthy controls, patients with depression showed a non-linear trajectory between age and hippocampal volume throughout the adult life span (see Fig. 2b). These results indicated that hippocampal atrophy may be dynamically impacted by depression at the early stages of adult life. Besides, no interaction effect between age-group and diagnosis is expected because, to our knowledge, no study found the regular group had a minor hippocampus volume than the patient group in different age conditions.

The present finding that right hippocampal reduction were associated with higher neuroticism in depressive patients younger than 30.65 years old (see Fig. 3b). It has been suggested that the hippocampus contains high levels of glucocorticoid receptors, which make it more vulnerable to stress than most other brain areas (Duman and Monteggia 2006). Translational studies further showed that the critical consequences of stress exposure on the hippocampus are suppressing neurogenesis in the dentate gyrus and dendritic remodeling in the cornu ammonis (McEwen 1999; Smith, Makino, Kvetnansky, and Post 1995). Hippocampal and hippocampal subfield volume reduction in depression may associate with early-life stress or childhood maltreatment. For example, Vythilingam et al. (2002), Gerritsen et al. (2015), and Saleh et al. (2017) reported significant associations between early-life adverse stress and reduced hippocampal volume (Gerritsen et al. 2015; Saleh et al. 2017; Vythilingam et al. 2002). Moreover, neuroticism was a vulnerability marker for depression and correlated a strong gene with depressive symptoms in non-clinical population samples (MDD) (Docherty et al. 2016; Genetics of Personality et al. 2015; Luciano et al. 2018; Okbay et al. 2016; D. J. Smith et al. 2016). Several behavior studies also found neuroticism to be strongly associated with a predisposition to experiencing adverse life events (Lehto, Mäestu, Kiive, Veidebaum, and Harro 2016; Vinkers et al. 2014). Thus, as one of the predisposing factors, neuroticism may play a critical role in hippocampal volume reduction in major depressive disorder. More importantly, the effects of neuroticism on hippocampal volume reduction only observed in depressive patients younger than 30 years old suggested that hippocampal volume reduction as a vulnerability factor for the early-onset and major geriatric depression may have a distinct different endophenotype. Previous studies also found that neuroticism was the primary trait domain showing changes in young adulthood (age 20–40) due to personality maturation (Roberts and Mroczek 2008; Roberts, Walton, & Wolfgang Viechtbauer 2006). Besides, a recent meta-analyses study indicated that neuroticism might be changed through clinical intervention and therapy (Roberts et al., 2017). Thus, future longitudinal work will need to examine the neuroticism changes in early-onset major depressive disorder treatment. Since only four patients older than 70 years old, the relationship among neuroticism, later adulthood, and hippocampal volume is hard to conclude even though a significant effect was found here.

Despite the strength of a large sample, the study also has limitations. The first limitation of our study is inherent in its cross-sectional design. In such a design, age-related changes in hippocampal volume reduction may be affected by potential cohort effects and limit our ability to examine the direction of causality, whether the smaller hippocampal volume precedes and confer vulnerability to or are the consequence of MDD. Secondly, the reduced hippocampal volume is not specific to MDD, as it has been observed in other psychiatric and neurodegenerative disorders, such as schizophrenia (Tamminga, Stan, & Wagner 2010), bipolar disorder (Blumberg et al. 2003), posttraumatic stress disorder (Bonne et al. 2001), and dementia (Small, Schobel, Buxton, Witter, and Barnes 2011). Some researchers suggested that psychiatric and neurodegenerative disorders differentially target distinct subfields of the hippocampal circuit (Small et al., 2011a). Moreover, neuroticism traits also is a risk factor for psychiatric and neurodegenerative disorders. Also, clinical research found that individual differences in neuroticism may affect the treatment resistance and outcomes in major depressive disorders. Thus, longitudinal studies will help clarify the causal relationships between hippocampal changes and neuroticism in MDD. Lastly, only very few patients with recurrent MDD were included in our sample, which probably could explain there was no significant effect on the bilateral hippocampal volume between the first-episode patients and recurrent MDD patients.

Future work will need to examine whether regional specificity of hippocampal volume reduction in various psychiatric and neurodegenerative disorders might be associated with neuroticism. Finally, we suggested that hippocampal volume reduction in geriatric depression might be a risk factor for dementia. This result needs to be interpreted with

caution because our study does not have collected information on cognitive aging in this relatively large sample.

Despite these limitations, the current findings are among the first to link a personality dysfunction (higher neuroticism) with hippocampal volume reduction in early adulthood depression. It provides a target for future work to examine the mechanisms responsible for neuroticism trait change in intervention and therapy in young adulthood. Moreover, patients with depression showed a non-linear trajectory between age and hippocampal volume in early adulthood. Future studies, especially longitudinal research in geriatric samples, need to confirm these findings.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10548-021-00846-0.

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Data Availability Data of this research is available from the corresponding author upon reasonable request.

Declarations

Conflict of interest All authors declare no competing interests.

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