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Research paper

Stress-induced alterations in resting-state functional connectivity among adolescents with non-suicidal self-injury

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ABSTRACT

Background: Non-suicidal self-injury (NSSI) is a major mental health problem among youth worldwide. Dysfunction in emotion regulation contributes to NSSI, but research on the underlying neurobiological mechanisms of NSSI is limited. Adolescents with emotion regulation difficulties are vulnerable to stress, making them susceptible to maladaptive coping mechanisms such as NSSI.

Methods: This study examined the functional neurocircuitry relevant to emotion regulation and stress coping in individuals with NSSI compared with healthy controls. This case-control study included 34 adolescents with NSSI (15.91 years) and 28 (16.0 years) unaffected controls. Participants underwent a functional magnetic resonance imaging scan before and after completing a laboratory stress-induction paradigm (the Montreal Imaging Stress Test). The effects of stress induction were quantified by both physiological measures and self-reports.

Results: Participants with NSSI showed distinctive alterations in functional resting-state following stress induction, which differentiated them from unaffected controls. Results show a reduction in functional connectivity between frontoparietal regions and the angular gyrus within the patient group compared to controls, as well as an increase in functional connectivity between visual regions, the insular cortex, the planum polare, and the central opercular cortex. After conditions of acute stress, adolescents with NSSI show changes in functional connectivity of regions associated with sensorimotor alertness, attention, and effortful emotion regulation.

Limitations: The patient group showed both NSSI and suicidal behavior, therefore results might be partly due to suicidality.

Conclusion: The findings emphasize the importance of targeting emotion regulation within therapeutic approaches to enhance stress coping capacity, which in turn may contribute to counteracting self-injurious behavior.

1. Introduction

Non-suicidal self-injury is the deliberate infliction of direct physical harm on one's own body without suicidal intent (Regier et al., 2013). In most cases, NSSI begins between the ages of 13 and 16, with injuries ranging from minor cuts to severe wounds, including biting, hitting, and burning oneself (Brunner et al., 2014; Kerr et al., 2010). NSSI is highly comorbid and co-occurs i.e. with mood and personality disorders as well as anxiety disorders and substance abuse (Plener, P., et al., 2018). The lifetime mean prevalence of NSSI is at around 28.2 % worldwide (Surace et al., 2021) with younger children exhibiting more severe self-injury and a wider range of methods than their older peers (Muehlenkamp et al., 2019).

Individuals who self-injure frequently display intense and overwhelming emotions (Klonsky et al., 2003, p.) which they find difficult to regulate. Therefore, adolescents with NSSI turn to maladaptive emotion regulation strategies such as self-injury to cope. For affected patients, NSSI feels functional as it reduces their negative affect (Claes et al.,

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2010) and increases their positive affect (Jenkins and Schmitz, 2012) in the short-term. Emotion regulation difficulties in NSSI are considered so severe that it is referred to as an emotion regulation disorder (Gross, 2014).

NSSI is a complex behavior with social, psychological, and biological risk factors contributing to its development (Wang et al., 2022). Kaess et al. (2021) state-trait model for NSSI categorizes risk factors and mechanisms of NSSI into three categories: distal biological traits, proximal biological traits, and biological states. Distal biological traits include biological predispositions or vulnerabilities to NSSI such as genetic predispositions or chronical stressors like childhood maltreatment that must either be present at birth or developed over a long period of time. Proximal biological traits include altered neuronal structures or functions and altered activity in the peripheral stress response system of moderate stability during existing NSSI symptomatology. In addition, biological states directly precede or follow NSSI and include reactions to acute stress or pain (Kaess et al., 2012; Koenig et al., 2017). Within this state-trait model the importance of stress processing in NSSI is apparent.

In NSSI emotion regulation and stress processing are fundamentally linked (Thayer et al., 2021). Both activate the hypothalamic–pituitary–adrenal axis, affecting heart rate and triggering cortisol release (Li et al., 2013; Zeman et al., 2006) and involve similar neural circuits. The fronto-limbic network, for example, is considered crucial in successful emotion regulation and stress coping. It involves areas such as the lateral and medial prefrontal cortex (PFC), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), hippocampus, anterior thalamus, insula, ventral striatum, periaqueductal grey (PAG) and amygdala (Etkin et al., 2015; Kohn et al., 2014; Raschle et al., 2019; Seminowicz et al., 2004).

Chronic stress is considered to affect brain development in fronto-limbic regions (Brañas et al., 2021; Cohodes et al., 2021; Etkin et al., 2015; Kim et al., 2013; Kohn et al., 2014; Mead et al., 2010; Raschle et al., 2019; Seminowicz et al., 2004), and results in changes in brain connectivity pattern associated with emotion regulation (Dark et al., 2020). Chronic stress also increases the risk of NSSI (Hankin et al., 2015; Miller et al., 2018), suicidal thoughts (Rosiek et al., 2016) and behavior (Pettit et al., 2011) in adolescents and young adults.

Unsurprisingly, altered functional resting-state connectivity (RSFC) in fronto-limbic circuits has also been found in patients with NSSI (Auerbach et al., 2021; Mayo et al., 2021; Westlund Schreiner et al., 2017). Additionally, alterations in insula activity (Mayo et al., 2021) and greater RSFC between amygdala, supplementary motor area (SMA) and dorsal anterior cingulate (Westlund Schreiner et al., 2017) have been found. And research has identified a negative association between fronto-limbic RSFC and cortisol levels in adolescents with depression and NSSI, revealing an abnormal interaction between neural connectivity and the neuroendocrine systems under acute stress (Thai et al., 2021). Furthermore, adolescents with NSSI exhibit an attenuated cortisol response compared to unaffected controls (Kaess et al., 2012), reduced physiological arousal to positive stimuli (Tatnell et al., 2018), but no differences in heart rate and affect rating (Kaess et al., 2012). Current research on adolescents stress levels during the COVID-19 pandemic revealed a link between higher pre-pandemic cortical overall responses to stress and emotion-induced amygdala activation to the persistence of NSSI behavior during the pandemic (Carosella et al., 2023), again highlighting the link between emotion and stress processing.

In children, emotion regulation and stress coping capability develop with increasing age and involves neuronal and physiological maturation (Thompson, 2014; Zeman et al., 2006). The development of emotion regulation is considered to increase a child's ability to cope with stressful situations (Southwick et al., 2011; Stansbury and Gunnar, 1994), leaving children with emotion regulation difficulties vulnerable to stressful situations, which in turn promotes NSSI behavior.

As stress exposure is a major health concern within each age group, various tasks to measure the effects of stress in laboratory settings have been developed (Akdeniz et al., 2014; Eisenbarth et al., 2016; Kirschbaum et al., 1993). The Montreal Imaging Stress Test (MIST) (Dedovic et al., 2005) consists of a sequence of mental arithmetic tasks and a social evaluative hazard component. It was designed for the magnetic resonance imaging (MRI) environment and enables research into the neuronal components of stress induction. Previous studies implementing the MIST have identified areas associated with stress induction, including the visual association cortex, angular gyrus (Dedovic et al., 2005), frontal regions (Chung et al., 2016; Dedovic et al., 2005; Goodman et al., 2018), subcortical regions (Dedovic et al., 2005; McEwen et al., 2016), and motor function regions (Dedovic et al., 2005). Despite the notable relationship between acute stress and emotion regulation, neuronal correlates of stress induction in patients with NSSI have not been sufficiently explored. Here, we aimed to add to the current understanding by conducting functional MRI scans in patients with NSSI before and after they completed MIST. We predicted that after the stress induction, adolescent patients with NSSI would show altered RSFC patterns in areas of emotion regulation and stress coping compared with matched unaffected controls.

2. Methods and materials

2.1. Participant recruitment

Patients engaging in NSSI were recruited via a specialized outpatient clinic for adolescent risk-taking and self-injurious behavior (AtR!Sk; University Hospital Heidelberg, Germany) (Kaess et al., 2017), or via inpatient units within the University Hospital Heidelberg. Patients who reported incidents of NSSI on 5 or more days within the last 12 months (criterion A in the Diagnostic and Statistical Manual of Mental Disorders [DSM] 5 (Regier et al., 2013)) were included. Exclusion criteria were acute psychotic episodes, neurological or medical conditions that could affect brain physiology (vascular and neurological diseases), acute suicidal tendencies, and IQ < 80. For the unaffected control participants, we contacted the citizens registration office at Heidelberg City Council, Germany and send letters to households ($n = 2398$) with children within the required age range. Our control participants were matched for age, handedness, sex, and level of school education and were not included if they had present or previous psychiatric disorders or abnormalities. All participants had to have sufficient understanding of German. In accordance with MRI safety regulations, pregnancy, claustrophobia, and metal implants, as well as a history of brain injury were considered to be exclusion criteria. Informed, written consent was obtained from participants as well as from their legal guardians (Ando et al., 2018). This study was approved by the ethics committee of the Medical Faculty of Heidelberg University (Study: ID S-046/2015) and conducted in accordance with the Declaration of Helsinki and its later amendments.

2.2. Psychological measurements

Prior to the MRI scanning session, demographic information, clinical diagnoses, and NSSI behavior from all participants were obtained (Ando et al., 2018). The Mini-International Neuropsychiatric Interview for Children and Adolescents 6.0 (Sheehan et al., 2010) was used to assess psychiatric disorders based on DSM-IV criteria and was administered no more than a week before MRI scanning. The borderline personality disorder module from the Structured Clinical Interview for DSM-IV, Axis II (Wittchen et al., 1997), also was performed on the same day before the scan, as was the Self-Injurious Thoughts and Behaviors Interview (Fischer et al., 2014), used to measure the extent of NSSI and suicidal behavior. Before the MRI scan we used the Edinburgh Handedness Inventory (Oldfield, 1971) to match groups for handedness. We used the State-Trait Anxiety Inventory (Kvaal et al., 2005) to investigate state and trait anxiety independent of depressive symptoms, and the Beck-Depression-Inventory II (Kühner et al., 2007) to measure the severity of depression. The following questionnaires were used both before and after the MIST stress induction: the 10-item Child Version of the Positive and Negative Affect Schedule (PANAS-C-SF) (Ebesutani et al., 2012) to evaluate positive and negative affect in performance situations, and the Dissociation-Tension Scale (DSS-4) (Stiglmayr et al., 2009) to assess dissociative states during neuroimaging, before and after stress induction. Using a visual analogue scale (VAS) from 0 to 100, we also asked participants to rate their current tension level and their performance evaluation after completing the measurement.

2.3. MIST paradigm

The MIST is a stress task designed for the MRI environment and consists of a sequence of mental arithmetic tasks, in addition to a social evaluative hazard component (Dedovic et al., 2005). In this study, participants underwent a 2-min practice session outside the scanner to familiarize themselves with the arithmetic task. Within the scanner, participants received 10 % less time to respond than they needed on average during the practice trials. The arithmetic task was designed for solutions to be an integer between 0 and 9, and answers could be given via a single keystroke. Participants were told that they needed to achieve 80 %–90 % correct answers as a minimum performance requirement and that the research staff would watch their performance. The fictional difference in their performance compared with other participants was visible as a comparison line on the monitor during the whole experiment. During MRI acquisition, pulse-to-pulse intervals were continuously recorded using the built-in Siemens MRI-compatible photoplethysmography on the right index finger at a sample rate of 50 Hz during each resting-state scan as well as during the MIST and were used for later analysis of heart rate variability (HRV) (Koenig et al., 2018). Functional resting-state sessions were acquired for 8 min before stress induction (RS1) and for 8 min after stress induction (RS2) via MIST to identify alterations in functional connectivity because of the stress induction. The MIST was performed while participants were lying inside the scanner.

2.4. MRI image acquisition

Images were acquired on a 3.0 T SIEMENS MAGNETOM Trio Tim syngo MR B17 scanner (Siemens TIM TRIO, Siemens, Erlangen) in the Neuroradiology Research Department at Heidelberg University Hospital, using a 32-channel head coil. First, anatomical T_1-weighted images in the sagittal plane were acquired with the following settings: 192 slices, 1 mm slice thickness, 1×1 mm^2 in-plane resolution, echo time = 2.52 ms, repetition time = 1900 ms, flip angle = 9°. Second, two functional resting-state runs using T^*_2-weighted echoplanar gradient echo sequences (180 measurements, 45 slices, 2.3 mm slice thickness, 2.3×2.3 mm^2 in plane resolution, echo time = 27 ms, repetition time = 2650 ms) were obtained before and after stress induction via MIST.

2.5. MRI preprocessing

Functional connectivity is defined as the statistical association between at least two anatomically distinct regions (Friston, 1994; Horwitz, 2003). To analyze collected functional resting-state data, we preprocessed images as follows. Extracranial tissues from T1-weighted images were removed using the brain extraction tool (BET) (Smith, 2002). Further preprocessing steps were done using FEAT as part of FSL (FMRIB Software Library 5.0) (Woolrich et al., 2009). Images were segmented into grey matter, white matter and cerebrospinal fluid (CSF) volume probability maps. Motion correction was done via the intramodal motion correction tool MCFLIRT (Jenkinson et al., 2002) and slice timing was corrected. Brain images were normalized into MNI152 (Montreal Neurological Institute) (Jenkinson and Smith, 2001; Maintz and Viergever, 1998; Zitová and Flusser, 2003). Images were smoothed with an 8-mm full-width-at-half-maximum kernel (Whitfield-Gabrieli and Nieto-Castanon, 2012).

2.6. Functional connectivity analysis

A first-level analysis was carried out using the CONN toolbox to perform spatial statistical analyses, with application of a weighted general linear model. Spatial maps and time sources for bivariate correlation measures were normalized into z-scores using Fisher's z transformation (inverse hyperbolic tangent function) (Fisher, 1915) to improve the normality assumptions of the second-level general linear model. A region of interest (ROI)-to-ROI analysis was performed for both groups and sessions and for pre- and post-stress induction. Children ages 12 years and older display functional connectivity patterns similar to those of young adults (Jolles et al., 2011), therefore ROIs were selected from CONN's standardized implemented HCP-ICA (1200 participants) and FSL Harvard-Oxford atlas of cortical and subcortical areas. As stress and emotion regulation involve neural processing steps that engage a divergent network of brain regions, we decided to include all ROIs for atlas and network analyses but focused on fronto-limbic regions such as the hippocampus, insula, amygdala, orbitofrontal cortex, prefrontal cortex and anterior and posterior cingulate cortex and their connectivity changes with various brain areas as well as networks associated with fronto-limbic regions like the fronto-parietal network and default mode network. Analyses were conducted for atlas-only connectivity, network-only connectivity, and shared connectivity (network + atlas regions), as ROIs can be connected to individual atlas regions or various nodes within a network. A network in this context describes a connection of atlas regions which show correlations in term of their fluctuating activity and therefore comprise a network. Common networks F-values for cluster-level inferences based on Gaussian random field theory (Worsley et al., 1996) were estimated. Results were corrected via false-discovery rate (FDR) p values (*p-FDR*) (Whitfield-Gabrieli and Nieto-Castanon, 2012). To analyze an interaction effect (group and resting state condition), a $2\text{-} \times -2$ mixed analysis of variance was carried out with a between-subject contrast [1–1] and a between condition contrast [1–1]. Group effects (NSSI group and control group) were analyzed using a two-sample t-test with a subject contrast of [1–1] and a condition contrast of [1]. Effects of condition (RS1 and RS2) were analyzed using a paired t-test with a subject contrast of [1] and a condition contrast of [1–1]. We performed a multiple regression with a fixed level of effect of both groups and checked for unique effects of age, HRV, depression, trait anxiety, borderline personality disorder, frequency of NSSI thoughts and behavior, and suicidality.

2.7. Further statistical analysis

Effects of stress induction via MIST within both groups were assessed using heart rate measures, DSS-4 values, and VAS and PANAS-C-SF scores, as well as functional MRI analysis. Pulse-to-pulse intervals were recorded for each resting state scan (RS1, RS2), as well as during the MIST. Measurements for each condition (RS1, MIST, RS2) were normally distributed. Because pulse-to-pulse intervals are a sufficient proxy for cardiac interbeat intervals, we used them for HRV analysis (Gil et al., 2010). Measurements were not normally distributed, so we used Mann–Whitney U tests for independent samples to evaluate group effects within the PANAS-C-SF ($N = 59$), the VAS ($N = 59$), and the DSS-4 ($N = 59$). Alpha levels were defined at 0.05. Multiple comparisons were corrected using corrected p-FDR values (Genovese et al., 2002).

3. Results

3.1. Demographic and psychometric measures

Of 62 participants, 34 met the diagnostic criteria of NSSI disorder according to the DSM-5 (section III, "Conditions for Further Study"), while the other 28 comprised unaffected controls (American Psychiatric Association and American Psychiatric Association, 2013, p. 5). For the experimental and control groups, demographic and diagnostic characteristics are described in detail in Table 1. Group comparisons revealed that adolescents with NSSI scored significantly higher on the Beck-Depression-Inventory II ($U = 33.00$, $p < .001$) and State-Trait Anxiety Inventory (state: $U = 181.00$, $p < .001$; trait: $U = 46.00$, $p < .001$) and were diagnosed with an average of 3.4 psychiatric disorders. The groups did not differ significantly in age ($t = -0.28$, $p = .78$). A correlation matrix of the psychometric measures can be viewed in supplementary results (Table S1).

3.2. *Effects of stress induction and heart rate variability*

A repeated-measures analysis of variance for the dependent variable HRV revealed a significant effect of the resting-state condition ($F = 166.62$; $p < .001$) and no significant main effect of group ($F = 0.69$; $p = .408$). There was a significant interaction effect of resting-state condition and group on HRV ($F = 8.36$; $p = .002$) (Fig. 1). In post hoc tests, we found a significant effect of condition between RS1 and MIST ($t = -13.14$; $p < .001$), MIST and RS2 ($t = 12.10$; $p < .001$), and RS1 and RS2 ($t = 2.54$; $p = .014$). To determine the direction of the interaction effect, post hoc tests were performed. No significant difference was found between the groups from stress induction (RS1: $t = -0.29$; $p = .773$; MIST: $t = -1.68$, $p = .101$; RS2: $t = -0.05$; $p = .958$). After FDR-corrected post hoc tests, all participants showed changes in the DSS-4 after stress induction (NSSI: $Z = -3.22$; $p = .001$; control: $Z = -3.47$; $p = .001$). The results of a Wilcoxon signed-ranks test indicated that patients with NSSI did not differ significantly in their positive affect rating (PANAS-CF: $Z = -1.49$; $p = .137$) or in their negative affect rating after stress induction ($Z = -0.26$; $p = .980$). In comparison, controls differed significantly in their positive affect rating ($Z = -2.63$; $p = .009$), with their positive affect decreasing because of stress induction but their negative affect rating remaining constant ($Z = -1.76$; $p = .078$). Group differences of DSS-4, VAS and PANAS for each resting-state condition are described in detail in Table 2.

3.3. *Resting-state functional connectivity*

The groups did not differ in RSFC before stress was induced, results that were consistent within network, ROI, and joint (network + ROI regions) analyses. A paired t-test across both groups to determine whether stress was induced (RS1 and RS2) revealed 25 clusters with altered connectivity effects in regions associated with stress induction, including the fronto-limbic network, default mode network, and cerebellum. Further details and descriptions of regions comprising mentioned networks are available in the supplementary results (Tables S2 and S3). Significant interaction effects were detectable between group and condition within the joint (network + ROI regions) connectivity analysis. We found a significant interaction effect (group*condition RS1 and RS2) between frontal regions and networks and the angular gyrus ($F(2,59) = 10.51$; p-FDR $= 0.02$). The involved frontal regions included the right middle frontal gyrus, right superior frontal gyrus, right frontal pole, and fronto-parietal network of the posterior parietal cortex and lateral prefrontal cortex. The right angular gyrus was connected to the frontal regions via the lateral prefrontal network, middle frontal gyrus, and right frontal pole. Compared with controls, the patient group showed reduced RSFC between these regions and networks after stress induction. Furthermore, we found a significant interaction effect among occipital visual regions and networks, the right planum temporale, the left central opercular cortex, and the insula ($F(2,59) = 10.39$; p-FDR $= 0.02$). The patient group showed increased functional connectivity between those regions after stress induction (Fig. 2).

None of the results could be explained by effects of age, suicidality, depression, trait anxiety, or borderline personality disorder symptomatology, and no results were associated with changes in HRV. An additional analysis without the male participants obtained the same results. Groups did not differ in head motion during measurement.

Table 1
Demographic and clinical characteristics.

	NSSI[a] Patients *N (%)*	*M(SD)*	Healthy Controls *N (%)*	*M(SD)*
Demographics				
Sex				
Female	32 (94 %)		28 (100 %)	
Male	2 (6 %)			
Age, years		15.91 (1.35)		16.0 (1.14)
Handedness				
left	3 (9 %)		3 (11 %)	
right	31 (91 %)		25 (89 %)	
School type[b]				
Hauptschule	5 (15 %)		1 (4 %)	
Realschule	4 (12 %)		5 (18 %)	
Gymnasium	20 (59 %)		20 (71 %)	
Vocational education	4 (12 %)		0 (0 %)	
Other	1 (3 %)		2 (7 %)	
Clinical Presentation				
DSM-5 NSSI disorder diagnosis	34 (100 %)		0 (0 %)	
BDI-II[c] (Depression)		28.65 (14.88)		4.14 (3.70)
STAI[d] (State Anxiety)		49.09 (10.94)		37.96 (6.61)
STAI(Trait Anxiety)		57.47 (12.28)		35.04 (5.90)
SCID-II[e] (BPD)	14 (41 %)		0 (0 %)	
SITBI-G[f]:				
Lifetime Thoughts of NSSI	34 (100 %)	92.56 (179.16)	0 (0 %)	0 (0)
Thoughts of NSSI (last 12 month)	34 (100 %)	28.03 (48.73)	0 (0 %)	0 (0)
Lifetime NSSI behavior	34 (100 %)	254.24 (402.17)	0 (0 %)	0 (0)
NSSI behavior (last 12 month)	24 (71 %)	65.03 (76.04)	0 (0 %)	0 (0)
Lifetime Suicidal thoughts	33 (97 %)	29.06 (56.50)	0 (0 %)	0 (0)
Suicidal thoughts (last 12 month)	32 (94 %)	28.03 (48.56)	0 (0 %)	0 (0)
Lifetime Suicide attempts	18 (53 %)	1.78 (1.31)	0 (0 %)	0 (0)
Suicide attempts (last 12 month)	14 (41 %)	1.21 (0.58)	0 (0 %)	0 (0)
ICD-10 Psychiatric diagnoses[g]				
F1 Mental and behavioural disorders due to psychoactive substance use	9 (27 %)		0 (0 %)	
F2 Schizophrenia, schizotypical and delusional disorders	1 (3 %)		0 (0 %)	
F3 Mood (affective) disorders	25 (74 %)		0 (0 %)	
F4 Neurotic, stress-related and somatoform disorders	20 (59 %)		0 (0 %)	
F5 Behavioural syndromes associated with physiological disturbances and physical factors	6 (18 %)		0 (0 %)	
F9 Behavioural and emotional disorders with onset in childhood and adolescent	6 (18 %)		0 (0 %)	
Medication	4 (12 %)		1 (4 %)	
SSRI/SNRI	3 (9 %)		0 (0 %)	
Neuroleptic	1 (3 %)		0 (0 %)	
Methylphenidate	0 (0 %)		1 (4 %)	
No medication	30 (88 %)		27 (96 %)	

Notes. Respective group characteristics.

[a] NSSI, Non-suicidal self-injury.

[b] After four years of elementary school the school system of Germany is divided into three levels according to academic performance. The Secondary General School (Hauptschule) prepares pupils for vocational training, the Intermediate Secondary School (Realschule) concludes with a general certificate of secondary education. The Gymnasium provides pupils with a general university entrance qualification. Matching education level allows for similar levels of intelligence.

[c] Beck Depression Inventory.

[d] State Trait Anxiety Inventory.

[e] Structured Clinical Interview for DSM-5 AXIS II Disorders.

[f] Self-Injurious Thoughts and Behavior Interview.

[g] ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision, Assessment via Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-Kid).

In addition, we identified significant interaction effects of condition (RS1 and RS2) and frequency of lifetime thoughts about NSSI (Cluster 1: $F(2,60) = 11.89$; p-FDR < 0.001; Cluster 2: $F(2,60) = 9.83$; p-FDR $<$ 0.001). Compared with controls, the patient group showed reduced RSFC between the fronto-parietal network (right posterior parietal cortex and lateral prefrontal cortex) and the right middle frontal gyrus, the right superior frontal gyrus, the right frontal gyrus, and the right angular gyrus. The patient group also showed reduced RSFC between the superior division of the lateral occipital cortex and the temporal pole (Fig. 3). Additionally, there was a significant interaction effect of resting-state condition and frequency of lifetime NSSI behavior (Cluster 1: $F(2,69) = 10.59$; p-z < 0.001; Cluster 2: $F(2,60) = 10.59$; p-FDR $<$ 0.001; Cluster 3: $F(2,60) = 9.40$; p-FDR < 0.001) between fronto-parietal atlas and network regions (Fig. 4).

4. Discussion

In the present study, we investigated stress-induced differences in RSFC, comparing a group of adolescents with NSSI to an unaffected group of adolescents. Both groups showed increased HRV during stress induction, which indicates stressing. Only the control group showed a reduced positive affect after completion of the MIST, suggesting a reflection on internal emotional changes from the stress induction. In contrast, the patient group did not change their positive and negative affect ratings. This invariability is consistent with some previous findings (Kaess et al., 2012; Tatnell et al., 2018) showing no difference in physiological arousal of participants with or without NSSI behavior during stress induction, but results are mixed (Nock and Mendes, 2008). This lack of subjective change in affective states may be explained by the positive association between NSSI and alexithymia (Greene et al., 2020), which is the inability to identify and describe feelings and distinguish them from physical sensation (Norman and Borrill, 2015). Although patients may have felt a shift in their affective state, they might not have been able to attribute it to the categories described by the PANAS.

With regard to functional connectivity patterns, two clusters could be identified, reflecting differences between patient and control groups following stress induction. The first cluster included various frontal regions and their connectivity to the angular gyrus. Patients showed reduced functional connectivity between these regions after stress induction. The angular gyrus previously has been described as a MIST-related region – a stress-independent area that additionally is activated when both social and temporal stressors are removed and only the mental arithmetic aspect remains (Dedovic et al., 2005). Although no task was presented within the resting-state condition, we found reduced functional connectivity between the angular gyrus and frontal regions in the patient group only. Because resting-state functional MRI was performed after completion of the MIST, and task specific changes should be equivalent in both groups, results in the current study cannot be task specific.

The reduced connectivity we observed could be interpreted in the context of effortful emotion regulation because reduced functional connectivity between frontal areas and the angular gyrus has been associated with effortful emotion regulation in patients with emotion regulation disorder (Raschle et al., 2019). For example, Kohn's (Kohn et al., 2014) core brain network model of emotional reactivity identifies

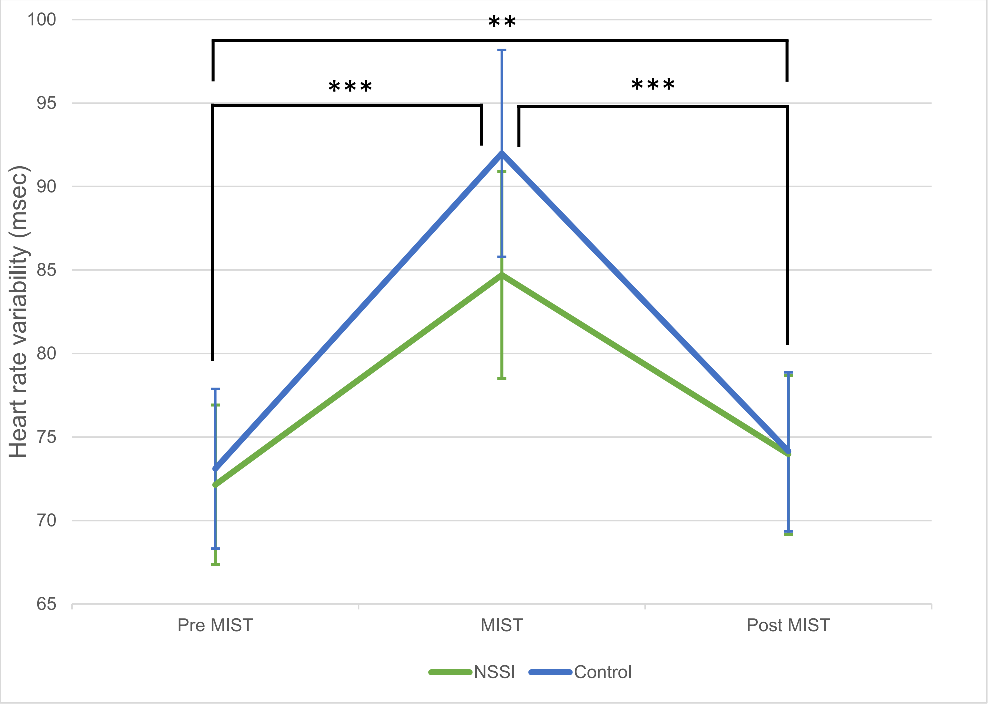

Fig. 1. Heart rate variability measure during magnetic resonance imaging via a pulse oximeter; Pre MIST: resting state 1; MIST: Montreal Imaging Stress Task; Post MIST: resting state 2; significant effect of condition between Pre MIST and MIST as well as MIST and Post MIST; significant effect of condition between Pre MIST and Post MIST; *** indicate a p-value $< .001$, ** indicate a p-value between 0.001 and 0.009.

Table 2
Psychological measurements before and after stress induction.

Logistic parameter	Pre MIST			Post MIST			Test Statistic Pre MIST		Test Statistic Post MIST	
	N	*M*	*SD*	*N*	*M*	*SD*	*U*	*p*	*U*	*p*
PANAS (PA)[a]							261.00	**0.001*****	302.00	0.051
NSSI[b]	33	12.06	3.58	33	11.0	3.56				
Control[c]	26	14.96	2.09	26	12.92	3.20				
PANAS (NA)[d]							223.50	**0.002****	307.50	0.062
NSSI	33	10.76	3.85	33	10.67	3.65				
Control	26	7.73	2.27	26	8.88	2.82				
DSS-4[e]							167.50	**0.001*****	246.00	**0.005****
NSSI	33	1.69	2.03	33	2.86	2.87				
Control	26	0.06	0.13	26	0.82	1.07				
VAS 1[f]									360.00	0.291
NSSI				33	70.61	12.39				
Control				26	64.54	18.07				
VAS 2[g]									310.50	0.070
NSSI				33	70.76	22.00				
Control				26	60.96	22.42				
VAS 3[h]									381.50	0.465
NSSI				33	81.52	18.20				
Control				26	87.42	9.12				
VAS 4[i]									199.50	**0.001*****
NSSI				33	18.33	15.25				
Control				26	35.38	19.25				

Notes. respective group differences. *** indicate a p-value $<$ .001, ** indicate a p-value between .001 and .009.

[a] Positive affect rating of the PANAS Children short form.

[b] NSSI: non-suicidal self-injury, experimental group.

[c] Control group.

[d] Negative affect rating of the PANAS Children short form.

[e] DSS-4:Dissociation-Tension Scale.

[f] VAS 1: How exhausting did you find the experiment?.

[g] VAS 2: How unpleasant did you find the experiment?.

[h] VAS 3: How much effort did you put into mastering the tasks?.

[i] VAS 4: How well do you rate your performance?

both frontal regions and the angular gyrus as core elements of emotion regulation, and the frontal cortex frequently appears in connection with regulatory processes of emotional processing (Barrash et al., 2000; Ochsner et al., 2002; Ochsner and Gross, 2005). Furthermore, the angular gyrus plays a role in early reappraisal, a strategy to alter the trajectory of emotional responses (Goldin et al., 2008). Reappraisal down-regulates emotional experience and behavior (Jackson et al., 2000), doing so by recruiting executive cognitive control processes via the prefrontal cortex (Ochsner et al., 2004; Phan et al., 2005). While NSSI is related to brain networks associated to difficulties in self-referential processing and future planning (Ho et al., 2021), the angular gyrus plays a role in the attempt to reach the desired emotional brain state (Kohn et al., 2014).

Our results might be indicative of effortful emotion regulation in response to stress induction in patients with NSSI. Emotion regulation and stress coping both entail an affective state (Gross, 2014). Against this background, it could be assumed that stressful situations trigger both an affect that requires imminent stress coping and an affect that requires emotion regulation in patients with NSSI. In the context of MIST, arithmetic tasks likely exert pressure to perform well, which may in turn trigger a stress response and activate coping mechanisms. Because coping is mostly unsuccessful in patients with NSSI, a heightened residual affective state remains (Tatnell et al., 2018). Concurrently, social evaluation adds an emotional stressor, which requires more complex affect regulation. Here, the situation is evaluated, and self-performance is assessed in comparison with a social group. Mistakes are presumably evaluated in the context of the social situation and possible consequences are assessed. If stress coping is not successful, for example, when NSSI is prevented (Willis et al., 2017), increased affect remains. Patients with NSSI show an interference in interoceptive awareness (Mürner-Lavanchy et al., 2022) and exhibit difficulties describing their feelings and distinguishing them from physical sensation (Greene et al., 2020; Sleuwaegen et al., 2017), therefore this residual affect may be additive with emotional affect, leading to more effortful emotion regulation.

Our secondary results showed reduced RSFC after stress induction between frontal regions and the angular gyrus in connection with frequency of lifetime thoughts about NSSI but not with NSSI behavior. This pattern indicates that effortful emotion regulation might be associated with the intensity of self-injurious thoughts but not with the behavior adolescents use to change their affective state.

Our second cluster identified functional connectivity changes between occipital visual regions and networks: the right planum temporale, left central opercular cortex, and insula. In accordance with Zhang and colleagues (Zhang et al., 2020), who identified stress-induced changes within the central-opercular and occipital modules associated with the sensorimotor and visual systems, respectively, our results show functional connectivity changes within occipital visual areas and the central opercular cortex. Zhang et al. (2020) identified those regions as a connector module under stress, arguing for enhanced capacity of the sensorimotor system in communication with other functional systems because of stress induction. In addition, we found increased functional connectivity between the abovementioned regions and the insula and right planum temporale, creating a link between a hypersensitized perception-action system (Auerbach et al., 2021; Zhang et al., 2020), stimulus-driven auditory attention (Hirnstein et al., 2013), and emotion processing (Giuliani et al., 2011; Grecucci et al., 2013) in stressed patients with NSSI. This finding may suggest that the experience of stress in patients with NSSI heightens focus on important stimuli and the emotional response, activating the fight-or-flight reaction in these patients and leading to an increased willingness to self-injure to reduce emotional arousal. These results are consistent with previous research (Haines et al., 1995) demonstrating that imagination of NSSI decreases the extent of physiological arousal among adolescent patients with the

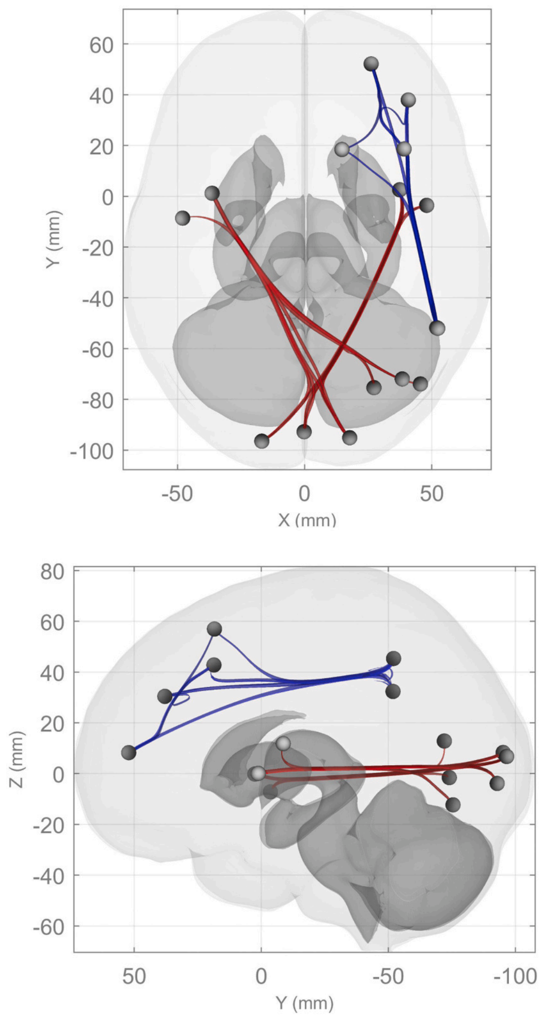

Fig. 2. Functional connectivity changes between Resting-State-Sessions pre and post stress induction. Interaction effects between group and condition: Red: Network: visual occipital cortex, right lateral visual cortex; Atlas: left & right occipital pole, right occipital fusiform gyrus, right lateral occipital cortex, left & right insular cortex, right planum polare, left central opercular cortex (NSSI > control & post > pre); Blue: Network: fronto-parietal: left & right lateral prefrontal cortex; right posterior parietal cortex; Atlas: right middle frontal gyrus, right superior frontal gyrus, right frontal pole, angular gyrus (control > NSSI & pre > post). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

condition.

4.1. Strengths

To date, the extent to which emotion regulation and stress coping are related is an ongoing debate, especially in stress-related psychiatric disorders. NSSI, as an emotion regulation disorder, with a symptomatology clustered in stressful situations, offers a unique opportunity to examine both constructs in relation to each other. We examined a well-characterized sample, representative of a typical treatment population of adolescents in child psychiatric inpatient and outpatient clinics. To our knowledge, this study is the first to use a stress-induction paradigm to examine RSFC in a clinical sample of adolescents engaging in NSSI. The findings thus provide deeper insights into the neurobiological underpinnings of stress and emotion processing in young patients with emotion regulation difficulties. Our findings underline the importance of targeting emotion regulation within the therapeutic setting to enhance adaptive coping strategies under distress and counteract self-injurious behavior in the early stages of adolescent development.

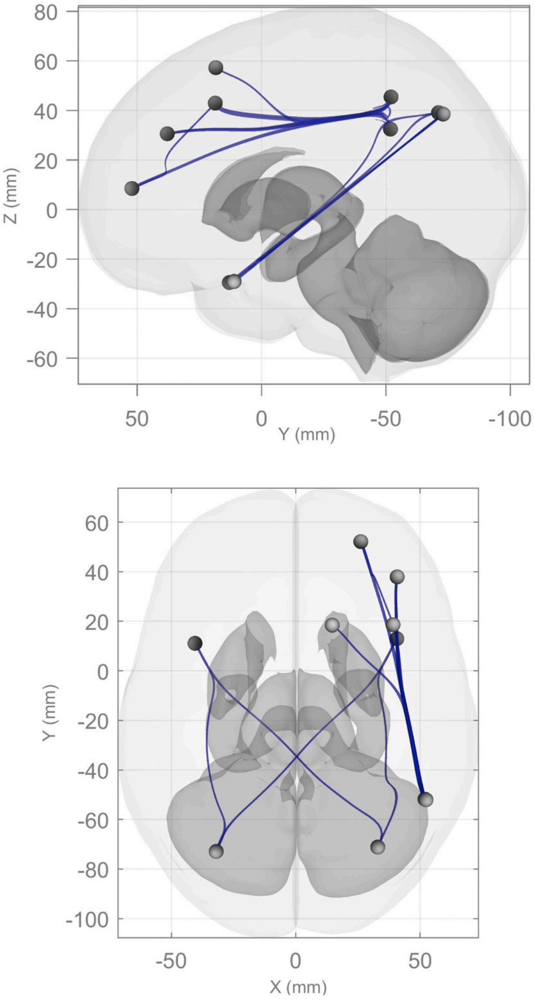

Fig. 3. Functional connectivity changes between Resting-State-Sessions pre and post stress induction. Interaction effects between lifetime NSSI thoughts and condition: Cluster 1: Atlas: right middle frontal gyrus, right angular gyrus, right superior frontal gyrus, right frontal gyrus; Network: fronto-parietal network: right posterior parietal cortex and left & right lateral prefrontal cortex; Cluster 2: Atlas: left & right superior division of the lateral occipital cortex, left & right temporal pole; (NSSI < control & post < pre).

4.2. Limitations

Despite several strengths, our study has some limitations. Our clinical sample was recruited based on their level of NSSI. NSSI is a major risk factor for suicidal behavior and both share some overlapping properties (Groschwitz et al., 2015). 41 % of our participants had attempted suicide within the past 12 months, and almost all of them reported suicidal ideation. Therefore, it cannot be ruled out that our results are, at least partly, due to suicidal behavior and not NSSI alone. The small number of boys in the total sample prohibited statistical analysis of possible sex effects. Potential sex differences thus could not be assessed and should be the subject of further studies. Furthermore, both left- and right-handed children and adolescents were included in the analysis. Handedness was not expected to have an influence because patients were matched according to handedness, but the possibility cannot be ruled out. We also must state that the groups differed greatly in their clinical characteristics, so we cannot exclude the possibility that differences arose because of patient status. And although our control subjects were examined by expert clinicians, one of the included control

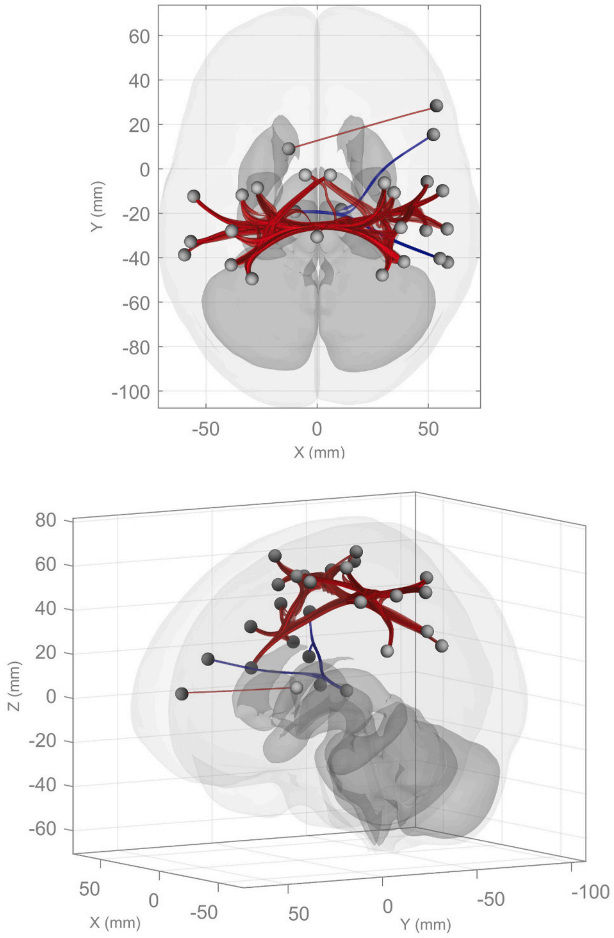

Fig. 4. Functional connectivity changes between Resting-State-Sessions pre and post stress induction. Interaction effects between lifetime NSSI behavior and condition: Cluster 1: red: Atlas: left & right anterior division of the supramarginal gyrus, right parietal operculum cortex, right central opercular cortex, left & right precentral gyrus, right supplementary motor cortex; Network: Salience Network: left supramarginal gyrus; (NSSI > control & post > pre); Cluster 2: red: Atlas: left & right postcentral gyrus, left & right precentral gyrus, left & right supplementary motor cortex, right parietal operculum cortex, right central opercular cortex, left & right superior opercular cortex; Network: Dorsal Attention Network left & right frontal eye field and left & right intraparietal sulcus, left & right lateral and superior Sensorimotor Network; (NSSI > control & post > pre); Cluster 3: blue: Atlas: left and right thalamus, left caudate, right inferior frontal gyrus, pars opercularis, right posterior division of the supramarginal gyrus; Network: Language Network: right posterior division of the superior temporal gyrus and right inferior frontal gyrus; (NSSI < control & post < pre); red: Atlas: left caudate, Network: Language Network: right inferior frontal gyrus; (NSSI > control & post > pre). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

participants was receiving methylphenidate. The difficulty of the arithmetic tasks was not adapted to participant performance level, so we cannot say with certainty that further connectivity changes would not be identifiable from more intensive stress. We did not conduct a low-stress control session to monitor task performance in the absence of stress, for that reason the perceived neurophysiological changes could be due to an effect other than stress. As an additional limitation, it cannot be ruled out that differences in HRV between Pre MIST and Post MIST occurred due to noise, as their error bars overlap. Nonetheless, our results offer promising insights into the acute stress response in patients with NSSI.

4.3. Main conclusion and further research prospects

Taken together, our RSFC results suggest that acute stress in patients with NSSI leads to increased affect, heightened focus on relevant stimuli and their emotional processing, and effortful emotion regulation, possibly increasing the likelihood of self-injurious behavior.

Further research may rely on repetitive transcranial magnetic stimulation of frontal regions involved in emotion regulation, measuring RSFC with the angular gyrus and the effect on effortful emotion regulation in patients with NSSI. This technique has been successfully used to improve emotion regulation in generalized anxiety disorder (Diefenbach et al., 2016). Future studies also should consider whether different levels of alexithymia within a group of self-injuring people impact the success of emotion regulation under acute stress because alexithymia could be a modulating factor in effortful emotion regulation under these conditions.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.07.032.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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