Resting-state functional brain network alternations related to non-suicidal and suicidal self-injurious behaviors in adolescents with depression

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Abstract

Background: Nonsuicidal self-injury (NSSI) and suicidal attempt (SA) frequently occur during depressed adolescents, but the underlying neurobiological mechanisms are poorly understood. This study sought to investigate neurobiological alternations that underpin adolescent NSSI with or without a history of SA, specifically using functional connectivity (FC) analysis.

Methods: We collected self-reported questionnaires and resting-state fMRI data from depressed adolescents (N = 114), and they were divided into three groups: clinical control (non-self-harm), NSSI-only, and NSSI+SA based on their history of self-harm. Alternations of FC patterns were identified through support vector machine-based classification.

Results: Adolescent NSSI with or without a history of SA exhibited both overlapping and divergent neurobiological alternations. Referring to the alternations of FC in the NSSI group, the alternations of intra-/inter-network FCs among the Control, SalVAtten, Limbic, and Default networks persist in depressed adolescents with a history of both NSSI and SA, while some new alternations appear, including inter-network FCs among the Limbic, DorsAttn, and Visual networks.

Limitations: Cross-sectional design. Retrospective self-report on the history of self-harm behaviors and severity of depression symptoms. The modest sample size.

Conclusions: The emphasis of this study on the network basis could extend the existing evidence at a circuit level, and may explain an underlying neurobiological mechanism pertaining to the continuum of self-destructiveness in adolescents.

Keywords: Adolescent; Nonsuicidal self-injury; Suicidal attempt; Depression; Resting-state Functional connectivity

1. Introduction

Adolescence is a critical period of physiological, psychological, and social changes [1]. Adolescents are highly vulnerable to mental disorders and maladaptive behaviors, including depression and self-injury behaviors. Nonsuicidal self-injury (NSSI) refers to intentional, self-inflicted damage to the surface of the body without intent to kill oneself, which is not socially sanctioned [2]. On the other hand, suicidal attempt (SA) refers to the engagement in potentially self-injurious behavior with at least some intent to end one's life [3]. Studies consistently demonstrate common heritable factors [4] and high levels of comorbidity [5] between non-suicidal and suicidal self-injury. NSSI and SA often emerge during adolescence and often co-occur, especially in clinical samples [6, 7]. Since NSSI is often used as an emotion regulation strategy for relieving emotional pain, some adolescents may experience depression first and subsequently develop NSSI as a maladaptive strategy for relieving emotional pain [8]. The prevalence rates of NSSI among the general population are estimated to be 17% among community samples [9] and more than 40% in clinical samples [10]. It has been suggested that high frequencies of NSSI incidents were associated with a significant increase in the risk of SA, although not all self-injurers will attempt suicide [11]. Adolescents with repeated NSSI who additionally reported a history of SAs presented greater severity of psychopathology compared to those with NSSI only [12]. Given that SA is associated with worse treatment courses and increased risk of mortality [13], it is important to understand why certain adolescents only engage in NSSI whereas others engage in SA. Because adolescence is a neurobiological critical period, investigating the neurobiological bases of these behaviors with this population could aid in early intervention and prevention strategies that promote healthy neurodevelopmental trajectories [14].

So far, a few neuroimaging studies examined NSSI or SA in adolescents (see reviews [15-17]) and reported complex and diverse neural underpinnings. Published youth SA research studies are characterized by alternations with prefrontal and limbic systems, whereby a comprised regulatory system may potentiate suicidal thinking, and perturbations in top-down and bottom-up connections may lead to SA [15, 16]. Youth NSSI research mainly focused on disruptions in the amygdala and anterior cingulate cortex activations and functional connectivity, which contributes to hyperarousal and reduced impulse control-center features of NSSI [16]. Among these studies, the majority were conducted with task-based fMRI and regions-of-interest based functional connectivity (FC) analysis. While these task-specific connectivity findings are important in beginning to elucidate the brain basis, these studies utilized disparate emotion processing tasks and obtained discrepant findings, signaling the need for understanding intrinsic (i.e., task-independent) neural networks associated with NSSI and SA.

Resting-state fMRI analysis provides advances in the understanding of intrinsic large-scale functional networks [18], and it is ideal for the investigation of whole-brain network-based perturbations in clinical conditions. Task-independent patterns of intrinsic functional signals derived from resting-state fMRI studies are relatively stable and have strong test re-test reliability [19]. However, compared with structural and task-based fMRI studies, the resting-state fMRI literature on adolescent NSSI and SA is smaller, and interpretations are challenging, given mixed methods and results [16]. Many of these studies are hypothesis-driven and are mainly focused on regions of interest (ROI), such as the amygdala [20] and post-cingulate cortex [21]. One recently published study applied data-driven approaches (e.g. independent component analysis) to explore brain networks, such as the Default network [22-26]. Therefore, -brain analysis can expand the coverage of brain networks under investigation and could achieve a more complete understanding of neurobiological underpinnings related to NSSI and SA of adolescents.

Studying these clinical phenomena of NSSI and SA can be challenging because while they sometimes manifest independently, they also frequently co-occur in adolescence [27]. According to the proposed Gateway Theory, suicidal behaviors stem from escalating NSSI behaviors [28]. The NSSI+SA pattern seems to constitute a potent signal of increased risk for subsequent suicidal behavior. Studies examining neurobiological correlates that may differentiate adolescents engaged in NSSI who attempt suicide from those who do not attempt suicide are needed to better inform current knowledge and clinical practice. There may be a complex neurobiological interaction and overlap in functional connectivity patterns between NSSI and SA. However, so far, almost no studies have performed a direct comparison between NSSI with NSSI+SA.

Here this study examined NSSI and/or SA within the context of depression. We inquired about previous SAs among adolescents presenting with NSSI, in order to address both overlapping and divergent patterns of self-harm behaviors (NSSI only, NSS+SA) compared with clinical controls. Findings based on a comparison between diagnostic controls and individuals with the same mental disorder plus NSSI or SB are more commonly reported in the literature and are more likely to reflect specific effects of these behavior in that disorder, whereas comparison with HCs may include more general effects of having a mental disorder". Whole brain resting-state functional connectivity alternations were extracted using data-driven support vector classification analysis, because machine learning approaches can help to overcome the multiple-comparison problems of their multivariate nature [29]. Based on the literature outlined above, we hypothesize that both overlapping and divergent patterns of resting-state functional connectivity alternations exist for different patterns of self-harm behaviors (NSSI only, NSS+SA) in depressed adolescents. A thorough investigation of the neural correlates of NSSI and SA may lead to a more comprehensive understanding of the nature of the link between these two types of behavior.

2. Materials and methods

2.1 Ethics

The protocol for this study was approved by the Research Ethics Committee of Shenzhen Kangning Hospital. All participants provided written informed consent in compliance with the code of ethics of the Declaration of Helsinki.

2.2 Participants

Depressed adolescents were recruited from the Department of Depression at Shenzhen Kangning Hospital. Inclusion criteria were as follows: (1) age 12 to 18 years, (2) was diagnosed with current depression by senior psychiatrists according to the Diagnostic criteria and Statistical Manual of Mental Disorder Fifth Edition (DSM-5). The exclusion criterion was a history of any serious neurological or intellectual disability, contraindications to MRI scanning, and meeting for a lifetime or current criteria for Mania, Psychosis, or any substance use disorders. In this study, 114 adolescents were recruited and finished MRI data collection.

The Chinese version of the Functional Assessment of Self-Mutilation (FASM) [30] was used to assess methods, frequency, and functions of self-reported self-harm in the past year. Participants were asked if they had engaged in any of the 10 listed self-harm behaviors in the past 12 months. Participants who answered "yes" were NSSI+ while those who answered "yes" were NSSI-. Besides, participants were asked if they had tried to take their life before. Participants who answered "no" were SA- while participants who answered "yes" were SA+ and made a further report about times of suicidal behavior. Patients were categorized into

three groups based on their self-harm and suicidal behavior history: depressed adolescents without NSSI and SA (diagnostic control group), depressed adolescents with NSSI but no SA (NSSI group), and depressed adolescents with a clinically significant history of both NSSI and SA (NSSI+SA group).

2.3 Data acquisition and preprocessing

All imaging studies were performed at the Department of Radiology at Shenzhen Kangning Hospital using a 3.0-Tesla scanner MRI (Prisma, Siemens, Germany). Resting-state fMRI was collected using an echo-planar imaging (EPI) sequence with the following parameters: TR/TE = 2000/30 ms; flip angle = 90□; slice thickness = 2.5 mm; acquisition matrix = 88×88; number of slices = 58; and 240 time points. During the scanning, each participant was asked to keep still with their eyes closed, and not to think about anything or fall asleep. High-resolution three-dimensional brain volume T1-weighted imaging was collected using the following parameters: TR/TE/IT = 2530/2.27/1100 ms; flip angle = 7□; slice thickness = 1 mm; acquisition matrix = 256×256; number of slices = 144.

The preprocessing of resting-state fMRI was performed using Data Processing Assistant for Resting-State fMRI Advanced Edition V2.2 (DPARSFA, http://rfmri.org/DPARSF) toolkit with Statistical Parametric Mapping (SPM8, https://www.fil.ion.ucl.ac.uk/spm/) in MATLAB (R2010b) (MathWorks, Natick, MA, USA). The main preprocessing steps were as follows: (1) The first 5 volumes were removed to allow for signal equilibration; (2) slice-timing correction was performed and the middle slice was used as the reference slice; (3) motion correction realignment was performed; five participants with excessive head motion, as operationalized by having a mean $FD_{Jenkinson}$>0.2mm, were excluded; (4) Spatial normalization was performed to the Montreal National Institute space (MNI) with a voxel size of $3\times3\times3mm^3$; (5) to reduce the effect of physiological noise, a series of nuisance covariates were regressed out using the Friston-24 model [31], including the mean signal of the white matter, cerebrospinal fluid signal, and head motion parameters; (6) temporal bandpass filtering (0.01-0.1 Hz) was further performed to reduce low-frequency drift and high-frequency noise; (7) spatial smoothing was performing using a 4 mm full-width at high maximum (FWHM) Gaussian kernel. Additionally, to ensure that residual motion was not a confound, mean framewise displacement was compared between groups, and no significant effect of motion was observed (one-way ANOVA, P = 0.599).

2.4 Functional network construction

To define network nodes, human brains were parcellated into 232 cortical and subcortical regions of interest (ROIs). The 200 Cortical ROIs were obtained from the scale-200 version of the whole-brain functional parcellation of Schaefer et al [32]. The 32 subcortical ROIs were obtained from a recent subcortical functional parcellation [33]. The 232 ROIs can be assigned into eight intrinsic connectivity networks (ICNs): (1) visual network, (2) somatomotor network (SomMot), (3) dorsal attention network (DorsAttn), (4) salience/ventral attention network (SalVAttn), (5) limbic network, (6) control network, (7) default mode network, and (8) subcortical network [18].

We extracted the averaged BOLD time series for each of the 232 ROIs for each subject. A 232×232 correlation matrix for each subject was subsequently constructed by calculating Pearson's correlation coefficients between the BOLD time series from all possible pairs of ROIs. A Fisher's r-to-z transformation was further applied to the correlation matrices. The feature vector of resting-state FC was constructed by vectorizing the upper triangular part of the correlation matrix of each subject.

2.5 Support vector machine training and classification

Considering the relatively higher dimensionality of whole-brain brain network features, machine learning approaches can help to overcome the multiple-comparison problem because of their multivariate nature [29]. Hence, different resting-state FC between groups was identified through support vector machine (SVM)-based classification. The application of SVM to fMRI data at the group level allows for identifying voxels or brain regions of interest that are informative for classifying different groups by accumulating the information more effectively across many spatial locations. Linear binary SVM classifiers [34] were trained to distinguish the NSSI group or NSSI+SA group from the control group. Feature sets of resting-state FC strength and topological nodal metrics were used separately.

Because the feature size was much larger than the sample size, a feature selection algorithm was applied to identify discriminating features between two groups and remove unnecessary information. In this study, the F-scores method was employed for feature ranking [35]. F score is simple, generally quite effective, and used in previous resting-state fMRI studies [36]. The F score of each feature is calculated by the ratio between the variance between groups and the variances within each of the two groups. For features of topological nodal metrics, the F score was first calculated for each metric and then averaged. The larger the F-score is, the more likely the feature is to be more discriminative between the two groups.

To identify the optimally differentiating features between the two groups, nested- leave-one-out-cross-validation (LOOCV) was applied. Prior to analysis, each feature was normalized across subjects in the training sample by subtracting the mean value and dividing by the standard deviation, and the same mean and standard deviation were used to scale the test data. The feature number of resting-state FC strength was tested from 20 to 3000 with a step of 20 (number of connections). For each LOOCV iteration, the data were divided into test and training samples. The F-scores of all features were calculated and then ranked within the training set. Specificity, sensitivity, and area under curve (AUC) were calculated to measure the performance of the selected classifier. The prediction performance was calculated for all the LOOCV iterations of each step of feature size, and the smallest step which achieved the highest prediction AUC value was chosen.

2.6 Evaluating contributions to a predictive model

Due to the use of linear kernel SVM classifiers, we can extract weights reflecting the importance of each feature for classification and derive the group-level differences of resting-state FC patterns. Utilizing of LOOCV strategy could get stable weights for each feature because the weights got from the training dataset were closer to the whole dataset. The final features used in the classification differed for each LOOCV iteration because feature ranking was based on a slightly different subset of the data. Consensus features (FCs) were defined as the common features always selected to form the final feature set for each LOOCV iteration. The weights of the consensus features were the average value of the classification weight across all iterations of LOOCV. Positive weights and negative weights were calculated separately. Then we only focused on the consensus features that exhibited at least one standard deviation greater weights than others.

To increase the interpretability of the network-level contributions, we examined the modular architecture of these consensus features at the brain location level. The 232 ROIs can be divided into eight modules (intrinsic brain networks: Visual, SomMot, DorsAttn, SalVAttn, Limbic, Control, Default, Subcortical). We calculated the mean weights and percentage of intra- and inter-modular discriminating FCs for each group. For each subject, the mean weights were calculated by averaging the weights of all the discriminating FC across all LOOCV loops within each module and between pairs of modules. We also calculated the percentage (density) of discriminating FCs occurring within and between different modules

(number of discriminating connections divided by the number of all possible connections). Then we only focused on the discriminating intra- and inter-modular discriminating FCs exhibited at least one standard deviation greater percentage than others (FC density). The predictive contributions of the consensus intra- and inter-modular features with both greater classification weights and densities were also visualized at the nodal level. Specifically, the weight of each region was calculated by summing one-half of the feature weights associated with that region [37]. Following this, the anatomical locations of the brain regions that play a more important role in the classification can be obtained.

2.7 Statistical analysis

All statistical analyses were performed using the SPSS (SPSS Statistics, IBM, Armonk, NY) or MATLAB (MathWorks Inc., MA) software. The Chi-square test and one-way analysis of variance (ANOVA) test were performed to analyze the group differences in the demographic data. $P < 0.05$ was considered statistically significant.

The statistical significance of selected classifiers based on resting-state FC was evaluated by the non-parametric permutation tests (5000 times). In each permutation, we randomly assigned the subjects' group labels and performed the above-mentioned classification procedure, including the feature selection and classification, and a null distribution of classification accuracies was obtained. The p-value was estimated as the proportion of the accuracies in the null distribution that were greater than or equal to the actual classification accuracy.

For NSSI and NSSI+SA groups, we extracted the mean intra- and inter-modular discriminating FC strength, and the partial Pearson's correlation analyses (age and gender were included as the confounding factors) were performed between these FC measures and clinical parameters.

3. Results

3.1 Demographic and clinical characteristics

The demographic and clinical characteristics of the participants are presented in Table 1. There were no significant group differences in age, gender, and education (all $P > 0.05$).

Table 1. Demographic and clinical characteristics of the participants

Item	Control	NSSI	NSSI+SA	P-value
	N = 34	N = 39	N = 36	
Gender (M/F)	9/25	6/33	5/31	0.332[a]
Age (years)	15.65±1.61	15.38±1.63	15.06±2.08	0.385[b]
Edu (years)	10.06±1.70	9.82±1.78	9.44±2.42	0.430[b]
PHQ scores	15.53±6.33	17.64±5.88	18.94±5.51	0.056[b]
GAD scores	11.41±5.76	12.79±5.26	13.06±5.72	0.419[b]
FD Jenkinson	0.068±0.023	0.073±0.029	0.075±0.031	0.599[b]

PHQ-Patient Health Questionnaire; a: chi-square test; b: one-way ANOVA.

3.2 Classification results based on resting-state FC

Different groups of patients were classified based on resting-state FC using linear SVM classifiers. Feature sets of different sizes were used and the optimal size with the highest classification performances was achieved (as shown in Figure 1). For resting-state FC-based classification, the AUC achieved the maximum value of 0.681 with 1520 features for classification between NSSI and control, and 0.686 with 2280 features for classification between NSSI+SA and control.

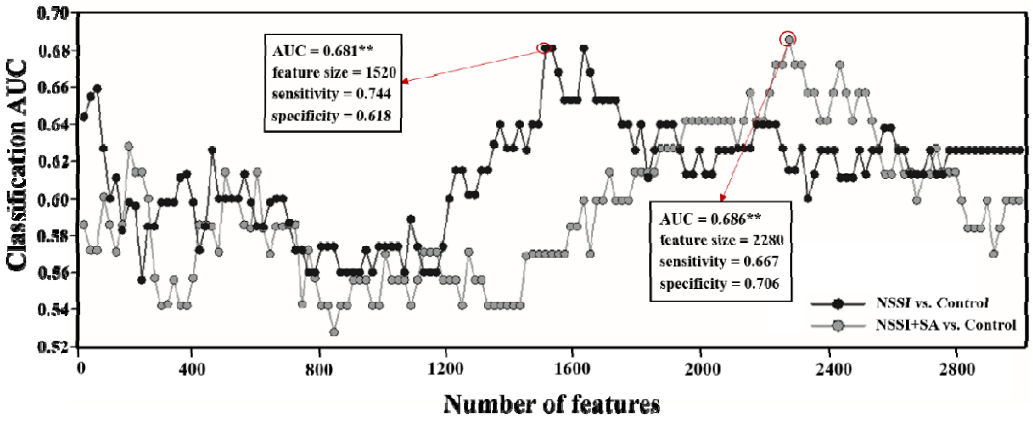

Figure 1. Classification performance with respect to the number of selected features. Each curve corresponds to the classification between different patient groups and the maximum value was selected. **p<0.005, as evaluated by the non-parametric permutation tests.

3.3 Group differences in resting-state FC patterns

Group differences across the entire functional connectome between groups were identified through support vector machine (SVM)-based classification. The linear SVM classifier can help identify discriminating resting-state functional connections with a higher contribution to the classification. As shown in Figure 2, the matrices on the left show the widely-distributed alternations of resting-state FC in the NSSI group and NSSI+SA group compared with the control group, respectively.

Here we focused on the modular architecture of the discriminating features at the brain location level. The circular plots in the middle of Figure 2 illustrate the predictive contributions of intra- and inter-modular resting-state FC features for the classification of the NSSI group and NSSI+SA group. The color of the line represents the mean weight and the thickness of the line represents the percentage of selected edges (normalized by the total number of edges within each modular or between two modules) to account for differences in network size. Therefore, inter- and intra-modular connections with darker and thicker lines indicate greater contribution (group differences).

Compared with clinical controls, the NSSI group showed relatively increased resting-state FC in the Limbic-Control, Limbic-SalVAtten, and decreased resting-state FC in the Control, SalVAttn, Control-SalVAttn, Limbic-Default, and Limbic-DorsAttn. For adolescents engaging in both NSSI and SA, similar alternations were observed in the Limbic-Control, Limbic-SalVAtten, SalVAttn, and Limbic-Default. Different from the pure NSSI group, increased FC was observed in Limbic-DorsAttn, Control-Visual, SalVAttn-Visual, and decreased FC was observed in Limbic-Visual, Limbic, DorsAttn-SalVAttn.

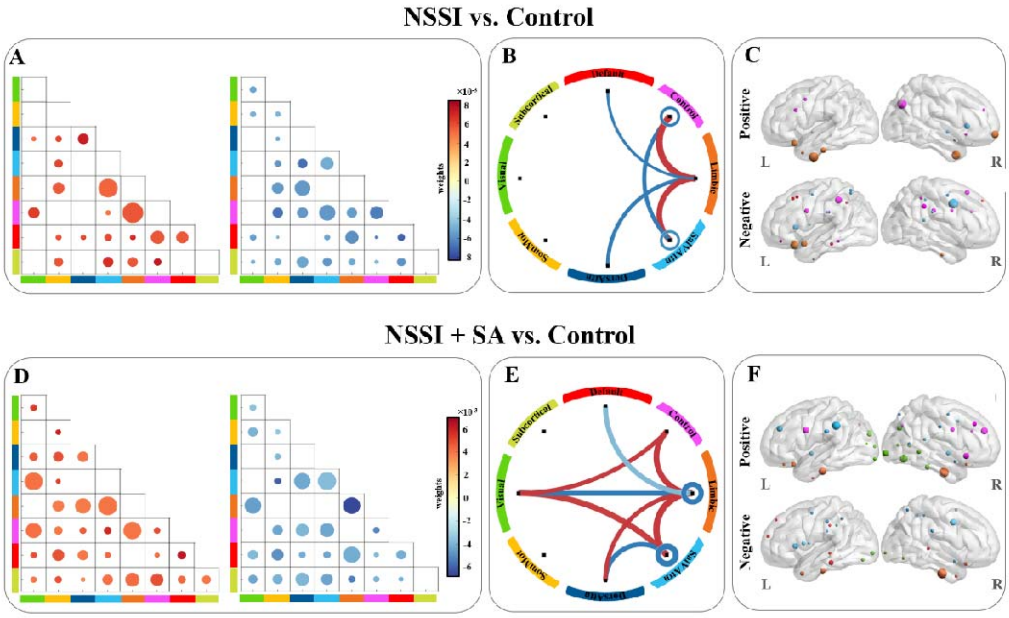

Figure 2. The resting-state FC contributed to the classification between the NSSI group and control group (top panel), and between the NSSI+SA group and control group (bottom panel). The matrices on the left (A and D) show the group-mean classification weights for consensus-discriminating features with greater weights. The circular graphs in the middle (B and E) show the modular architecture of these consensus features with a greater percentage of connections within each module and between pairs of modules. Dots (in the matrices) and lines (in the circular graphs)with warm color represent positive discriminating weights in NSSI or NSSI+SA compared with the control group, and the reverse for dots with cold color. The line thickness is in proportion to the percentage of discriminating functional connections. The 3D glass brain representations on the right (C and F) show the brain regions which contributed more to the classification between groups. The colors of nodes represented the different modules of brain functional networks and the node size is in proportion to the mean discriminating weight.

The brain regions which contributed more to the classification between groups are shown in the 3D glass brain representations of Figure 2 and listed in the supplementary table S1. For the NSSI group, brain regions with positive weights localized predominantly to the insular cortex (SalVAttn), orbital frontal cortex and temporal pole (Limbic), and prefrontal cortex (Control); brain regions with negative weights localized predominantly to the frontal eye fields (DorsAttn), superior temporal gyrus and insular cortex (SalVentAttn), temporal pole (Limbic), cingulate and supramarginal gyrus (Control), and middle frontal cortex and precuneus (Default).

For the NSSI+SA group, brain regions with positive weights localized predominantly to the frontal eye fields, superior parietal gyrus, postcentral gyrus and middle temporal gyrus (DorsAttn), insular cortex and prefrontal cortex (SalVentAttn), orbital frontal cortex and temporal pole (Limbic), cingulate and prefrontal cortex (Control), occipital cortex (Visual); brain regions with negative weights localized predominantly to the frontal eye fields and inferior parietal gyrus (DorsAttn), insular cortex and parietal operculum (SalVentAttn), the temporal pole (Limbic), the medial prefrontal cortex and middle temporal gyrus (Default), the middle occipital cortex, calcarine, fusiform gyrus (Visual).

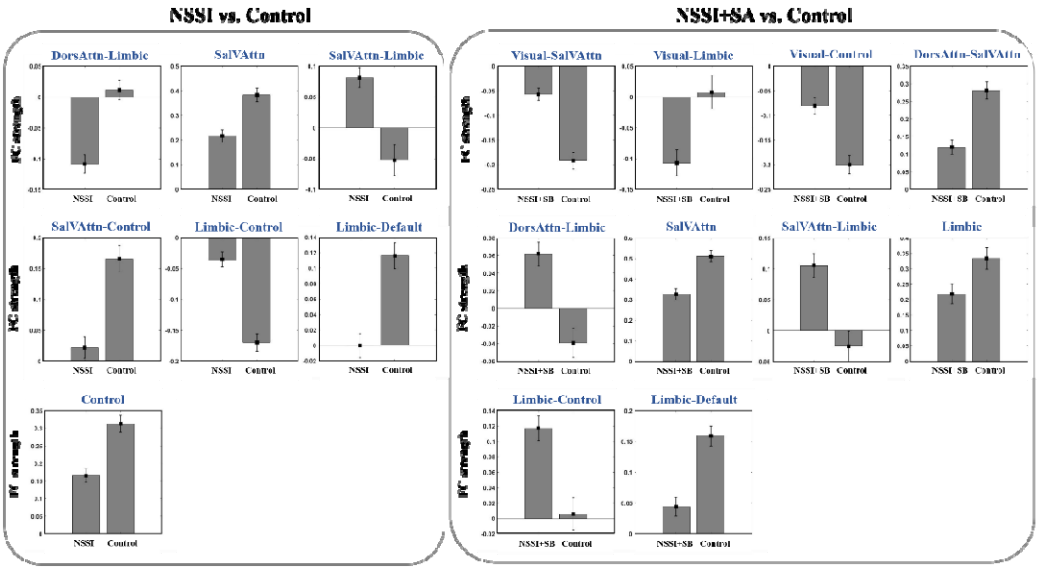

Figure 3. The mean resting-state FC strength changes between groups for intra- and inter-modular discriminating features.

3.4 Correlation between discriminating FC strength and clinical parameters

For the NSSI+SA group, the increased resting-state FC between the DorAttn and Limbic showed a significant positive correlation with PHQ depression rating scores (R = 0.44, P = 0.008, Figure 4). No significant correlation was observed between the discriminating FC and any of the clinical parameters for the NSSI group.

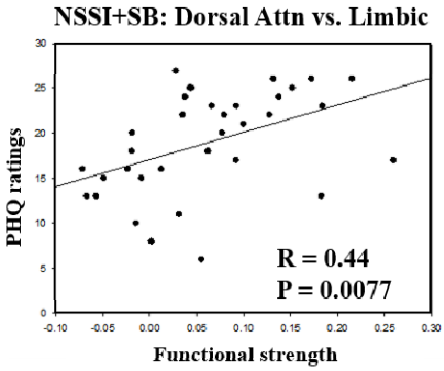

Figure 4. Correlation between discriminating FC strength and clinical parameters.

4. Discussion

Existing evidence suggests that the predisposition to suicidal and non-suicidal behaviors in adolescents is at least partly mediated by neurobiological factors. The altered cerebral function might play a key biological role in maladaptive behaviors, such as NSSI and SA, in depressed adolescents [15-17, 38]. The present study was the first to examine both overlapping and divergent neurobiological alternations that underpin adolescent NSSI with or without a history of SA compared with age-matched clinical controls. Compared with the clinical control group, commonly and widely distributed aberrant intrinsic network FC was

identified not only between the three core neurocognitive intrinsic brain networks (the SalVAttn, Control, and Default networks) proposed as the triple network model of psychopathology [39] but also between these core neurocognitive intrinsic brain networks and other networks (such as the Limbic and DorsAttn networks). Referring to the alternations of FC in the NSSI group, the alternations of intra-/inter-network among the Control, SalVAtten, Limbic, and Default networks persist in depressed adolescents with a history of both NSSI and SA, while some new alternations appear, including inter-network FC among the Limbic, DorsAttn, and Visual networks. Besides, the severity of depressive symptoms only showed a significant correlation with increased FC in Limbic-DorAttn networks, strengthening the fact that these observed alternations of FC might not be caused by increased depression severity in these adolescents engaging both NSSI and SA. We discuss potential interpretations of these findings below.

Our focus on networks is important, not only because individual brain regions do not function in isolation, but also because the maturation of network connectivity is a central feature of brain development during adolescence [40, 41]. Studies of normative development have shown that functional brain networks increasingly segregate through adolescence [42], making it a vulnerable period for emotional problems [43]. Importantly, the neural networks that support these processes continue to mature in adolescence [40, 41] and are aberrant in depressed adolescents [44]. Our account of NSSI in adolescence is supported by a substantial body of developmental cognitive and affective neuroscience [45]. According to existing evidence, the source of abnormal FC within seed-networks tended to be spatially distributed, highlighting the importance of considering anatomical regions within functional networks. Menon et al critically reviewed the fMRI literature and proposed a triple-network model (SalVAttn, Control, and Default network) for neuropsychiatric disorders and these three neurocognitive intrinsic brain networks are obviously connected with emotional regulation and cognitive processing [39]. NSSI or SA is a maladaptive strategy among adolescents that stems from greater difficulty with emotional awareness and regulation [46]. Specific patterns of network dysfunction of core neurocognitive intrinsic brain networks may contribute to core deficits in cognitive and affective functioning that are believed to underlie these behaviors.

The Affective network (AN) and the ventral attention network (VAN), sometimes together called the SalVAttn network, are involved in processing emotion or monitoring salient events [18]. The SalVAttn network, primarily based in the anterior insular and cingulate cortex, plays a critical role in identifying biologically and cognitively salient events necessary for guiding attention and goal-directed behaviors [47]. We found decreased intra-network FC of the SalVAttn and inter-network FC between SalVattn and Control networks. Increased sensitivity to socioaffective pain contributes to the onset of NSSI in adolescence and it is largely believed that it is a product of an imbalance between elevated response to affective information in the environment by the SalVAttn network [48, 49], and blunted regulation by the Control network associated with effortful emotion regulation and cognitive control [50]. Besides, the Salience network also plays a critical role in processing emotion in connection with the Limbic network [47]. Therefore, increased FC between the SalVAttn and Limbic networks could be explained by the excessive emotional responses to salient external stimuli (i.e., behaviorally relevant and potentially threatening), and SalVAttn-Control hypoconnectivity may represent difficulty in the regulation of negative affect in adolescents with NSSI.

Adolescents with NSSI showed alternations in inter-network FC of Limbic with the Control, Default, and DorsAttn networks. The limbic network has two main nodes including the orbitofrontal cortex (Limbic-OFC) and temporal pole (Limbic-TempPole) [18]. OFC is a key

region for integrating emotional information and is associated with emotional regulation in emotional disorders. In NSSI participants, greater activation was found in the OFC during the emotional processing task [51-53]. As part of an extended limbic system, the temporal pole has some role in both social and emotional processes, and dysfunction of the temporal pole has been observed in clinical disorders with socioemotional regulation [54]. The Control network is involved in the top-down regulation of attention and emotion [55], and the Default [56] and DorsAttn [57] networks are involved in internally or externally oriented attention, respectively. Therefore, our results here are in congruent with the deficits in the socioemotional regulation associated with NSSI.

The relationship between NSSI and SA is complicated and both of them lie along a spectrum of self-destructive actions [28]. Initial findings support the view that NSSI and SA in adolescents are characterized by abnormal rsFC, but inconsistent patterns of resting-state functional alterations were reported for adolescents with NSSI and SA [16]. NSSI is a key risk factor for future SAs, and some of the same neurobiological systems have been implicated in both NSSI and SA. According to our results, both NSSI and NSSI+SA groups showed increased FC in Limbic-Control, and Limbic-SalVAttn, and decreased FC in SalVAttn and Limbic-Default. This observation emphasizes theories about a potential continuum of self-destructiveness [58] and indicates that indeed there is a potential neurobiological underpinning of the continuum from self-injury to suicidal behavior.

It has also been proposed that individuals who engage in both NSSI and SA have more complex psychopathology [59]. As expected, in addition to these above-mentioned common alternations, adolescents engaging both in NSSI and SA showed widespread FC alternations involving the dorsal Visual network. In the context of NSSI, adolescents show difficulties with social cue interpretation and deficits in interpersonal problem-solving, and they are prone to negatively interpreting social situations [60]. There have been consistent findings that adolescents with repeated NSSI who additionally reported a history of SAs presented greater severity of psychopathology such as a lower level of functioning compared to those with NSSI only [12]. During the maintenance of NSSI, heightened negative bias may contribute to the development of SA [59]. Hence, our findings of alternation FC associated with the Visual network in the NSSI+SA group could be interpreted from an “information processing” perspective [61, 62]. Vision is an important part of the selective attention process, and the dorsal Visual network is associated with spatial awareness and guidance of actions [63]. Hence, the processing bias in adolescents with NSSI+SA may be initiated as a perceptual visual bias, and then eventually cause a series of cognitive and affective symptoms.

Limitations and future directions

While the findings add to understanding NSSI and SA, there are some limitations. First, a key study limitation is a cross-sectional design. The findings raise several questions that we cannot answer here: when did these aberrant FC patterns emerge? The interpretation of the observed findings remains a hypothesis until it can be confirmed with longitudinal studies to examine within-person change over time. Second, this study used retrospective self-report to collect data on self-harm behaviors and depression symptoms, and it may be affected by reporting and recall biases. Third, while studying a sample of depressed adolescents reduces clinical heterogeneity, the alternated FC patterns identified in our study may not be representative of the neural circuits underpinning NSSI and SA in adolescents more broadly; thus, it will be important in future studies to examine self-harm behaviors transdiagnostically.

Conclusions

In summary, the present study was the first to examine both overlapping and divergent neurobiological alternations that underpin adolescent NSSI with or without a history of SA. Although further investigation is needed, the emphasis of this study on the network basis could extend the existing evidence at a circuit level, and may explain an underlying neurobiological mechanism pertaining to the continuum of self-destructiveness in adolescents. Besides, our results can potentially aid in the identification of those at risk for SA in adolescents engaging NSSI and contribute to the development of neurobiologically informed interventions.

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Conflict of interest

The authors declare that they have no competing interests.

Ethics approval

The study protocol was approved by the Human Research Ethics Committee of Shenzhen Kangning Hospital. Informed, written consent was obtained from all participants and their caregivers prior to participation in the study.

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Supplementary materials

Table S1. Information on brain regions contributed more to the classification between groups.

NSSI vs. Control				NSSI+SA vs. Control			
ROI	**x**	**y**	**z**	**ROI**	**x**	**y**	**z**
Positive weights				***Positive weights***			
LH_SalVentAttn_FrOperIns_1	-40	-4	-4	LH_Vis_5	-26	-96	-12
RH_SalVentAttn_FrOperIns_1	40	6	-16	LH_Vis_9	-22	-96	6
RH_SalVentAttn_FrOperIns_2	46	-4	-4	LH_Vis_11	-40	-84	10
RH_SalVentAttn_FrOperIns_3	36	24	4	LH_Vis_13	-6	-88	28
LH_Limbic_OFC_1	-24	22	-20	LH_Vis_14	-24	-88	24
LH_Limbic_TempPole_1	-30	-6	-40	RH_Vis_1	38	-34	-24
LH_Limbic_TempPole_2	-44	-20	-30	RH_Vis_3	28	-68	-12
LH_Limbic_TempPole_3	-28	10	-34	RH_Vis_7	16	-46	-2
RH_Limbic_OFC_3	14	64	-8	RH_Vis_8	30	-94	-4
RH_Limbic_TempPole_1	30	8	-38	RH_Vis_9	8	-76	8
LH_Cont_PFCl_4	-44	20	28	RH_Vis_10	22	-60	8
LH_Cont_PFCl_5	-42	6	44	RH_Vis_15	32	-74	32
LH_Cont_pCun_1	-10	-74	38	RH_DorsAttn_Post_2	52	-60	10
RH_Cont_PFCv_1	34	22	-8	RH_DorsAttn_Post_3	60	-16	34
RH_Cont_PFCl_5	30	48	28	RH_DorsAttn_Post_6	14	-74	52
RH_Cont_pCun_1	14	-70	36	RH_DorsAttn_FEF_1	34	-4	52
Negative weights				LH_SalVentAttn_ParOper_2	-62	-26	28
LH_DorsAttn_Post_8	-30	-60	60	LH_SalVentAttn_ParOper_3	-60	-40	36
LH_DorsAttn_Post_9	-6	-60	56	LH_SalVentAttn_FrOperIns_1	-40	-4	-4
LH_DorsAttn_FEF_1	-32	-4	54	LH_SalVentAttn_PFCl_1	-28	42	32
RH_DorsAttn_FEF_1	34	-4	52	RH_SalVentAttn_TempOccPar_2	60	-38	16
LH_SalVentAttn_ParOper_2	-62	-26	28	RH_SalVentAttn_FrOperIns_1	40	6	-16
LH_SalVentAttn_FrOperIns_2	-34	20	6	RH_SalVentAttn_FrOperIns_2	46	-4	-4
LH_SalVentAttn_FrOperIns_3	-38	0	10	RH_SalVentAttn_Med_1	8	10	42
RH_SalVentAttn_TempOccPar_2	60	-38	16	LH_Limbic_OFC_1	-24	22	-20
RH_SalVentAttn_TempOccPar_3	60	-26	28	LH_Limbic_OFC_2	-10	36	-20
RH_SalVentAttn_PrC_1	50	4	40	LH_Limbic_TempPole_1	-30	-6	-40
RH_SalVentAttn_Med_2	10	-36	46	LH_Limbic_TempPole_2	-44	-20	-30
LH_Limbic_OFC_1	-24	22	-20	RH_Limbic_OFC_2	28	22	-20
LH_Limbic_TempPole_1	-30	-6	-40	RH_Limbic_TempPole_2	46	-12	-34
LH_Limbic_TempPole_4	-42	8	-18	RH_Limbic_TempPole_3	26	-10	-32
RH_Limbic_TempPole_2	46	-12	-34	LH_Cont_pCun_1	-10	-74	38
LH_Cont_Par_3	-46	-42	46	LH_Cont_Cing_1	-4	-28	28
LH_Cont_Temp_1	-60	-42	-14	LH_Cont_Cing_2	-4	4	30
LH_Cont_OFC_1	-32	42	-14	RH_Cont_PFCv_1	34	22	-8
LH_Cont_Cing_1	-4	-28	28	RH_Cont_PFCl_5	30	48	28
LH_Cont_Cing_2	-4	4	30	RH_Cont_PFCl_6	40	34	38
RH_Cont_Par_1	62	-38	36	RH_Cont_pCun_1	14	-70	36
RH_Cont_Par_2	52	-42	48	RH_Cont_Cing_2	4	2	30
RH_Cont_Cing_1	6	-24	30	RH_Cont_PFCmp_1	8	30	28
RH_Cont_Cing_2	4	2	30	***Negative weights***			
RH_Cont_PFCmp_1	8	30	28	LH_Vis_2	-26	-78	-14
RH_Cont_PFCmp_2	8	24	56	LH_Vis_7	-6	-92	-4
LH_Default_PFC_11	-40	18	50	RH_Vis_3	28	-68	-12
LH_Default_PFC_12	-24	24	48	RH_Vis_8	30	-94	-4
LH_Default_pCunPCC_4	-6	-54	42	LH_DorsAttn_Post_4	-54	-26	42
LH_Default_PHC_1	-26	-32	-18	LH_DorsAttn_Post_6	-32	-48	46
RH_Default_PFCdPFCm_5	16	46	44	LH_DorsAttn_FEF_1	-32	-4	54
				RH_DorsAttn_Post_4	46	-38	50
				RH_DorsAttn_Post_7	34	-48	50
				RH_DorsAttn_Post_8	26	-62	58
				RH_DorsAttn_FEF_2	26	8	58
				LH_SalVentAttn_ParOper_2	-62	-26	28
				LH_SalVentAttn_ParOper_3	-60	-40	36

LH_SalVentAttn_FrOperIns_2	-34	20	6
LH_SalVentAttn_FrOperIns_3	-38	0	10
LH_SalVentAttn_FrOperIns_4	-52	8	10
RH_SalVentAttn_TempOccPar_3	60	-26	28
RH_SalVentAttn_PrC_1	50	4	40
RH_SalVentAttn_FrOperIns_1	40	6	-16
LH_Limbic_TempPole_2	-44	-20	-30
LH_Limbic_TempPole_3	-28	10	-34
RH_Limbic_OFC_2	28	22	-20
RH_Limbic_TempPole_1	30	8	-38
RH_Limbic_TempPole_2	46	-12	-34
RH_Limbic_TempPole_3	26	-10	-32
LH_Default_Temp_4	-58	-30	-4
LH_Default_PFC_7	-8	60	20
LH_Default_PFC_9	-12	48	44
LH_Default_pCunPCC_3	-4	-30	36
LH_Default_PHC_1	-26	-32	-18
RH_Default_Temp_5	52	-32	2