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Smaller putamen volumes are associated with greater problems in external emotional regulation in depressed adolescents with nonsuicidal self-injury

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ABSTRACT

The functions of nonsuicidal self-injury (NSSI) consist of social and emotional aspects (Social influence, Sensation seeking, Internal and External emotion regulation). Previous studies have indicated that dysfunction in reward-related brain structures especially the striatum might drive this habitual behavior. However, no studies to date have investigated the associations between striatum and different functions for adolescents engaging in NSSI behaviors. Here, we recruited 35 depressed adolescents with recent NSSI behaviors and 36 healthy controls and acquired structural brain images, depressive symptoms, social, academic and family environments assessments, in addition to NSSI functions in patients only. Subcortical volumes and cortical thickness were estimated with FreeSurfer. Mixed linear regressions were performed to examine associations between striatal structures (caudate, putamen, nucleus accumbens, pallidum) and NSSI functions, with age, sex, total intracranial volume, hemisphere and depression severity included as covariates. Effect of environmental factors and potential associations with cortical thickness and other subcortical volumes were also tested. We found that, among the four functions, external emotional regulation represented the main function for NSSI engagement. Increased external emotion regulation was significantly associated with smaller putamen volume. No environmental factors biased the association with putamen. No associations with other cortical or subcortical regions were observed. Our findings suggested that smaller putamen might be a biomarker of NSSI engagement for depressed adolescents when they regulated frustrated or angry emotions. The results have potentially clinical implications in early identification and brain intervention of NSSI in youth.

1. Introduction

As a vital developmental period, adolescence comes with increasing risk behaviors, such as suicidal behavior and nonsuicidal self-injury (NSSI). NSSI is a direct, deliberate, and habitual injury on one's own body without suicidal attempt (Nock and Favazza, 2009). NSSI typically onsets in early adolescence, then increases sharply with age and peaks in middle to late adolescence. Recent surveys revealed a prevalence of NSSI at approximately 19.4% worldwide (Lim et al., 2019), and even 27.4% in China (Wang et al., 2020a). NSSI is highly associated with suicide attempts, depression and other psychiatric disorders (Tuisku et al., 2014). In addition, NSSI behaviors were related to decreased clinical and social improvement of several psychiatric disorders (Victor et al., 2016). Thus, increasing knowledge of NSSI, especially delineating specific reasons or motivations why individuals perform NSSI, are of critical importance for responsibly treating and dealing with adolescents.

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Considerable research has indicated that NSSI servers to satisfy various functional needs. According to prior theoretical models of NSSI functions (Bentley et al., 2014; Chapman et al., 2006; Hooley and Franklin, 2018; Klonsky, 2007), interpersonal and intrapersonal factors could be distinguished among them. Interpersonal functions mainly relate to social influence and sensation seeking (Guerin-Marion et al., 2018). Social influence reflects motivations to evoke responses or changes in social contexts, which could enable individuals to attract others' attention, seek help and gain others' understanding. Sensation seeking refers to individuals' willingness and preference to attain novel experiences (Kentopp et al., 2021). Greater sensation seeking might be accompanied by more NSSI engagement. Intrapersonal functions relate to emotion-regulation for gaining stress relief and increasing or re-establishing self-esteem (Tatnell et al., 2014). Emotion regulation can be further divided into internal and external functions according to specific symptoms (Guerin-Marion et al., 2018). The former relates to regulating internalizing symptoms, such as sadness and suicidal ideation, while the latter relates to externalizing symptoms, such as frustration and anger. As compared to interpersonal functions, intrapersonal functions seem to be more common in individuals engaging in NSSI (Taylor et al., 2018). In this study, we considered the classical four NSSI functions of Social influence, Sensation seeking, Internal and External emotion regulation, as featured in the established Ottawa self-injury inventory (Nixon et al., 2015; Zhang et al., 2015).

NSSI can be considered a habitual and repetitive behavior acquired by reinforcement learning (Hepp et al., 2020). NSSI was conceptualized as a behavioral addiction because negative reinforcement perpetuated the behavior, as suggested by the addictive model of NSSI (Blasco--Fontecilla et al., 2016; Nixon et al., 2002). Ventral/striatal–dorsomedial/striatal network might be the neural circuits supporting the acquisition of new behaviors (Everitt and Robbins, 2013; Walsh, 2013). With repeated or prolonged engagement in a certain behavior, habituation sets in, often accompanied by reduced sensitivity to previously functional reward (Liu, 2017) and by a stronger involvement of nucleus accumbens (NAcc) and anterior dorsolateral striatum (Everitt and Robbins, 2013). The transition from explicitly intended behaviors (operant conditioning) to more implicit, habitual behaviors might be associated with a shift of striatal locus of control from the ventral to dorsal striatum (Everitt and Robbins, 2013; Walsh, 2013). Another remarkable characteristic of NSSI is the transformation of what should be an aversive experience of pain into a reinforcing behavior. Again, the dorsal striatum, together with the thalamus and precuneus, seems to contribute to individuals' relief from painful experiences (Osuch et al., 2014). Taken together, various lines of evidence emphasize the possible involvement of the striatum in the engagement in self-harm behaviors.

Many neuroimaging studies have investigated NSSI-related brain atypicalities, mostly by comparing individuals who do and who do not engage in NSSI (Auerbach et al., 2021). Research on brain structures has reported reduced gray matter volume in insula in adolescents with NSSI (Ando et al., 2018), and both NSSI and reduced gray matter volumes were associated with emotional dysregulation (Beauchaine et al., 2019). Bonenberger et al. (2015) focused on the insular pain processing functions in NSSI-engaging individuals and found a reduced inability to modulate distressing stimuli as compared to healthy controls. Poon et al. (2019) found early NSSI thoughts in healthy adolescents was associated with increased activation in bilateral putamen in response to monetary rewards. Another study indicated that NSSI severity was related with characteristic patterns of the communication between amygdala and prefrontal cortex (Basgoze et al., 2021). However, the observed deficits in amygdala-frontal cortex communication were possibly driven by depression rather than NSSI (Westlund Schreiner et al., 2017). In summary, previous studies have indicated brain atypicalities associated with emotion regulation, reward processing and pain processing in individuals showing NSSI behaviors, despite some inconsistencies involved. Such inconsistencies might be due to differences across studies in clinical samples. Most previous studies were conducted in mixed clinical samples with major depressive disorder (MDD), borderline personality disorder, or obsessive-compulsive disorder (Leone et al., 2021; Osuch et al., 2014; Westlund Schreiner et al., 2017). Different symptom profiles, comorbidity, and medication use in various disorders might confound the associations between NSSI and brain structures. Hence, there is a clear need to study NSSI in highly homogeneous samples (Zhang et al., 2022).

A drawback of most neuroimaging studies on NSSI is their neglect of possible effects of environment factors, such as parental characteristics, school environment, and social isolation (Auerbach et al., 2021). Ecological systems theory suggests five environmental systems with which an individual would interact, and significantly impact child's development (Bronfenbrenner, 1979). At the microsystem's level, family, school and peers are the institutions/groups that impact adolescents' development most directly and immediately. Multiple studies confirmed the link between family adverse environments and the onset/persistence of NSSI behavior (Bean et al., 2021; Gatta et al., 2017). That might be because affect-related parental behavior, such as aggression, anxiety, and depression, impacts the children's emotional development (Gavic et al., 2018; Mammen et al., 2002). Baetens et al. (2021) found that unsatisfactory academic performance was negatively associated with NSSI behavior, suggesting that adolescents experience low-self-esteem/self-efficacy (sense of defeat) if their or their parents' expectations are not met (Madjar et al., 2017), which in turn motivates NSSI. At last, high social isolation, or low level of peer acceptance, comes with increased feeling of loneliness in adolescence (Q. Wang et al., 2020).

Taken altogether, this study aimed to investigate the associations between the four key NSSI functions and striatal-related brain structures (caudate, putamen, NAcc and pallidum). Considering the high prevalence of NSSI in depressed adolescents (Csorba et al., 2009; Hawton et al., 2013), we focused on depressed adolescents with a history of NSSI engagement. We hypothesized that functions of NSSI might be associated with the volume of striatal regions. We also assessed if various environmental variables could influence potential associations between NSSI functions and striatal structures. Identifying NSSI-related individual variability in brain structures serves to more general goals: to get a better grip of the neural underpinnings of NSSI and to develop clinically useful structural biomarkers of NSSI and NSSI functions—which both will be useful for our understanding of the condition and the development of successful interventions for its treatment.

2. Materials and methods

2.1. Participants

Thirty-five first-episode depressive adolescents (33 females) aged from 12.84 to 18.47 years (mean age: 15.46 ± 1.54) were recruited from the inpatient and outpatient department of the Shandong Mental Health Center. Another thirty-six healthy controls (29 females) aged from 10.61 to 18.84 (mean age: 16.20 ± 2.77) were recruited via public advertisements. All patients in this study were diagnosed with current MDD according to DSM-5 by two clinical psychiatrists, and were under medication with selective serotonin reuptake inhibitors (SSRIs) antidepressants, for instance, Escitalopram and Sertraline. These patients also met the diagnostical criteria of NSSI behavior, which was an engagement in NSSI on five or more days in the past year (Zetterqvist, 2015). Among them, 3 patients (8.57%) had daily NSSI behavior, 14 (40%) engaged in NSSI at least once a week, and 7 of them (20%) had NSSI at least once a month. More detailed information about NSSI behaviors in depressive patients was summarized in Supplemental Table S1. In the current study, we defined these participants as the group of NSSI patients. By contrast, healthy controls did not have any prior or current episode of any psychiatric disorder or NSSI based on DSM-5 at the time of investigation.

Exclusion criteria for all participants included 1) premenarchal status (for females), 2) a history of any lifetime concussion with loss of consciousness, 3) contraindications to magnetic resonance imaging (MRI) scanning (e.g. metal implants or claustrophobia), 4) serious neurological or intellectual disorders that could interfere with the participant's ability to complete the study components, and 5) lifetime or current diagnosis of bipolar disorder, schizophrenia, attention deficit hyperactivity disorder or alcohol dependence. This study was approved by the institutional review boards at the Shandong Normal University. Written assent and informed consent were provided by each participant's father or mother.

2.2. Clinical assessments

Clinical psychiatrists interviewed each depressed adolescent and assessed their eligibility in two domains, depression severity and NSSI history. Depression severity was assessed by the Children's Depression Inventory (CDI)-Chinese version (Wu et al., 2010) and it was characterized for the past 2 weeks. This questionnaire consists of 27 items assessing children's negative mood, interpersonal problem, ineffective, negative self-esteem and interpersonal behaviors. The total CDI score ranges from 0 to 54, with higher scores indicating more severe depressive mood. The Chinese version of the CDI demonstrated good reliability and validity (Cronbach's α coefficient = 0.88; test-retest Pearson's r = 0.81) (Wu et al., 2010).

OSI inventory is a widely-used self-report tool that provides a comprehensive evaluation of adolescents' NSSI behavior (Martin et al., 2013; Nixon et al., 2015; Rodav et al., 2014). It has also been used to determine the prevalence and features of adolescents' NSSI in China (Zhang et al., 2019). This scale measures four functional domains of NSSI behaviors, including Social influence, Sensation seeking, Internal and External emotion regulation. The four functions largely cover the wide range of overarching functions described by a past review (Klonsky, 2007). For each function, a mean score was calculated by averaging corresponding items. Each function ranged from 0 to 4, with higher scores indicating higher likelihood of this reason contributing to NSSI behaviors. Of note is that NSSI patients were required to report the functions as they were when they first engaged in NSSI behavior. Following the initial clinical interview session, eligible participants were invited to complete MRI scan and psychological assessments.

2.3. Psychological assessments

Loneliness for all adolescents was assessed by Children's Loneliness Scale (Asher et al., 1984). This scale measured the feelings of social dissatisfaction. It consisted of 24 items and required participants to specify their level of agreement to each statement in 5-point Likert scale. It has shown high reliability and has been widely used in previous research (Ma et al., 2020; Tan et al., 2016).

Sense of defeat in the academic environment was assessed by the Defeat Scale (Gilbert and Allan, 1998). It assessed the feelings of struggle, failure and frustration in these adolescents. It asked participants to respond to 16 items about the extent to which they felt they had failed, e.g., "I feel that I have not succeeded in my learning". This scale showed high internal consistency and external reliability (Taylor et al., 2011).

2.4. Parental assessments

For each participant, demographic characteristics of one parent and psychological assessments including marital conflict resolution, level of aggression, severity of depression and anxiety were collected at the same time. Recruiting one parent might lead to loss of some information. However, couples are at a high likelihood for affective concordance, particularly for depression and anxiety (Walker et al., 2017). Here, the ineffective arguing inventory (IAI) was used (Kurdek, 1994) to assess how well the respondent and his/her partner handle arguments as a couple. A higher score indicates a lower likelihood of conflict solving. Moreover, parents' level of aggression was assessed by the Buss Perry Aggression Questionnaire (BPAQ) (Buss and Perry, 1992), and anxiety and depression were assessed by the 14-item Hamilton anxiety rating scale (HAMA) and 24-item Hamilton depression rating scale (HAMD) separately.

2.5. Brain images acquisition and segmentation

Acquisition parameters of brain scans were provided in supplemental materials. For each participant, brain structural images were preprocessed using complete FreeSurfer recon-all pipeline (supplemental material). Volumes of striatum regions, including caudate nucleus, putamen, pallidum and NAcc were extracted, in addition to other subcortical regions (hippocampus, amygdala and thalamus). Mean cortical thickness was extracted for each of the 31 regions in the Desikan-Killianny-Tourville atlas (Klein and Tourville, 2012). Cortical thickness was calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl and Dale, 2000). All brain measures (Supplemental Table S2) were transformed to z-scores and there were no outliers beyond 2.5 standard deviations.

2.6. Statistical analyses

All analyses were conducted in StataMP 17. We firstly identified the main function of adolescents' NSSI and examined the correlations between NSSI functions and other variables of interest in NSSI patients. Then, we performed an ANCOVA analysis to test whether the striatal volumes differed between NSSI patients and healthy controls. We defined the group (NSSI and healthy controls) and hemisphere (left and right) as the independent variables, three variables (age, sex, and total intracranial volume (TIV)) as the covariables, four striatal volumes as the dependent variables. The Bonferroni method ($p < 0.013$) was applied for correction of multiple comparisons.

Subsequently, mixed linear regression models were conducted to examine the associations between each NSSI function (independent variable) and striatal structures (caudate, putamen, NAcc, pallidum, dependent variable). The model has been commonly used in neuroimaging studies with left and right homologous structures regarded as repeated measures (Neilson et al., 2019; Shen et al., 2021; Zhu et al., 2021). Interaction between hemisphere and NSSI functions on regional volume was tested at first using model: StructuralVolume ~ NSSIfunction + Hemisphere + NSSIfunction x Hemisphere + Sex + Age + TIV + (1 | Subject), where xmeant interaction between variables. If there is a significant interaction, separate tests of bilateral brain values would be performed additionally. If not, hemisphere would be included in the models as a fixed factor. Age, sex, TIV and depression severity were also included as covariates (StructuralVolume ~ NSSIfunction + Hemisphere + Sex + Age + TIV + ChildrenDepression + (1 | Subject)). For detailed models and the logic, please refer to the Supplemental Fig. S1. P–P plot and Q-Q plot were also performed for checking normality of residuals. For significant associations, we validated the results by (1) repeating analyses in randomly selected subsamples (N = 20), and (2) performing a leave-one-out analysis using same regression models and (3) excluding male participants and sex variable from the analysis. Bonferroni correction ($p < 0.05/n$, n = 4, which indicated 4 striatal regions) was conducted to control for multiple comparisons.

Finally, we examined the potential impact of social, academic and family environmental factors (loneliness, sense of defeat in learning, parental conflict, aggression level, severity of depression and anxiety) on the associations between NSSI functions and striatal structures (StructuralVolume ~ NSSIfunction + Hemisphere + Sex + Age + TIV + ChildrenDepression + Loneliness + Defeat + ParentalConflict + ParentalAggression + ParentalAnxiety + ParentalDepression + (1 |

Subject)). Because of a large number of variables, multicollinearity was also examined by computing variance inflation factors (VIFs). In addition, we explored the associations with regional cortical thickness and another three subcortical volumes (amygdala, hippocampus and thalamus), in order to test the specificity of the potential association with the striatum. The Bonferroni method was also applied to correct for multiple comparisons ($p < 0.05/n$, $n = 34$, which included 3 subcortical and 31 cortical regions).

3. Results

3.1. Descriptive statistics

Demographics, clinical, and parental characteristics for all participants were presented in Table 1. There were no significant differences in age ($t = 1.38$, $df = 70$, $p = 0.173$), sex ($\chi^2 = 3.02$, $df = 1$, $p = 0.082$) and TIV ($t = 0.58$, $df = 70$, $p = 0.563$) between the two groups. NSSI patients had higher scores in depression ($t = 12.08$, $df = 70$, $p < 0.001$), loneliness ($t = 10.67$, $df = 70$, $p < 0.001$), and sense of defeat ($t = 11.10$, $df = 70$, $p < 0.001$). Also, parents of NSSI patients demonstrated a higher severity of anxiety ($t = 4.64$, $df = 70$, $p < 0.001$) and depression ($t = 3.78$, $df = 70$, $p < 0.001$) than those of healthy controls.

Table 1
Demographic characteristics and clinical information for 35 NSSI participants and 36 healthy controls.

Variables	NSSI participants	Healthy controls	t/χ^2	p
Age (M ± SD)	15.46 ± 1.54	16.20 ± 2.78	1.38	0.173
Sex (F/M)	33/2	29/7	3.02	0.082
Children depression (M ± SD)	27.91 ± 8.50	7.67 ± 5.30	12.08	<0.001
Loneliness (M ± SD)	51.71 ± 12.20	25.44 ± 8.20	10.67	<0.001
Sense of defeat (M ± SD)	43.06 ± 13.77	14.25 ± 7.17	11.10	<0.001
Duration of depression (months, M ± SD)	15.60 ± 11.65			
Age of depressive episode onset (M ± SD)	13.97 ± 1.56			
Age of first NSSI (M ± SD)	14.12 ± 1.1.38			
Nonsuicidal self-Injury functions				
Social influence (M ± SD)	1.26 ± 1.07			
Sensation seeking (M ± SD)	0.97 ± 1.03			
Internal emotion regulation (M ± SD)	2.09 ± 0.91			
External emotion regulation (M ± SD)	2.35 ± 1.09			
Parental information				
Parental age (M ± SD)	43.53 ± 4.14	43.91 ± 4.15	0.38	0.702
Parental conflict (M ± SD)	24.74 ± 7.75	22.97 ± 5.22	1.13	0.261
Parental aggression (M ± SD)	68.06 ± 15.86	67.61 ± 13.96	0.13	0.899
Parental anxiety (M ± SD)	6.54 ± 4.93	2.36 ± 2.18	4.64	<0.001
Parental depression (M ± SD)	6.96 ± 5.42	2.91 ± 3.39	3.78	<0.001
Treatment information				
Time with drug use (days, M ± SD)	25.73 ± 16.49			
Under psychotropic medication	35(100%)			
Antidepressant drugs (SSRIs)	35(100%)			
Benzodiazepine	27(77.14%)			
Brain Stimulation[a]	29(82.86%)			

SSRIs, Selective serotonin reuptake inhibitors; NSSI, nonsuicidal Self-Injury.
[a], Brain stimulation includes electroconvulsive therapy and transcranial magnetic stimulation.

Among the NSSI functions, intrapersonal functions represented the main reasons for adolescents' NSSI behaviors, with external emotional regulation scoring highest (2.35 ± 1.09), followed by internal emotional regulation (2.09 ± 0.91). Pairwise comparisons across four functions showed significant differences between external emotional regulation and internal emotional regulation ($t = 2.16$, $df = 34$, $p = 0.038$), social influence ($t = 6.00$, $df = 34$, $p < 0.001$) and sensation seeking ($t = 7.18$, $df = 34$, $p < 0.001$).

Correlation analyses showed that depression severity was significantly correlated with the four NSSI functions ($r = 0.44$–0.56, $df = 33$, all $p_s < 0.01$). Sense of defeat in learning was also linked to social influence ($r = 0.42$, $df = 33$, $p = 0.011$), sensation seeking ($r = 0.35$, $df = 33$, $p = 0.037$), and external emotional regulation ($r = 0.35$, $df = 33$, $p = 0.040$). Loneliness and parental characteristics showed no significant correlation with any of the NSSI functions. A correlation matrix of our primary outcomes of interest and covariates was presented in Table 2.

3.2. Differences in striatal structures between NSSI patients and healthy controls

Regarding group differences, ANCOVA analyses showed no significant interactions between group and hemisphere (Table S3). NSSI patients had significantly decreased volumes in caudate (controls, 3822.76 ± 384.65; NSSI, 3611.04 ± 435.91; $F_{(1,135)} = 13.17$, $p_{Bonferroni} < 0.05$), putamen (controls, 5492.76 ± 458.15; NSSI, 5238.78 ± 449.48; $F_{(1,135)} = 5.66$, $p_{Bonferroni} = 0.08$), pallidum (controls, 2094.52 ± 218.55; NSSI, 1968.71 ± 197.38; $F_{(1,135)} = 9.99$, $p_{Bonferroni} < 0.05$), and NAcc (controls, 539.10 ± 73.60; NSSI, 503.75 ± 89.97; $F_{(1,135)} = 5.99$, $p_{Bonferroni} = 0.06$).

3.3. Higher external emotional regulation was associated with smaller putamen volumes

There was no interaction between hemisphere and any NSSI functions on the four striatal volumes (Table S4). Thus, in the subsequent mixed regression models, we included hemisphere as a fixed factor, and age, sex, TIV, and depression severity as the covariates. For external emotional regulation, we found a negative association with putamen volume ($\beta = -0.39$, $z = -3.36$, $p_{Bonferroni} < 0.05$, Fig. 1), but not caudate ($\beta = -0.03$, $z = -0.19$, $p_{Bonferroni} > 0.05$), NAcc ($\beta = -0.21$, $z = -1.51$, $p_{Bonferroni} > 0.05$) or pallidum ($\beta = -0.04$, $z = 0.27$, $p_{Bonferroni} > 0.05$). Residuals of the putamen model were close to a normal distribution (P–P plot and Q-Q plot shown in Supplemental Fig. S2). For social influence, sensation seeking and internal emotional regulation, we did not find any associations with any of the striatal volumes (Table 3).

In subsamples of NSSI patients, we replicated the negative relationship between external emotional regulation and putamen (supplementary results, Table S5). The leave-one-out analysis also demonstrated such an association (supplementary results; Table S6). In the analysis after excluding male participants, negative association between external emotional regulation and putamen was robust and significant ($\beta = -0.41$, $z = -3.45$, $p_{Bonferroni} < 0.05$; Table S7).

3.4. Impact of social, academic and family factors on the association between putamen and external emotional regulation

When social, academic, and family environmental factors were added as covariates in regression analyses, the association between putamen and external emotional regulation remained significant (Table 4). Multicollinearity test showed that VIFs of all independent variables were <10 and 1/VIF were >0.1, suggesting that there was no serious collinearity among them. Sense of defeat in learning, loneliness, parental conflict, aggression, anxiety and depression showed no significant effects in the model (all $p_s > 0.05$) after Bonferroni correction.

Table 2
Correlation between depression severity, NSSI functions, loneliness, sense of defeat and family environment factors of NSSI patients.

Variables	1	2	3	4	5	6	7	8	9	10	11
1. Children depression	1										
2. Social influence	0.56**	1									
3. Sensation seeking	0.44**	0.54**	1								
4. Internal emotional regulation	0.44*	0.52**	0.52**	1							
5. External emotional regulation	0.44**	0.51**	0.43*	0.75***	1						
6. Loneliness	0.52**	0.14	0.18	0.14	−0.06	1					
7. Sense of defeat	0.70***	0.42*	0.35*	0.33	0.35*	0.38*	1				
8. Parental conflict	0.10	−0.04	−0.11	−0.06	−0.08	−0.03	−0.14	1			
9. Parental aggression	0.03	−0.13	−0.08	0.05	−0.14	0.06	−0.21	0.41**	1		
10. Parental anxiety	−0.06	−0.23	−0.13	−0.02	−0.28	0.17	−0.38*	0.44**	0.52**	1	
11. Parental depression	−0.15	−0.15	−0.03	−0.12	−0.32	0.13	−0.32	0.3	0.28	0.75***	1

*p < 0.05; **p < 0.01; ***p < 0.001.

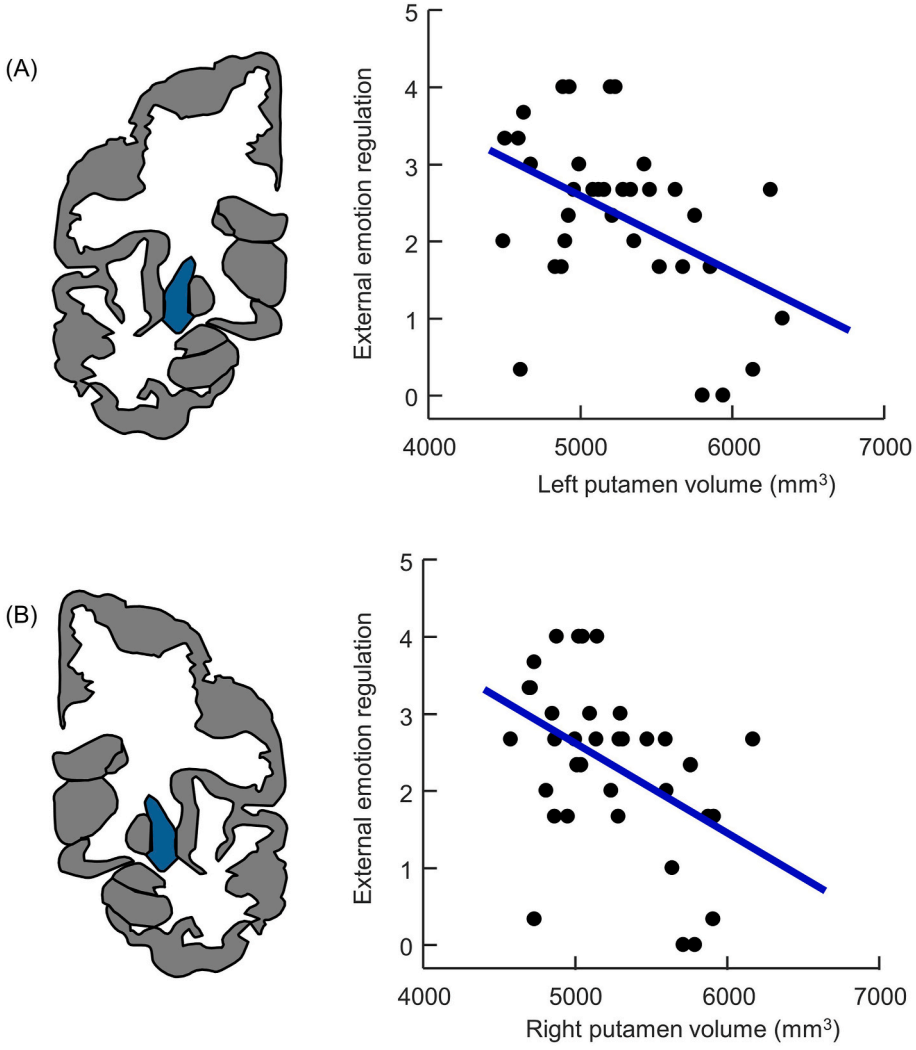

Fig. 1. Smaller gray matter volume of the left (A) and right (B) putamen are associated with higher external emotional regulation of performing NSSI. For the purposes of visualization, raw brain and behavior data points and their trends are depicted without adjustment of covariates.

3.5. Association between NSSI functions and other cortical and subcortical structures

To examine the specificity of the association with putamen, we also examined the associations between 4 NSSI functions and another 3 subcortical structures (i.e., amygdala, hippocampus and thalamus), as well as the 31 cortical regions. We found increased social influence of performing NSSI behaviors was associated with decreased cortical thickness in inferior parietal lobule ($\beta = -0.50$, $z = -3.40$, $p_{Bonferroni} = 0.05$, Table S8). None of the other NSSI functions showed significant associations with any of the 31 cortical regions or another three subcortical structures (Tables S8–S11). Specifically, regarding insula, for which significant associations have been demonstrated in previous literature, we did not find significantly associations with any of the four NSSI functions (social influence, $\beta = -0.06$, $z = -0.32$, $p_{Bonferroni} > 0.05$; sensation seeking, $\beta = 0.05$, $z = 0.27$, $p_{Bonferroni} > 0.05$; internal

Table 3
Associations between striatal volumes and social influence, sensation seeking, and internal emotional regulation functions.

		Social influence				Sensation seeking				Internal emotional regulation			
		Coef.	SE.	z value	$p_{Bonferroni}$	Coef.	SE	z value	$p_{Bonferroni}$	Coef.	SE	z value	$p_{Bonferroni}$
	NSSI function	**0.35**	**0.15**	**2.39**	**0.068**	**0.29**	**0.14**	**2.00**	**0.184**	**0.25**	**0.15**	**1.67**	**0.384**
Caudate	Hemisphere	0.12	0.06	2.21	0.108	0.12	0.06	2.21	0.108	0.12	0.06	2.21	0.108
	Sex	0.02	0.56	0.04	1.000	−0.43	0.60	−0.72	1.000	−0.32	0.60	−0.54	1.000
	Age	−0.19	0.13	−1.52	0.512	−0.20	0.13	−1.57	0.468	−0.22	0.13	−1.70	0.356
	TIV	0.50	0.13	3.79	<0.001	0.50	0.14	3.73	<0.001	0.58	0.14	4.15	<0.001
	Children depression	−0.49	0.15	−3.32	0.004	−0.43	0.14	−3.01	0.012	−0.42	0.15	−2.84	0.020
	NSSI function	**−0.03**	**0.14**	**−0.18**	**1.000**	**0.04**	**0.14**	**0.32**	**1.000**	**−0.21**	**0.14**	**−1.57**	**0.464**
Putamen	Hemisphere	−0.03	0.08	−0.40	1.000	−0.03	0.08	−0.40	1.000	−0.03	0.08	−0.40	1.000
	Sex	−1.09	0.54	−2.02	0.176	−1.14	0.57	−2.01	0.176	−0.87	0.54	−1.61	0.432
	Age	0.04	0.12	0.30	1.000	0.04	0.12	0.31	1.000	0.06	0.12	0.46	1.000
	TIV	0.56	0.13	4.35	<0.001	0.55	0.13	4.30	<0.001	0.51	0.13	4.07	<0.001
	Children depression	−0.01	0.14	−0.05	1.000	−0.04	0.14	−0.30	1.000	0.08	0.13	0.60	1.000
	NSSI function	**0.17**	**0.14**	**1.21**	**0.912**	**0.11**	**0.13**	**0.81**	**1.000**	**0.17**	**0.14**	**1.23**	**0.880**
Pallidum	Hemisphere	−0.78	0.10	−8.12	<0.001	−0.78	0.10	−8.12	<0.001	−0.78	0.10	−8.12	<0.001
	Sex	−0.43	0.53	−0.82	1.000	−0.62	0.56	−1.10	1.000	−0.65	0.55	−1.19	0.944
	Age	−0.19	0.12	−1.56	0.472	−0.19	0.12	−1.58	0.452	−0.21	0.12	−1.72	0.344
	TIV	0.39	0.13	3.15	0.008	0.40	0.13	3.14	0.008	0.44	0.13	3.46	0.004
	Children depression	−0.36	0.14	−2.57	0.040	−0.32	0.14	−2.37	0.072	−0.35	0.14	−2.59	0.040
	NSSI function	**0.13**	**0.15**	**0.83**	**1.000**	**0.05**	**0.15**	**0.33**	**1.000**	**−0.07**	**0.15**	**−0.45**	**1.000**
NAcc	Hemisphere	0.63	0.12	5.36	<0.001	0.63	0.12	5.36	<0.001	0.63	0.12	5.36	<0.001
	Sex	−0.91	0.58	−1.58	0.460	−1.00	0.61	−1.65	0.396	−0.87	0.60	−1.46	0.58
	Age	−0.11	0.13	−0.84	1.000	−0.11	0.13	−0.86	1.000	−0.11	0.13	−0.82	1.000
	TIV	0.29	0.14	2.10	0.144	0.29	0.14	2.13	0.132	0.28	0.14	2.03	0.168
	Children depression	−0.33	0.15	−2.14	0.128	−0.28	0.15	−1.93	0.216	−0.23	0.15	−1.53	0.500

Coef. = coefficient, SE = standard error, TIV = total intracranial volume. p-value indicates the corrected value after multiple comparison correction with Bonferroni method.

Table 4
Association between putamen volume and external emotional regulation score of performing NSSI. Results are shown with covariates in mixed-effects maximum likelihood regression models.

Variables	Coefficient	SE	z value	$p_{Bonferroni}$	95% CI	
					Lower	Upper
External emotional regulation	−0.47	0.12	−3.98	<0.001[a]	−0.70	−0.24
Hemisphere	−0.03	0.08	−0.40	1.000	−0.19	0.13
Sex	−0.49	0.48	−1.03	1.000	−1.43	0.45
Age	0.05	0.10	0.46	1.000	−0.15	0.24
TIV	0.44	0.11	4.13	<0.001[a]	0.23	0.64
Children depression	0.42	0.17	2.46	0.056	0.09	0.75
Loneliness	0.07	0.12	−0.54	1.000	−0.30	0.17
Sense of defeat	−0.23	0.16	−1.47	0.572	−0.54	0.08
Parental conflict	−0.10	0.11	−0.94	1.000	−0.31	0.11
Parental aggression	0.07	0.11	0.58	1.000	−0.16	0.29
Parental anxiety	−0.43	0.18	−2.41	0.064	−0.78	−0.08
Parental depression	0.31	0.15	2.10	0.144	0.02	0.61

SE = standard error, TIV = total intracranial volume. p-value indicates the corrected value after multiple comparison correction with Bonferroni method.
[a] indicates $p_{bonferroni}$ <0.05. CI means confidence interval.

emotional regulation, β = 0.30, z = 1.72, $p_{Bonferroni} > 0.05$; external emotional regulation, β = 0.36, z = 1.98, $p_{Bonferroni} > 0.05$).

4. Discussion

In the current study, we investigated four different functions of NSSI in depressive adolescents and examined their associations with striatum and other brain regions. Our results indicated that external emotion regulation was the main function for depressive adolescents to engage in NSSI behavior. In addition, higher external emotion regulation scores were associated with smaller putamen volumes—i.e., participants with smaller putamen volumes were more likely to report external emotion regulation as a motive to engage in NSSI. The association was also independent of potential confounding factors including depressive symptoms, social loneliness, sense of defeat in learning, as well as some family environmental factors. Our findings highlight the role of the putamen in adolescents' NSSI behaviors, indicating that smaller putamen might serve as a biomarker for depressive adolescents who engage NSSI behavior for external emotion regulation.

Our results are consistent with previous neuroimaging studies that reported abnormalities in reward-related brain regions (Auerbach et al., 2021; Marchand et al., 2013; Osuch et al., 2014) and deepen our understanding of the neural basis of NSSI. In particular, the key NSSI function of external emotion regulation was unrelated to regions involved in emotion processing (e.g., amygdala, anterior cingulate cortex, prefrontal cortex, etc.) proper but rather related to the striatum, a classical reward-related structure. This suggests a strong association between deficits in reward processing and NSSI behaviors, and probably a causal role of the former in the latter.

These observations can be interpreted in the context of classical dual-pathway approaches to intentional action (e.g., O'Doherty et al., 2004). These approaches are based on the idea that behavioral control emerges from a competition between an intentional route, in which action decisions are based on expected utility and reward, and a more automatic route, which relies on overlearning and is not or less sensitive to reward (for an overview, see (Watson et al., 2018)). According to dual-pathway logic, overlearning increases the impact of the automatic route, which dominates action control in habitual action, including addiction and similar pathological behavioral tendencies. Even though the implication that habitual action should be considered non-intentional can be questioned (Hommel and Wiers, 2017), there is strong evidence that the control of habitual, strongly overlearned behavior differs systematically from the control of novel actions (Watson et al., 2018). Importantly for our purposes, the intentional route is assumed to rely on the ventral striatum, the major hub in computing predicted reward—which the intentional route relies on; whereas the habitual route is assumed to rely on the dorsal striatum (Burton et al., 2015; O'Doherty et al., 2004)—the

habit hub. Our findings show that engaging in NSSI for the purpose of dealing with challenges of external emotion regulation was related to dorsal rather than ventral striatal structures, which according to dual-pathway logic fits with considering NSSI as an overlearned habit that is no longer sensitive to action consequences. Indeed, NSSI behavior is assumed to be triggered by automatically registered NSSI that take over behavioral control (Riquino et al., 2020). Our findings also suggest interesting links between NSSI and other risky behaviors. Because of the association between atypicalities in reward pathways and NSSI and repeated engagement in NSSI, researchers have proposed that NSSI may be similar to substance use (Poon et al., 2019) and perhaps to dietary decisions (Morawetz et al., 2020). Although these ideas are still controversial (Victor et al., 2012), the reward circuit should be the focus of future NSSI studies.

Previous studies have demonstrated that depressive symptoms, loneliness, academic defeat, and poor family environment had effects on NSSI behaviors (Hawton et al., 2013; Nemati et al., 2020; Russell et al., 2020; Wang et al., 2020b). These factors were also associated with cortical and subcortical brain areas, which might bias the association between brain structure and NSSI. Recent longitudinal studies suggested that adolescent striatum functional connectivity related with depressive level and predicted future risk for depressive disorder and the severity of anhedonia (Pan et al., 2017, 2022). Another functional MRI study using a monetary reward task showed that depression severity was associated with blunted response of cortico-striatal circuits to anticipation (Rappaport et al., 2020). In addition, a study about family environment highlighted that parents' past aggression associated with reduced activation in the insula and NAcc when children rating their parents' emotions. The association between parental aggression and subsequent adolescents' aggression toward their parents was mediated by the right amygdala (Saxbe et al., 2016). In our study, we recruited the adolescent patients with depression and controlled these potential confounding factors. Thus, the association with putamen we found might primarily be driven by external emotion regulation. Such consistent results help to identify the role of putamen as a neurobiological marker of NSSI.

This study has several limitations. Firstly, this study has a small sample size and it is cross-sectionally designed. However, even with a limited sample, this study could serve as a basis for future research about brain mechanisms of NSSI functions. Secondly, more factors that associated with NSSI and emotion regulation should be considered. For instance, dissociation was positively associated with maladaptive domains of emotion regulation. Patients with dissociation disorder had a higher possibility of engaging in NSSI behaviors (Rossi et al., 2019). There is a need to test whether dissociation could be linked to striatum and NSSI (Cavicchioli et al., 2021). Thirdly, although our homogenous sample may eliminate some variation associated with psychiatric symptoms, whether our findings can be generalized beyond depressed adolescents remains a concern. Recent evidence suggested common abnormalities of brain networks among various psychiatric disorders (Li et al., 2021; Xia et al., 2019), especially the brain reward circuits (McTeague et al., 2020; Sharma et al., 2017), which indicated that dorsal striatum might be the specific biomarker of NSSI across disorders. Future studies should be conducted in other psychiatric diagnoses. Fourth, the time period between their first engagement in NSSI and the brain scan was about 1 year, which might affect the results to some extent, although functions of the NSSI and brain structure could be moderately stable in an one-year interval (Daukantaite et al., 2020; Hedman et al., 2012; You et al., 2013).

5. Conclusions

In conclusion, external emotion regulation is a critical function of NSSI in depressive adolescents, and it is significantly correlated with reduced volume in putamen. When depressed adolescents regulate emotions of frustration or anger, putamen might be a biomarker that initiates NSSI behaviors. Identifying NSSI-related brain structural markers implicates the potential development of preventive intervention programs for reducing the likelihood of this risk-taking behavior.

Disclosures

All authors declare they have no conflicts of interest.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2022.09.014.

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