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Cortical morphological alterations in adolescents with major depression and non-suicidal self-injury

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ABSTRACT

Background: Non-suicidal self-injury (NSSI) involves repetitive self-harm without suicidal intent and is common among adolescents, often linked to major depressive disorder (MDD). NSSI can lead to physical harm, cognitive impairments, interpersonal issues, violent behavior, and increased risks of psychological disorders and suicide attempts later in life.

Methods: Voxel-based morphometry (VBM) and surface-based morphometry (SBM) were performed on 44 NSSI patients and 44 healthy controls (HCs). Differences in GMV, CT, and cortical complexity were compared using the two-sample *t*-tests and correlated with neuropsychological scales.

Results: NSSI patients exhibited significant GMV atrophy in multiple regions, including the left insula, left anterior cingulate cortex, left putamen, left middle frontal gyrus, and right superior frontal gyrus showing increased GMV in the cerebellum posterior lobe. NSSI patients had increased CT in multiple left hemisphere regions and decreased CT in the right middle frontal gyrus. Additionally, they exhibited reduced cortical complexity, including decreased SD in the right frontal gyrus, and lower GI in the left insula. There were no significant differences between the two groups in terms of fractal dimension (FD). NSSI patients showed negative correlation between the CT of the right middle frontal gyrus and the anger dimension of the BPAQ, as well as the SD of the right superior frontal gyrus and the hostility dimension of the BPAQ.

Conclusion: NSSI patients have significant structural changes in the insular cortex, prefrontal cortex, precentral and postcentral gyrus, temporal lobe, putamen, and anterior cingulate cortex, offering a morphological perspective on the pathophysiology of NSSI in MDD.

1. Introduction

Non-suicidal self-injury (NSSI) is defined as the deliberate, repetitive harm done to one's body without a contemplated suicide (Qu et al., 2023). Statistical data indicate that the prevalence rate in developing countries ranges from 11.5 % to 33.8 %, while the overall prevalence rate among Chinese secondary school students is 22.4 % (Jin et al., 2023; Mannekote Thippaiah et al., 2021). NSSI patients demonstrate several characteristic features, including behaviors such as intentional scratches, hitting hard objects with one's head, hitting oneself with fists or other hard objects, and intentional pinching. These behaviors are reported notably associated with childhood maltreatment (Xie et al., 2024). NSSI is prevalent among adolescents and is often associated with major depressive disorder (MDD) (Weissman et al., 2006), the incidence of depression in adolescents with NSSI behavior was relatively high (Niu et al., 2024). Apart from causing physical harm, NSSI is associated with a variety of adverse outcomes, including cognitive impairments, impaired interpersonal relationships, and violent behavior (Maciejewski et al., 2014; Richmond-Rakerd et al., 2019). NSSI in early adolescence may predict psychological disorders in later adolescence, such as depression,

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anxiety, and eating disorders (Mars et al., 2014; Wilkinson et al., 2018). Furthermore, NSSI is associated with suicidal ideation and suicide attempts among adolescents (Guan et al., 2012). It is estimated that individuals who engage in NSSI are several times more likely to attempt suicide compared to the general population (Iskric et al., 2020). The classification of non-suicidal self-injury (NSSI) subtypes is still a subject of ongoing research. Indicators for these subtypes include NSSI symptoms, personal characteristics, functions of NSSI, and psychological pain (Wang et al., 2024). The reasons behind adolescent NSSI are complex and not entirely understood, involving a multitude of factors including genetic, biological, psychological, physiological, social, and cultural influences (Hawton et al., 2012). Therefore, developing more targeted and effective prevention strategies may require the identification and validation of reliable biological risk markers for NSSI.

With the rapid development of neuroimaging, magnetic resonance imaging (MRI) has increasingly been used as a non-radiative and non-invasive technique to examine brain structure and function, especially among adolescents (Kim et al., 2021; Maza et al., 2023; Yeo et al., 2024; Zuidema et al., 2024). Functional MRI (fMRI) and structural MRI (sMRI) can be used to analyze the pathological connectivity of brain regions associated with depression and suicidal ideation as well as suicidal behavior (Nawaz et al., 2023). fMRI provides dynamic information on brain activity and enables analysis of functional connectivity between brain regions. Accurately delineating brain tissue anatomy and providing direct evidence of structural changes is essential for comprehending brain structure under pathological conditions, with structural MRI (sMRI) serving as an optimal modality. sMRI offers excellent spatial resolution, allowing for precise measurement of anatomical brain structures, such as gray matter volume, cortical thickness, and sulci and gyri. Compared to functional imaging, sMRI results are relatively stable and are less affected by short-term fluctuations in individual states.

Structural MRI studies primarily involve voxel-based morphometry (VBM) (Ashburner & Friston, 2000) and surface-based morphometry (SBM) (Dahnke et al., 2013), both techniques objectively illustrate structural changes in the central nervous system, offering new insights into the pathophysiological mechanisms, diagnosis, and prognosis of various diseases. VBM utilizes 3D T1-weighted structural images to quantitatively analyze gray matter volume (GMV) and white matter volume (WMV) on a voxel-by-voxel basis. This method is highly effective in detecting local variations in brain morphology. VBM has been widely used in the study of NSSI and MDD (Lee et al., 2023; Liu et al., 2024; Serra-Blasco et al., 2021; Wang et al., 2023). Although VBM can provide comprehensive measures of apparent gray matter density or volume, it cannot distinguish the geometric basis of cortical changes. SBM analysis relies on brain tissue segmentation and cortical reconstruction to calculate indices such as cortical thickness (CT), gyrification index (GI), fractal dimension (FD), and sulcal depth (SD) (Dahnke et al., 2013). The indicators obtained from SBM analysis quantify the morphological structure of gray matter, estimate various features of the cortical surface, and reflect the complexity and folding characteristics of the cortex. The combination of these two methods offers a broader scope of structural information, potentially revealing specific regional alterations related to NSSI behavior.

This study aimed to concurrently use VBM and SBM to analyze adolescents with MDD who exhibit NSSI behaviors. We measured and analyzed GMV, CT, and cortical complexity across the whole brain. Additionally, we correlated clinical scale scores with neuroimaging indices. We hypothesized that there were significant differences in gray matter volume, cortical thickness, and cortical complexity between NSSI patients and healthy adolescents, and these neuroimaging changes might be correlated with clinical scale scores.

2. Material and methods

2.1. Participants

Adolescents with MDD were consecutively recruited from the Department of Psychology and Sleep Medicine of the Second Affiliated Hospital of Anhui Medical University, China. Inclusion criteria: (1) possesses the ability and intelligence to comprehend and complete the questionnaires, (2) diagnosis of depressive disorder as per the DSM-V, (3) written informed consent from all participants or their legal guardians. Exclusion criteria: (1) study dropout, (2) adolescents with acute psychotic symptoms, acute suicidality, pervasive developmental or psychotic disorders, unstable medical illnesses, or those with a contraindication to MRI (e.g. claustrophobic, mental implants, history of brain injury), (3) history of organic brain disorders, (4) with other comorbidities. Healthy participants who had never engaged in NSSI and who had neither received a psychiatric diagnosis in their lifetime nor undergone psychiatric treatment were recruited through community recruitment. The study was approved by the Ethics Committee of Anhui Medical University and was conducted by the Declaration of Helsinki (study number: 83230422).

2.2. Clinical assessments

After obtaining informed consent, all participants were assessed by trained clinicians according to a comprehensive diagnostic protocol. We used the 17-item Hamilton Depression Rating Scale (HAMD) to assess the severity of depression in NSSI group and HCs (Hamilton, 1967). We assessed the severity of NSSI using the Clinician-Rated Severity of Non-Suicidal Self-Injury (CRSNSSI) (American Psychiatric Association and Association, 2013). The CRSNSSI evaluates NSSI behaviors over the past year on a 5-point scale: 0 (None), 1 (Subthreshold), 2 (Mild), 3 (Moderate), and 4 (Severe). “None” indicates fewer than 3 days of NSSI with no urge to self-injure again. “Subthreshold” refers to 2–4 days of NSSI or past NSSI on 5 or more days with urges to self-injure again. “Mild” describes 5–7 days of NSSI using a single method without requiring surgical treatment. “Moderate” includes 8–11 days of NSSI using a single method or 5–7 days using multiple methods, both without requiring surgical treatment. “Severe” involves NSSI requiring surgical treatment, or 12 or more days of NSSI using a single method, or 8 or more days using multiple methods. Additionally, we used the Adolescent Non-Suicidal Self-Injury Assessment Questionnaire (ANSAQ) to evaluate the number and primary methods of self-injury behaviors in patients over the past year (Yuhui et al., 2018). We also used the Buss-Perry Aggression Questionnaire (BPAQ) to measure levels of aggression, which may be closely related to NSSI. High levels of aggression, particularly inward-directed anger and hostility, can increase the risk of NSSI behaviors. As part of the BPAQ, 29 items have been divided into four subscales: Physical aggression, Verbal aggression, Anger, and Hostility. This questionnaire provides valuable insights into the aggression profiles that may contribute to self-injurious behavior (Buss and Perry, 1992). Clinical and demographic data are shown in Table 1.

2.3. MRI image acquisition

MRI scans were acquired utilizing a 3.0-Tesla MR system (Discovery GE750; GE Healthcare, Buckinghamshire, UK) equipped with an 8-channel head coil at the University of Science and Technology of China (USTC). To reduce scanner noise, earplugs were used, and comfortable foam padding was used to minimize head movement. A head-neck coil was used to acquire high-resolution T1-weighted images. The scanning parameters were as follows: repetition time = 8.16 ms, echo time = 3.18 ms, inversion time = 450 ms, flip angle = 12°, field of view = 256 × 256 mm^2, slice thickness = 1 mm, voxel size = 1 × 1 × 1 mm^3, and number of sections = 188. All scanned images were verified by more than two experimenters to confirm that the whole brain area, including the

Table 1
Demographic and clinical measurements of NSSI patients and HCs.

Characteristic	NSSI (n = 44)	HCs (n = 44)	Statistics	*p*-value
Age (years)	16 (15, 17)	16.5 (15.25, 17.75)	$z = -0.78$[a]	0.44
Gender (male/female)	9/35	16/28	$\chi 2 = 2.74$[b]	0.10
Education level (years)	10 (9, 11)	11 (10, 11)	$z = -1.69$[a]	0.09
HAMD	24.05±6.41	1 (0, 3)	$z = 8.08$[a]	< 0.001
CRSNSSI	2 (2, 3)	0 (0, 0)	$z = 8.08$[a]	< 0.001
BPAQ	32			
Physical aggression	43.9±21.74	17.86 (7.14, 28.57)	$z = 5.12$[a]	< 0.001
Verbal aggression	43.41 ±24.75	22.84±11.58	$t = 4.99$[c]	< 0.001
Anger	59.5±22.31	20.83 (8.33, 33.33)	$z = 6.57$[a]	< 0.001
Hostility	60.15 ±21.26	23.46±15.26	$t = 9.30$[c]	< 0.001
NSSI frequency				
1–5 acts	1	NA	NA	NA
6–10 acts	2	NA	NA	NA
11–20 acts	11	NA	NA	NA
21^{+}	30	NA	NA	NA
NSSI ways		NA	NA	NA
Cutting	34	NA	NA	NA
Interfere with wound	43	NA	NA	NA
Severe scratching	17	NA	NA	NA
Hair pulling	39	NA	NA	NA
Bagging/hitting self	31	NA	NA	NA

Note: Data are presented as mean ± SD or median (Q1, Q3). [a]Mann-Whitney *U*-tests, [b]Pearson chi-squared test, [c]two-sample *t*-test. Abbreviations: HAMD, Hamilton rating scale of depression; CRSNSSI, Clinician-Rated Severity of Non-Suicidal Self-Injury; BPAQ, Buss-Perry Aggression Questionnaire; NA, not applicable.

cerebellum, was covered during the scanning.

2.4. VBM and SBM analysis

Data preprocessing was conducted through several steps: (1) MRI images were converted from DICOM format to NIFTI format using MRIcro software. (2) The CAT12 toolbox (Computational Anatomy Toolbox) within SPM12 (*https://www.fil.ion.ucl.ac.uk/spm/software/spm12/*) on MATLAB 2013b was utilized to process MRI images from both NSSI and HC participants. By analyzing images and normalizing them in standard space, we produced relative volume maps of gray matter, white matter, and cerebrospinal fluid using the diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) algorithm (Ashburner and Friston, 2000). In addition, SBM analysis was conducted using segmentation, cortical reconstruction, topology correction, spherical registration, and spatial normalization using the DARTEL algorithm, generating left- and right-sided central surface representations (Dahnke et al., 2013). CT was estimated by calculating the distance between the pial and white matter surfaces by means of a projection-based methodology. (3) Visual inspection and SPM data quality checks were conducted on the acquired images. (4) Using the "Surface tool" within CAT12, we extracted measures of GI, FD, and SD from the central surfaces of the right and left hemispheres. (5) The images were smoothed using an 8 mm Gaussian kernel for GMV, a 15 mm Gaussian kernel for CT, and a 20 mm Gaussian kernel for GI, FD, and SD. The smoothed images were used for statistical analysis.

2.5. Statistical analysis

A two-sample *t*-test was used for normally distributed data and a Mann-Whitney *U* test for non-normally distributed data, in order to compare the demographics and clinical characteristics of NSSI patients and HCs. Chi-squared test was used to analyze gender differences. SPSS 23.0 software package (SPSSInc., Chicago, III., USA) was used to perform these statistical analyses.

To determine structural differences in VBM image data, a two-sample *t*-test was conducted on the normalized gray matter images using SPM12. Age, sex, and total intracranial volume were included as covariates in the analysis. Statistical significance for group differences was set at $p < 0.05$, corrected for multiple comparisons using cluster-level family-wise error (FWE) correction.

For SBM image data, a two-sample *t*-test was conducted to analyze cortical differences between groups for CT, FD, GI, and SD indicators, with age and gender included as covariates. The resulting spmT maps were further compared and calibrated using CAT12. Based on the cluster-level FWE method, multiple comparisons were corrected resulting in a cluster-defining threshold of $p = 0.001$ and a corrected cluster significance of $p < 0.05$.

We defined regions of interest (ROIs) for those brain regions that showed significant differences between the groups in the VBM and SBM analyses. A correlation analysis was conducted between GMV, CT, and cortical complexity indices in these ROIs and neuropsychological scale scores in patients with NSSI. Those variables that conformed to a normal distribution were analyzed using Pearson correlation analysis, and those that did not conform to a normal distribution were analyzed using Spearman correlation analysis. Multiple comparisons were corrected using the Bonferroni method, with significance set at $p < 0.05$.

3. Results

3.1. Demographic and clinical characteristics

Table 1 presents demographic and clinical information on NSSI patients and HCs. Neither NSSI nor HC groups differed significantly in age, gender, or education (all $p > 0.05$). The HAMD ($z = 8.08$, $p < 0.001$, Cohen's $d = 4.65$) and CRSNSSI ($z = 8.08$, $p < 0.001$, Cohen's $d = 5.53$) scores in the NSSI group were significantly higher than those in the HCs. Further, the NSSI group showed higher scores on all subscales of the BPAQ than the HCs (all $p < 0.001$). The medication usage for each patient has been meticulously documented in Supplementary Table S1.

3.2. VBM analysis

Compared with HCs, NSSI patients exhibited reduced GMV in multiple brain regions. In particular, significant reductions in GMV were observed in the left insula gyrus, left anterior cingulate cortex, left putamen, and left middle frontal gyrus. A significant increase in GMV was also observed in the posterior lobe of the cerebellum in NSSI patients as compared to HCs (all $p < 0.05$, FWE-corrected). Further cluster details are presented in Table 2 and illustrated in Fig. 1.

3.3. SBM analysis

In comparison to HCs, NSSI patients exhibited significantly increased CT in the left superior temporal gyrus, left transverse temporal gyrus, left postcentral gyrus, left precentral gyrus, and left pars opercularis, while the CT in the right middle frontal gyrus was significantly decreased (all $p < 0.05$, FWE-corrected, Table 3 and Fig. 2a). In the cortical complexity analysis, the NSSI group exhibited significantly reduced SD in the right superior frontal gyrus and rostral middle frontal gyrus compared to the HC group ($p < 0.05$, FWE-corrected, Table 4 and Fig. 2b). Additionally, the NSSI group showed a significantly lower GI in the left insula compared to the HC group ($p < 0.05$, FWE-corrected, Table 5 and Fig. 2c). No significant differences in FD were observed between the two groups ($p > 0.05$, FWE-corrected).

Table 2
Differences in GMV between NSSI patients and HCs.

Clusters	Brain regions	Cluster size	MNI (X, Y, Z) mm	Peak *t* value	*p*-value (FWE-corrected)
NSSI > HCs					
Cluster 1	Cerebellum posterior lobe (L)	1335	−18, −82, −42	5.3477	0.004
NSSI < HCs					
Cluster 1	Insula gyrus (L)	10,126	−30, 12, −9	−5.5775	< 0.001
	Anterior cingulate cortex (L)				
	Putamen (L)				
Cluster 2	Middle frontal gyrus (L)	1905	−38, 58, −6	−8.5764	0.001
Cluster 3	Superior frontal gyrus (R)	941	32, 62, 8	−4.9387	0.017

Abbreviations: MNI, Montreal Neurological Institute. (X, Y, Z), locations of the primary peaks in the MNI space; FWE, family-wise error; L, left; R, right.

3.4. Correlation analysis

In the correlation analysis, we found that the CT of the right middle frontal gyrus in NSSI patients was negatively correlated with the anger dimension of the BPAQ (r = -0.403, p = 0.007, uncorrected, Fig. 3a). Simultaneously, the SD of the right superior frontal gyrus was negatively correlated with the hostility dimension of the BPAQ (r = -0.422, p = 0.004, uncorrected, Fig. 3b). However, after correcting for multiple comparisons, any significant correlation between ROI-based mean imaging values and clinical scores was not observed (all $p > 0.05$, Bonferroni corrected).

4. Discussion

Our study utilized SBM and VBM methods to systematically investigate the differences in GMV, CT, and cortical complexity between NSSI patients and HCs. The study found that the NSSI group had significantly higher scores in depression, self-injury, and aggression compared to the HC group. Whole-brain GMV analysis revealed extensive GMV reductions in the NSSI group, primarily in the left insula, left anterior cingulate cortex, left putamen, left middle frontal gyrus, and right superior frontal gyrus. In contrast, the NSSI group showed significantly higher GMV in the cerebellum posterior lobe than the HC group. Furthermore, analysis of CT and cortical complexity showed that the NSSI group had significantly increased CT in the left superior temporal gyrus, left transverse temporal gyrus, left postcentral gyrus, left precentral gyrus, and left pars opercularis compared to the HC group, whereas CT was significantly reduced in the right middle frontal gyrus. Additionally, the NSSI group exhibited significantly lower SD in the right superior frontal gyrus and a lower GI in the left insula compared to the HC group. Based on these findings, we may be able to gain a greater understanding of the underlying mechanisms of NSSI.

Current research has mainly focused on gray matter volume changes in adolescents with depression and NSSI (Yi et al., 2024; Ando et al., 2018), while the aspect of cortical complexity remains largely overlooked. Our study provides a significant advancement by analyzing brain structural features in NSSI individuals, specifically investigating the interrelationships among CT, GMV, and cortical complexity. Unlike prior studies that primarily addressed overall or regional atrophy, we uniquely report an increase in CT across multiple regions of the left hemisphere, a finding that is relatively rare in the literature. Additionally, we found a notable negative correlation between reduced CT in the right middle frontal gyrus and the dimension of anger. This insight highlights the potential role of structural changes in the cortex in emotional regulation and self-injurious behaviors, suggesting that such alterations may contribute to the emotional dysregulation frequently observed in NSSI patients.

We found widespread GMV reductions in NSSI patients, primarily located in the left insula, left anterior cingulate cortex, left putamen, left middle frontal gyrus, and right superior frontal gyrus. As an important center for the integration of sensory information from both internal and external sources, the insula cortex establishes extensive connections with various cortical and subcortical regions. This integrative function is crucial for the regulation of sensory, emotional, motivational, and cognitive functions (Craig, 2009; Menon and Uddin, 2010). Given that the insula cortex is an essential emotional center in the brain, damage to the insula cortex directly leads to abnormalities in emotional regulation. Prefrontal cortex contains both the middle and superior frontal gyri. The prefrontal cortex is primarily responsible for higher cognitive functions. Damage or dysfunction in this area can lead to a range of cognitive and behavioral issues, such as poor impulse control, difficulty in decision-making, and abnormal social behavior (Miller, 2000). Several studies have found that NSSI patients exhibit functional abnormalities in the prefrontal cortex, and these abnormalities are closely related to self-injurious behavior (Guo et al., 2024; Koenig et al., 2021). Therefore, we hypothesize that structural damage to the prefrontal cortex may lead to functional abnormalities. As part of the striatum, the putamen is involved in motor control, emotion regulation, and cognitive functions. Previous studies have identified a reduction in the GMV of the putamen in NSSI patients, which is associated with the external emotional regulation of performing NSSI (Wang et al., 2022). These findings are consistent with our research results. The anterior cingulate cortex (ACC) has been identified as an important brain region involved in depression (Rolls et al., 2019; Wu et al., 2022). Due to its location, the ACC is interconnected with both the remaining limbic system structures and the

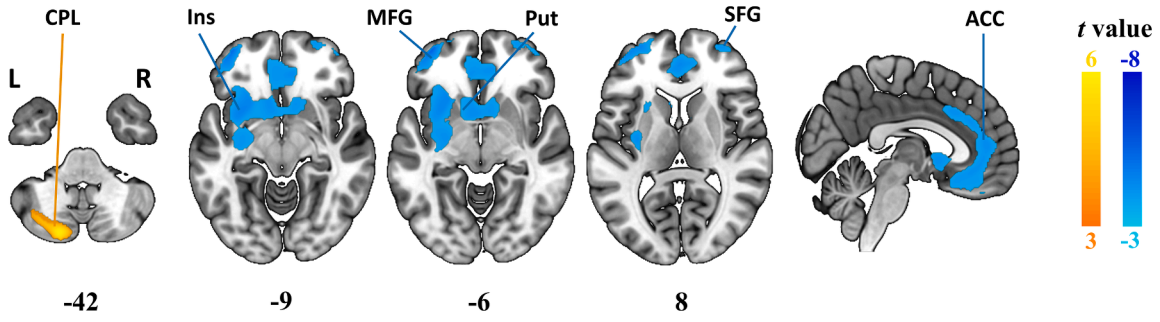

Fig. 1. Results of VBM analyses using two-sample *t*-tests between the NSSI and HCs ($p < 0.05$, cluster-level FWE correction). The GMV in certain brain regions differs significantly between the NSSI and the HCs. The color bar represents the *t*-values from the between-group analysis. Warm color indicates higher GMV in the NSSI group compared to the HCs, while cool color indicates lower GMV in the NSSI group compared to the HCs. Abbreviations: CPL, cerebellum posterior lobe; Ins, insula; MFG, middle frontal gyrus; Put, putamen; SFG, superior frontal gyrus; ACC, anterior cingulate cortex; L, left; R, right.

Table 3
Differences in CT between NSSI patients and HCs.

Clusters	Overlap of DK atlas region	Cluster size	MNI (X, Y, Z) mm	Peak *t* value	*p*-value (FWE-corrected)
NSSI > HCs					
Cluster 1	73 % superior temporal (L) 27 % transverse temporal (L)	1397	−55, 40, −8	4.6	0.00001
Cluster 2	70 % postcentral (L) 30 % precentral (L)	835	−60, 31, 6	5.0	< 0.0001
Cluster 3	76 % pars opercularis (L) 24 % precentral (L)	817	−37, 47, 2	3.8	0.00013
NSSI < HCs					
Cluster 1	52 % caudal middle frontal (R) 48 % rostral middle frontal (R)	1418	39, 44, 33	−5.4	< 0.0001

Note: Atlas labeling was conducted using the Desikan-Killiany atlas.
Abbreviations: CT, cortical thickness; MNI, Montreal Neurological Institute. (X, Y, Z), locations of the primary peaks in the MNI space; DK, Desikan–Killiany; L, left; R, right.

Table 4
Differences in SD between NSSI patients and HCs.

Clusters	Overlap of DK atlas region	Cluster size	MNI (X, Y, Z) mm	Peak *t* value	*p*-value (FWE-corrected)
NSSI < HCs					
Cluster 1	79 % superior frontal (R) 21 % rostral middle frontal (R)	956	18, 78, 17	−4.9	< 0.0001

Note: Atlas labeling was conducted using the Desikan-Killiany atlas.
Abbreviations: SD, sulcus depth; MNI, Montreal Neurological Institute. (X, Y, Z), locations of the primary peaks in the MNI space; DK, Desikan–Killiany; R, right.

Table 5
Differences in GI between NSSI patients and HCs.

Clusters	Overlap of DK atlas region	Cluster size	MNI (X, Y, Z) mm	Peak *t* value	*p*-value (FWE-corrected)
NSSI < HCs					
Cluster 1	100 % insula (L)	1192	−36, 37, −15	−5.0	< 0.0001

Note: Atlas labeling was conducted using the Desikan-Killiany atlas.
Abbreviations: GI, gyrification index; MNI, Montreal Neurological Institute; (X, Y, Z), locations of the primary peaks in the MNI space; DK, Desikan–Killiany; L, left.

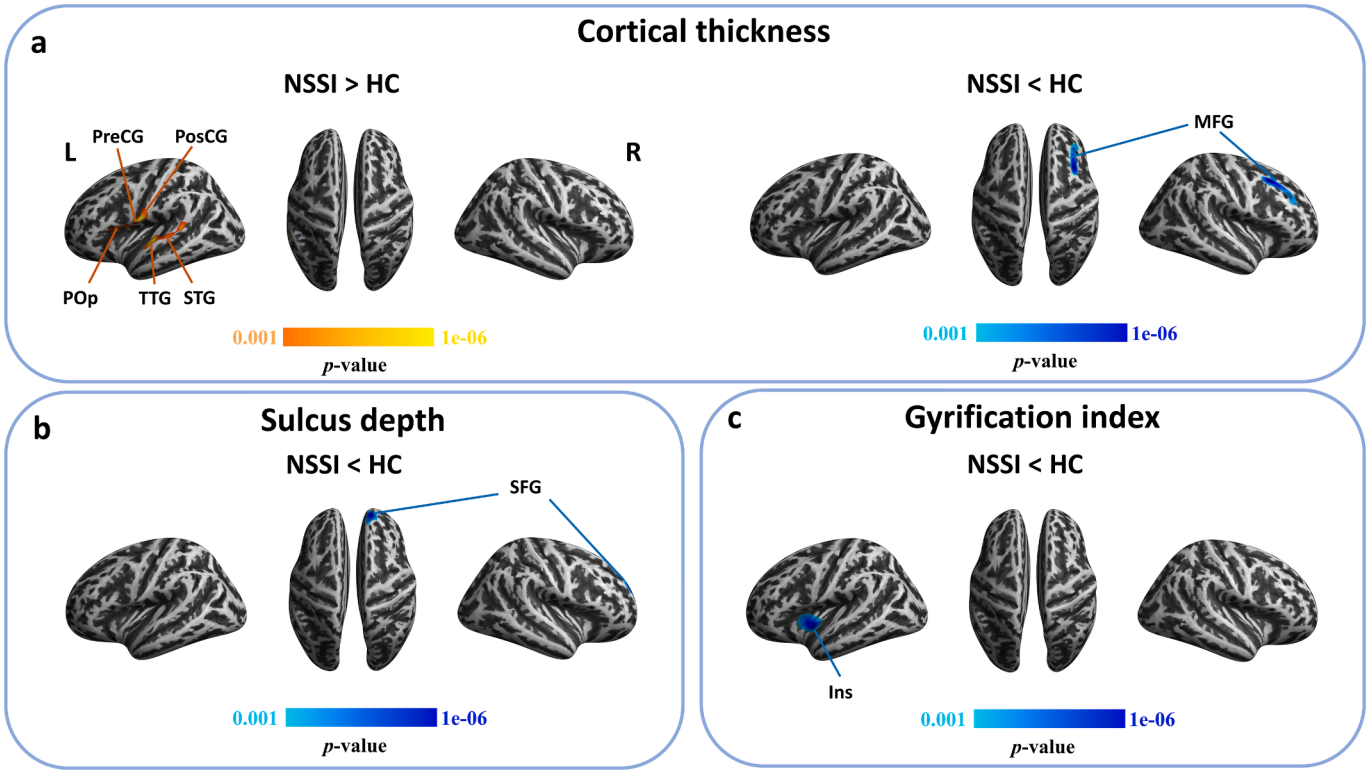

Fig. 2. Results of SBM analyses using two-sample *t*-tests between the NSSI and HC groups ($p < 0.05$, cluster-level FWE correction) revealed significant differences in brain regions. Specifically, (a) significant differences in CT were observed between the NSSI and HCs, (b) significant differences in SD were found between the groups, and (c) significant differences in the GI were noted. The color bar represents the *p*-values from the between-group analysis, where warm colors indicate higher CT in the NSSI group compared to the HCs, while cool colors indicate lower CT, SD, or GI in the NSSI group compared to the HCs. Abbreviations: Pop, pars opercularis; PreCG, precentral gyrus; PosCG, postcentral gyrus; TTG, transverse temporal gyrus; STG, superior temporal gyrus; MFG, middle frontal gyrus; SFG, superior frontal gyrus; Ins, insula.

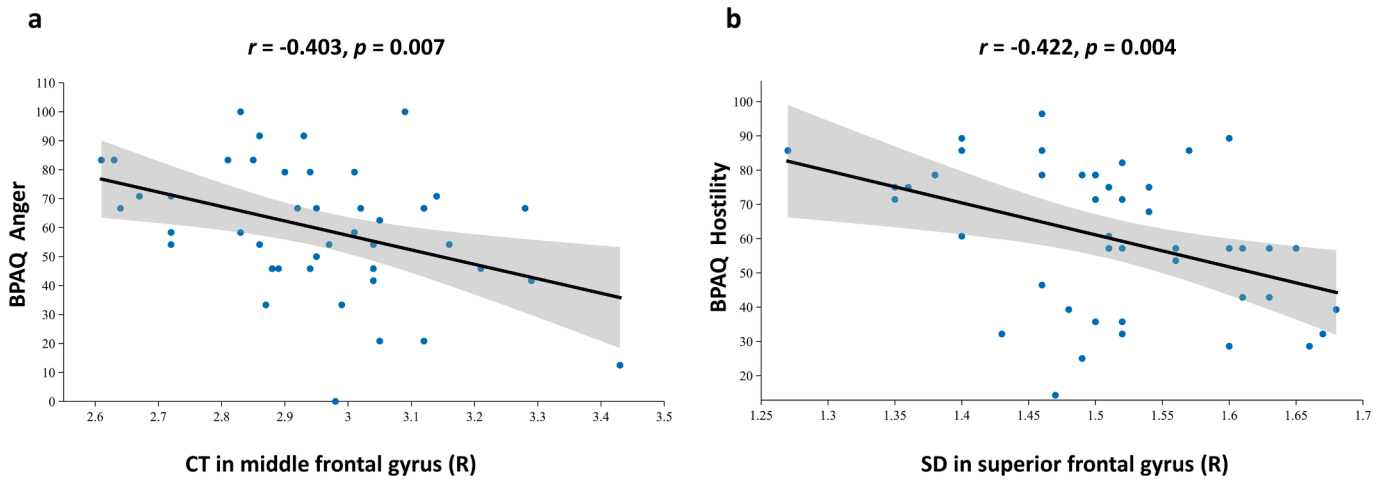

Fig. 3. Analysis results of the correlation between clinical scale scores and morphological indicators. (a) Scatter plot of CT in right middle frontal gyrus negatively associated with the BPAQ Anger score. (b) Scatter plot of SD in right superior frontal gyrus negatively associated with the BPAQ Hostility score. The reported results are not adjusted for multiple comparisons. After Bonferroni correction, all p-values > 0.05.

prefrontal and frontal cortex areas involved in decision-making. These connections have been linked to various psychological issues, including antisocial behavior, violence, and suicidal tendencies (Stevens, Hurley, & Taber, 2011; Wagner et al., 2012). A task-based functional MRI study found that, compared to controls, individuals with NSSI exhibited significantly stronger brain responses in the anterior cingulate cortex when viewing emotional images (Plener et al., 2012). Structural damage to the anterior cingulate cortex may lead to abnormalities in emotional regulation and self-injurious behavior. Additionally, we found increased GMV in the cerebellum posterior lobe in the NSSI group. The cerebellum posterior lobe plays a crucial role in emotion processing and regulation, influencing emotional and motivational states through its connections with the limbic system and prefrontal cortex (Rudolph et al., 2023). According to Kang and colleagues, the cerebellum-center function network is more important than other factors in predicting NSSI behavior in MDD patients, indicating that cerebellar circuits may play a crucial role in NSSI (Kang et al., 2022). The increase in GMV in the cerebellum posterior lobe may therefore indicate a compensatory mechanism. Nevertheless, GMV changes are only one aspect of gray matter alterations, and examining density and other variables can contribute to a greater understanding of gray matter changes. MDD patients have variable cerebellum posterior lobe GMV, but it is unclear whether this reflects compensatory adaptations or a causal deficit leading to NSSI.

CT undergoes dynamic changes throughout life due to normal development and disease processes (Frangou et al., 2022; Messina et al., 2013). Changes in CT are closely related to cell number; studies on the cortical surfaces of four different animals show that thinner regions contain fewer glial cells (Carlo & Stevens, 2013). According to a study of gene expression data and 3D-T1 brain images of 45 NSSI adolescents, the CT differences between the two groups were related to differences in the morphogenesis of astrocytes and excitatory neurons (Cai et al., 2023). In the SBM analysis, NSSI patients exhibited significantly increased CT in the left superior temporal gyrus, left transverse temporal gyrus, left postcentral gyrus, left precentral gyrus, and left pars opercularis compared to healthy controls. These regions may have abnormal neuron density or glial cell proliferation increases, though these hypotheses require further experimental validation. Recent studies have identified structural and functional changes in the temporal lobe associated with NSSI. Firstly, abnormal GMV in the superior temporal gyrus can help predict NSSI behavior in MDD (Kang et al., 2022). Additionally, MDD patients with NSSI behavior exhibit weaker regional homogeneity (ReHo) activity in the transverse temporal gyrus compared to those without NSSI behavior (Huang et al., 2024). Finally, the temporal lobe function in NSSI patients is overly active during self-referential processing (Nam et al., 2022). In summary, our study demonstrates structural abnormalities in the temporal lobe associated with NSSI. Previous research found that adolescents engaging in NSSI showed lower participation and gateway coefficients in pars opercularis. The frequency of NSSI and the number of previous suicide attempts were associated with lower integration and efficiency of the pars opercularis resting-state functional connectivity (RSFC) and higher clustering in the frontal networks (Mürner-Lavanchy et al., 2021). In this study, we found abnormal CT in the left pars opercularis, which may serve as the structural basis for the observed abnormalities in pars opercularis RSFC. In CT analysis, we also found increased CT in the precentral and postcentral gyrus. The precentral gyrus, primarily responsible for motor control, shows functional and structural abnormalities in NSSI patients, which may be related to impulsivity and increase the risk of self-harm (Yan et al., 2022). The postcentral gyrus, which processes tactile information, exhibits functional abnormalities in NSSI individuals, potentially affecting their pain perception and processing. Some studies have found that NSSI individuals may respond differently to pain compared to healthy individuals, likely due to these functional abnormalities in the postcentral gyrus (Li et al., 2022). This study also found that the right middle frontal gyrus CT was reduced in the NSSI group and negatively correlated with anger scores on the BPAQ. The middle frontal gyrus serves multiple functions, including emotion regulation, attention, memory, and executive functions (Ohira et al., 2006). Previous research has shown that changes in the CT of the middle frontal gyrus are associated with symptoms of MDD in adolescents (Reynolds et al., 2014). Therefore, structural deficits in the middle frontal gyrus may lead to functional abnormalities, impacting emotion regulation and cognitive functions. This makes it more difficult for patients to regulate their emotions and process information such as language in social activities, which may contribute to the motivation behind self-injurious behavior in adolescent MDD patients.

SBM analyses confirmed that the SD in the right superior frontal gyrus was significantly reduced in the NSSI group compared to the HC group, and it showed a negative correlation trend with the hostility scores on the BPAQ scale. The superior frontal gyrus is situated at the upper part of the prefrontal cortex and encompasses several cytoarchitecturally distinct subregions, including Brodmann areas (BAs) 4, 6, 8, 9, and 32 (Li et al., 2013). Research has shown that the SFG plays a crucial role in regulating emotional responses by processing emotion-related information and working in coordination with other brain regions such as the amygdala and anterior cingulate cortex (Etkin et al., 2015). Additionally, the superior frontal gyrus is part of the executive function

network, which encompasses attention, working memory, and decision-making processes, helping individuals stay focused and respond appropriately to complex tasks (Miller, 2000). Seok and colleagues discovered structural defects in the right superior frontal gyrus of adolescents with severe irritability, which may be related to its role in inhibitory control (Seok et al., 2021). Therefore, damage to the superior frontal gyrus may lead to abnormalities in emotion regulation and inhibitory control. SD is an important indicator of cortical complexity, closely associated with brain function and structural intricacy (Deng et al., 2014). During individual development, SD increases, particularly during childhood and adolescence, correlating with cortical thickening and the complexity of neural networks (Sowell et al., 2004). The reduction in SD might result from the contraction of local gyri or could be a consequence of overall tissue changes or contractions in distant regions. Abnormal cortical folding may lead to functional abnormalities in the associated sulci. Therefore, we speculate that the reduction in SD in NSSI may lead to abnormalities in emotional processing and impairments in executive control functions.

Based on SBM analyses, the GI of the left insula cortex was significantly lower in the NSSI group than in the HC group. GI refers to the amount of cortex that is buried within the sulcal folds, compared to how much cortex is visible on the outer surface. In contrast, a low GI indicates a limited amount of cortical folding. Based on the tension-based theory of cortical morphogenesis, a decreased GI implies a decrease in deep white matter fibers, as tension along the axons in white matter refers to cortical folding (Luders et al., 2006). Consequently, we speculate that the reduction in GI of the insula is due to damage to deep white matter fibers, which may result in abnormal emotional information processing and depressive symptoms in patients with NSSI.

Lastly, current research reports indicate that patients with MDD typically exhibit abnormalities in gray matter volume and cortical thickness, particularly atrophy in regions such as the left insula and anterior cingulate cortex (Sambataro et al., 2018, Webb et al., 2018). The specific changes observed in certain brain regions in our study, such as the increase in gray matter volume in the posterior cerebellum, are significantly correlated with emotional dimensions like anger and hostility. These findings are not commonly reported in studies focused solely on MDD, suggesting that these alterations may be linked to the unique emotional regulation challenges faced by individuals with NSSI. Therefore, we plan to recruit a sufficient number of participants with MDD without NSSI behavior for further investigation into cortical morphological alterations in adolescents.

5. Conclusion

In conclusion, our study demonstrates that NSSI patients exhibit extensive cortical structural changes in multiple brain regions, including the insular cortex, prefrontal cortex, precentral gyrus, postcentral gyrus, temporal lobe, putamen, and anterior cingulate cortex. These findings not only provide a crucial morphological perspective for understanding the pathophysiological mechanisms underlying NSSI in MDD but also offer new directions for future intervention and treatment strategies. In future research, we aim to investigate the associations between brain structural changes and emotional dimensions in NSSI patients, utilizing larger sample sizes and longitudinal studies to understand the dynamics of emotional regulation. Additionally, integrating multimodal neuroimaging with behavioral indicators may enhance insights into emotional regulation mechanisms and aid in developing personalized interventions.

6. Limitations

There are a few limitations to be noted. First, the sample size in this study is relatively moderate, which might introduce bias into our results. Larger sample sizes are necessary to validate the reproducibility of the VBM and SBM findings. Second, the current results may be confounded by factors such as medication use. Future studies should aim to recruit more drug-naive first-episode NSSI patients to address this issue. Third, our study did not include participants with MDD without NSSI behavior. Including such participants would help distinguish between pure MDD and self-injurious behavior. Future research should aim to recruit more adolescents with MDD alone.

7. Statement of ethics

Participants in the study gave their written informed consent before participating. Under the approval number [83230422], the protocol for the study was approved by the Research Ethics Committee at Anhui Medical University (AHMU).

CRediT authorship contribution statement

Xiaonan Pang: Writing – original draft, Methodology, Investigation. **Dongpeng Wu:** Writing – original draft, Methodology, Investigation. **Hongping Wang:** Writing – original draft, Methodology, Investigation, Conceptualization. **Jiahua Zhang:** Resources, Investigation, Conceptualization. **Yue Yu:** Investigation, Conceptualization. **Yue Zhao:** Investigation, Conceptualization. **Qianqian Li:** Investigation, Conceptualization. **Liangping Ni:** Investigation, Conceptualization. **Kai Wang:** Supervision, Project administration, Conceptualization. **Dai Zhang:** Writing – review & editing, Investigation, Formal analysis, Data curation, Conceptualization. **Yanghua Tian:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Data curation, Conceptualization.

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Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2024.103701.

Data availability

Data will be made available on request.

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