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# Revealing complexity: segmentation of hippocampal subfields in adolescents with major depressive disorder reveals specific links to cognitive dysfunctions

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## Research Article

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## Abstract

**Background.** Hippocampal disruptions represent potential neuropathological biomarkers in depressed adolescents with cognitive dysfunctions. Given heterogeneous outcomes of whole-hippocampus analyses, we investigated subregional abnormalities in depressed adolescents and their associations with symptom severity and cognitive dysfunctions.

**Methods.** MethodsSeventy-nine first-episode depressive patients (ag = 15.54 ± 1.83) and 71 healthy controls (age = 16.18 ± 2.85) were included. All participants underwent T1 and T2 imaging, completed depressive severity assessments, and performed cognitive assessments on memory, emotional recognition, cognitive control, and attention. Freesurfer was used to segment each hippocampus into 12 subfields. Multivariable analyses of variance were performed to identify overall and disease severity-related abnormalities in patients. LASSO regression was also conducted to explore the associations between hippocampal subfields and patients' cognitive abilities.

**Results.** Depressed adolescents showed decreases in dentate gyrus, CA1, CA2/3, CA4, fimbria, tail, and molecular layer. Analyses of overall symptom severity, duration, self-harm behavior, and suicidality suggested that severity-related decreases mainly manifested in CA regions and involved surrounding subfields with disease severity increases. LASSO regression indicated that hippocampal subfield abnormalities had the strongest associations with memory impairments, with CA regions and dentate gyrus showing the highest weights.

**Conclusions.** Hippocampal abnormalities are widespread in depressed adolescents and such abnormalities may spread from CA regions to surrounding areas as the disease progresses. Abnormalities in CA regions and dentate gyrus among these subfields primarily link with memory impairments in patients. These results demonstrate that hippocampal subsections may serve as useful biomarkers of depression progression in adolescents, offering new directions for early clinical intervention.

## Introduction

Major depressive disorder (MDD) during adolescence is a critical global mental health challenge that affects approximately 25% of all adolescents worldwide [1]. When depression manifests during adolescence, it may have far-researching implications, leading to substantial disruptions in school performance and interpersonal relationships, and affecting later life [2, 3]. These adverse outcomes can be mainly attributed to the cognitive impairments and neuroanatomical irregularities associated with depression. Prior research has shown that adolescents with MDD experience cognitive impairments in many domains, including memory [4], emotion recognition [5], attention, and cognitive control [6]. At the neuroanatomical level, substantial evidence from adolescent patients has implicated abnormalities of the hippocampus [7], a core region of the limbic system that is intricately linked to cognitive abilities. However, studies examining the global hippocampus volume in adolescent patients with MDD have revealed heterogeneous findings, with some indicating decreased volume and others reporting no significant changes [8-11]. The multifaceted nature of the hippocampus may have contributed to these mixed outcomes, pointing to the importance of examining distinct structural subfields. Additionally, variability in the severity of patients' symptoms and subtypes of depression may have contributed to the discrepancies in prior volumetric findings [12, 13]. Hence, there is an urgent need to



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identify hippocampal subfield abnormalities in adolescent MDD patients and to investigate their associations with disease severity and cognitive dysfunctions.

The hippocampus exhibits cytoarchitectural differences among subfields [14], which may lead to functional distinctions across them. Connectomic and neurophysiological studies have shown differences in the regions they connect to and the directions of connections [15, 16]. These differences may be due to genetic determinants, as hippocampal subfields have unique genetic correlates that are associated with specific biological processes [17, 18]. This suggests that analyzing the hippocampus at a subfield level could crucially enhance the sensitivity in detecting diagnostic effects as compared to whole-structure analyses [19]. In vivo, segmentation of the hippocampus into subfields has been made possible based on structural T1 weighted scans. Volumetric measures of different subfields have already been extensively examined in relation to various neurodegenerative and psychiatric diseases, such as Alzheimer's disease, schizophrenia, and depression [20, 21]. However, the hippocampus is a subcortical nucleus, which is located at a deep location and is susceptible to imaging artifacts. Studies have suggested that adding T2-weighted images can aid in the identification of different subfields, as T2 images show lower signal intensity in this area, contributing to specific subfield distinctions [22]. Thus, we suggest utilizing both T1 and T2 images to increase the accuracy of subfield segmentation.

MDD is a highly heterogeneous condition and patients could differ in symptom manifestations, severity, duration of the illness, and comorbidities. Heterogeneity in patient groups has significantly contributed to the inconsistency in neuroimaging findings [23]. Indeed, early studies examining hippocampal subfields have predominantly examined depression as a unitary disease entity [21, 24-26]. Few studies have started to pay attention to the hippocampal differences in relation to MDD heterogeneity. For instance, Roddy et al. (2019) reported the progressive patterns of hippocampal subfields by comparing first-episode and recurrent adult patients [27]. Kraus et al. (2019) examined the effects of disease status (acute versus remitted patients) and found that remitted adult patients had larger volumes compared with acute patients [28]. A growing number of studies have focused on the heterogeneity in MDD, especially in adolescent patients [29-32]. Although research from the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium found adult patients with early-onset MDD (<21 years) showed reduced hippocampus volume when compared to controls [10], it did not provide direct evidence on adolescent patients. Additionally, features such as overall symptom severity, self-harm behavior, and suicidality should also be considered to draw a fuller picture of hippocampal abnormalities in relation to MDD heterogeneity.

The hippocampus has been shown to be closely associated with various cognitive domains. In addition to its well-established links to working and spatial memory, the human hippocampus is also involved in emotion recognition, attention [33], and cognitive control [34]. These associations have been established in both adult populations [35] and typically developing children and adolescents [36]. In adolescents with MDD, associations between cognitive disruption [37, 38] and hippocampal volume have also been reported. Barch et al. [4] investigated cognitive control, memory, attention, and language in adolescent MDD patients and found reduced hippocampal volume being associated with worse episodic memory and emotion recognition. However, it remains unknown which hippocampal subfields have mainly contributed to such associations.

In the current study, we used both T1 and T2 weighed high-resolution structural images to identify the abnormalities of hippocampal subfields in first-episode depressed adolescents. We also examined associations between subfield volumes and overall depressive severity, illness duration, self-harm, and suicidality. Given the role of the hippocampus in various cognitive functions, we also investigated to which extent these subfields were linked to MDD patients' cognitive impairments in memory, attention, emotion recognition, and cognitive control.

## Methods

### *Participants*

This study included a total of 150 participants from our ongoing *Shandong Adolescent Neuroimaging of Depression* project. Among them, 79 adolescents (62 females; mean age = 15.54 ± 1.83, ranging from 11.69 to 20.11 years) were diagnosed with MDD by two clinical psychiatrists from the Shandong Mental Health Center, based on the standard DSM-V criteria. These patients also underwent a comprehensive assessment at the time of enrollment, which included an evaluation of their psychiatric history, confirming that they were experiencing their first episode. All of them were also administered antidepressant medication when being enrolled. The other 71 age- and gender-matched healthy controls (48 females; mean age = 16.18 ± 2.85, range from 9.24 to 19.36 years) were recruited through social media advertisements.

Exclusion criteria for all participants included: (1) contraindications to magnetic resonance imaging scan (e.g., metal implants or claustrophobia); (2) current or past neurological or intellectual disorders that may interfere with the cognitive assessments; and (3) current or past use of addictive substances (e.g., marijuana or heroin). All healthy controls completed the Children's Depression Inventory (CDI) and Multidimensional Anxiety Scale for Children and scored below 12 for depression and below 48 for anxiety. This study received approval from the local ethics committee at Shandong Normal University and all participants and their parents provided signed informed consent forms.

### *Clinical and cognitive assessments*

Before the brain scanning, we conducted face-to-face interviews with all participants to assess their clinical and cognitive characteristics. Depressive severity was assessed using (Table 1): (a) overall depressive severity, assessed with the total score of CDI scale [39]; (b) illness duration; (c) suicidal ideation, assessed by the total score of Beck Scale for Suicide Ideation (BSI) scale [40]; (d) suicide risk, quantified using the total score of nurses' global assessment of suicide risk (NGASR) scale [41]; (e) self-injury behavior, assessed with Ottawa Self-injury Inventory (OSI) and quantified as the number of self-harm incidents [42]. To identify disease severity-related abnormalities of the hippocampus, we classified depressed patients into two groups with relatively mild or severe symptoms based on each of these five measures. Detailed information about the classification criteria and severity of subgroups were shown in Table 2 and Supplemental Methods.

Cognitive assessments including memory, emotional recognition, attention bias, and cognitive control abilities were performed with a battery of widely used and validated tasks. Memory abilities for all participants were tested on working memory using the digit Nback test (1back and 2back) [43], spatial memory using the four mountains test [44, 45], and short-term memory storage capacity

**Table 1.** Demographic and clinical characteristics of adolescents with MDD and healthy controls

| Variables | Adolescents with MDD (*N* = 79) | Healthy controls (*N* = 71) | $t/\chi^2$ | $\eta^2$ | *p* value |
|---|---|---|---|---|---|
| Age, years | 15.54 (1.83) | 16.18 (2.86) | 2.69 | 0.05 | 0.10 |
| Gender, male/female | 17/62 | 23/48 | 2.26 | – | 0.13 |
| Height, m | 1.67 (0.08) | 1.63 (0.09) | 2.44 | 0.04 | 0.02 |
| Weight, kg | 62.24 (18.45) | 53.61 (11.09) | 3.42 | 0.07 | <0.01* |
| BMI, kg/m$^2$ | 22.31 (6.16) | 19.94 (2.82) | 2.97 | 0.06 | <0.01* |
| eTIV, cm$^3$ | 1560.70 (145.88) | 1563.60 (156.82) | 0.01 | 0.00 | 0.91 |
| Age of onset, years | 14.18 (1.51) | – | – | – | – |
| Illness duration, months | 17.29 (12.51) | – | – | – | – |
| Antidepressant medication, % | 100% | – | – | – | – |
| Depression score[a] | 23.2 (9.09) | 7.56 (4.9) | 336.22 | 1.00 | <0.001* |
| Suicide risk[b] | 5.18 (4.42) | 0.49 (1.36) | 328.60 | 1.00 | <0.001* |
| Suicidal ideation[c] | 9.38 (6.23) | – | – | | – |
| Self-injurious behavior[d] | 8.89 (5.35) | – | – | | – |

*Note:* MDD, major depressive disorder; BMI, body mass index; eTIV, estimated total intracranial volume. For controls, we assessed their suicidal ideation and self-injurious behavior and found that none of the participants had these behaviors. *p* values with "*" indicated the significance with <0.05.
[a]Depression score was assessed by the children's depression inventory.
[b]Suicide risk was assessed by the nurses' global assessment of suicide risk scale.
[c]Suicidal ideation was assessed by the Beck scale for suicide ideation.
[d]Self-injurious behavior was assessed using the Ottawa self-injury inventory and expressed as the number of self-harm incidents.

**Table 2.** Assessments of depressive severity and characteristics for each level of severity

| Depressive severity assessments | Group name | Criteria | Mean (SD), range | Number of patients | | | Age | | | | CDI score | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *N* (female) | $\chi^2$ | *p* value | Mean (SD) | *t* | $\eta^2$ | *p* value | Mean (SD) | *t* | $\eta^2$ | *p* value |
| Overall depressive severity[a] | Group 1 | <25 | 16.50 (5.32), 4 ~ 24 | 42 (28) | 7.41 | 0.006 | 15.78 (1.89) | −1.27 | 0.02 | 0.208 | 16.50 (5.32) | 11.32 | 0.62 | <0.001 |
| | Group 2 | ≥25 | 30.81 (5.92), 25 ~ 50 | 37 (34) | | | 15.26 (1.75) | | | | 30.81 (5.92) | | | |
| Illness duration[b] | Group 1 | <15.3 | 8.16 (4.37), 0.13 ~ 14.77 | 35 (28) | 0.05 | 0.819 | 14.87 (1.60) | 3.67 | 0.16 | <0.001 | 22.63 (9.24) | 0.16 | 0.00 | 0.876 |
| | Group 2 | ≥15.3 | 26.17 (11.39), 15.30 ~ 70.37 | 36 (28) | | | 16.30 (1.71) | | | | 22.94 (7.69) | | | |
| Suicidal ideation[c] | Group 1 | <10 | 3.71 (3.27), 0 ~ 9 | 35 (26) | 0.85 | 0.357 | 15.92 (2.04) | −1.80 | 0.04 | 0.076 | 18.20 (7.75) | 5.20 | 0.27 | <0.001 |
| | Group 2 | ≥10 | 14.22 (3.40), 10 ~ 20 | 41 (34) | | | 15.17 (1.58) | | | | 27.49 (7.77) | | | |
| Suicide risk[d] | Group 1 | ≤5 | 5.63 (5.55), 0 ~ 5 | 23 (14) | 6.93 | 0.008 | 15.97 (1.91) | −1.14 | 0.02 | 0.259 | 18.13 (9.42) | 2.73 | 0.09 | 0.008 |
| | Group 2 | >5 | 9.73 (5.04), 6 ~ 20 | 55 (48) | | | 15.39 (1.91) | | | | 24.74 (8.45) | | | |
| Self-injurious behavior[e] | Group 1 | <1 | 0 (0), 0 | 22 (15) | 0.91 | 0.340 | 15.06 (2.01) | 1.38 | 0.02 | 0.171 | 21.71 (9.21) | 0.90 | 0.01 | 0.370 |
| | Group 2 | ≥1 | 7.06 (3.63), 1 ~ 15 | 57 (44) | | | 15.71 (1.77) | | | | 23.83 (9.11) | | | |

Abbreviations: CDI, children's depression inventory; SD, standard deviation.
[a]General depressive severity was assessed using the total score of CDI scale and classified into two groups, as suggested by Bang et al. [39].
[b]These patients were classified into two groups based on the median duration of illness.
[c]Suicidal ideation was quantified using the total score of BSI scale and classified into two groups with the mediation score of 10.
[d]Suicide risk was assessed using the total score of the NGASR scale and classified into two groups, following the findings of Cutcliffe et al. [41].
[e]We classified these patients into two groups: self-injurious and non-injurious individuals.

using the digit span test [46]. Emotional recognition was examined using the facial emotional recognition task where participants were shown with positive (happiness) and negative (sadness) emotional faces [47]. Attention bias was examined using the dot-probe task, with positive, negative, and neutral facial emotions as attracting stimuli [47, 48]. Finally, cognitive control abilities were tested with classic and emotional Go/No-Go task (inhibition) [49], Eriksen Flanker task (cognitive monitoring) [50], Stroop color and word task (response selection) [51], and task switching (target selection) [52]. These tasks are described in detail in Table 3 and Supplemental Methods.

### *Structural data acquisition, preprocessing, and segmentation of hippocampal subfields*

Both high-resolution T1 (voxel size = 0.875 × 0.875 × 0.90 mm$^3$) and T2 (voxel size = 0.438 × 0.438 × 0.90 mm$^3$) weighted structural images were scanned on a 3.0 T SIMENS scanner for each

**Table 3.** Profiles of cognitive performances of depressed adolescents and healthy controls

| Cognitive domains | Cognitive tests | Cognitive measures | Adolescents with MDD (*N* = 79) | Healthy controls (*N* = 71) | *t* | $\eta^2$ | *p* value |
|---|---|---|---|---|---|---|---|
| Memory | Nback test | Nback (1back), ACC | 0.73 (0.21) | 0.88 (0.13) | −5.14 | 0.15 | <0.001* |
| | | Nback (2back), ACC | 0.61 (0.19) | 0.79 (0.14) | −6.22 | 0.21 | <0.001* |
| | 4 mountain test | Spatial memory (direction), ACC | 0.71 (0.13) | 0.76 (0.11) | −2.70 | 0.05 | 0.008** |
| | | Spatial memory (position), ACC | 0.73 (0.16) | 0.84 (0.11) | −4.77 | 0.13 | <0.001* |
| | | Spatial memory (arrangement), ACC | 0.68 (0.17) | 0.83 (0.12) | −6.25 | 0.21 | <0.001* |
| | Digit span test | Digit span memory, length | 14.20 (2.26) | 14.77 (1.68) | −1.74 | 0.02 | 0.083 |
| Emotion recognition | Facial emotion recognition task | Emotion recognition (sadness), RT | 3.30 (0.73) | 2.85 (0.60) | 4.03 | 0.10 | <0.001* |
| | | Emotion recognition (happiness), RT | 3.28 (0.78) | 2.71 (0.66) | 4.79 | 0.13 | <0.001* |
| Attention | Dot probe task | Attentive selection (S-H), RT | 0.54 (0.17) | 0.48 (0.15) | 2.21 | 0.03 | 0.029* |
| | | Attentive selection (H-S), RT | 0.50 (0.15) | 0.49 (0.19) | 0.25 | <0.01 | 0.801 |
| | | Attentive selection (S-N), RT | 0.52 (0.14) | 0.47 (0.13) | 2.03 | 0.03 | 0.044* |
| | | Attentive selection (N-S), RT | 0.53 (0.15) | 0.47 (0.12) | 2.86 | 0.05 | 0.005* |
| | | Attentive selection (H-N), RT | 0.54 (0.17) | 0.47 (0.12) | 2.79 | 0.05 | 0.006* |
| | | Attentive selection (N-H), RT | 0.53 (0.16) | 0.48 (0.14) | 2.00 | 0.03 | 0.048* |
| Cognitive control | Go/No-Go task | Emotional Go/No-Go, ACC | 0.93 (0.05) | 0.96 (0.03) | −4.46 | 0.12 | <0.001* |
| | | Classic Go/No-Go, ACC | 0.97 (0.03) | 0.99 (0.01) | −3.78 | 0.09 | <0.001* |
| | Flanker task | Flanker, RT | 0.08 (0.17) | 0.07 (0.05) | 0.12 | < 0.01 | 0.906 |
| | Stroop task | Stroop, RT | 0.13 (0.14) | 0.12 (0.11) | 0.91 | 0.01 | 0.363 |
| | Task switching | Task switching, RT | −0.08 (0.14) | −0.05 (0.18) | −1.12 | 0.01 | 0.266 |

*Note:* Cognitive performances were shown with mean ± SD values. *p* values with "*" indicated the significance with <0.05.
Abbreviations: MDD, major depressive disorder; RT, reaction time (s); ACC, accuracy; S-H, sad (attractive emotion)-happy; H-S, happy (attractive emotion)-sad; S-N, sad (attractive emotion)-neutral; N-S, neutral (attractive emotion)-sad; H-N, happy (attractive emotion)-neutral; N-H, neutral (attractive emotion)-happy.

participant. Detailed acquisition parameters for these images were described in the Supplemental Methods. Both T1 and T2 images were preprocessed using the automated recon-all pipeline of FreeSurfer v6.0. This involved motion correction, skull stripping, Talairach transform, segmentation of white and gray matter volumetric regions, and surface extraction [53]. The images were registered to a spherical atlas and the cerebral cortex was then parcellated. The T2 images were particularly useful in improving pial surfaces, as they provided a different contrast compared to T1 data [54]. Next, the hippocampus was segmented and volumes of bilateral 12 subfields were measured [21], as shown in Figure 1. These 12 subfields consisted of Cornu Ammonis region 1 (CA1), CA2/3, CA4, dentate gyrus, subiculum, presubiculum, parasubiculum, fimbria, fissure, molecular layer, tail, and hippocampus-amygdala transition area (HATA). The volumes of these hippocampal subfields were extracted for subsequent statistical analyses.

Before preprocessing, we visually inspected both T1 and T2 images for the presence of encephalopathy, motion artifacts, and issues with full brain coverage. After completing the preprocessing, we carefully examined the registration, pial and white surface, and segmentation of subcortical structures to ensure accuracy against the structural image. Additionally, all hippocampal subfield volumes were within five standard deviations from the mean. We also repeated the analyses using the ENIGMA quality control protocol [55], excluding participants with values that exceeded three standard deviations from the mean (Figures S1 and S2, Table S3).

### Statistical analysis

To investigate the overall effect of depression on hippocampal subfield volumes, mixed-model analyses of covariance (ANCOVA) were performed to compare volume differences between the MDD group and healthy controls. Diagnosis (MDD, healthy controls) was regarded as the between-subject factor; hemisphere (left, right) was included as the within-subject factor, and age, gender, and estimated total intracranial volume (eTIV) were included as covariates. Multiple comparison correction was performed using the false discovery rate (FDR) method (*p*.adjust function from R) separately for the main effects (diagnosis, hemisphere) and the interaction effects involving these 12 subfields.

The groups with mild and severe symptoms were then compared to identify severity-related abnormalities (Table 2). For each symptom severity measure, mixed ANCOVA analyses were performed to compare the two groups with healthy controls. The same covariates were included in these analyses. To correct for multiple comparisons, we also used the FDR method across the 12 subfields for the main effects (diagnosis, hemisphere) and the interaction effects.

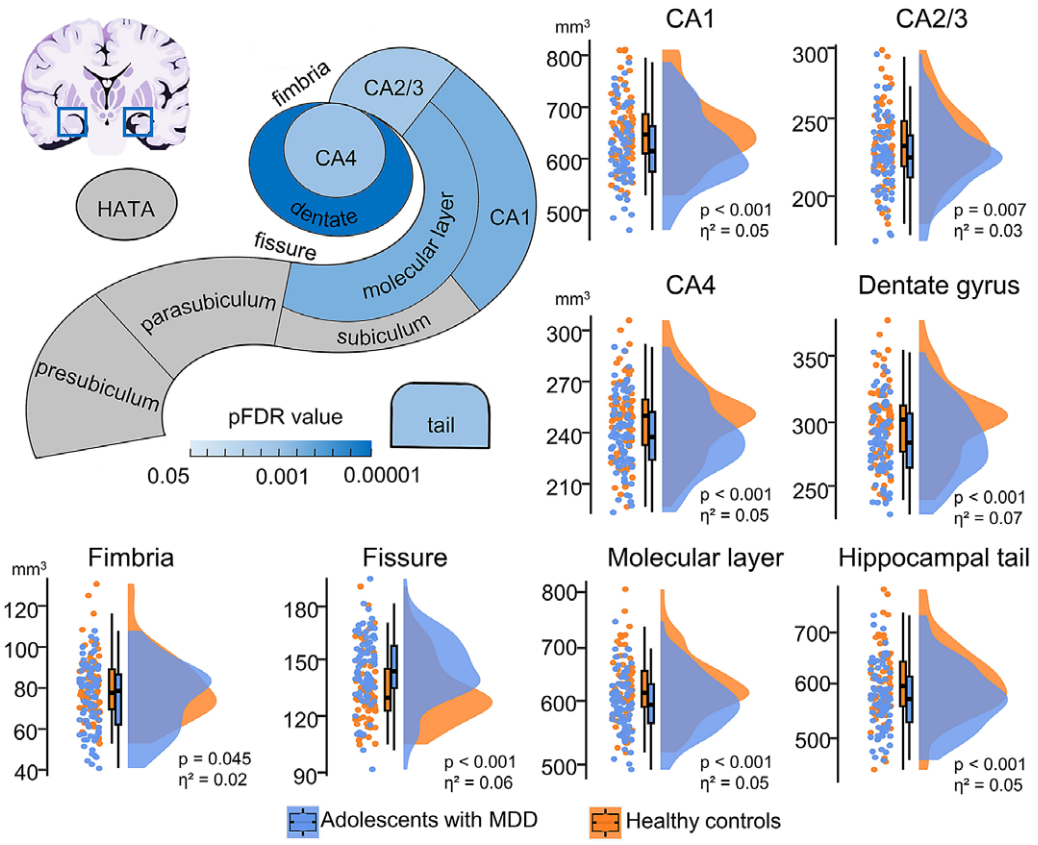


**Figure 1.** Volumetric differences in 12 hippocampal subfields between all adolescents with MDD and healthy controls. The significances (after FDR correction) of these substructure volume changes in depression were presented graphically on a Freesurfer hippocampus segmentation schematic. Raincloud plots were also created for those eight significant subfields with volume sizes of substructures in both depressive patients and healthy controls. Of them, patients showed significantly decreased volumes in seven subfields and increased volume in only fissure subfield. MDD, major depressive disorder; CA, cornu ammonis; HATA, hippocampal amygdalar transition area; FDR, false discovery rate.

To assess the robustness, we performed sensitivity analyses including (1) measuring subfield volumes using only the T1-weighted image (Supplemental Methods), (2) excluding age and gender as covariates (only including eTIV as a covariate), and (3) adding body mass index (BMI) as an additional covariate (age, gender, eTIV, and BMI).

To examine the extent to which specific hippocampal substructures have effects on cognitive impairments in adolescents with MDD, we conducted a Least Absolute Shrinkage and Selection Operator (LASSO) regression. LASSO is ideal here to avoid multicollinearity, as it selects variables using sparse solutions. The L1 penalty in LASSO could set coefficients of non-relevant predictors to 0, rather than just shrinking the coefficients. It has therefore widely been employed in recent research on between brain and behavior associations [56]. The analysis was performed in R, using the "cv.glmnet" function from the "glmnet" package and setting $\alpha = 1$, as suggested in a prior study [57]. All cognitive indices were regarded as "y" variables, and all hippocampus subregion volumes were included as "x" variables. Age, gender, and eTIV were entered as covariates. To estimate the coefficient weights for each predictor in the model, we performed 10-fold cross-validation to optimize the regularization parameter ($\lambda$). This $\lambda$ parameter controls the strength of the penalty and L1 influences the minimization of mean squared error (MSE). Finally, we summed the absolute values of the weights of each subfield to represent its overall associations with cognition and also summed the absolute values for each cognitive measure to identify its overall link with hippocampal subfields.

## Results

### Descriptive statistics

Demographics, clinical characteristics, and depression severity scores for all participants are presented in Table 1. There were no significant differences in age ($t = 2.69$, $\eta^2 = 0.05$, $p = 0.10$), gender ($\chi^2 = 2.26$, $p = 0.13$), or eTIV ($t = 0.01$, $\eta^2 = 0.00$, $p = 0.91$) between the MDD group and healthy controls. When compared to healthy controls, adolescents with MDD scored higher on depression ($t = 336.22$, $\eta^2 = 1.00$, $p < 0.001$, Table 1), suicide risk ($t = 328.60$, $\eta^2 = 1.00$, $p < 0.001$), and BMI ($t = 2.97$, $\eta^2 = 0.06$, $p < 0.01$) and scored lower on working ($ps < 0.001$, Table 3) and spatial memory ($ps < 0.008$), facial emotional recognition ($ps < 0.001$), attentive selection ($ps < 0.05$) and cognitive control (Go/No-Go, $ps < 0.001$, Table 3). Descriptive values of bilateral hippocampus subfields for the MDD group and healthy controls are shown in Table S1.

The group with severe symptoms scored higher than the group with mild symptoms on all five measures (Table 2, $ps < 0.001$; illness duration, $t = 8.75$, $\eta^2 = 0.53$; CDI score, $t = 11.32$, $\eta^2 = 0.62$; suicidal ideation, $t = 13.66$, $\eta^2 = 0.72$; suicide risk, $t = 12.61$, $\eta^2 = 0.68$; self-injury behavior, $t = 8.87$, $\eta^2 = 0.51$).

### Abnormalities of hippocampal subfields in patients and their associations with depressive severity

Compared to healthy controls, depressed adolescents had smaller dentate gyrus ($F = 20.62$, $\eta^2 = 0.07$, $p < 0.001$), CA1 ($F = 15.28$,

$\eta^2$ = 0.05, $p$ < 0.001), CA2/3 (F = 8.51, $\eta^2$ = 0.03, $p$ < 0.010), CA4 (F = 14.10, $\eta^2$ = 0.05, $p$ < 0.001), molecular layer (F = 15.39, $\eta^2$ = 0.05, $p$ < 0.001), fimbria (F = 4.77, $\eta^2$ = 0.02, $p$ < 0.045), tail (F = 13.80, $\eta^2$ = 0.05, $p$ < 0.001) and larger fissure (F = 19.33, $\eta^2$ = 0.06, $p$ < 0.001) (Figure 1 and Table 4). Significant main effects of the hemisphere were found in the tail, presubiculum, parasubiculum, molecular layer, dentate gyrus, CA1, CA2/3, CA4, fimbria, and HATA ($p$s < 0.05, Table S2). No significant interactions were observed between the diagnosis and hemisphere.

When the mild and severe groups were compared to healthy controls separately, we found those with greater overall depressive severity ($p$s < 0.001), illness duration over 15.3 months ($p$s < 0.003), higher suicidal ideation ($p$s < 0.012), higher suicidal risk ($p$s < 0.006) or more self-injury behaviors ($p$s < 0.018) had more significant reductions in the CA regions and such abnormalities trended to extend to surrounding subfields (Figure 2 and Table 4). Consistent patterns were observed for all five severity measures, suggesting heterogeneity of hippocampal abnormalities in MDD patients.

We also analyzed the hippocampal volumes that were segmented using T1 images only. Similar abnormalities in these subfields in depressed adolescents were observed (Figure S3), and these abnormalities were associated with depressive severities (Figure S4, Table S4). Additionally, we also identified abnormalities in these subfields and their relations with depressive severities when including eTIV only as the covariate (Figures S5 and S6, Table S5). Furthermore, adding the BMI as an additional covariate did not change these findings in subfields (Figures S7 and S8, Table S6).

### *Associations between hippocampal subfield volumes and cognitive abnormalities*

Using 10-fold cross-validation, LASSO regression analysis revealed the optimal regularization parameter with minimized MSE (1 back, $\lambda_{min}$ = 0; 2 back, $\lambda_{min}$ = 0.04; spatial memory, $\lambda_{min}$ = 0.03 ~ 0.18; digit span memory, $\lambda_{min}$ = 0.14; emotion recognition, $\lambda_{min}$ = 0.06 ~ 0.21; attentive selection, $\lambda_{min}$ = 0.07 ~ 1.00; cognitive control, $\lambda_{min}$ = 0.17 ~ 1.00) and created sparse models. The coefficient weights of hippocampal substructures on predicting cognitive measurements are shown in Figure 3. Hippocampal subfields showed the strongest associations with working memory and spatial memory, with many coefficients for subfields not being 0. Then, we summed absolute coefficient weights for each memory measure. We found that hippocampal subfield volumes had the largest magnitude in predicting n back (1back) score, which was followed by two back and spatial memory. For attentive selection, emotion recognition, and cognitive control, hippocampal subfield volumes showed relatively low magnitude in prediction.

Additionally, we also summed coefficient weights for each of the hippocampal subfields and found that dentate gyrus and CA4 showed the largest magnitude, followed by presubiculum, tail, molecular layer, CA2/3, CA1, parasubiculum, HATA, and subiculum (Figure 3B).

## Discussion

This study investigated the hippocampal subfield abnormalities in adolescents with depression using high-resolution T1 and T2 structural images. We found significant hippocampal decreases in CA1–4, dentate gyrus, and fimbria in adolescent MDD patients. As depression severity increased, such abnormalities showed an extending pattern that spread from the CA regions to peripheral subfields. The groups with severe symptoms showed more extensive abnormalities and the pattern was similar across all five severity assessments. Moreover, hippocampal abnormalities had the strongest associations with short-term memory deficits. Within all the subfields, CA4 and dentate gyrus showed the strongest links with cognitive functions. These results may reflect the progressive deterioration of the hippocampus in adolescents with MDD, indicating potential early biomarkers for adolescent depression and providing guidance on early clinical intervention.

Our primary findings demonstrate that hippocampal abnormalities are widespread in depressed adolescents, involving the dentate gyrus, CA regions, and surrounding fimbria and molecular layer. These results are consistent with some studies in adult patients with MDD [10, 27] and adolescents [58]. For instance, first-episode adult MDD patients have been found to show CA1 to CA4 volume reduction [27]. Research from the ENIGMA consortium also found that adult patients with early-onset MDD had lower thickness and surface area in hippocampal subfields [59]. In adolescent patients, reduced hippocampal subfields have also been reported [58], even though some studies did not observe any differences [21]. Such mixed findings were probably due to differences in methodology and the sample sizes. Most studies have segmented the hippocampus based on T1 images only [21, 58]. However, as we did here, including both T1 and T2 weighted images could take advantage of both image contrasts and produce smoother and more accurate segmentation of the hippocampus [22]. Additionally, we recruited a relatively large sample consisting of a homogeneous group of clinically depressed patients, in which the hippocampal abnormalities might be more extensive as compared to smaller sample sizes [60] and individuals with subthreshold/high-risk depression [61-63]. Hence, our results extend previous findings by directly examining hippocampal subfield volumes in adolescent patients, suggesting that depressed adolescents may exhibit atypical brain development.

Hippocampal changes in depressed adolescents may depend on symptom severity. We found the volumetric reductions to be more pronounced and more extensive from CA regions to peripheral subregions in patients with greater depressive severity, longer illness duration, higher suicide risk, more suicidal ideation, or more self-injury behaviors. Subiculum regions may be recruited later as MDD progresses further. These results are in line with another study that found a similar extension of hippocampal abnormalities from first presentation to recurrent episodes in adult MDD patients [27]. Our results in first-episode adolescent patients replicate such progressive patterns of hippocampal abnormalities, which may represent disease severity-related changes. The progressive patterns from CA regions to peripheral subregions are also consistent with neural circuits of the hippocampus [64, 65], in which neurons in the dentate gyrus receive afferent inputs from the medial temporal cortex, then project to CA2/3 and CA1 through fibers, and finally goes to subiculum regions. Our findings highlight the need for early intervention during the early stage of MDD [66], so to mitigate the progression of MDD and hippocampal abnormalities.

Hippocampal abnormalities may contribute to cognitive disruption, particularly in memory. The associations with memory were more pronounced as compared to emotion recognition, attention, and cognitive control abilities. The cognitive model theory of depression posits that biased memory could interact with other cognitive functions to directly contribute to the development of depressive symptoms in at-risk individuals [67]. Hence, it is important to understand what may underlie biased cognition

**Table 4.** Abnormalities of hippocampal subfield volumes in adolescents with MDD and its associations with severity

| | Overall differences | | Overall severity | | | | Illness duration | | | | Suicidal ideation | | | | Suicide risk | | | | Self-injurious behavior | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All patients versus HC | | Patients with CDI score (<25) versus HC | | Patients with CDI score (≥25) versus HC | | Patients with illness duration (< 15.3 months) versus HC | | Patients with illness duration (≥ 15.3 months) versus HC | | Patients with BSI score (<10) versus HC | | Patients with BSI score (≥10) versus HC | | Patients with NGASR score (≤5) versus HC | | Patients with NGASR score (>5) versus HC | | Patients with NSSI time (<1) versus HC | | Patients with NSSI time (≥1) versus HC | |
| Hippocampal subfields | *p* value | $\eta^2$ | *p* value | $\eta^2$ | *p* value | $\eta^2$ | *p* value | $\eta^2$ | *p* value | $\eta^2$ | *p* value | $\eta^2$ | *p* value | $\eta^2$ | *p* value | $\eta^2$ | *p* value | $\eta^2$ | *p* value | $\eta^2$ | *p* value | $\eta^2$ |
| Tail | <0.001* | 0.05 | 0.022* | 0.03 | 0.001* | 0.05 | 0.002* | 0.06 | 0.003* | 0.05 | 0.089 | 0.02 | 0.003* | 0.05 | 0.202 | 0.01 | 0.002* | 0.05 | 0.159 | 0.01 | 0.002* | 0.05 |
| Dentate gyrus | <0.001* | 0.07 | 0.006* | 0.05 | 0.001* | 0.08 | 0.050* | 0.03 | <0.001* | 0.12 | 0.003* | 0.06 | 0.003* | 0.06 | 0.002* | 0.07 | 0.002* | 0.05 | 0.004* | 0.06 | 0.002* | 0.05 |
| CA1 | <0.001* | 0.05 | 0.018* | 0.03 | 0.001* | 0.07 | 0.061 | 0.02 | <0.01* | 0.08 | 0.014* | 0.04 | 0.005* | 0.04 | 0.064 | 0.03 | 0.002* | 0.05 | 0.077 | 0.02 | 0.002* | 0.05 |
| CA2/3 | 0.007* | 0.03 | 0.165 | 0.01 | 0.001* | 0.06 | 0.167 | 0.01 | 0.001* | 0.05 | 0.089 | 0.02 | 0.012* | 0.03 | 0.293 | 0.01 | 0.005* | 0.05 | 0.130 | 0.02 | 0.018* | 0.03 |
| CA4 | <0.001* | 0.05 | 0.019* | 0.03 | 0.001* | 0.06 | 0.129 | 0.02 | <0.001* | 0.10 | 0.019* | 0.04 | 0.006* | 0.04 | 0.013* | 0.05 | 0.006* | 0.04 | 0.052 | 0.03 | 0.004* | 0.04 |
| Molecular layer | <0.001* | 0.05 | 0.018* | 0.03 | 0.001* | 0.07 | 0.037* | 0.03 | <0.01* | 0.08 | 0.038* | 0.03 | 0.003* | 0.06 | 0.163 | 0.02 | 0.001* | 0.06 | 0.052 | 0.03 | 0.002* | 0.05 |
| Presubiculum | 0.802 | <0.01 | 0.958 | <0.01 | 0.753 | 0.00 | 0.485 | <0.01 | 0.990 | <0.01 | 0.824 | <0.01 | 0.775 | <0.01 | 0.502 | <0.01 | 0.764 | <0.01 | 0.552 | <0.01 | 0.782 | <0.01 |
| Parasubiculum | 0.272 | <0.01 | 0.745 | <0.01 | 0.024* | 0.03 | 0.107 | 0.02 | 0.726 | <0.01 | 0.808 | <0.01 | 0.041* | 0.02 | 0.828 | <0.01 | 0.173 | 0.01 | 0.552 | <0.01 | 0.271 | 0.01 |
| Subiculum | 0.205 | 0.01 | 0.165 | 0.01 | 0.598 | 0.00 | 0.683 | <0.01 | 0.049* | 0.02 | 0.349 | 0.01 | 0.492 | <0.01 | 0.502 | <0.01 | 0.293 | 0.01 | 0.552 | <0.01 | 0.273 | 0.01 |
| Fimbria | 0.045* | 0.02 | 0.018* | 0.04 | 0.725 | 0.00 | 0.129 | 0.01 | 0.073 | 0.02 | 0.038* | 0.03 | 0.314 | 0.01 | 0.293 | 0.01 | 0.069 | 0.03 | 0.071 | 0.03 | 0.244 | 0.01 |
| HATA | 0.122 | 0.01 | 0.508 | 0.00 | 0.099 | 0.02 | 0.867 | <0.01 | 0.049* | 0.02 | 0.122 | 0.01 | 0.400 | <0.01 | 0.502 | <0.01 | 0.173 | 0.02 | 0.144 | 0.02 | 0.273 | 0.01 |
| Fissure | <0.001* | 0.06 | <0.001* | 0.09 | 0.015* | 0.03 | 0.002* | 0.06 | <0.01* | 0.07 | <0.001* | 0.08 | 0.004* | 0.05 | <0.001* | 0.11 | 0.005* | 0.04 | <0.001* | 0.11 | 0.008* | 0.03 |

*Note:* $\eta^2$ describes effect size; the *p* value is corrected with FDR method and "*" indicated the significance with <0.05.
Abbreviations: MDD, major depressive disorder; HC, healthy controls; CDI, children's depression inventory; NSSI, non-suicidal self-injury; BSI, beck scale for suicide ideation; NGASR, nurses' global assessment of suicide risk scale; CA, cornu ammonis; HATA, hippocampal amygdalar transition area.

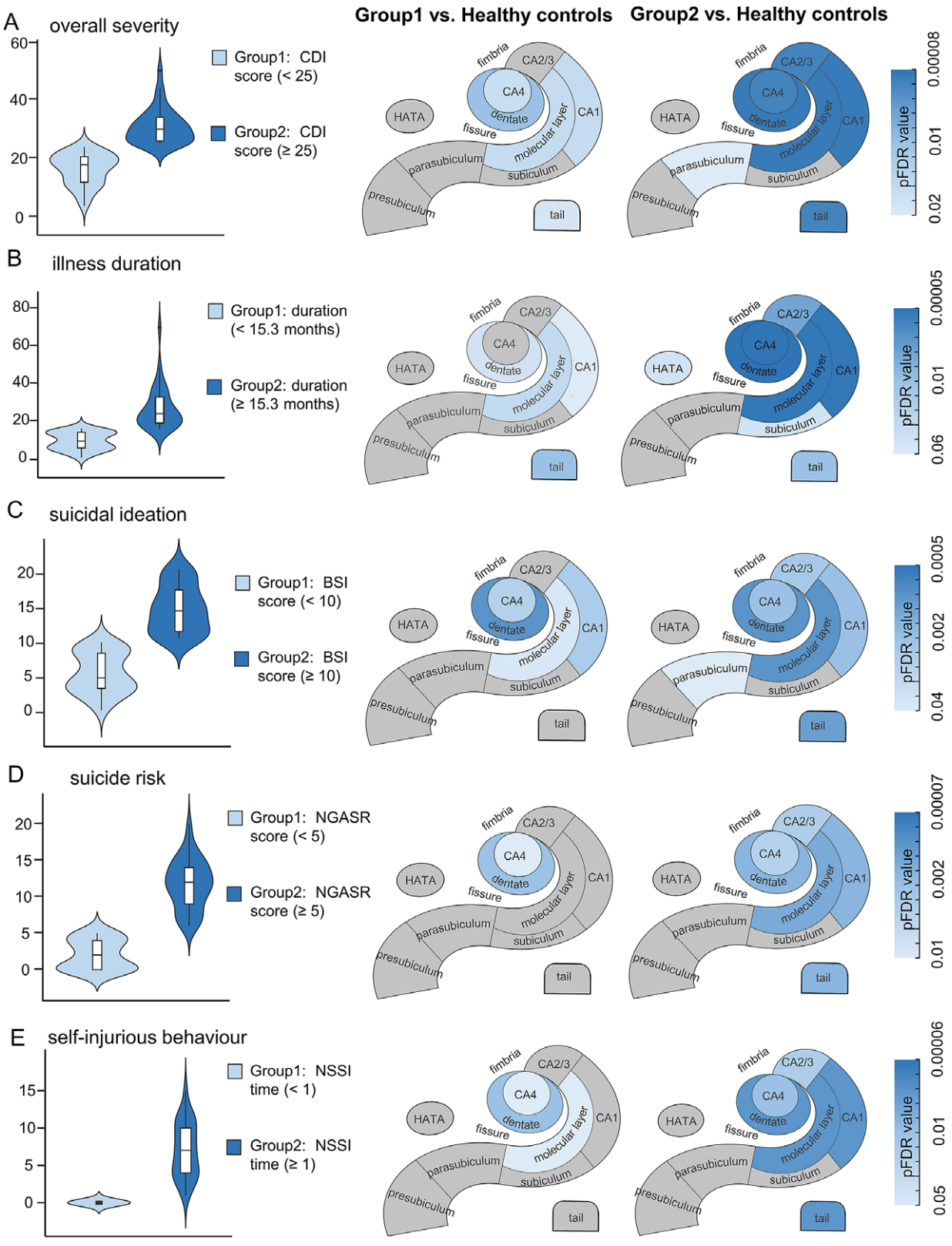


**Figure 2.** Abnormalities of hippocampal subfield volumes extend from CA regions to surrounding areas as depressive severity increases. We assessed depressive severities from five perspectives, including overall depressive severity (A), illness duration (B), suicidal ideation (C), suicide risk (D), and self-injury behavior (E). Regardless of the methods used to assess severity, hippocampal substructures consistently demonstrated a tendency to exhibit progressive decrease, starting from the CA regions and extending towards the peripheral regions. CA, cornu ammonis; HATA, hippocampal amygdalar transition area; NGASR, nurses' global assessment of suicide risk; NSSI, nonsuicidal self-injury; FDR, false discovery rate.

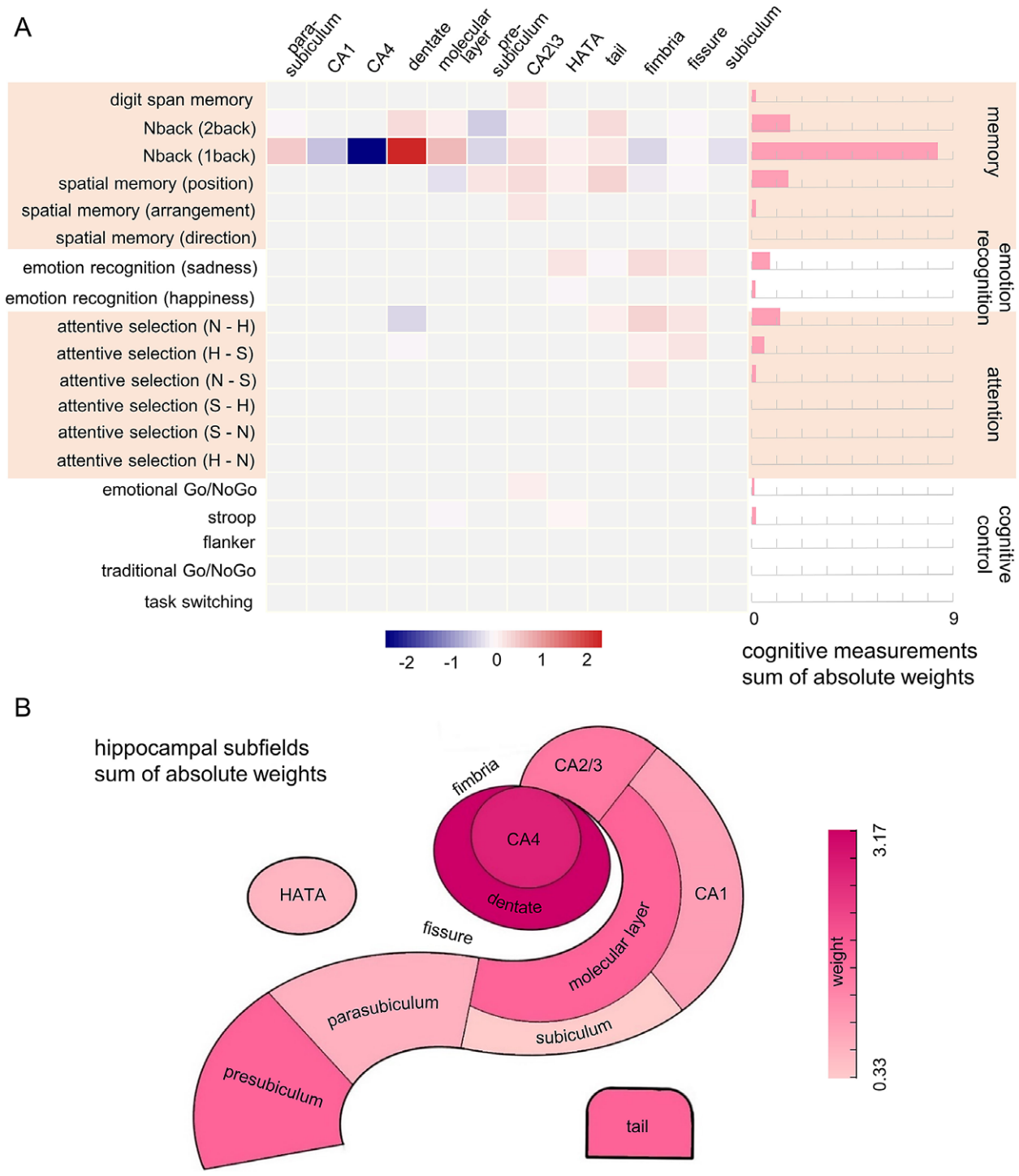


**Figure 3.** Associations between hippocampal subfield volumes and cognitive abnormalities in adolescents with MDD. We identified the optimal regularization parameters from the LASSO regression analysis using 10-fold cross-validataion. The coefficient weights of core CA region volumes (B) had the relatively largest magnitudes in associations with memory (working and spatial memory, A), following by attentive selection, emotional recognition and cognitive control abilities. For the different cognition and hippocampus substructures, coefficient weights were summed by the corresponding absolute values. CA, cornu ammonis; HATA, hippocampal amygdalar transition area; attentive selection (N), neutral emotion; attentive selection (H), positive emotion; attentive selection (S), negative emotion; in dot probe task, left stimuli was defined as the attractive one.

during the development of MDD [68, 69]. Here, we provided evidence for the potential contribution of hippocampal subfields, especially the dentate gyrus and CA regions, to memory deficits in early-onset adolescent patients. Interventions aimed at improving memory may target these subfields or the functional circuits involving them. Considering that memory impairment is not regarded as a core symptom of MDD, it is important to determine whether such abnormalities are specific to depressed patients or common in other disorders, such as autism and anxiety disorders [70, 71]. Furthermore, given that the hippocampus is a deep structure within the subcortex, it is challenging to utilize neuro-interventional methods to modulate its activity [72]. Therefore,

future research should also explore the disruption of effective functional circuits in different subfields in these patients [73], and consider utilizing other cortical targets to exert interventions to hippocampal subfields [74].

There are several limitations in this study. Firstly, although the severity of MDD was assessed using five different measures, all of them were cross-sectional. We thus cannot determine the causality between depression and volume reductions in the hippocampus. Volumetric changes in the hippocampus have been found to predict the later onset of depression from early to mid-adolescence [75]. Future longitudinal studies are warranted to reveal to which extent hippocampal subregions could predict the onset and development of MDD. Secondly, despite the high-resolution images and robust segment method, we only focused on the substructure volumes and ignored the long-axis specialization of the hippocampus [76, 77]. Noval shape analyses may provide more morphometric and quantitative brain measures and greater power to detect disease effects [78, 79]. Thirdly, considering this study focused on the hippocampus and its associations with cognition, particularly in relation to multifaceted memory, future research should consider other tests for declarative memory, delayed recall, and recognition memory. Fourthly, adolescent depression is significantly influenced by adverse childhood environments [80]. Early-life stress may contribute to hippocampal abnormalities [81] by inducing alterations in epigenetic programming such as DNA methylation progression [62]. However, it is still unclear whether the abnormal hippocampal tissues in depressed adolescents are a result of adverse environments and abnormal DNA expression processes [82, 83].

In conclusion, this study has focused on hippocampal subfields in adolescent MDD patients and successfully identified significant volumetric reductions in several subregions. The results on the severity of the symptoms supported the importance of core hippocampal structures in the pathophysiology of depression. Hippocampal subfields also showed associations with cognition impairments in MDD patients, especially in the cognitive domain of memory. These findings underscore the necessity of effective early therapeutic interventions in adolescent depression to potentially mitigate progressive hippocampal damage.

**Supplementary material.** The supplementary material for this article can be found at http://doi.org/10.1192/j.eurpsy.2024.15.

**Data availability statement.** The data that support the findings of this study are available on request from the corresponding author, Kangcheng Wang.

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**Author contribution.** Yinxin Zhang: Conceptualization, study design, data collection, formal analysis, and writing. Xuan Liu: Data collection, study design, and formal analysis. Ying Yang: Study design and data collection. Yihao Zhang: Data collection. Qiang He: Data collection. Feiyu Xu: Data collection. Xinjuan Jin: Data collection. Junqi Gao: Data collection. Dexin Yu: Data collection. Bernhard Hommel: Writing. Xingxing Zhu: Study design and writing. Kangcheng Wang: Conceptualization, study design, methodology, formal analysis, and writing. Wenxin Zhang: Conceptualization, study design, and data collection.

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**Competing interest.** All authors declare they have no conflicts of interest.

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