

Research paper

Large scale brain functional networks underlying non-suicidal self-injury behavior, addiction and functions in youth psychiatric disorders

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ABSTRACT

Background: Non-suicidal self-injury (NSSI) is a common high-risk behavior in adolescents and it occurs in various psychiatric disorders, especially major depressive disorder (MDD). It remains largely unknown whether and which brain functional networks contribute to NSSI across youth mental disorders.

Methods: This study analyzed brain functional data acquired from 156 adolescents (MDD + NSSI group, $n = 44$, age = 15.32 ± 1.51 ; MDD-NSSI group, $n = 32$, age = 15.36 ± 1.96 ; healthy controls, $n = 80$, age = 15.92 ± 2.72). NSSI behavior, four NSSI functions (internal and external emotion regulation, social influence and sensation seeking), as well as the addictive feature were assessed using the Ottawa Self-injury Inventory. Using support vector machine recursive feature elimination classification and regression models, we investigated the brain functional networks that predicted NSSI. External validations were performed in an ADHD cohort ($n = 40$) and a transdiagnostic psychiatric cohort ($n = 40$).

Results: The brain networks related to NSSI behavior were mainly composed of inter-network connections between the fronto-parietal, motor, limbic, basal ganglia networks. These networks were also associated with it four functions and the additive feature. Notably, the fronto-parietal network was involved in all NSSI components. External validations in both the ADHD and the transdiagnostic cohorts validated the associations of these functional networks with NSSI severity.

Conclusions: Our results demonstrate that the fronto-parietal, motor, limbic and basal ganglia networks play key roles in NSSI among youth with psychiatric disorders, offering insights into potential brain targets for prevention and intervention.

1. Introduction

Non-suicidal self-injury (NSSI) refers to individuals intentionally inflicting repeated and direct harm upon their bodies without any suicidal intent. This behavior encompasses various actions, including but not limited to cutting, scratching, and burning the skin, leading to direct damage to body tissues (Klonsky, 2011; Nock, 2009; Wang et al., 2022). Currently, NSSI is a common problematic behavior in adolescents. The prevalence of NSSI among adolescents reaches 20 %, and it is up to 30 %

to 82 % among adolescents with psychiatric disorders (Lucena et al., 2022; Wang et al., 2024). Considering that NSSI is a prevalent symptom in various psychiatric disorders (Bentley et al., 2015; Patel et al., 2021; Swanson et al., 2014), and that psychiatric disorders link with altered brain functional networks, there is a need to explore the brain functional network alterations underlying NSSI among adolescents with distinct psychiatric disorders. In addition, as NSSI is a multifactorial behavior, it is important not only to observe its occurrence but also to examine potential addiction/repeatability and the interpersonal and intrapersonal

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motivations (i.e. functions) it may serve (Manca et al., 2014; Taylor et al., 2018). Identifying the brain functional network associations of NSSI occurrence, repeatability and functions may potentially provide valuable targets for neuromodulation-based intervention for those with NSSI behavior across psychiatric disorders.

Most previous imaging studies focused on the NSSI behavior per se, and examined functional connectivity associations by comparing individuals that do or do not engage in NSSI. Researchers have found alterations in multiple brain networks, such as the fronto-parietal, default mode, limbic, and reward networks. In the fronto-parietal and limbic networks, individuals engaging in NSSI exhibited altered functional connectivity between frontal lobe regions, the anterior cingulate, insula, parahippocampal gyrus, and the amygdala (Reitz et al., 2015; Santamarina-Perez et al., 2019; Schreiner et al., 2017). In the default mode network, abnormal functional connectivity has been found between angular gyrus and frontoparietal regions, and between anterior cingulate gyrus and the paracentral gyrus (Mürner-Lavanchy et al., 2023; Otto et al., 2023). In the reward circuits, NSSI patients showed stronger functional connectivity between the putamen and angular gyrus, cingulate gyrus, insula, and superior frontal gyrus when compared with healthy controls (Chen et al., 2023; Yi et al., 2023). In addition, functional connectivity between nucleus accumbens and inferior cerebellum was positively associated with NSSI severity (Chen et al., 2023). These findings suggested that NSSI associated with widespread brain functional networks. However, it should be noted that previous brain network studies on NSSI have mainly utilized seed-based analyses and independent component analyses (Chen et al., 2023; Ho et al., 2021; Reitz et al., 2015; Santamarina-Perez et al., 2019; Schreiner et al., 2017; Yi et al., 2023; Zhang et al., 2025), which mainly rely on prior knowledge and assumptions. This may add to inconsistent results between studies and miss other important brain regions or functional networks (Bookstein, 2001; Davatzikos, 2004; Lv et al., 2018). To gain a full picture of NSSI-related brain networks, it is crucial to examine the whole brain large-scale functional brain networks.

NSSI is characterized by addictive feature, including a strong urge to self-harm and repetitive behavior, similar to craving in substance use disorders (Victor et al., 2012). The typical characteristics of NSSI addiction include: the individual gradually becomes dependent on engaging in NSSI, cannot effectively control the thoughts of NSSI, shows obvious tolerance to NSSI, and continues to harm themselves despite the negative effects (Buser and Buser, 2013; Nixon et al., 2002). Accordingly, in reward-related brain regions such as the ventral striatum, NSSI participants showed significantly increased activation during gambling tasks and the monetary reward task (Sauder et al., 2016). Amygdala, putamen, and frontal cortex showed reduced activation, which was associated with an increased frequency of NSSI thoughts (Mayo et al., 2021; Poon et al., 2019; Reitz et al., 2015). Hence, it is clear that addiction is an important feature of NSSI, but the large-scale brain networks underlying NSSI addiction have been rarely investigated.

NSSI may serve to satisfy different motivations or functional demands, including interpersonal and intrapersonal functions (Klonsky et al., 2015; Turner et al., 2012). The intrapersonal function plays a key role in emotion regulation, including internal and external emotion regulation (Guérin-Marion et al., 2018). Studies based on emotional tasks indicate that certain regions in the prefrontal cortex and the basal ganglia structures such as amygdala and putamen are involved in the emotional regulation function of NSSI (Mayo et al., 2021; Poon et al., 2019; Reitz et al., 2015). Interpersonal function includes social influence and sensation seeking (Guérin-Marion et al., 2018). The motivation of social influence is to exert influence within a social context and provoke a response from others. Sensation seeking refers to the pursuit of sensory stimulation or excitement through NSSI (Guérin-Marion et al., 2018; Heath et al., 2009; Kentopp et al., 2021; Knorr et al., 2013). Interpersonal functions encompass brain regions associated with the reward system, social cognition, and emotional resonance, including the limbic system and prefrontal cortex (Groschwitz et al., 2016; Osuch et al.,

2014). Few studies have investigated the structural alterations associated with NSSI functions. Smaller volumes in the anterior insula, putamen and secondary somatosensory cortex are associated with frequent engagement in NSSI for emotion regulation and sensation seeking functions (Lee et al., 2023; Wang et al., 2022). However, it remains largely unknown whether these NSSI functions are associated with large-scale brain networks.

This study sought to identify functional networks associated with NSSI behavior, its four functions and the addictive feature. Our primary cohort consisted of adolescents diagnosed with depression, considering the high prevalence of NSSI among them (Csorba et al., 2009; Hawton et al., 2013). To examine whether potential biomarkers were robust and replicable, we also included two validation cohorts: adolescents with attention deficit hyperactivity disorder (ADHD) (Hinshaw et al., 2012; Meza et al., 2016) and a transdiagnostic sample (Bentley et al., 2015; Swanson et al., 2014). Based on previous studies, we hypothesized that NSSI behavior, addiction, and functions relate to multiple brain functional networks, such as the fronto-parietal, reward and default mode networks.

2. Methods

2.1. Participants

The primary dataset (Dataset 1) included 156 participants from the Shandong Adolescent Neuroimaging of Depression (SAND), our ongoing project to examine the associations among brain imaging, cognition, and adolescent depression (Wang et al., 2022; Zhang et al., 2024). Of these, 44 were diagnosed with major depressive disorder (MDD) and engaged in NSSI (MDD + NSSI group), 32 were MDD patients without NSSI (MDD-NSSI group), and 80 were healthy controls. Both patient groups were assessed by two psychiatrists from Shandong Mental Health Center using the DSM-5 criteria and were receiving medication treatment with selective serotonin reuptake inhibitors (SSRIs) antidepressants, including Escitalopram and Sertraline. None of the patients had comorbid psychiatric disorders, such as schizophrenia, ADHD, alcohol use disorder, or autism. The detailed diagnostic and inclusion criteria were provided in supplemental material. Written informed consent was obtained from all participants and their parents. The study obtained approval from the ethics committee at Shandong Mental Health Center and Shandong Normal University.

Validation datasets included 40 patients with ADHD (Dataset 2) and 40 patients with transdiagnostic psychiatric disorders (Dataset 3). All these patients had a history of NSSI and were from the Healthy Brain Network project (releases 1–9, http://fcon_1000.projects.nitrc.org/indi/cmi_healthy_brain_network/index.html). This project is a comprehensive study aiming at exploring the trajectory of brain development and identifying biomarkers associated with mental health (Alexander et al., 2017). The HBN protocol has received ethical approval from the Chesapeake Institutional Review Board, and informed written consent was obtained from the legal guardians of all participants.

2.2. Clinical assessments

In the primary dataset (Dataset 1), the Ottawa Self-injury Inventory was utilized to evaluate patients' NSSI behavior, addiction and four NSSI functions: internal emotion regulation, external emotion regulation, social influence, and sensation seeking (Nixon et al., 2015; Rodav et al., 2014). Chinese version of this inventory has been proven effective in measuring related indicators of NSSI in adolescents (Zhang et al., 2019). For each subdimension, the score was obtained by calculating the mean score of all items within that dimension. The higher a patient scored on a specific function, the more likely they were to perceive that function as the primary motivation to engage in NSSI (Wang et al., 2022). The Children's Depression Inventory was utilized to assess the severity of depression, with a focus on the total score. A higher score indicated a

more severe depressive condition.

In validation datasets (Dataset 2 and 3), the Repetitive Behavior Scale was used to measure the severity of NSSI (Bodfish et al., 1999; Lam and Aman, 2007). This scale contained a total of 43 items, with items 7 to 14 serving as NSSI subscales. The parent report version was adopted based on a 4-point Likert scale ranging from “0 - behavior did not occur” to “3 - behavior did occur and is a serious problem.” When filling out the scale, respondents were instructed to refer to the child’s situation over the previous month. The NSSI severity score was calculated by summing the scores of each item within the NSSI subscale.

2.3. Functional network construction and feature selection

Functional brain data were acquired and preprocessed in a standard pipeline (see supplemental material). We constructed the functional connectivity matrix for each subject based on the Shen functional atlas of 268 nodes (Shen et al., 2013). The functional connectivity between nodes (i.e., edges) was defined as the Pearson correlation coefficient, followed by a Fisher-Z transformation for each edge. Finally, a 268*268 matrix was obtained for each subject.

After constructing the functional connectivity matrix, we performed feature selection by *t*-test (MDD + NSSI vs. MDD-NSSI, uncorrected, $p < 0.01$). Edges showing significant differences were selected to build up the feature set. We also performed the same feature selection between the healthy controls and two MDD groups.

2.4. Functional networks associated with NSSI behavior, addition, and its functions

After feature selection, we first constructed a classification model to identify the functional networks that were associated with NSSI behavior, using functional connectivity to classify the MDD-NSSI group and the MDD + NSSI group in Dataset 1. Here, we employed the linear kernel support vector machine recursive feature elimination (SVM-RFE) classification model (Ding et al., 2015; Richhariya et al., 2020). The core principle lied in iteratively removing the features (i.e., edges) that contribute minimally to classification. This process progressively refined the optimal feature subset, thereby enhancing both the model’s predictive performance and generalization capability. SVM-RFE, compared to SVM, was particularly suitable for handling high-dimensional data. The detailed steps of SVM-RFE classification were provided in the supplemental methods. For healthy controls and two MDD group, SVM classification models were performed to investigate whether healthy controls vs. MDD + NSSI group would exhibit more abnormal brain functional connectivities compared to healthy controls vs. MDD-NSSI group. We employed accuracy to evaluate the classification performance and utilized permutation tests ($n = 1000$, $p < 0.05$) to determine the significance.

Based on the optimal feature set derived from the SVM-RFE classification model, we utilized an SVM-RFE regression model to predict the NSSI addiction scores and the four function scores of NSSI in the MDD + NSSI group (Dataset 1). The detailed steps of SVM-RFE regression were provided in the supplemental materials. We utilized the root mean square error (RMSE) to evaluate the prediction performance, and employed leave-one-out cross-validation and permutation test to determine the model significance. The functional connectivities with best prediction performance were depicted as brain functional networks associated with NSSI addiction and its functions.

2.5. Internal validation and external validation

For internal validation, we employed a stricter threshold for feature selection (MDD + NSSI vs. MDD-NSSI, uncorrected $p < 0.005$) in Datasets 1 and re-classified the MDD + NSSI group and the MDD-NSSI group using a SVM classification model. Similarly, if the model was statistically significant, the feature set represented the brain functional

network associated with NSSI behavior. The internal validation was conducted by assessing the similarity between this network (with a threshold of $p < 0.005$) and our main findings of NSSI behavior-related network (with a threshold of $p < 0.01$). In addition, to address the issue of limited and imbalanced sample sizes, we implemented the Synthetic Minority Oversampling Technique (SMOTE) (see supplementary methods) to verify the robustness of our classification models (MDD + NSSI vs. MDD – NSSI and MDD + NSSI vs. healthy controls). SMOTE is a widely used method that generates synthetic minority samples through feature-space interpolation, thereby improving model performance in class-imbalanced datasets.

Regarding external validation, we employed the SVM-RFE regression model to predict the severity of self-injury in both the ADHD cohort (Dataset 2) and the transdiagnostic cohort (Dataset 3). Specifically, we extracted the functional connectivities from the optimal SVM classification model for NSSI behavior in Dataset 1 as the feature set. We then used this feature set to predict NSSI severity in both the ADHD cohort and the transdiagnostic cohort. If all or part of these functional connectivities demonstrated significant predictive power for NSSI severity in these two external datasets, it would indicate that the brain functional networks associated with NSSI behavior identified in this study possess strong generalizability and external validity.

3. Results

3.1. Demographic and clinical characteristics

In Dataset 1, there were no significant differences in sex and age among the MDD + NSSI group, the MDD-NSSI group, and the healthy controls. These three groups showed significant differences in depression severity ($F = 114.71$, $p < 0.001$, Table 1): MDD + NSSI group scored higher than MDD-NSSI group ($p < 0.001$) and healthy controls ($p < 0.001$); MDD-NSSI group scored higher than healthy controls ($p < 0.001$). Illness duration between the MDD + NSSI group and the MDD-NSSI group was not significantly different ($t = -1.96$, $p = 0.054$). Among the four NSSI functions, internal emotion regulation had the highest mean score (Table 1). Demographic and diagnostic information for Datasets 2 and 3 are presented in Tables S1 and S2.

Table 1

Demographic characteristics and clinical information for MDD + NSSI patients, MDD-NSSI patients and healthy controls (Dataset 1).

Characteristics	MDD + NSSI	MDD-NSSI	Healthy controls	$F/\chi^2/t$	p
Age (Mean $\pm$ SD, year)	15.32 $\pm$ 1.51	15.36 $\pm$ 1.96	15.92 $\pm$ 2.72	1.28	0.28
Sex (Female/Male)	8\36	12\20	27\53	4.31	0.12
Children depression (Mean $\pm$ SD)	26.80 $\pm$ 8.96	19.97 $\pm$ 8.60	7.51 $\pm$ 4.81	114.71	<0.001
Illness duration (Mean $\pm$ SD, month)	14.67 $\pm$ 9.21	20.37 $\pm$ 16.00		-1.96	0.054
NSSI addiction (Mean $\pm$ SD)	13.36 $\pm$ 7.66				
NSSI functions					
Internal emotion regulation (Mean $\pm$ SD)	10.80 $\pm$ 9.01				
Social influence (Mean $\pm$ SD)	7.59 $\pm$ 8.05				
External emotion regulation (Mean $\pm$ SD)	4.98 $\pm$ 4.57				
Sensation seeking (Mean $\pm$ SD)	2.89 $\pm$ 3.75				

SD = standard deviation. NSSI = nonsuicidal self-injury. MDD = major depressive disorder.

3.2. Functional brain networks related to NSSI behavior

In Dataset 1, *t*-tests between the MDD + NSSI and MDD-NSSI groups yielded 153 edges as the feature set (uncorrected $p < 0.01$). After SVM-RFE classification, we obtained a network containing 60 edges related to NSSI behavior (accuracy = 91.30 %, AUC = 0.92), and the SVM classification model based on these 60 edges passed the permutation test ($p = 0.002$). Fig. 1A shows the distribution of these 60 edges that were related to NSSI behavior. This network primarily consisted of inter-network connections between the fronto-parietal and limbic, basal ganglia, motor, visual association, visual I, and cerebellum networks; between the motor and limbic, default mode, and cerebellum networks; and between the basal ganglia and limbic networks. In general, the fronto-parietal, motor, limbic, and basal ganglia networks had more inter-network connections with other networks.

The SVM classification models for edges that emerged from healthy controls vs. MDD + NSSI/MDD-NSSI groups showed high classification accuracy (healthy controls vs. MDD-NSSI: 314 edges, accuracy = 97.06 %, AUC = 0.99, $p = 0.001$, Fig. S2A; healthy controls vs. MDD + NSSI: 701 edges, accuracy = 81.08 %, AUC = 0.94, $p = 0.003$, Fig. S2B). The main differences between the two classification results were the presence of more disturbed brain functional connectivity in healthy controls vs. MDD + NSSI group, primarily involving the fronto-parietal, motor and basal ganglia networks, which had more connections with other networks.

To further investigate the impact of controlling for covariates on our results, we conducted two additional analyses. During the feature selection stage, we incorporated two sets of covariates (first: age and sex; second: age, sex, and illness duration) and performed between-group comparisons using a general linear model ($p = 0.01$, uncorrected) to

select features. This process yielded 127 edges (first analysis) and 158 edges (second analysis), respectively. Based on these edges, we reapplied the SVM-RFE classification model (MDD + NSSI group vs. MDD-NSSI group). The results showed that models containing 59 edges (first analysis, Fig. S3) and 57 edges (second analysis, Fig. S4) achieved optimal classification performance (first: accuracy = 91.30 %, AUC = 0.93, $p = 0.003$; second: accuracy = 91.30 %, AUC = 0.95, $p = 0.002$). The distribution of these edges was largely consistent with our main findings, indicating that the fronto-parietal, basal ganglia, motor, and limbic networks exhibit a greater number of inter-network connections with other networks.

Given that the between-group difference in illness duration was marginally significant (MDD + NSSI group = 14.67 ± 9.21 ; MDD-NSSI group = 20.37 ± 16.00 ; $t = -1.96$; $p = 0.054$, Table 1), we further investigated whether illness duration influenced our main findings. To clarify this, we performed support vector regression using the 60 edges associated with NSSI behavior from our main results to predict illness duration across all MDD subjects. The results showed very poor predictive performance (RMSE = 1.62, $r = 0.15$, permutation test $p = 0.20$), demonstrating that these 60 edges are relatively specific to NSSI.

3.3. Functional brain networks related to NSSI addiction

Based on the 60 edges related to NSSI behavior, we built the SVM-RFE regression model for NSSI addiction. The results showed that a model with 12 edges had the best prediction performance (RMSE = 0.66, $p = 0.001$). Fig. 1B shows these 12 edges related to NSSI addiction. These edges mainly involved inter-network connections between fronto-parietal and limbic and motor networks, as well as between the cerebellum and motor networks.

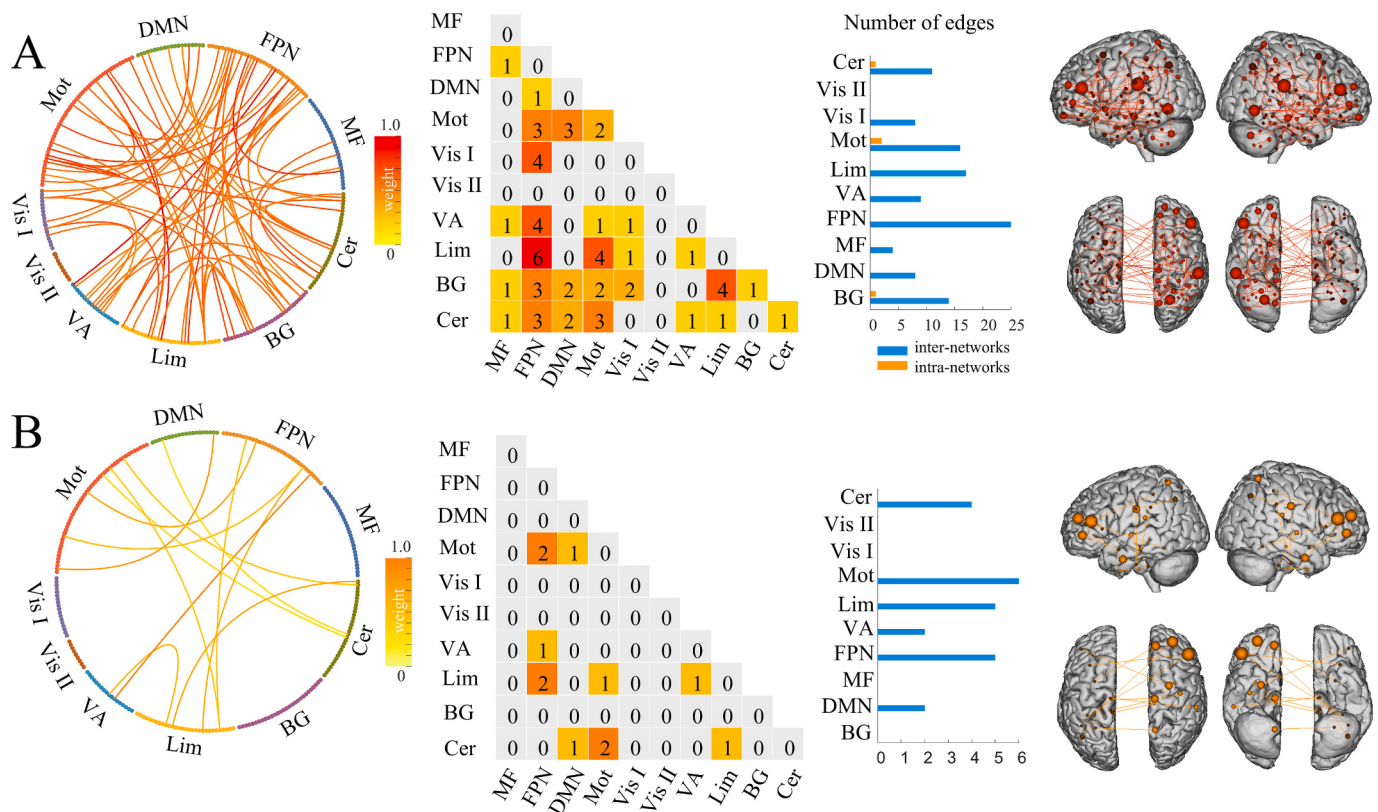


Fig. 1. Functional brain networks that associated with NSSI behavior and its addiction. 60 functional edges are related to NSSI behavior (A), mainly constructed with inter-network connections between the fronto-parietal and limbic, basal ganglia, motor, visual association, visual I, and cerebellum networks, particularly connections between the fronto-parietal and limbic networks. 12 functional edges are related to NSSI addiction (B), most of which involve inter-network connections between the fronto-parietal, limbic and motor networks, as well as between the cerebellum and motor networks. MF = Medial Frontal, FPN = Fronto-parietal, DMN = Default Mode, Mot = Motor, Vis I = Visual I, Vis II = Visual II, VA = Visual Association, Lim = Limbic, BG = Basal Ganglia, Cer = Cerebellum.

3.4. Functional brain networks related to four NSSI functions

Similarly, the SVM-RFE regression models for the four NSSI functions were built based on the 60 edges related to NSSI behavior. For internal emotion regulation, the SVM regression model with 21 edges had the best prediction performance ($RMSE = 0.65$, $p = 0.001$; Fig. 2A). For social influence, the SVM regression model with 17 edges had the best prediction performance ($RMSE = 0.66$, $p = 0.001$; Fig. 2B). Regarding external emotion regulation, the SVM regression model with 28 edges had the best prediction performance ($RMSE = 0.66$, $p = 0.001$; Fig. 2C). As to sensation seeking, the SVM regression model with 22 edges had the best prediction performance ($RMSE = 0.72$, $p = 0.001$; Fig. 2D).

Similar patterns of brain networks were observed for the four NSSI functions. The frontal-parietal, limbic, motor, basal ganglia, cerebellar and other networks exhibited many inter-network connections, indicating consistently high participation. Specifically, for internal emotion regulation, there were many inter-network connections between the frontal-parietal and limbic networks, between the basal ganglia and visual I networks, and between the motor and default mode and basal ganglia networks. For social influence, there were many inter-network connections between the frontal-parietal and motor networks, along with intra-network connections in the motor network. For external emotion regulation, there were many inter-network connections between the frontal-parietal and visual association, limbic, basal ganglia, and cerebellar networks, between the motor and limbic networks, and between the cerebellar and basal ganglia networks. For sensation seeking, there were many inter-network connections between the frontal-parietal and visual association networks, between the motor and cerebellar networks, and between the basal ganglia and visual I and limbic networks.

3.5. Internal validation: performing feature selection using a stricter threshold

We conducted internal validation by constructing the SVM classification model using a stricter threshold (uncorrected $p < 0.005$) for the t -test between the MDD + NSSI and MDD-NSSI groups. A total of 69 edges were identified and they effectively distinguished the two groups (accuracy = 95.65 %, $AUC = 0.96$, $p = 0.001$, Fig. S1). Similar to the main results, this network was mainly composed of inter-network connections between the fronto-parietal and limbic networks, between the default mode and basal ganglia and motor networks, and between the cerebellum and motor networks. In addition, SMOTE results demonstrated robust and consistent classification performance, further supporting the reliability of our main analyses (see Supplementary Results).

3.6. External validation: prediction of NSSI severity in the ADHD cohort and the transdiagnostic cohort

The 60 edges associated with NSSI behavior in Dataset 1 were used to construct SVM-RFE regression models for NSSI severity in the ADHD cohort and the transdiagnostic cohort.

A network with 23 edges showed the best prediction performance in the ADHD cohort ($RMSE = 0.62$, $p = 0.001$). Fig. 3A shows the distribution of these brain networks, which were similar to our main results and mainly involved the frontal-parietal, limbic, basal ganglia, motor, cerebellar and other networks. The most connections were observed between the limbic network and frontal-parietal network and between the cerebellar network and motor network.

In the transdiagnostic cohort, we found a network comprising 31 edges demonstrated the best prediction performance ($RMSE = 0.37$, $p = 0.001$). Fig. 3B shows the distribution of these brain networks, which were generally consistent with our main findings. Brain networks associated with NSSI severity in the transdiagnostic cohort involved inter-network connections between the frontal-parietal, limbic, basal ganglia, motor and other networks. The most connections were observed

between the limbic network and frontal-parietal and between the limbic network basal ganglia network.

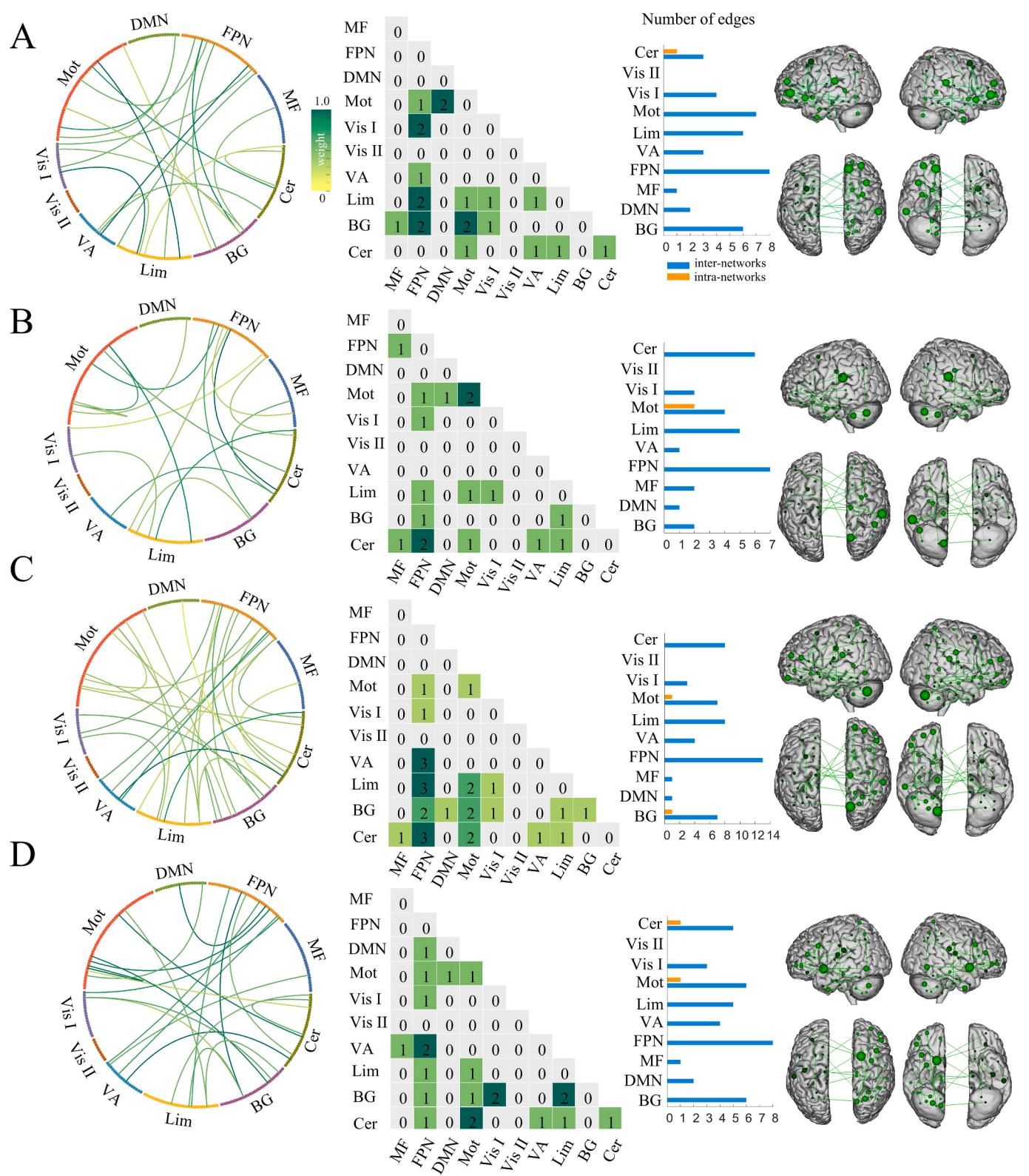
4. Discussion

In the present study, we investigated brain functional networks underlying NSSI behavior in adolescent depression, from a large-scale brain functional network perspective. The brain networks related to NSSI behavior mainly involved connections between the fronto-parietal, limbic, motor and basal ganglia networks and other networks. We found these functional connectivities could successfully predict NSSI addiction and the four related functions (internal emotion regulation, social influence, external emotion regulation, and sensation seeking). These results were validated both internally and externally. In the ADHD and transdiagnostic samples, some functional connections identified in the primary dataset successfully predicted the severity of NSSI.

We found the involvement of the fronto-parietal, limbic, basal ganglia, and motor networks, despite that specific connectivity patterns were different for NSSI behavior, addiction, and functions. This was validated internally and in the external ADHD and transdiagnostic datasets (Dataset 2 and 3). The neuroanatomy of the network found in the present study mirrored previous fMRI studies of NSSI, which reported lesions of the connectivity in the fronto-parietal, limbic, basal ganglia and motor networks (Chen et al., 2023; Groschwitz et al., 2016; Plener et al., 2012; Schreiner et al., 2017; Yan et al., 2022). This was in line with the NSSI patients' difficulties in dealing with negative emotions (Brañas et al., 2021; Otto et al., 2023), and their reliance on physical movement or sensory feedback (Oldehinkel et al., 2019; Scott, 2016). These problems may further make them more likely to feel self-rewarded by NSSI behavior and thus increase the likelihood of the occurrence of NSSI (Haber and Knutson, 2010; Halicka-Maslowska et al., 2020).

Among the brain networks associated with NSSI, the fronto-parietal network showed consistently high involvement. This suggests that abnormalities in the fronto-parietal network might represent the core neural underpinnings of NSSI, despite differences in the severity of NSSI among patients or their motivation to engage in NSSI. Previous NSSI studies have also found abnormalities in the fronto-parietal network. Specifically, NSSI adolescents showed abnormal activation in regions within the fronto-parietal network, such as the superior frontal gyrus, cingulate gyrus, and dorsolateral prefrontal cortex, when performing tasks involving social feedback (Dahlgren et al., 2018; Osuch et al., 2014; Perini et al., 2019), which is often associated with abnormal functioning of inhibitory control and emotional regulation (Kim et al., 2020). The large number of inter-network connections between fronto-parietal and other networks (e.g., the limbic network) in our results also fit with the observation that NSSI patients exhibit defects in the expression and regulation of emotion behaviors (Weir et al., 2012). Hence, abnormalities in the fronto-parietal network may serve as potential intervention targets for treating NSSI.

Similar to NSSI behavior, our analyses on NSSI addiction and functions also suggested associations with functional brain networks. In addition to the fronto-parietal, limbic, basal ganglia, and motor networks, we found abnormal connections of vision-related (visual association and visual I) networks to be involved in NSSI functions (Zhou et al., 2022), especially their inter-network connections with the fronto-parietal network. This may reflect a synergistic effect between cognitive control and visual processing involving in NSSI (Noseda et al., 2019; Parlatini et al., 2017; Wang et al., 2014). The identified functional connectivity patterns involving the fronto-parietal network may reflect its role in modulating cognitive evaluations related to NSSI, potentially through regulating attention and decision-making processes. Concurrently, the visual network's interactions with fronto-parietal regions could facilitate the integration of perceptually salient stimuli that may be relevant to NSSI behaviors. The involvement of limbic networks in NSSI addiction and functions may underlie NSSI patients' functional



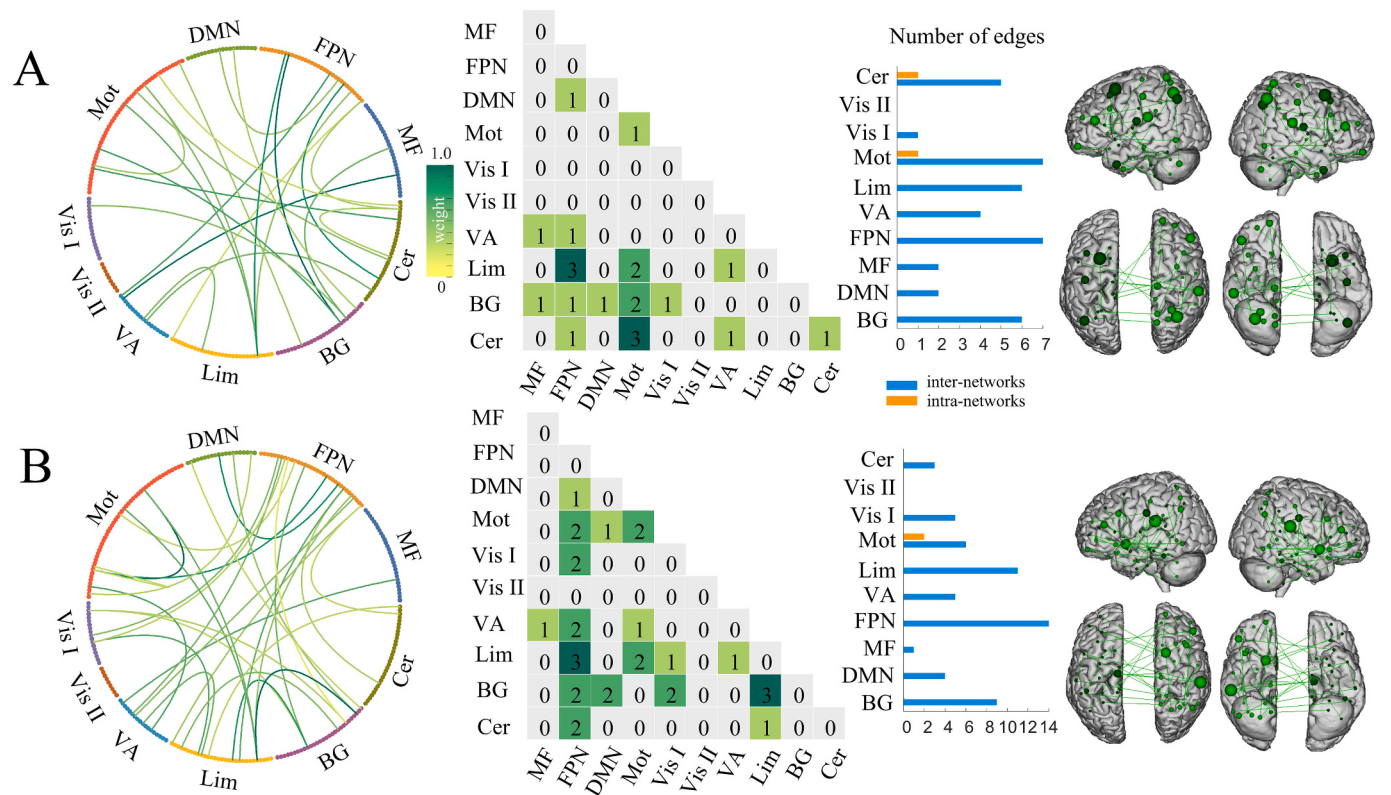


Fig. 3. Functional brain networks that associated with NSSI severity in external datasets. In the ADHD cohort, 23 edges are associated with NSSI severity (A). In the transdiagnostic cohort, 31 edges are associated with NSSI severity (B). In these two results, the fronto-parietal, basal ganglia, motor and limbic networks exhibit a greater number of inter-network connections with other networks. These findings are generally consistent with our main results. MF = Medial Frontal, FPN = Fronto-parietal, DMN = Default Mode, Mot = Motor, Vis I = Visual I, Vis II = Visual II, VA = Visual Association, Lim = Limbic, BG = Basal Ganglia, Cer = Cerebellum.

impairments in reward processing and emotional regulation. NSSI addiction and functions could provide us with a deeper understanding of NSSI and should receive more attention in future neuroimaging studies of NSSI.

The brain networks associated with NSSI identified in this study shared key commonalities with those implicated in depression and anxiety, while also exhibiting features that were distinct from NSSI. The fronto-parietal, limbic, and basal ganglia networks—core components of the NSSI-related network—have been consistently reported as dysfunctional in mental disorders such as depression and anxiety (Bryant et al., 2024; Macpherson and Hikida, 2019; Ren et al., 2025; Tse et al., 2024). These networks support emotional regulation and cognitive control, and abnormalities in their inter-network connectivity (e.g., fronto-parietal–limbic dysconnectivity) were well-documented transdiagnostic neural markers of mood disorders, reflecting overlapping mechanisms underlying emotional dysregulation. Importantly, the NSSI-related network also exhibited unique characteristics. The NSSI-specific edges showed poor predictive performance for depression duration, suggesting they were relatively specific to NSSI rather than reflecting depression-related processes. Furthermore, NSSI related sub-networks—such as inter-network connections between the fronto-parietal and motor networks, and between visual networks and basal ganglia networks—highlighted mechanisms unique to NSSI, likely supporting the motor execution of self-injurious acts and the sensory integration required for processing self-injury-related stimuli.

Our findings provide some possible guidance for clinical practice by identifying fronto-parietal, limbic, basal ganglia, and motor networks as potential neural targets for NSSI intervention. Notably, the consistent involvement of the fronto-parietal network across all NSSI dimensions (behavior/addiction/functions) highlights it as a unified therapeutic target. Non-invasive neuromodulation (e.g., TMS) aimed at enhancing

top-down cognitive control could therefore simultaneously mitigate multiple NSSI mechanisms. Furthermore, motor network involvement provides a potential biological substrate for developing sensorimotor based interventions. Replicated network patterns validated in ADHD and transdiagnostic cohorts support their utility as biomarkers for early identification of at-risk youth through accessible neuroimaging protocols (e.g., fNIRS-based school screenings). While further validation is required for clinical translation, this network framework offers potential mechanistically-grounded stratification of prevention strategies, for example, fronto-parietal network-focused cognitive training for affective subtypes versus motor circuit modulation for impulsive phenotypes.

This study has several limitations. First, the cross-sectional design precludes causal inferences and longitudinal tracking of neural developmental changes of NSSI behavior. Second, the relatively small sample size in both the primary depressive sample and the external ADHD and transdiagnostic cohorts limits our capacity to fully characterize the heterogeneity of NSSI, including its types and frequency. Third, potential confounding factors, such as types of self-injury and treatment period (hospitalization or pharmacotherapy), could not be systematically controlled due to clinical sample constraints. Fourth, the absence of task-based fMRI limits our ability to directly assess brain functional networks during specific cognitive and emotional processes relevant to NSSI, such as emotion regulation, impulsivity, and cognitive control. While resting-state fMRI captures context-independent neural signatures that remain stable across conditions, it cannot replace task-based measures of process-specific brain function. Fifth, medication effects could not be excluded in the current study, as the NSSI patients had comorbid depression and were receiving SSRI treatment; ethical considerations prevented the use of drug washout protocols. Finally, although externally validated, the modest sample size warrants replication in larger cohorts. Future research could extend these findings by integrating

multimodal neuroimaging approaches, such as intrinsic local brain activity and structural-functional coupling (Chen et al., 2025; Deco et al., 2022; Fotiadis et al., 2024), alongside large-scale longitudinal studies and task-based fMRI paradigms (Du et al., 2025; Nakua et al., 2025), ultimately delineating a more comprehensive neurobiological framework for NSSI.

5. Conclusion

In conclusion, our study identified functional brain networks associated with NSSI behavior, addiction and functions in adolescents with MDD. We found evidence that the fronto-parietal, limbic, motor, and basal ganglia networks represent the neural underpinnings of NSSI and the fronto-parietal network may be the key neural marker involving in different aspects of NSSI. These results comprehensively capture the brain network abnormalities underlying NSSI and point to potential targets for early identification, intervention and treatment.

CRedit authorship contribution statement

Xuan Liu: Writing – original draft, Visualization, Investigation, Formal analysis, Data curation, Conceptualization. **Ying Yang:** Resources, Data curation. **Jiahui Chen:** Data curation. **Yihao Zhang:** Data curation. **Duanwei Wang:** Data curation. **Chunyan Lu:** Data curation. **Feiyu Xu:** Data curation. **Junqi Gao:** Data curation. **Yuan Yao:** Data curation. **Bernhard Hommel:** Writing – review & editing. **Xingxing Zhu:** Writing – review & editing. **Kangcheng Wang:** Writing – review & editing, Software, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Wenxin Zhang:** Data curation.

Ethical approval

The Ethics Committees of School of Psychology at Shandong Normal University and Shandong Mental Health Center approved the research. The protection and treatment of patient data in our research comply with the Helsinki Declaration.

Code availability

Upon request from the corresponding author (Kangcheng Wang with email wangkangcheng@sdnu.edu.cn).

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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.jad.2025.120552>.

Data availability

For the primary data (dataset 1) of this study, they are available on request from the corresponding author, Kangcheng Wang. For the dataset 2 and 3, they are released from the website, https://fcon_1000.projects.nitrc.org/indi/cmi_healthy_brain_network/.

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