Journal of Psychiatric Research 184 (2025) 17–26

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Altered brain structure and function correlate with non-suicidal self-injury in children and adolescents with transdiagnostic psychiatric disorders

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ARTICLE INFO

Keywords:
Non-suicidal self-injury
Children and adolescents
Brain alterations
Transdiagnostic psychiatric disorders

ABSTRACT

Non-suicidal self-injury (NSSI) is a prevalent mental problem among children and adolescents, cutting across psychiatric disorders. Studies in specific disorders such as depression and ADHD have revealed associations with alterations in brain regions responsible for reward processing and emotion regulation. However, it remains largely unknown whether such associations are shared among different disorders. Here, we aimed to examine brain structural and functional associations with NSSI in a transdiagnostic psychiatric cohort of children and adolescents. A total of 386 patients (age = 10.72 ± 3.53, range = 5.04 to 21.22) diagnosed primarily with ADHD, autism and generalized anxiety disorder from the Healthy Brain Network study were included. Using linear regression models, we examined brain volumes (N = 386) and functional connectivities (N = 277) associated with NSSI and whether potential alterations could moderate/mediate the links between internalizing/externalizing symptoms and NSSI. We found that increased severity of NSSI was associated with decreased bilateral putamen volumes, and reduced connectivities of the left putamen with bilateral regions of temporoparietal junction and of the right putamen with the left temporoparietal junction, demonstrating the role of putamen in NSSI behavior. Moreover, some of these associations played moderating roles: in patients with lower putamen volumes or weaker functional connectivities, increased internalizing/externalizing symptoms were associated with higher NSSI severity. Our findings suggest that transdiagnostic NSSI is linked to structural alterations and functional dysfunctions in putamen, highlighting that putamen may serve as a neural marker of NSSI and as a potential target for neuromodulation treatments across mental conditions.

1. Introduction

Non-suicidal self-injury (NSSI) refers to deliberate, self-inflicted harm to one's body without suicidal intention. It includes behaviors such as cutting, burning, hitting, and scratching (Wang et al., 2022b). Repetition is a distinctive feature of NSSI behavior. A recent large-scale clinical study reported that individuals hospitalized for initial self-harm faced the highest risk of both subsequent repeat self-harm and suicide (Qian et al., 2023). Compared to occasional NSSI, repetitive NSSI occurs at a higher frequency and exhibits stronger addictive tendencies. NSSI typically begins around preschool age (Luby et al., 2019) and shows a significant increasing trend during early adolescence. It reaches a peak during middle to late adolescence and often persists into early adulthood (Andover, 2014; Hankin and Abela, 2011). Recent reports have indicated a global prevalence of NSSI of 19.4% in the general population (Lim et al., 2019). Among children and adolescents, the prevalence was 17.2% worldwide and up to 50% among those with psychiatric disorders (Plener et al., 2018). NSSI was particularly prominent in borderline personality disorder (Chapman et al., 2005) and also presented in other disorders such as attention deficit hyperactivity disorder (ADHD), depression, anxiety, and autism spectrum disorders (Bentley et al., 2014; Swanson et al., 2014). The frequency of NSSI has been found to be closely associated with ADHD, anxiety, and depression (Bentley et al., 2015; Patel et al., 2021), highlighting the transdiagnostic nature of NSSI. A comprehensive understanding of NSSI-related brain mechanisms necessitates the inclusion of transdiagnostic cohorts.

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https://doi.org/10.1016/j.jpsychires.2025.02.051
Received 6 October 2023; Received in revised form 25 January 2025; Accepted 27 February 2025
Available online 27 February 2025

At the neurobiological level, NSSI was found to be associated with deficits in brain regions involved in reward processing and emotion regulation (Branas et al., 2021; Hepp et al., 2020; Plener et al., 2012). Once engaged in NSSI behavior, patients may frequently harm themselves to achieve emotional regulation, which may, in turn, contribute to a higher likelihood of addiction (Wang et al., 2022a). Adolescents who engaged in NSSI showed reduced gray matter volume in reward-related brain regions, such as the ventral prefrontal cortex, orbitofrontal cortices, striatum, and amygdala (Ando et al., 2018; Auerbach et al., 2021; Beauchaine et al., 2019; Branas et al., 2021). Previous fMRI studies using reward tasks, such as the monetary incentive delay task, also found altered activation in the putamen and orbitofrontal cortex in adolescents with NSSI, when compared to non-NSSI controls (Poon et al., 2019; Sauder et al., 2016; Vega et al., 2018). Moreover, lower activation in the putamen, amygdala, and frontal regions (Mayo et al., 2021; Poon et al., 2019; Reitz et al., 2015) may contribute to more NSSI thoughts (Poon et al., 2019). Concurrently, studies of functional connectivity during resting-state and task fMRI reported alterations in frontal-limbic networks in individuals with NSSI (Reitz et al., 2015; Santamarina-Perez et al., 2019; Vega et al., 2018; Westlund Schreiner et al., 2017). Together, these studies demonstrated specific brain structural and functional alterations associated with NSSI and highlighted the role of reward- and emotion-related brain circuits.

At the behavioral level, NSSI was closely related to both internalizing and externalizing problems. The prevalence of NSSI behavior increased when adolescents experienced these issues (Mancinelli et al., 2022). Prior research has revealed strong associations between NSSI and internalizing problems, particularly difficulties with emotion regulation (Wolff et al., 2019). These difficulties may lead individuals to resort to NSSI as a maladaptive strategy for managing their emotions (Yang et al., 2022). Regarding externalizing problems, the relationships with NSSI may be bidirectional: individuals with NSSI were more prone to externalizing problems, and those with externalizing problems were also more likely to exhibit NSSI (Meszaros et al., 2017; Victor and Klonsky, 2014). Importantly, both internalizing and externalizing problems reflected disruptions in brain regions involved in reward processing and emotion regulation. Depression and anxiety have consistently been associated with abnormalities in fronto-striatal circuits (Auerbach et al., 2022; Ng et al., 2019). Additionally, externalizing symptoms in ADHD were also related to changes in the reward system (Hoogman et al., 2017; Plichta and Scheres, 2014). These findings suggest that internalizing and externalizing problems might promote NSSI behavior, and the shared brain alterations related to reward processing and emotion regulation might explain the underlying processes connecting NSSI behavior with these problems.

Although many neuroimaging studies on NSSI in children and adolescents were available, they suffered from at least one of two shortcomings that we aimed to address in the present study. Most previous studies have primarily focused on specific psychiatric disorders and/or were conducted with small sample sizes (Auerbach et al., 2021; Lai et al., 2021; Wang et al., 2022a). Considering the similarities in brain structural and functional abnormalities across different psychiatric diagnoses (Li et al., 2022; Opel et al., 2020; Vanes and Dolan, 2021), the brain correlates of NSSI may manifest at a transdiagnostic level, which is very important for the design of future brain-based interventions with greater generalizability. Additionally, sample sizes in previous studies have been relatively small, ranging from 9 to 168 participants (Case et al., 2021; Osuch et al., 2014; Plener et al., 2012; Schreiner et al., 2017). The transdiagnostic similarities or differences identified previously may therefore not be true. Accordingly, a large sample with transdiagnostic psychiatric disorders would be ideal to identify generalizable neurological features of NSSI, thus revealing possible common neural circuits and pathogenesis that cut across disorders (Vanes and Dolan, 2021).

To sum up, we aimed to identify the associations of NSSI behavior with brain structure and functional connectivity in a transdiagnostic cohort of children and adolescents. Voxel-based morphometry analysis was utilized to investigate brain structural alterations associated with NSSI severity. The functional connectivities of regions identified in the brain structure analyses were then examined in relation to NSSI severity. We also tested whether the potential brain associations could play the roles in the relationships between internalizing and externalizing problems and NSSI severity. Based on previous research (Auerbach et al., 2021; Wang et al., 2022a), we hypothesized that some reward- and emotion-related brain regions, especially the putamen, might be associated with NSSI. Due to the lack of literature, no specific hypotheses (moderating or mediating) were made regarding the role of brain alterations in the relationships between internalizing/externalizing problems and NSSI severity.

2. Materials and methods

2.1. Participants

All participants were from the Healthy Brain Network project (HBN, release 1–9, http://fcon_1000.projects.nitrc.org/indi/cmi_healthy_brain_network/index.html), a large-scale study examining the progression of brain development and identifying biomarkers linked to mental health. The HBN project provided open-access clinical and imaging data of children and adolescents, encompassing a wide range of psychiatric diagnoses (Alexander et al., 2017). This study included a total of 386 patients (mean age = 10.72 ± 3.53, range = 5.04 to 21.22; 271 males;

Table 1
Demographic characteristics and diagnostic information of study participants.

Characteristics	All participants[b] (n = 386)
Age (Mean ± SD)	10.72 ± 3.53
Sex (Female/Male)	115/271
Socioeconomic Status (Mean ± SD)	49.03 ± 13.65
Internalizing problems (Mean ± SD)	62.21 ± 9.19
Externalizing problems (Mean ± SD)	59.65 ± 11.59
NSSI severity score (Mean ± SD)	2.25 ± 1.85
Race/ethnicity	**N (%)**
White/Caucasian	207 (53.63%)
Multiracial people	68 (17.62%)
Black/African American	46 (11.92%)
Hispanic	37 (9.59%)
Asian	13 (3.37%)
Indian	4 (1.04%)
Unknown	11(2.85%)
Primary Diagnosis	**N (%)**
ADHD-combined type	99 (25.65%)
ADHD-inattentive type	80 (20.73%)
ADHD-hyperactive/impulsive type	12 (3.11%)
Autism spectrum disorder	46 (11.92%)
Generalized anxiety disorder	30 (7.77%)
Major depressive disorder	18 (4.66%)
Learning disorder	16 (4.15%)
Social anxiety	14 (3.63%)
Other disorders[a]	71 (18.39%)

Note.
[a] Other disorders including non-specified ADHD (n = 7), oppositional defiant disorder (n = 6), separation anxiety (n = 6), borderline intellectual functioning (n = 5), disruptive mood dysregulation disorder (n = 5), obsessive-compulsive disorder (n = 5), specific phobia (n = 5), non-specified anxiety disorder (n = 4), posttraumatic stress disorder (n = 4), excoriation (skin-picking) disorder (n = 3), intellectual disability-mild (n = 3), bipolar ii disorder (n = 2), non-specified depressive disorder (n = 2), persistent (chronic) motor or vocal tic disorder (n = 2), tourettes disorder (n = 2), adjustment disorders (n = 1), bulimia nervosa (n = 1), conduct disorder-childhood-onset type (n = 1), cyclothymic disorder (n = 1), enuresis (n = 1), other specified disruptive, impulse-control, and conduct disorder (n = 1), reactive attachment disorder (n = 1), schizophrenia (n = 1), selective mutism (n = 1), speech sound disorder (n = 1).
[b] All these participants were included in the structural analysis, with 277 of them included in the functional analysis (refer to Table S1). ADHD, attention-deficit/hyperactivity disorder. SD = standard deviation.

Table 1). Of these, 225 participants were from the CitiGroup Cornell Brain Imaging Center, 150 from the Brain Imaging Center at Rutgers University, and the remaining 11 from the Advanced Science Research Center at the City University of New York. Our study included individuals who exhibited a history of NSSI behavior and had a diagnosis of mental disorders such as ADHD, autism spectrum disorder, generalized anxiety disorder, depression, learning disorder, social phobia, and other disorders (Table 1). The detailed inclusion and exclusion criteria and numbers of participants for the following statistical analyses were shown in a flow chart (Supplemental Fig. S1).

All participants underwent the computerized web-based version of the Schedule for Affective Disorders and Schizophrenia—Children's version (KSADS). This semi-structured psychiatric review, rooted in DSM-5 criteria, was used for clinical diagnoses. The KSADS interviews were administered by licensed clinicians, incorporating inputs from both parents and children. These interviews generated automated diagnoses, which were synthesized by the clinical team to formulate a consensus on DSM-5 diagnoses (Alexander et al., 2017). Our study included participants whose diagnoses reached consensus by different clinicians. Their comorbidity diagnosis information was presented in Supplemental Table S1.

The study protocol of the HBN received ethical approval from the Chesapeake Institutional Review Board. Before data collection, informed written consent was obtained from the legal guardians of all participants. All procedures were conducted in accordance with relevant guidelines and regulations. Throughout the consent procedure, participants explicitly consented to share their data through protocols approved by the Chesapeake Institutional Review Board.

2.2. Psychological assessments

The severity of NSSI was assessed using the Repetitive Behavior Scale (Bodfish et al., 1999; Lam and Aman, 2007), which provided a quantitative, continuous measure of repetitive behaviors. This scale consisted of 43 items, with items 7–14 specifically designed as a subscale to assess the severity of NSSI. Scores were reported by the participants' parents or primary caregivers on a four-point Likert scale ranging from "0 - The behavior did not occur" to "3 - The behavior occurred and is a serious problem". Evaluators were instructed to consider the previous month's conditions when completing this scale.

Internalizing and externalizing problems were assessed using the Child Behavior Checklist (CBCL/6–18; Achenbach and Edelbrock, 1991), which was completed by parents or primary caregivers of the children. It utilized a 0–2 scale and consisted of 113 items that primarily described the children's behavior. Internalizing and externalizing problems were 2 s-order dimensions from this scale (Carneiro et al., 2016). The former encompassed subjective psychological problems, including withdrawal, anxiety, somatic complaints, and depression; the latter primarily focused on various forms of conflict, such as attention problems and aggressive behavior. In addition, the total score of CBCL could reflect an individual's overall psychosocial functioning and behavior (Minde et al., 2003; Sievert et al., 2021). We also examined the CBCL total score in supplementary analyses to explore the potential mediating and moderating effects of brain abnormalities.

Socioeconomic status was measured by the Barratt Simplified Measure of Social Status (BSMSS) Questionnaire (Barratt, 2006), which was completed by their parents. In this questionnaire, maternal and paternal years of education and their occupations were used to represent socioeconomic status. We added up the scores for each item to obtain the total socioeconomic score. This measure was regarded as a more reliable and objective indicator of socioeconomic status.

2.3. Brain images acquisition and preprocessing

Acquisition parameters of the structural and functional images for the three scanning sites have been provided in a prior study (Alexander et al., 2017), the online HBN imaging protocol (http://fcon_1000.projects.nitrc.org/indi/cmi_healthy_brain_network/), and our supplemental materials. Structural data preprocessing was performed with CAT12 toolbox (http://www.neuro.uni-jena.de/cat/) in Matlab (2019a) (MathWorks, Natick, MA). For the segmentation and normalization processes of all structural scans, we implemented an optimized voxel-based morphometry protocol using the DARTEL (Diffeomorphic Anatomical Registration using Exponentiated Lie algebra). The standard MNI152 brain template was then utilized to achieve normalization to the standard space. The voxel size for normalized images was set to $1.5 \times 1.5 \times 1.5$ mm^3. The probabilistic gray matter images were eventually smoothed using an 8 mm full-width at half-maximum Gaussian kernel. The total intracranial volume (TIV) of each participant was also extracted and included as a covariate.

Resting-state functional data were preprocessed using Brant (BRAinNetome Toolkit https://brant.brainnetome.org/en/latest). Detailed preprocessing steps for all functional scans were as follows. First, we discarded the first 5 vol for each scan and performed slice timing correction and head motion correction. Next, we normalized the functional images to the MNI152 template and regressed out factors from white matter, cerebrospinal fluid, global signals, and head motion. Then, we applied temporal bandpass filtering between 0.01 and 0.08 Hz and smoothed the images with a gaussian kernel of 6 mm full width at half maximum. Regarding head motion, volumes with a mean framewise displacement greater than 0.50 were scrubbed (Siegel et al., 2014), and participants with less than 70 percent useable volumes were excluded. A total of 277 patients were included in the functional analyses (Table S2).

2.4. Statistical analyses

Linear regression models in SPM12 were used to identify structural volume alterations associated with NSSI severity, with NSSI severity score regarded as the independent variable. Age, age^2, sex, site, and TIV were included in the model as covariates. Results were corrected using the Gaussian random field (GRF) correction method at a voxel level of $p < 0.001$ and a cluster level of $p < 0.05$. To further verify the stability of potential findings, we repeated the analysis in randomly selected 50% subsamples 100 times. We also performed a two-sample *t*-test by comparing participants with an NSSI severity score of 1 (low severity score group) to those with a score ≥ 2 (high severity score group) and examined whether race/ethnicity or socioeconomic status changed potential associations.

Functional connectivity abnormalities were examined with voxel-wise whole-brain analyses. Because brain regions with structural changes may have a high likelihood of functional deficits, structural alterations that survived GRF correction in the above analyses were regarded as the regions of interest (i.e., bilateral putamen), as suggested by prior studies (Cao et al., 2022; Wang et al., 2014). Voxel-wise functional connectivity was calculated for each region of interest, and Fisher's Z-transformation was subsequently performed. Similar to structural analysis, linear regression models were created to identify abnormal functional connectivity patterns. NSSI severity score was the independent variable; age, age^2, sex, site, and head motion (framewise displacement value) were included as covariates. The GRF method was utilized to correct for multiple comparisons (voxel-level $p < 0.001$ and cluster-level $p < 0.05$). Validation analyses were also performed by randomly selecting 50% subsamples 100 times, in addition to the comparison between high and low NSSI severity groups.

We also examined how brain alterations may contribute to the relationships between internalizing/externalizing symptoms and NSSI severity. We extracted the gray matter volumes of significant brain regions (i.e., bilateral putamen) and their functional connectivities that were significantly associated with NSSI severity. Moderation and mediation models were then tested separately. Internalizing and externalizing problems were the independent variables, and NSSI severity was the dependent variable. Gray matter volumes and functional

connectivities served as moderators and mediators, respectively. The schematic diagram of the moderation and mediation models was provided in Supplemental Fig. S2. In both models, prior covariates for brain structural analysis (age, age^2, sex, site, and TIV) and functional connectivity analysis (age, age^2, sex, site, and head motion) were also included in the corresponding analyses. Tests were performed in SPSS 26.0 using PROCESS v4.1, with the Bootstrap method used to determine the significance of moderating and mediating effects.

3. Results

3.1. Clinical demographics

Demographics and clinical characteristics of study participants are provided in Table 1. 65.54% of the participants (N = 253) were diagnosed with neurodevelopmental disorders (20.73% inattentive type ADHD; 3.11% hyperactive-impulsive type ADHD; 25.65% combined type ADHD; 11.92% autism spectrum disorder; 4.15% learning disorder), and 16.06% of the participants (N = 62) were diagnosed with mood disorders (7.77% generalized anxiety disorder; 4.66% major depressive disorder; 3.63% social anxiety). The remaining participants were diagnosed with oppositional defiant disorder, separation anxiety, and other unspecified disorders (Table 1). The mean score of NSSI severity was 2.25 ± 1.85. The average scores of internalizing symptoms and externalizing symptoms were 62.21 ± 9.19 and 59.65 ± 11.59, respectively. Regression analyses of internalizing ($\beta = 0.281$, $t = 5.651$, $p < 0.001$) and externalizing symptoms ($\beta = 0.275$, $t = 5.553$, $p < 0.001$) on NSSI severity revealed significantly positive associations, after adjusting for age and sex.

3.2. Gray matter volumes associated with NSSI severity

Higher severity of NSSI was found to be associated with reduced gray matter volumes in the bilateral putamen (left: number of voxels: 1636; MNI coordinates, x = −31.5, y = −3, z = 6; peak Z value = −5.228; right: number of voxels: 701; MNI coordinates, x = 31.5, y = −3, z = 9; peak Z value = −5.233; Fig. 1, Table 2), with both extending to the insula and pallidum. In the supplementary analyses of randomly selected 50% of participants, reductions in gray matter volume in the bilateral putamen were also found (left: t = −4.245, right: t = −4.010; Supplemental Fig. S3, Table S3). To further test the stability of the results, we then randomly selected 50% of participants 100 times for supplementary analyses. We calculated the mean t-value for each voxel as well as the frequency of significant occurrence of each voxel ($p <$

Table 2
Brain regions in the structural and functional connectivity analyses that significantly associated with the severity of NSSI.

Analysis	Significant brain regions	MNI coordinate x, y, z	Voxels	Peak Z value
Structural voxel-based morphometry analyses (gray matter volume; n = 386)	Left putamen	−31.5, −3, 6	1636	−5.228
	Left insula		372	
	Left pallidum		43	
	Right putamen	31.5, −3, 9	701	−5.233
	Right insula		56	
	Right pallidum		36	
Functional connectivity analyses (seed: left putamen; n = 277)	Left temporoparietal junction	−45, −36, 0	232	−5.142
	Left superior temporal gyrus		109	
	Left middle temporal gyrus		87	
	Left angular gyrus		61	
	Right temporoparietal junction	48, −27, 3	174	−5.306
	Right superior temporal gyrus		104	
	Right middle temporal gyrus		53	
Functional connectivity analyses (seed: right putamen; n = 277)	Left temporoparietal junction	−51, −39, 6	52	−4.548
	Left superior temporal gyrus		42	
	Left middle temporal gyrus		43	

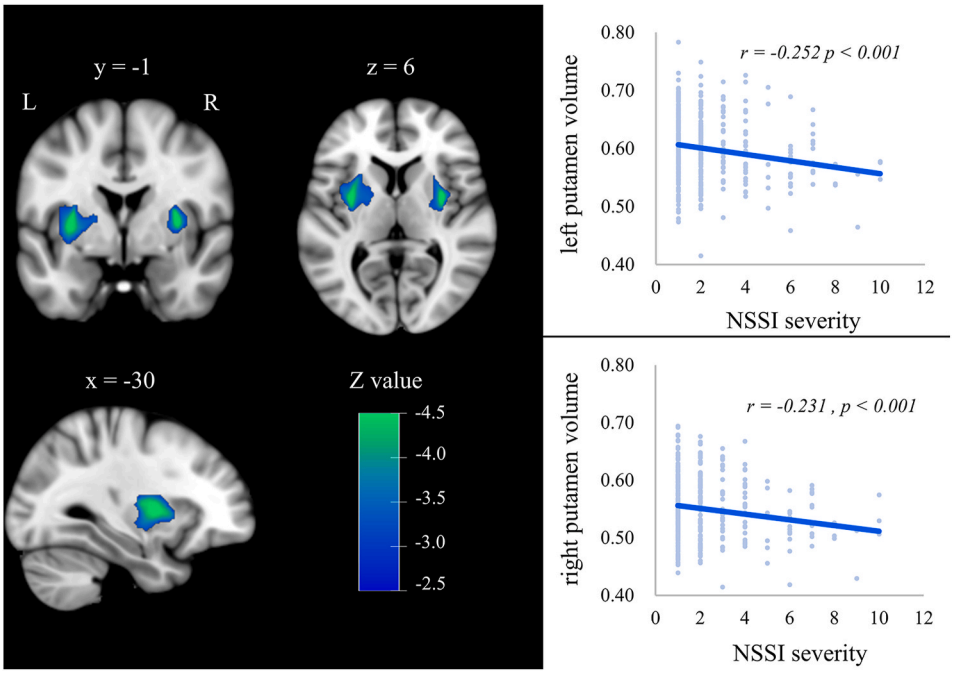

Fig. 1. Increased NSSI severity associated with decreased volumes in bilateral putamen. On the left panel, these results were shown after Gaussian random field correction. On the right panel, scatter plots depicted the negative correlations between both left and right putamen volumes and NSSI severity.

0.01, uncorrected). There were also the reductions of gray matter volume in bilateral putamen (Supplemental Figs. S4 and S5). The high and low severity groups also differed in putamen volumes (left: t = −4.030, right: t = −3.417; Supplemental Fig. S6, Table S3). When race/ethnicity or socioeconomic status was included as an additional covariate, similar associations with putamen were found (Supplemental Figs. S7 and S8).

3.3. Abnormal functional connectivities associated with NSSI severity

Increased NSSI severity was related to decreased functional connectivities of the bilateral putamen. For the left putamen, connectivities with bilateral regions of the temporoparietal junction were reduced (TPJ; left: number of voxels: 232, MNI coordinates, x = −45, y = −36, z = 0, peak Z value = −5.142; right: number of voxels: 174, MNI coordinates, x = 48, y = −27, z = 3; peak Z value = −5.306; Fig. 2, Table 2), involving the superior and middle temporal gyri and the angular gyrus. For the right putamen, reductions were found for the left TPJ (number of voxels: 52, MNI coordinates, x = −51, y = 39, z = 6; peak Z value = −4.548; Fig. 2, Table 2), including the superior and middle temporal gyri. Similar associations were observed in the supplementary analysis consisting of randomly selected 50% of participants (Supplemental Fig. S9, Table S4) and in the comparisons between high and low NSSI severity groups (Supplemental Figs. S14 and S15, Table S4). We also randomly selected 50% of participants 100 times, then calculated the mean t-value for each voxel and the frequency of significant occurrence of each voxel ($p < 0.01$, uncorrected). The reduced functional connectivity between the putamen and the TPJ region was also observed (Supplemental Figs. S10–S13).

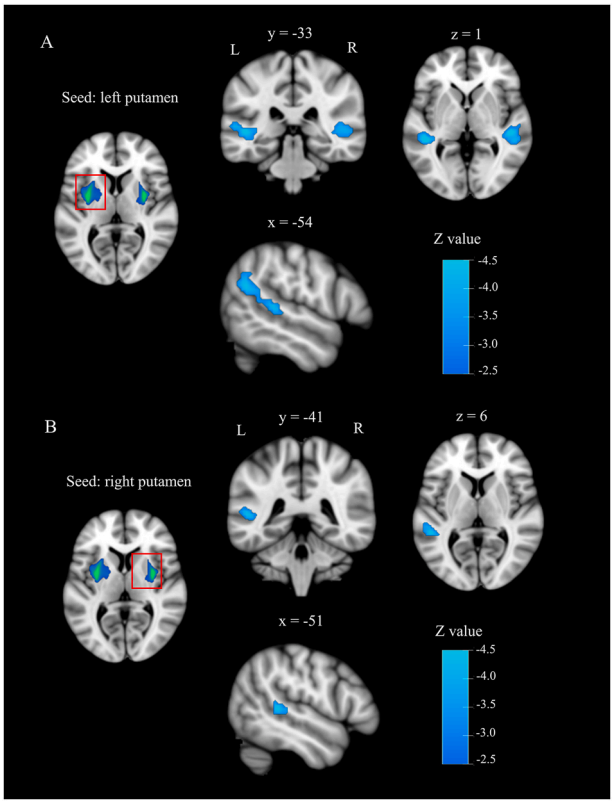

Fig. 2. Increased NSSI severity associated with putamen related abnormal brain functional connectivities. Higher severity linked with decreased connectivities of (A) left putamen and bilateral TPJ regions, and of (B) right putamen and left TPJ region. These functional results were shown after Gaussian random field correction. TPJ = temporoparietal junction.

3.4. Associations of NSSI severity with putamen and its functional connectivities in different diagnostic groups

To test whether the structural and functional associations with NSSI were shared among different diagnoses, we conducted multiple group regression analyses and ANOVA for putamen volume and functional connectivities. Diagnostic groups included ADHD-combined type (N = 99), ADHD-inattentive type (N = 80), ADHD-hyperactive/impulsive type (N = 12), autism spectrum disorder (N = 46), generalized anxiety disorder (N = 30), major depressive disorder (N = 18), learning disorder (N = 16), social anxiety (N = 14), and other disorders (N = 71). We found that the interactions between diagnostic groups and NSSI severity were not significant for bilateral putamen volumes (left putamen: p = 0.63; right putamen: p = 0.85; Supplemental Fig. S16) or the functional connectivities with left putamen (left putamen - left TPJ, p = 0.59; left putamen - right TPJ, p = 0.43; Supplemental Fig. S16). The only significant interaction was found for the functional connectivity between right putamen and left TPJ region ($p < 0.001$).

3.5. The roles of brain alterations in the relationships between internalizing/externalizing problems and NSSI severity

For putamen volumes, significant moderating effects were observed (β = −0.53 to −0.44, t = −3.83 to −2.58, ps < 0.01; Fig. 3, Table 3). In patients with smaller putamen volumes, internalizing and externalizing problems were associated with greater NSSI severity, compared to those with larger putamen volumes. No mediating effects were significant (Supplemental Table S5).

For the functional connectivities of putamen, we found significant moderating effects of left putamen to bilateral TPJ and of right putamen to left TPJ (β = −0.17 to −0.11, t = −3.13 to −2.46, ps < 0.02; Fig. 4, Table 4). Simple slope analyses showed both internalizing and externalizing problems were more associated with greater NSSI severity in participants with lower functional connectivities, compared to those with higher functional connectivities (Fig. 4). Similarly, no significant mediating effects were observed (Supplemental Table S5).

Furthermore, we found consistent results in the supplementary analyses of the CBCL total score. Putamen volumes and the functional connectivities of putamen showed significant moderating effects in the associations between total CBCL score and NSSI severity (Supplemental Figs. S17 and S18, Table S6). No significant mediating effects were observed (Supplemental Table S7).

4. Discussion

In this study, we investigated NSSI-related brain structural alterations and functional connectivity in a transdiagnostic psychiatric sample of children and adolescents. We also explored the role of brain alterations in the relationships between internalizing/externalizing problems and NSSI severity. We found that increased NSSI severity was significantly linked with reduced bilateral putamen volumes, as well as decreased functional connectivities between the putamen and TPJ regions. Moreover, smaller putamen volumes and reduced functional connectivities showed moderating effects in the relationships between internalizing/externalizing problems and NSSI severity. Our results demonstrated that putamen might be a promising neural marker of NSSI that cuts across psychiatric disorders.

The severity of NSSI was related to structural abnormalities in the putamen, a critical region within the brain reward circuit. The results agreed with prior neuroimaging findings that have focused on specific disorders, highlighting abnormalities in reward-related brain regions among individuals engaging in NSSI behavior (Marchand et al., 2013; Wang et al., 2022a). The dorsal striatum, composed of putamen and caudate nucleus, was considered a central hub for habitual behavior (Everitt and Robbins, 2013). It may directly influence decision-making, action selection, inhibition, and the establishment and engagement of

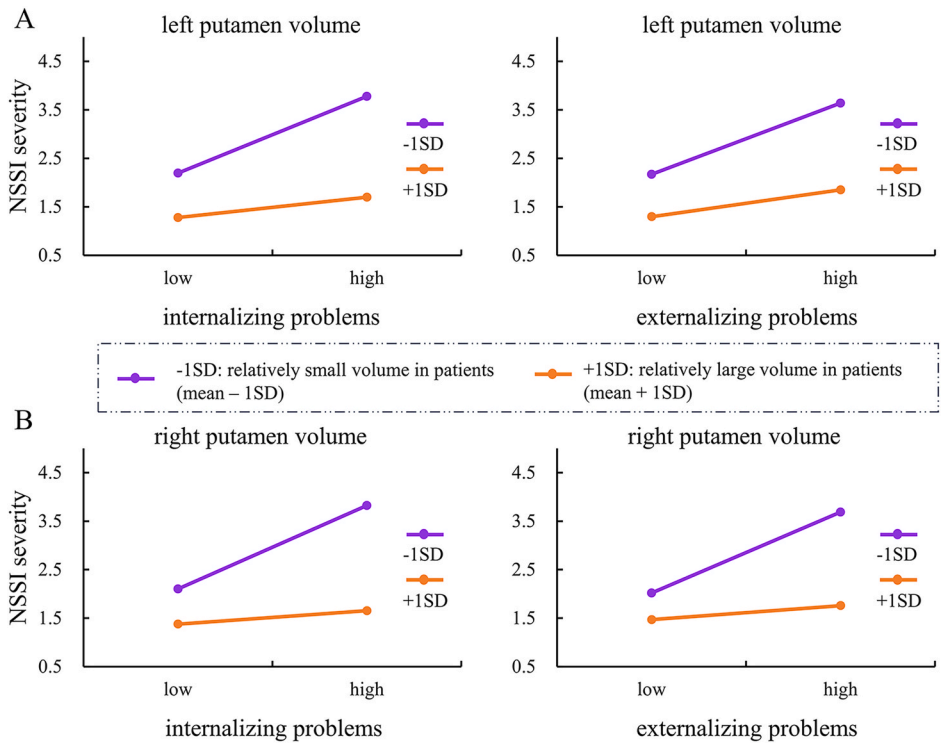

Fig. 3. Bilateral putamen volumes moderated the associations between both internalizing and externalizing problems and NSSI severity. In patients with relatively small left (A, purple) and right (B, purple) putamen volumes (mean - 1SD), both internalizing and externalizing problems showed increased associations with NSSI severity; while in patients with relatively large putamen volumes (A and B, orange, mean + 1SD), the positive associations were relatively weak. SD = standard deviation. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 3
Moderation results with putamen volumes as moderators in the associations between both internalizing and externalizing problems and the severity of NSSI.

Models	Coefficient	SE	t	p	Lower CI	Upper CI
Internalizing × left putamen volume	**−0.53**	**0.16**	**−3.39**	**< 0.001**	**−0.83**	**−0.24**
Internalizing	0.05	0.01	5.68	<0.001	0.03	0.07
Left putamen volume	−12.57	2.35	−5.36	<0.001	−18.00	−7.64
Internalizing × right putamen volume	**−0.44**	**0.17**	**−2.58**	**0.01**	**−0.76**	**−0.14**
Externalizing	0.06	0.01	5.67	<0.001	0.03	0.08
Right putamen volume	−11.76	2.47	−4.76	<0.001	−17.18	−7.04
Externalizing × left putamen volume	**−0.52**	**0.14**	**−3.83**	**< 0.001**	**−0.79**	**−0.26**
Externalizing	0.04	0.01	5.72	<0.001	0.03	0.06
Left putamen volume	−12.14	2.33	−5.20	<0.001	−17.23	−7.40
Externalizing × right putamen volume	**−0.53**	**0.16**	**−3.39**	**< 0.001**	**−0.82**	**−0.23**
Externalizing	0.04	0.01	5.54	<0.001	0.03	0.06
Right putamen volume	−10.94	2.46	−4.44	<0.001	−15.94	−6.27

Note: 386 participants were included in these moderation analyses. "×" indicated interaction between variables. Bootstrap sample size = 5000. Lower CI = Bootstrap lower limit of confidence interval. Upper CI = Bootstrap upper limit of confidence interval. Age, age^2, gender, site, and total intracranial volume were included as the covariates for these analyses.

habitual behaviors (Burton et al., 2015; Haber and Knutson, 2010). When considered separately, the caudate nucleus may be involved in goal-directed behavior by monitoring behavior-outcome related brain connections. The putamen, in turn, was likely to be engaged in habitual behavior and operate based on stimulus-response contingencies, in collaboration with motion-related regions such as the sensorimotor cortex (Wang et al., 2023; Yin et al., 2006). In both animal and human models, putamen has also been associated with the transition from goal-oriented behavior to habitual patterns, including behaviors like drug use and binge eating (Everitt and Robbins, 2013; Favier et al., 2020; McKim et al., 2016; Zapata et al., 2010). Our results highlighted the role of putamen in NSSI, which may contribute to the transition from adaptive emotion regulation strategies to habitual NSSI behavior in participants engaging in NSSI.

Our functional connectivity results revealed that increased NSSI severity was associated with reduced connectivities between putamen and TPJ regions. The TPJ was considered a key region responsible for attentional control (Geng and Vossel, 2013; Wilterson et al., 2021), and played a vital role in updating internal models based on new external information and initiating new actions for upcoming events, akin to top-down adjustments. In behavioral research, individuals with NSSI behaviors demonstrated a more pronounced attentional bias toward negative and NSSI-specific stimuli compared to individuals who had not engaged in self-injury (Riquino et al., 2021; Tonta et al., 2023). The biased attention in individuals with NSSI might be associated with their reduced attention control ability (Tonta et al., 2022). Our study found that higher severity of self-injury was associated with reduced connectivities between TPJ regions and putamen. This suggested that deficits in

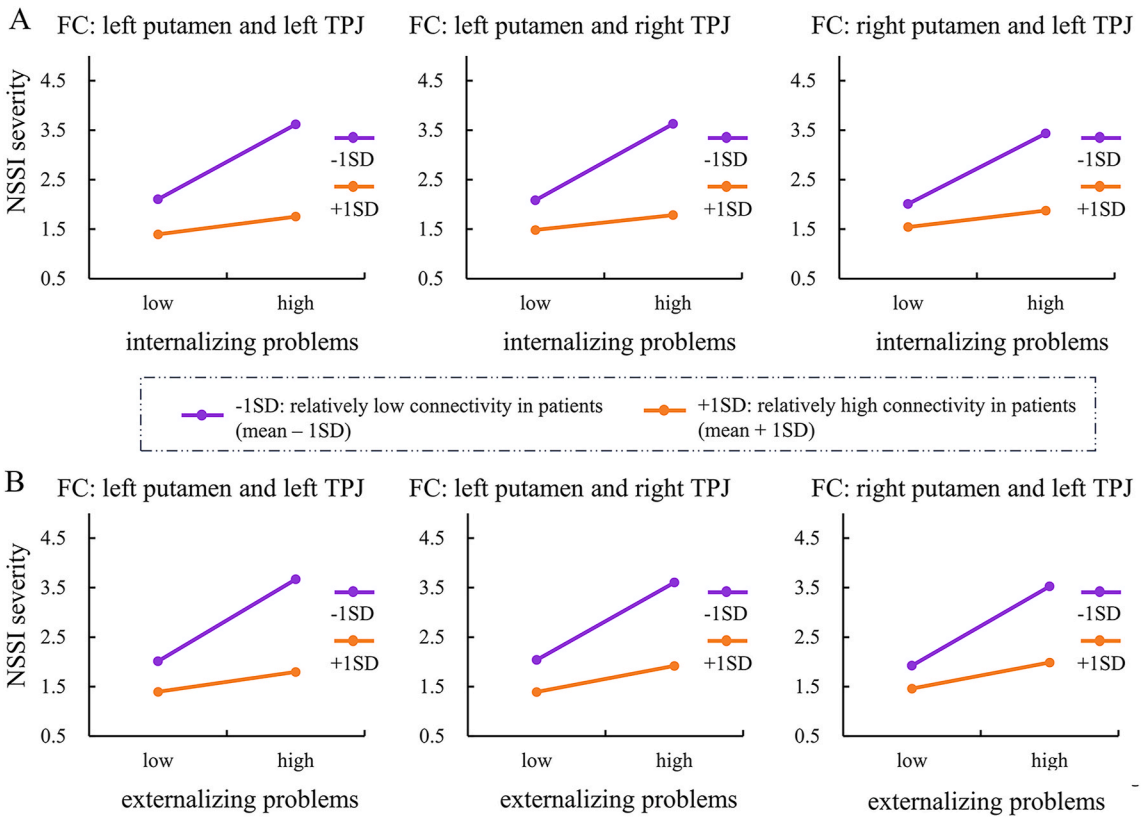

Fig. 4. Putamen related functional connectivities moderated the associations between both internalizing (A) and externalizing problems (B) and NSSI severity. In patients with relatively low functional connectivities (purple, of left putamen and bilateral TPJ, and of right putamen and left TPJ, mean – 1SD), both internalizing and externalizing problems showed increased associations with NSSI severity; while in patients with relatively high connectivity (orange, mean + 1SD), the positive associations were relatively weak. FC = functional connectivity; TPJ = temporoparietal junction; SD = standard deviation. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

attention control and attentional biases might serve as predisposing factors for individuals to routinely resort to self-injurious behaviors as a means to regulate their emotions (Herzog et al., 2023). Individuals with NSSI may not be able to shift their attention toward positive external stimuli or employ adaptive coping strategies (Thomassin et al., 2017). Consequently, they may increasingly engage in NSSI behavior, ultimately affecting reward-associated brain regions, particularly the putamen (Wang et al., 2022a).

We additionally identified moderating effects of brain alterations in the relationships between internalizing and externalizing problems and NSSI severity. Prior studies have shown significant associations between internalizing and externalizing problems and NSSI (Liu et al., 2018; Mancinelli et al., 2022), in line with the present study. Here, our results extended previous research at the neurobiological level, suggesting that effects of internalizing and externalizing symptoms might be more pronounced in individuals with structural or functional alterations in putamen. Specifically, in individuals with smaller putamen volumes and lower connectivities between putamen and TPJ, the association between internalizing/externalizing problems and NSSI severity was significantly stronger. This indicates that brain abnormalities involving putamen may play a prominent role in promoting NSSI behavior, irrespective of mental conditions. Taken together, structural abnormalities and decreased functional connectivities of putamen may contribute to NSSI severity.

Our study has several limitations. Firstly, it was cross-sectionally designed, which meant we could not determine the causal relationships between the observed brain abnormalities and NSSI behavior. Future longitudinal research involving drug therapy, neuromodulation treatment, and brain lesion studies are warranted to provide more conclusive results. Secondly, the self-injurious subscale in Repetitive Behavior Scale provided a general assessment of NSSI severity, but it did not account for the emotional and motivational components of NSSI. This may have limited the reliability of this subscale in measuring NSSI when considered alone. The frequency of NSSI was also overlooked. Future studies with more accurate reports of NSSI frequency may provide further insights. Thirdly, the severity of NSSI was based on parental reports. As parents may not always be aware of NSSI engagement and the recency of this engagement (Gratch et al., 2022), incorporating reports from both parents and adolescents would reduce bias and improve the robustness of NSSI assessment. Fourthly, our sample consisted of patients with mostly neurodevelopmental disorders, which may limit the generalizability of our findings to other psychiatric disorders, such as depression. Future studies with larger cohorts of adolescents with mood disorders are warranted to shed light on NSSI-related transdiagnostic biomarkers. Finally, our analyses relied on univariate regression only, while multivariate analyses, like machine learning, are more informative and may offer greater sensitivity in identifying potential hub regions involved in NSSI behavior.

5. Conclusions

In conclusion, we investigated NSSI-related brain structural and functional alterations in a transdiagnostic sample of children and adolescents with psychiatric disorders. Our findings suggested that the putamen may serve as a biomarker for NSSI behavior. Structural and functional abnormalities of the putamen also moderated the associations between internalizing and externalizing problems and NSSI severity. These results highlighted the importance of the putamen in potential interventions and treatments for transdiagnostic disorders in children and adolescents.

Table 4
Moderation results with putamen related functional connectives as moderators in the associations between both internalizing and externalizing problems and the severity of NSSI.

Models	Coefficient	SE	T	p	Lower CI	Upper CI
Internalizing × FC: left putamen - left TPJ	**−0.16**	**0.06**	**−2.89**	**< 0.001**	**−0.26**	**−0.07**
Internalizing	0.05	0.01	4.57	<0.001	0.03	0.07
FC: left putamen - left TPJ	−3.33	0.55	−6.07	<0.001	−4.53	−2.24
Internalizing × FC: left putamen - right TPJ	**−0.17**	**0.05**	**−3.13**	**< 0.001**	**−0.30**	**−0.06**
Internalizing	0.05	0.01	4.51	<0.001	0.03	0.07
FC: left putamen - right TPJ	−3.08	0.51	−5.99	<0.001	−4.29	−1.91
Internalizing × FC: right putamen - left TPJ	**−0.16**	**0.06**	**−2.52**	**0.01**	**−0.31**	**−0.02**
Internalizing	0.05	0.01	4.19	<0.001	0.02	0.07
FC: right putamen - left TPJ	−2.72	0.57	−4.81	<0.001	−4.10	−1.40
Externalizing × FC: left putamen - left TPJ	**−0.14**	**0.04**	**−3.32**	**< 0.001**	**−0.23**	**−0.06**
Externalizing	0.04	0.01	5.11	<0.001	0.02	0.06
FC: left putamen - left TPJ	−3.22	0.54	−5.97	<0.001	−4.35	−2.12
Externalizing × FC: left putamen - right TPJ	**−0.11**	**0.05**	**−2.46**	**0.01**	**−0.23**	**0.00**
Externalizing	0.05	0.01	5.17	<0.001	0.03	0.06
FC: left putamen - right TPJ	−2.94	0.51	−5.73	<0.001	−4.18	−1.72
Internalizing × FC: right putamen - left TPJ	**−0.12**	**0.05**	**−2.53**	**0.01**	**−0.23**	**−0.01**
Externalizing	0.05	0.01	5.19	<0.001	0.03	0.07
FC: right putamen - left TPJ	−2.70	0.56	−4.84	<0.001	−3.95	−1.42

Note: 277 participants were included in these moderation analyses. "×" indicated interaction between variables. FC = functional connectivity. "-" of the FC indicated the connectivity between two regions. Bootstrap sample size = 5000. Lower CI = Bootstrap lower limit of confidence interval. Upper CI = Bootstrap upper limit of confidence interval. TPJ = temporoparietal junction region. Age, age^2, gender, site, and head motion (framewise displacement value) were included as the covariates for these analyses.

CRediT authorship contribution statement

Xuan Liu: Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Yixin Zhang:** Software, Data curation, Conceptualization. **Jiahui Chen:** Data curation. **Mingyan Xie:** Data curation. **Lijun Pan:** Data curation. **Bernhard Hommel:** Writing – review & editing, Writing – original draft. **Ying Yang:** Conceptualization. **Xingxing Zhu:** Writing – review & editing, Writing – original draft, Conceptualization. **Kangcheng Wang:** Writing – review & editing, Writing – original draft, Software, Methodology, Conceptualization. **Wenxin Zhang:** Conceptualization.

Data availability statements

The data that support our findings are openly available in Healthy Brain Network Data Portal (http://fcon_1000.projects.nitrc.org/indi/cmi_healthy_brain_network/).

Fundings

This research was supported by the National Natural Science Foundation of China (32000760), China Postdoctoral Science Foundation Funded Project (2019M662433, 2023T160397), Postdoctoral Innovation Project in Shandong Province (239735), Youth Innovation Team in Universities of Shandong Province (2022KJ252) and Shandong Provincial Natural Science Foundation (ZR2024QH085).

Declaration of Competing interest

All authors declare they have no conflicts of interest.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2025.02.051.

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