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Associations between parental rearing style and amygdala and hippocampal subfield abnormalities in drug-naive females with anorexia nervosa

Yu Wang[1], Min Xie[1], Linli Zheng[1], Jing Ma[1], Meiou Wang[1] and Lan Zhang[1*]

Abstract

Background Altered volumes in the hippocampus and amygdala have been linked to anorexia nervosa (AN). This study aimed to investigate amygdala and hippocampal subfields volume abnormalities in AN patients, and their associations with parental rearing practices and clinical psychological characteristics.

Methods This study included twenty-nine drug-naive females with AN from West China Hospital of Sichuan University, China, and fifty-nine age- and gender-matched healthy controls (HCs) recruited through advertisement. All participants underwent T1-weighted imaging. Amygdala and hippocampal subfields volume was calculated using FreeSurfer 7.0. The Core Self-Evaluation Scale (CSES) and Rosenberg Self-Esteem Scale (RSES) were used to assess the psychological characteristics of AN patients. The Egna Minnen av Barndoms Uppfostran (EMBU) was employed to evaluate parental rearing practices. Group differences in brain volumes were analyzed with covariates like age and total intracranial volume (TIV). Partial correlation analysis explored the correlations between brain region volumes and clinical psychological characteristics.

Results AN patients exhibited lower RSES and CSES scores, and more adverse parental rearing style than healthy norms. After adjusting for covariates, AN patients showed decreased gray matter volume (GMV) in the left medial (Me) and cortical (Co) nucleus, as well as in the right hippocampal-amygdala transition area (HATA). GMV in the left Me was correlated with years of education among HCs but not among AN patients. GMV in the right HATA was positively correlated with paternal penalty and severity, as well as maternal overinterference.

Conclusion This study supports structure abnormalities in amygdala and hippocampus in AN patients and suggests that parental rearing practices may be associated with hippocampal abnormalities, potentially contributing to the pathophysiology of AN. Addressing appropriate parental rearing styles may offer a positive impact on AN.

Keywords Anorexia nervosa, Neuroimaging, Amygdala, Hippocampus, Subfield, Parental rearing style

*Correspondence:
Lan Zhang
huaxizhanglan@126.com
[1]Mental Health Center, West China Hospital of Sichuan University, Dianxin South Street, 28#, Wuhou District, Chengdu, Sichuan 610041, P. R. China

Introduction

Anorexia Nervosa (AN) is a complex and serious eating disorder that primarily affects young women, characterized by an intense fear of gaining weight and a distorted body image [1, 2]. These characteristics of AN often leads to life-threatening emaciation and devastating psychological burdens [3, 4], resulting in the highest standardized mortality rate among psychiatric disorders [5], with a five-fold or greater increase in mortality risk compared to the general population [6]. In addition, AN is frequently associated with other psychopathologies and role impairment, and is often under-treated [7]. According to the Global Burden of Diseases (GBD) 2019, eating disorders (specifically anorexia nervosa and bulimia nervosa) accounted for 2.9 million disability-adjusted life-years (DALYS) globally in 2019, equivalent to 37.6 per 100,000 people [8]. Most individuals with AN experience a profound impact on social functioning and impose a substantial economic burden on patients, families, and society [5, 9].

Accumulated evidence indicates that alterations in gray matter volume (GMV) are associated with AN [10, 11], particularly in the hippocampus and the amygdala overall [12–14]. Researchers have reported a reduction in bilateral total hippocampal volume in patients with active AN [15, 16]. The hippocampus, known for its role in memory, learning, and visuospatial processes, is increasingly recognized to play a significant role in regulating food intake [17]. However, it's essential to note that the hippocampus is a heterogeneous structure with multiple cell layers and distinct "hippocampal subfields" (HS) that differ in both structure and function [18, 19]. In a pioneering study, Burkert et al. investigated alterations in hippocampal subfield volume in 21 females with AN and 21 age-matched healthy controls (HCs), and they observed a noteworthy decrease in the volume of the hippocampal fimbria, as well as a significant enlargement of the hippocampal fissure [20]. Another study involving 58 female adolescents, including 30 active AN and 28 HCs, reported that adolescents with AN exhibited a decreased GMV in all hippocampal subfields except for the fissure [21]. In summary, there is evidence to suggest that altered hippocampal subfield volume may be implicated in AN.

Previous structural MRI (sMRI) studies have also reported reductions in GMV in the amygdala as a whole in individuals with AN [22, 23]. However, increasing evidence suggests the presence of phylogenetic, histological, and functional diversity within the amygdala, particularly in the amygdaloid complex [24]. These findings emphasize the importance of considering amygdala substructures in translational and clinical research [24, 25]. It is possible that alterations in specific subregions of the amygdala may differ from general gray matter volume (GMV) alterations observed in AN, highlighting their potential clinical significance. Enhanced version of automated tools, which also segment the nuclei of the amygdala, such as those found in FreeSurfer 7, has facilitated pilot studies investigating alterations in amygdala nuclei among psychiatric populations [24, 26, 27]. A recent study revealed a global reduction in most amygdala nuclei volumes in AN patients, with four specific nuclei (accessory basal, cortical, medial nuclei, and corticoamygdaloid transition in the rostral-medial amygdala) exhibiting greater volumetric reductions compared to the GMV of the whole amygdala, while basal, lateral, and paralaminar nuclei showed lesser reduction [28]. To sum up, investigating alterations in amygdala subregions in individuals with AN holds potential as a specific area of interest in neurobiological approaches to understanding the disorder.

Until now, few studies have examined the GMV differences in the hippocampus and amygdala subregions between Chinese Han females with AN and HCs, as well as the association between altered GMV, paternal rearing practices, and clinical psychological characteristics. This study aimed to compare GMV in the hippocampus and amygdala subregions in Chinese Han female with AN, and to explore the relationship between altered GMV, paternal rearing practices, and clinical psychological characteristics.

Methods

Participants

Twenty-nine females with current AN and 59 age-matched female HCs were also included in the study. All participants were of Chinese Han ethnicity, right-handed, and aged between 13 and 30 years. Two psychiatrists independently assessed and diagnosed all participants based on the DSM-5 criteria [2]. We did not categorize patients into the restrictive type or the binge-eating/purging type. Current AN was defined as a body mass index (BMI) <17.5 kg/m^2 or <10th age percentile (if younger than 18 years). To minimize the potential influence of medication, all patients in this study were required to be psychotropic medication-naive (never having taken any psychotropic medication) or psychotropic medication-free for at least 3 months before enrollment. All HCs had no history of mental disorders, substance abuse, or neurological illnesses. Patients were excluded if they had severe physical diseases such as neurogenic diseases, endocrine diseases, or metabolic disorders. Additionally, comorbidity with other severe psychiatric disorders, such as schizophrenia, bipolar disorder, major depressive disorder, alcohol or drug abuse, or history of loss of consciousness, was also an exclusion criterion.

Clinical psychological assessment

Core self-evaluation was assessed using the Chinese version of the Core Self-Evaluation Scale (CSES) [29]. The CSES comprises 10 items, rated on a five-point scale. The total score ranged from 10 to 50, with higher scores indicating more frequent core self-evaluations. It showed acceptable reliability and validity, with a Cronbach's alpha of 0.81. The national norm for Chinese undergraduate female on the CSES was reported as 36.05±5.21, and we compared the CSES scores of our patients to this norm.

The revised Chinese version of the Rosenberg Self-esteem Scale (RSES) was used to assess overall feelings about self-worth and self-acceptance [30]. The scale consisted of 10 items, each item scored on a 4-point scale, with higher scores indicating higher levels of self-esteem. The RSES has demonstrated good reliability and validity across multiple studies, with a Cronbach's alpha value of 0.85 [31, 32]. We compared the RSES scores of our patients to the mean RSES score of 28.73±4.48 reported for undergraduates in Beijing [33].

The Parental Rearing Practices Evaluation Scale (EMBU - Egna Minnen av Barndoms Uppfostran) was developed by Carlo Perris and colleagues to assess individuals' own memories of parental rearing behaviour [34]. In 1993, 115-item EMBU was translated and revised, providing normative scores for each dimension [35]. The revised scale includes 58 items for the father's parenting style, divided into six dimensions: warmth and understanding (51.54±8.89), penalty and severity (15.84±3.98), overinterference (20.92±3.66), favoritism (9.82±3.83), rejection and denial (8.27±2.40), and overprotection (12.43±3.12). The mother's parenting style includes 57 items divided into five dimensions: warmth and understanding (55.71±9.31), penalty and severity (11.13±2.84), overinterference and overprotection (36.42±6.02), favoritism (9.99±3.81), and rejection and denial (11.47±3.26). Each item is scored on a 4-point scale, with higher scores indicating more frequent parental behaviors in that particular factor.

MRI data acquisition and processing

All participants underwent MRI scans between 4:00 PM and 6:00 PM. MR images were obtained using a Philips 3.0 T system. All subjects underwent 3D T1-weighted volumetric scanning with the following parameters: orientation, sagittal; matrix size, 256×256; field of view (FOV), 256×256 mm; slice thickness, 1 mm; gap, none; flip angle, 7°; repetition time (TR), 8.2 ms; echo time (TE), 3.8 ms; voxel size, 1×1×1 mm. During MRI, all subjects were instructed to relax, keep their eyes closed without falling asleep, and maintain their head as motionless as possible, while avoiding focusing on any particular thoughts. The method of MRI data acquisition has also been described previously [36]. All scans were reviewed by two practicing neuroradiologists to exclude any gross brain abnormalities. The total intracranial volume (TIV) of each participant was estimated.

MRI data were processed in a fully automated manner (online SM 1.4) using FreeSurfer (http://surfer.nmr.mgh.harvard.edu, version 7.1.1) to achieve cortical surface reconstruction and volumetric brain segmentation, including subcortical processing streams [24, 37, 38].

Subfields for the amygdala and hippocampus

FreeSurfer calculated the overall volumes of the hippocampus and amygdala, as well as their subfields bilaterally [24, 38]. In the hippocampus, 14 subregion volumes were generated and analyzed separately for the left (lh) and right (rh) brain hemispheres: head, body, tail, CA1, CA3 (including CA2), CA4, the molecular and granule cell layers of the dentate gyrus (GC-ML-DG), the molecular layer (ML), subiculum, presubiculum, parasubiculum, fimbria, fissure, and the hippocampal-amygdala transition area (HATA) [39]. In the amygdala, volumes of nine subregions were generated and analyzed separately for both left (lh) and right (rh) brain hemispheres: lateral (La), basal (Ba), accessory basal (AB), anterior amygdaloid area (AAA), central (CeA), medial (Me), cortical (Co), corticoamygdaloid transition (CAT), and paralaminar nuclei [39]. In our analysis, the head and body volumes were combined to reflect the whole hippocampal volume, and the whole amygdala was also computed and compared.

Statistical analysis

All analyses were performed using IBM SPSS version 26. Group comparisons for demographic data were performed using independent t-tests for continuous variables. Three Multivariate Analyses of Covariance (MANCOVAs) was employed to examine the differences in the amygdala and hippocampal volumes between AN patients and HCs. The first MANCOVA compared the whole volumes of four regions: left and right amygdala, as well as left and right hippocampus. The second and third MANCOVA explored differences in volumes among amygdala and hippocampus subfields, respectively. Age and TIV were included as covariates in all three analyses. The significance threshold was set at $p<0.05$, and False Discovery Rate (FDR) correction was used to account for multiple comparisons in the study. Partial Correlations between AN-associated altered GMV and clinical characteristics were analyzed, with age and TIV as covariates, and a significance level of 0.05 was set for all two-tailed tests.

Results

Clinical and demographic characteristics

The groups did not differ significantly in age or years of education, but AN patients had a lower BMI than HCs. Compared to the healthy population norms, patients showed lower RSES and CSES scores, as well as lower levels of parental warmth and understanding and higher levels of parental penalty and severity, favoritism, and rejection and denial. Additionally, paternal overinterference and overprotection were lower, while maternal overinterference and overprotection were higher. Table 1 summarizes the demographics and clinical characteristics of AN patients and HCs.

Altered GMV in AN patients

There were no significant differences in TIV between AN patients and HCs. After adjusting for age, years of education, and TIV, no significant differences were observed in the volume of bilateral amygdala between AN patients and HCs ($P_{FDR} > 0.05$). Subregional analyses revealed a significant reduction in the volume of the left medial nucleus (F=6.57, $P_{FDR} = 0.024$) and cortical nucleus (F=5.44, $P_{FDR} = 0.044$) in AN patients compared to HCs (Fig. 1).

As for hippocampus, there was no significant difference in GMV of the bilateral whole hippocampus between AN patients and HCs ($P_{FDR} > 0.05$). Subsequent subregional analyses revealed that AN patients exhibited a significant decrease in GMV in the right HATA (F=4.97, $P_{FDR} = 0.028$). (Fig. 2).

Altered GMV correlated with clinical characteristics

After controlling for age and TIV, partial correlation analysis revealed a significant positive correlation between the volume of the left medial nucleus and years of education among HCs ($r=0.36$, $p=0.037$), but not among AN patients ($r=0.28$, $p=0.068$) (see Fig. 3a-b). The volume of the right HATA was positively correlated with paternal penalty and severity ($r=0.41$, $p=0.038$), as well as maternal overinterference and overprotection ($r=0.41$, $p=0.036$) (see Fig. 3c-d). No significant correlations were observed between altered subfields and BMI, age, age of onset, duration of illness, or total score on the RSES and CSES.

Discussion

To the best of our knowledge, this is the first study conducted on drug-naive Chinese Han females with AN to examine the GMV abnormalities in the amygdala and hippocampus subregions, as well as the correlation between AN-associated altered GMV and clinical and psychological characteristics.

This study revealed no significant GMV reduction in the bilateral whole amygdala among AN patients, which contrasts with prior research indicating GMV reduction in the whole amygdala in AN patients [13, 22, 23, 28]. The differences may be attributed to the homogeneity

Table 1 Demographic, clinical characteristics of the participants

	AN ($n=29$)	HC ($n=59$)	Z	*p*
Age	19.00 (16.00, 22.00)	20.00 (18.00, 22.00)	0.625	0.532
BMI (kg/m^2)	16.13 (14.41, 17.36)	19.81 (19.01, 20.73)	6.429	**<0.001**
Education (years)	12.00 (9.00, 15.00)	14.00 (12.00, 16.00)	2.345	0.054
Onset age	16.00 (14.13, 20.00)	-	-	-
Duration of illness (years)	2.00 (1.00, 2.75)	-	-	-
RSES total score	26.00 (20.00, 29.75)	-	-	-
CSES total score	32.00 (28.25, 35.75)	-	-	-
Paternal parenting style				
Warmth and understanding	43.00 (37.25, 54.75)	-	-	-
Penalty and severity	16.50 (14.00, 21.75)	-	-	-
Overinterference	18.00 (16.00, 20.00)	-	-	-
Favoritism	12.00 (8.00, 17.50)	-	-	-
Rejection and denial	9.00 (7.00, 12.75)	-	-	-
Overprotection	11.50 (10.00, 14.00)	-	-	-
Maternal parenting style				
Warmth and understanding	50.00 (41.25, 61.50)	-	-	-
Penalty and severity	33.00 (30.00, 42.50)	-	-	-
Overinterference and overprotection	14.00 (10.00, 18.50)	-	-	-
Favoritism	12.50 (10.00, 15.75)	-	-	-
Rejection and denial	14.00 (8.50, 17.00)	-	-	-
TIV (mm^3)	1236752.25 (1087700.06, 1460410.99)	1361570.41 (1149031.34, 1517691.39)	1.488	0.142

Note: Data are presented as as median (P25, P75). Z are the effect sizes of the Mann-Whitney U test. BMI, body mass index; RSES, Rosenberg Self-Esteem Scale; CSES, Core Self-evaluation Scale; TIV, total intracranial volume

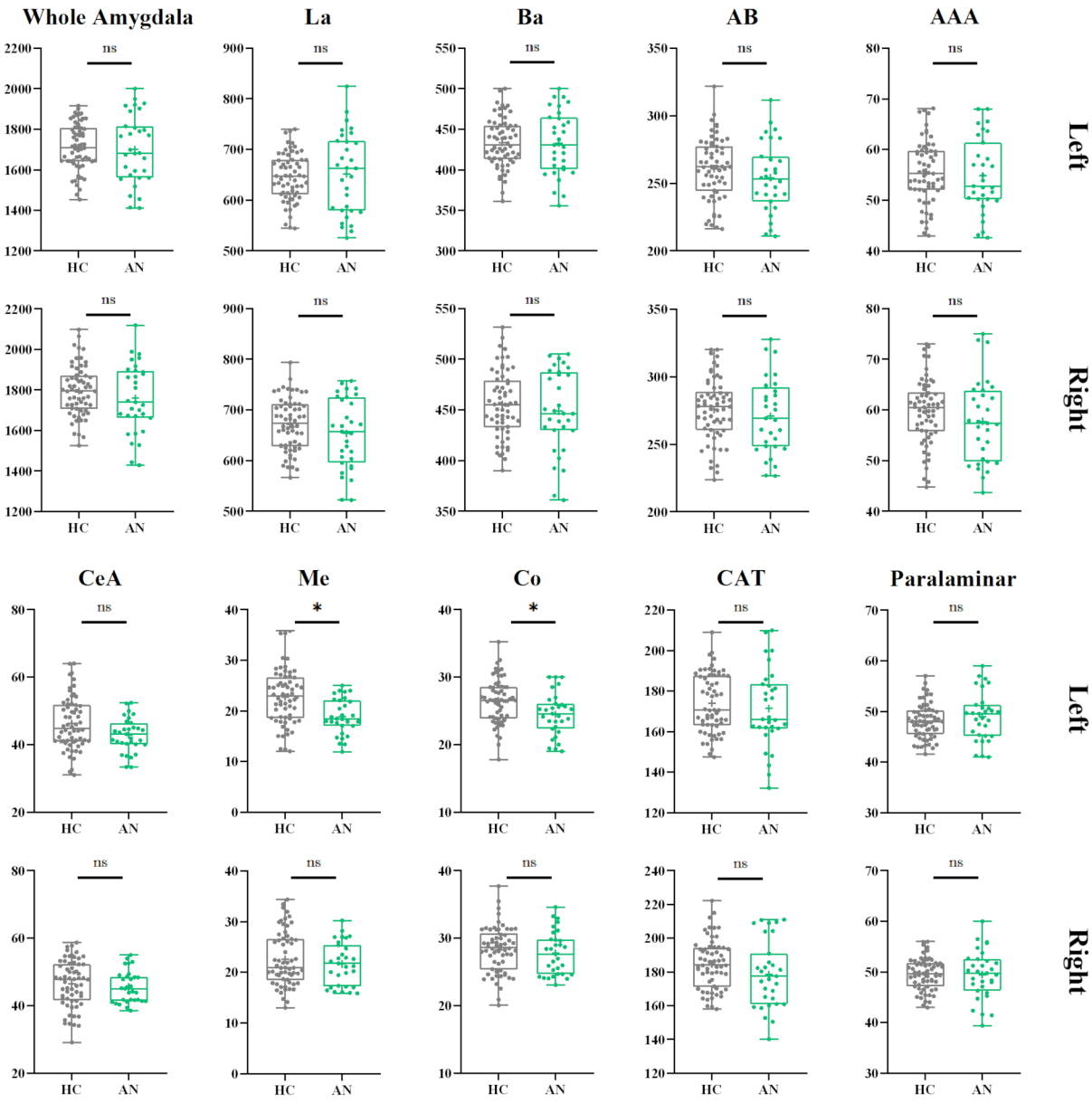

Fig. 1 Box-plots of volumes of the amygdala subregions in AN patients and healthy control (HC). Statistical significance at False Discovery Rate (FDR) level: *, $P_{FDR} < 0.05$; ns, non-significant ($P_{FDR} > 0.05$)

of our sample, consisting of drug-naive Chinese females with AN, as well as the relatively small sample size. AN patients did show reduced GMV in the left amygdala medial and cortical nucleus, consistent with findings of reductions in the accessory basal nucleus, medial nucleus, cortical nucleus, corticoamygdaloid transition, and others [28]. Accumulated evidence suggested that evolutionarily conserved structures, such as the accessory basal, cortical, medial nuclei, and corticoamygdaloid transition communicate with the olfactory cortex and exert emotional control over food intake [24, 25]. Specifically, the medial nuclei is a component of the amygdalar complex that plays a pivotal role in innate emotional behaviors by relaying olfactory information to hypothalamic nuclei involved in reproduction and defense [40]. It also contributes to various social behaviors, encompassing sensory and behavioral attributes, and is functionally linked to an extensive network of limbic regions spanning the entire brain [41]. Meanwhile, the cortical amygdala is necessary for innate aversive and appetitive behaviors [42]. It is well known that these neural processes are closely associated with eating disorders.

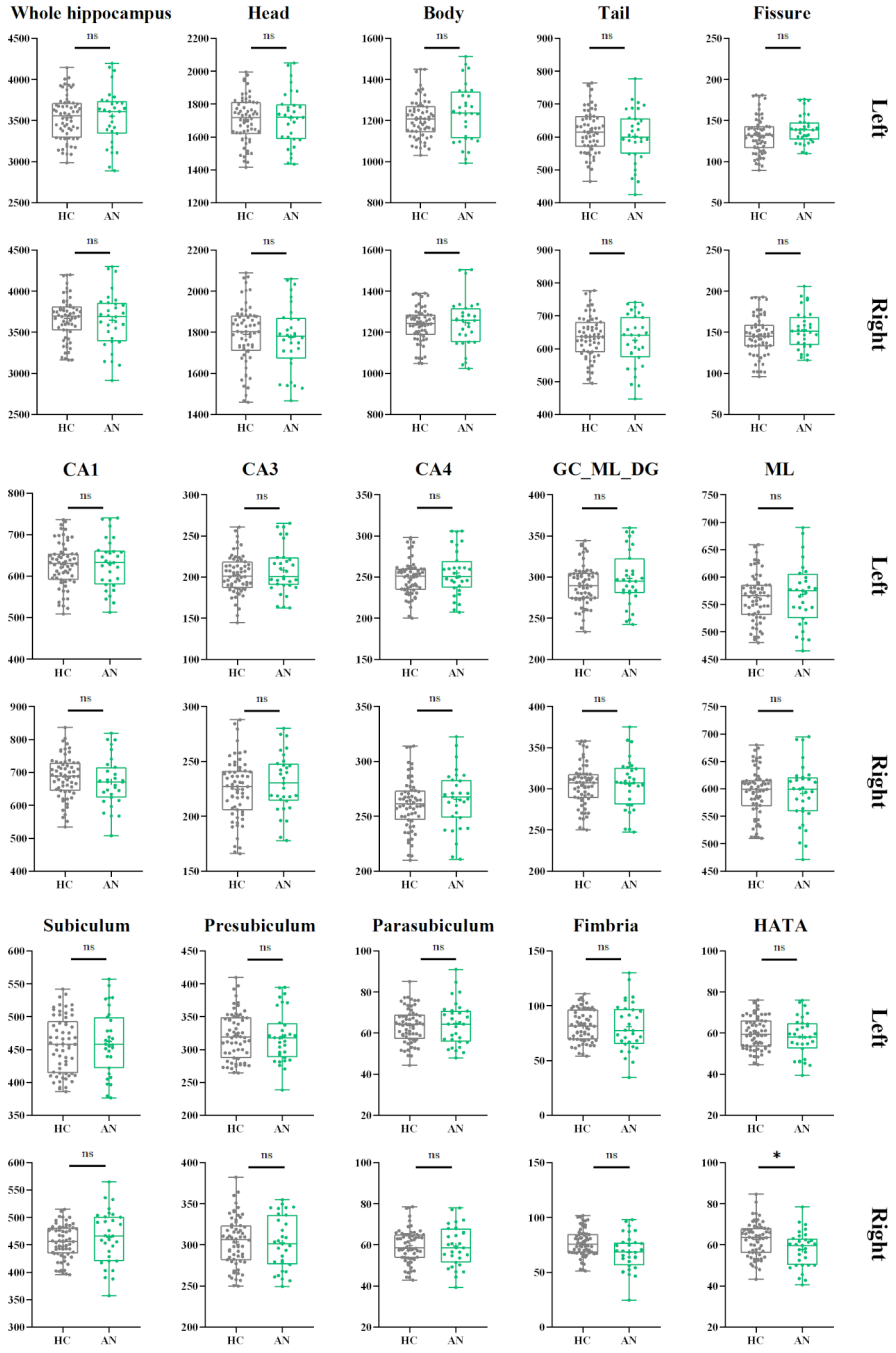

Fig. 2 Box-plots of volumes of the hippocampus subregions in AN patients and healthy control (HC). Statistical significance at False Discovery Rate (FDR) level: *, $P_{FDR} < 0.05$; ns, non-significant ($P_{FDR} > 0.05$)

Furthermore, in line with the previous studies, no significant correlations were found between GMV in the amygdala subfields and clinical variables (e.g., age, BMI, years of education, duration of illness, and onset age) [28].

In this study, we did not find significant differences in the bilateral whole hippocampal GMV between individuals with AN and HCs. This finding contrasts with previous research suggesting a reduction in total hippocampal volume among patients with AN [16, 43, 44]. Regarding the hippocampal subfields, the study indicated decreased GMV in the right HATA among AN patients. This finding is partially consistent with Myrvang et al., who reported that adolescents with AN exhibited a decreased volume in all hippocampal subfields except

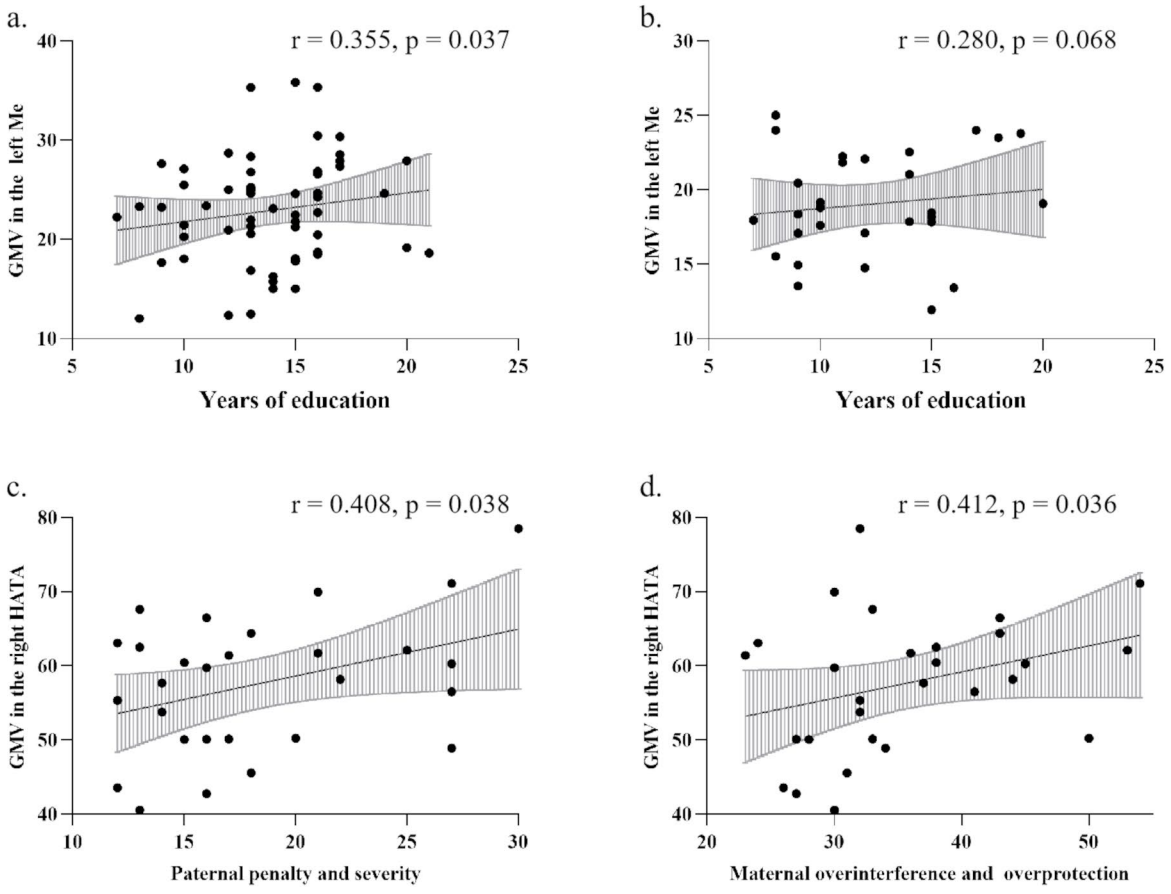

Fig. 3 Association between GMV reduction, education years, and parental rearing in AN patients. GMV in the left medial nucleus was significantly correlated with education years in HCs (**a**) but not in AN patients (**b**). GMV in the right HATA was significantly positively correlated with paternal penalty and severity (**c**), as well as maternal overinterference and overprotectiveness (**d**)

for the fissure [21]. Although the factors contributing to the heterogeneity of these results remain unclear, potential contributing factors may include the omission of statistical control for key variables (e.g., age, TIV, duration of illness, medication use) [45–47]. Furthermore, the hippocampus stands out as a brain region with lifelong neurogenesis and increased vulnerability to malnutrition due to its heightened metabolic demands [48]. Some longitudinal studies have observed a normalization in total hippocampal volume, or specifically in the left hippocampus volume after treatment or weight recovery [13, 49]. Asami et al. reported that AN patients had a sustained decrease in hippocampal volume during the weight-recovered phase [44]. In this study, BMI, a crucial nutritional indicator, did not exhibit any significant correlation with hippocampal volume. The discrepancy is thought to be possibly linked to symptom improvement [13]. Besides, Beadle et al. reported that women with AN, who had engaged in prior excessive exercise and restricted food intake, exhibited larger hippocampus volumes compared to HCs. The increased volume was more marked in those with AN who exercised excessively and experienced starvation [50]. In the present study, all patients were drug-naive Chinese Han females, with over 90% of the patients (28/31) engaging in excessive exercise and restricted food intake, which may contribute to the differences observed in comparison to these previous studies.

The HATA is located in the medial region of the hippocampus and is the transitional area between the hippocampus and amygdala. The atrophy of the HATA might disrupt the integrity of the hippocampal-amygdala network, which is in charge of information processing [51]. The HATA is closely related to memory function [51], and previous studies have reported a significant volume decrease in HATA in participants with cognitive impairment, and the size of the HATA was positively correlated with the score on the Montreal Cognitive Assessment (MoCA) [52, 53]. The volume of the HATA was predictive of the transition from normal cognition to mild

cognitive impairment [53]. In addition, the HATA plays an important role in fear regulation, the underlying mechanism of situational learning and emotional memory [54]. These pieces of evidence suggested that HATA might be involved in emotional processing and cognitive function, potentially contributing to the pathophysiology of AN. Further research is needed to confirm this hypothesis.

As expected, AN patients had lower scores on the RSES and CSES compared to healthy norms, indicating a common AN symptom of body image dissatisfaction which is linked to low self-esteem. Focusing on self-esteem within cognitive-behavioral therapy (CBT) proves advantageous in tackling self-esteem issues and serves as a catalyst for transforming AN psychopathology [55]. AN patients also showed lower parental emotional warmth and paternal overinterfering, along with higher parental penalty and severity, favoritism, rejection and denial, and maternal overinterfering and overprotection compared to HCs, consistent with the previous studies [56]. Paternal rejection was predictive of drive for thinness, bulimia, and body dissatisfaction which aligns with its relevance to eating disorders [57]. Females perceive greater parental favoritism than males, which may be culturally influenced, such as in Chinese families where higher expectations are often placed on boys [58]. Furthermore, this study also observed that AN-associated GMV decrease in the right HATA was correlated with paternal penalty and severity, as well as maternal overinterference and overprotection. According to our intuition, higher parental penalty and severity in AN patients may indicate a more pronounced impact on brain, potentially correlating with a greater GMV decrease in the right HATA. However, it's noteworthy that counterintuitive network-behavioral relationships have been reported in multiple psychiatric disorders. Although the underlying mechanism remains unclear, it has been hypothesized that the brain might engage compensatory mechanisms in response to abnormal conditions [59]. Besides, this study represents an initial exploration of the link between hippocampal GMV and parental rearing style; prior research has indicated a connection between adverse environmental conditions, neurodevelopment, and mental disorders [60]. Therefore, we speculate that both the hippocampal structure and parental rearing style play roles in the pathophysiology of AN.

The present study has several limitations. First, the study focused exclusively on females, potentially limiting the generalizability of the findings to all individuals with AN. Secondly, some of our patients exhibited mild anxiety and depressive symptoms based on clinical assessment, which might have confounded our results. Nevertheless, it is important to note that this could also enhance the representativeness of our sample, reflecting the broader AN patient population [61]. Third, the sample size was relatively small, which might have led to insufficient statistical power. Fourth, the reliance on self-reported and retrospective measures for parental rearing style may introduce recall bias and subjective reporting inaccuracies. Finally, the lack of longitudinal follow-up prevented us from investigating changes in the hippocampus and amygdala subregions after treatment, such as weight restoration and nutritional improvement. Therefore, longitudinal follow-up studies with larger samples are warranted to elucidate whether the observed GMV abnormalities are the result of AN pathology or the consequence of underweight.

Conclusion

In conclusion, our findings highlight significant structural abnormalities in the amygdala and hippocampus subfields among patients with AN, alongside lower self-esteem scores and adverse parental rearing experiences. Notably, GMV in the right HATA correlated with paternal penalty and severity, as well as maternal overinterference and overprotection, which sheds light on their potential role in the pathophysiological mechanisms of AN. These results underscore the importance of addressing parental rearing styles as a potential therapeutic avenue to positively impact individuals with AN and further emphasize the intricate interplay between brain structure and psychosocial factors in the etiology of AN.

Abbreviations

AN	Anorexia nervosa
DALYS	disability-adjusted life-years
GMV	Grey matter volume
HS	hippocampal subfields
HCs	health controls
MRI	Magnetic resonance imaging
sMRI	structural MRI
BMI	Body mass index
CSES	Core Self-Evaluation Scale
RSES	Rosenberg Self-Esteem Scale
EMBU	Egna Minnen av Barndoms Uppfostran
TIV	Total intracranial volume
GC-ML-DG	granule cell layers of the dentate gyrus
ML	molecular layer
HATA	hippocampal-amygdala transition area
La	lateral
Ba	basal
AB	accessory basal
AAA	anterior amygdaloidarea
CeA	central
Me	medial
Co	cortical
CAT	corticoamygdaloid transition
SPSS	Statistical Package for the Social Sciences
MANCOVA	multivariate analysis of covariance
FDR	false discovery rate

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Author contributions
LZ, and YW designed this study. YW, LLZ, JM, and MOW conducted this study. YW and MX conducted data analysis. YW wrote the first draft of the paper, and LZ and MX critically revised the manuscript. All authors participated in the data collection, and made contributions to critical revision of the manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All participants and guardians (if younger than 18 years) were fully informed of the details and purpose of the study and provided written informed consent before their participation. The study was approved by the Ethics Committee of West China Hospital of Sichuan University and was conducted according to the Helsinki Declaration.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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