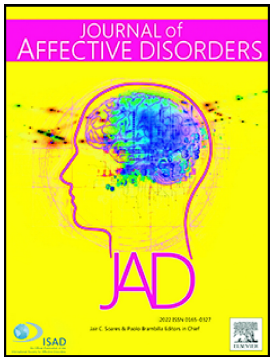

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Resting-state functional connectivity predicting clinical improvement following treatment in female adolescents with non-suicidal self-injury

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Keywords: *Non-suicidal self-injury; psychological intervention; therapy; outcome; resting-state connectivity; adolescents*

Abstract

Background: Non-suicidal self-injury (NSSI) is highly prevalent among adolescents and predicts future psychopathology including suicide. To improve therapeutic decisions and clinical outcome of patients engaging in NSSI, it seems beneficial to determine neurobiological markers associated with treatment response. The present study investigated whether resting-state functional brain connectivity (RSFC) served to predict clinical improvements following treatment in adolescents engaging in NSSI.

Methods: *N*=27 female adolescents with NSSI took part in a baseline MRI exam and clinical outcome was assessed at follow-ups one, two and three years after baseline. During the follow-up period, patients received in- and/or outpatient treatment. Mixed-effects linear regression models were calculated to examine whether RSFC was associated with clinical improvement.

Results: Patients' clinical outcome improved across time. Lower baseline RSFC between left paracentral gyrus and right anterior cingulate gyrus was associated with clinical improvement from baseline to one-year and from two-year to three-year follow-up. Lower and higher baseline RSFC in several inter- and intrahemispheric cortico-cortical and cortico-subcortical connections of interest were associated with clinical symptomatology and its severity, independent from time.

Limitations: A relatively small sample size constrains the generalizability of our findings. Further, no control group not receiving treatment was recruited, therefore clinical changes across time cannot solely be attributed to treatment.

Conclusions: While there was some evidence that RSFC was associated with clinical improvement following treatment, our findings suggest that functional connectivity is more predictive of severity of psychopathology and global functioning independent of time and treatment. We thereby add to the limited research on neurobiological markers as predictors of clinical outcome after treatment.

Introduction

Non-suicidal self-injury (NSSI) denotes deliberate self-inflicted bodily injury without suicidal intent (American Psychiatric Association, 2013), and includes self-cutting, scratching and bruising, which is not socially or culturally accepted (Plener et al., 2016). With a prevalence rate of 17.2%, single events of NSSI are highly common in population samples of adolescents (Swannell et al., 2014). *NSSI disorder*, characterized by repetitive acts of NSSI, has been introduced in the 5th version of the Statistical and Diagnostic Manual of Mental Disorders (DSM-5) as a research diagnosis requiring further research (American Psychiatric Association, 2013), reflecting both clinical and scientific interest in the phenomenon. Diagnostic criterion A of the disorder is met when an individual engages in self-injury without suicidal intent on at least five days within the past year. While a prevalence rate of 4% has been found for NSSI disorder in adolescent community samples (Plener et al., 2016) prevalence of around 50% has been found among adolescent in-patient samples (Glenn and Klonsky, 2013; Groschwitz et al., 2015). Females are more likely to report a history of NSSI than males, in particular in clinical samples (Bresin and Schoenleber, 2015), which might be due to female patients being more likely to seek help (Haavik et al., 2019). Engagement in NSSI has serious negative consequences, as NSSI history is associated with future NSSI, suicide attempts (Asarnow et al., 2011) and an increased risk for suicide (Hawton et al., 2015). NSSI has also been found to be one of the strongest predictors of Borderline Personality Disorder (BPD) development (Ghinea et al., 2019), and recent research suggests that NSSI is a transdiagnostic risk marker of psychopathology in general (Ghinea et al., 2020).

Many psychiatric disorders already emerge in childhood and half of all mental illnesses begin before the age of 14 years (Merikangas et al., 2009). However, response rates to mental health treatment are concerning, with high rates of partial or no response (Menke, 2018). As a result, young patients may experience heightened distress and may require several episodes of treatment, which in turn are linked with increasing health care costs (Kessler, 2018). It is possible that determining patients' responses to therapy, might optimize treatment outcomes in adolescent psychiatric patients (McMahon, 2014). The diagnostic and therapeutic process is however, mostly based on subjective clinical judgment (McMahon, 2014), and patient characteristics (e.g., treatment adherence,

sociodemographic, psychosocial) which may additionally influence treatment outcomes. Therefore, the prediction of treatment response is a challenging endeavor (Kessler, 2018; McMahon, 2014), however recent scientific initiatives (e.g. the research domain criteria; RDoC; (Cuthbert, 2015)) suggest addressing this problem by focusing on dimensions of observable behavior and objective neurobiological measures. That is to say, finding more objective predictors of treatment outcome might allow for a more appropriate selection of, and more favourable responses to, treatment (Chang et al., 2020; Jeong et al., 2020; Ng and Weisz, 2016).

To that end, neuroimaging research has so far mainly focused on proximal neurobiological traits in individuals engaging in NSSI (Kaess et al., 2021). Findings to date have highlighted the important roles of frontolimbic brain circuitry and alterations in prefrontal and limbic brain structure associated with NSSI (Ando et al., 2018; Dahlgren et al., 2018; Groschwitz et al., 2016; Koenig et al., 2021; Niedtfeld et al., 2010; Plener et al., 2012; Schär et al., 2022; Vega et al., 2018). Previous resting-state functional magnetic resonance imaging (rsfMRI) studies assessing resting-state functional connectivity (RSFC) in adolescents with NSSI have demonstrated both higher and lower RSFC between frontal and limbic brain regions: Female adolescents with NSSI (13 – 21 years old, n = 29) showed higher right amygdala - dorsal anterior cingulate cortex (ACC) RSFC and higher amygdala - supplementary motor area (SMA) RSFC than healthy controls (Westlund Schreiner et al., 2017). In the same study, lower negative amygdala RSFC with lateral occipital and angular gyri, frontal pole, and inferior and middle temporal regions were found in comparison with healthy controls (Westlund Schreiner et al., 2017). Another group of 12 – 17-year-olds with NSSI (n = 24) showed reduced seed-based RSFC between the amygdala and the ACC, paracingulate gyrus, subcallosal cortex, right insula and right planum temporale, and between the medial PFC and left insula, as well as pre- and postcentral gyri, in comparison with healthy controls (Santamarina-Perez et al., 2019). Adopting a graph theory approach to whole brain RSFC, we previously identified longer average path lengths and a smaller number of weighted hubs globally, as well as lower efficiency and worse integration in an orbitofrontal region in n = 33 adolescents (aged 12 – 17 years) engaging in NSSI (Mürner-Lavanchy et al., 2022).

Given the potential of neuroimaging as an objective measure, it is of particular interest as to

whether brain function might serve to predict clinical and treatment outcomes in adolescents engaging in NSSI (Westlund Schreiner et al., 2019). The first study investigating whether brain connectivity predicted treatment outcome in NSSI patients, used a seed-based approach to examine baseline amygdala RSFC in 12-17 year-olds (Santamarina-Perez et al., 2019). The study found that lower connectivity between the amygdala and ACC as well as the prefrontal cortex, was associated with greater clinical improvement following treatment in NSSI patients after four months of Dialectical Behavior Therapy for Adolescents (DBT-A) and treatment as usual (n = 24) (both treatment arms were combined to increase statistical power). The authors suggested that 'top-down' regulation of the amygdala by the prefrontal cortex might be beneficial for treatment outcome. A second study relating seed-based RSFC with clinical outcomes after an 8-week open-label N-acetylcysteine trial in 13-21 year-old NSSI patients (n = 18) found decreases in left amygdala–right supramarginal gyrus and right nucleus accumbens–left superior medial frontal cortex RSFC, and increases in right amygdala–right inferior frontal cortex RSFC to be associated with reductions in NSSI frequency after treatment (Cullen et al., 2020). The finding of changes in RSFC associated with pharmaceutical treatment suggests amygdala and nucleus-accumbens-based circuits as potential treatment targets.

The purpose of the present study was to expand the sparse literature on neuroimaging precursors of treatment outcome by investigating whether baseline RSFC is associated with clinical change across three years in female adolescents engaging in NSSI. Our aim was to exploratively investigate whether RSFC between several a priori defined regions of interest predicted treatment outcome at one, two- and three-years' follow-up.

Methods and Materials

Participants and procedure

Two existing datasets were merged for the present investigation. Data on clinical outcome stem from a clinical cohort study designed to evaluate an outpatient clinic specialized in adolescent risk-taking and self-harm behavior (AtR!Sk; "Ambulanz für Risikoverhalten & Selbstschädigung", University Hospital Heidelberg, Germany; Kaess et al., 2017). Adolescents between the age of 12 and 17 years who presented at this specialized outpatient clinic were consecutively recruited to participate

in this cohort study and underwent structured clinical assessments by specifically trained clinicians.

A subsample of patients recruited into the clinical cohort study between 2015 and 2016 were also invited to participate in a cross-sectional neuroimaging study. Both study protocols (clinical cohort study ID: S-449/2013; neuroimaging study ID: 983 6087 8915) were approved by the ethics committee of the Medical Faculty, University of Heidelberg, Germany and were conducted according to the Declaration of Helsinki ("World Medical Association Declaration of Helsinki," 2013). Written informed consent was obtained from participants and their primary caregivers prior to study participation.

Within the clinical cohort study, yearly clinical assessments were performed by trained clinicians in child and adolescent psychiatry. In the current report, data from three follow-up time-points were included. For further follow-ups, sample sizes were too small due to drop-out. Follow-up assessments occurred at approximately 12 months, 24 months, and 36 months post baseline. Patients received psychotherapeutic treatment either at inpatient units of the Clinic of Child and Adolescent Psychiatry, University Hospital Heidelberg, at the AtR!Sk outpatient clinic, or with licensed psychotherapists. Treatment at the outpatient clinic AtR!Sk followed a structured treatment protocol and consisted of a cognitive-behavioral oriented short-term therapy (10 sessions) and/or dialectic-behavioral therapy. A minor proportion of patients received additional inpatient treatment.

General inclusion criteria were presentation in the AtR!Sk outpatient clinic, written informed consent of adolescents and their caregivers, age between 12 and 17 years and fluent German language. Exclusion criteria for both studies were acute psychotic symptoms, acute suicidality, pregnancy, endocrine disorders, and prescription of glucocorticoid medication. For the cross-sectional neuroimaging study, patients were additionally excluded if they had known vascular and neurological diseases (potentially influencing brain function), claustrophobia, metal implants, and a history of brain injury.

Clinical assessment

During the clinical assessment, sociodemographic information was obtained, including sex, date of birth, handedness (using the Edinburgh Handedness Inventory (Oldfield, 1971)), body mass index

(BMI: weight(kg)/ height(m)²), medication and drug use. Further, information on treatment received since the last clinical assessment was obtained.

The Mini-International Neuropsychiatric Interview for Children and Adolescents (M.I.N.I.-KID 6.0) (Sheehan et al., 2010) was used as an extensive assessment of psychiatric diagnoses. The German version of the Self-Injurious Thoughts and Behavior Interview (SITBI, (Nock et al., 2007)), the SITBI-G (Fischer et al., 2014) was used to assess NSSI. This version has shown good reliability and convergent validity (Fischer et al., 2014). The variable of interest for the present study was the number of days with NSSI incidents during the month preceding the interview (henceforth abbreviated as "NSSI incidents"). The Clinical Global Impression Scale (CGI-S), a one-item clinician-rated measure was used to assess the severity of Psychopathology during the past seven days at all follow-up assessments (Busner and Targum, 2007). Further, the Global Assessment of Functioning (GAF) Scale was used to estimate global psychosocial functioning (Moos et al., 2000), where clinicians were required to make an overall judgement regarding a patient's current level of psychological, social, and occupational functioning based on a 1 – 100 rating scale at all follow-up time-points. Other clinical measures obtained but not used in the statistical analyses are described in the *Supplementary material*.

Neuroimaging

The neuroimaging procedure has been described previously (Mürner-Lavanchy et al., 2022). Anatomical T_1-weighted images and T_2*-weighted echo planar images were acquired using a Magnetom TRIO 3 Tesla scanner (Siemens, Erlangen, Germany) with a 32-channel-head coil. T1-weighted images were acquired in the sagittal plane with the following parameters: 192 slices with 1mm thickness, 1x1mm^2 in-plane resolution, echo time, TE = 2.52 ms, repetition time, TR = 1900 ms and flip angle = 9°). T2*-weighted echo planar images were acquired during a resting state, during which patients were asked to keep their eyes open. Each of the three runs lasted for approximately 8 minutes (TE = 27 ms, TR = 2650 ms, FoV = 220 mm, Flip angle = 90°, slices = 45).

Image processing

T1-weighted images were automatically segmented using the Desikan-Killiany-Tourville atlas (Klein and Tourville, 2012) in FreeSurfer version 6.0 (Reuter et al., 2010). The volume-based segmentation process is performed as follows: 1) labelling of brain structures by registration to MNI305 space 2) segmentation based on a subject-independent probabilistic atlas and subject-specific measured values 3) classification of each voxel to a label. After segmentation, all images underwent a visual quality check by trained researchers. Details of FreeSurfer segmentation have previously been described (Fischl et al., 2004, 2002). The volumes of regions which are labelled as a particular structure are then calculated by FreeSurfer and can further be used in statistical analyses.

FMRIB's Software Library (FSL 5.0, Oxford, 2012) was used for standard preprocessing of rsfMRI data and included the following steps: motion correction using MCFLIRT, brain extraction with BET, slice time correction, spatial smoothing with a full-width-half-maximum 6 mm Gaussian kernel, as well as high-pass temporal filtering. The FMRIB linear image registration tool was used for linear registration of functional images with the processed brain extracted images and finally, FNIRT was used to co-register the functional images non-linearly with MNI standard space.

Connectivity network

All nodes were used to create a connectivity matrix. In this matrix, the connection of two nodes is equal to the squared partial correlation of the time series, which is controlled for the time series of all other nodes (this serves to control for indirect connections between the connections of interest) as well as cerebrospinal fluid and white matter.

Regions of Interest (ROI) were selected from the Deskan-Killiany atlas provided by FreeSurfer (Desikan et al., 2006). The nine cortical ROIs assessed in the present study included caudal anterior cingulate cortex, rostral anterior cingulate cortex, lateral orbitofrontal cortex, medial orbitofrontal cortex, rostral middle frontal gyrus, caudal middle frontal gyrus, superior frontal gyrus, paracentral cortex, pericalcarine cortex (each left and right hemisphere). The two subcortical ROIs included the amygdala and the hippocampus (each left and right hemisphere, for an overview of all ROIs studied, see Supplementary Figure 1). The aforementioned ROIs have been previously associated with the

neurobiology/neuroanatomy of NSSI in adolescents and adults (Ando et al., 2018; Koenig et al., 2021; Mürner-Lavanchy et al., 2022; Santamarina-Perez et al., 2019). Connections of interest (COI) between each possible combination of ROIs, were used as RSFC predictors in the statistical analyses.

Statistical analyses

First, descriptive analyses were calculated, and data was explored visually. Then, variables were checked for normal distribution and log transformation was applied where necessary (i.e., for the variable NSSI incidents). The analyses of our main aims were conducted with mixed-effects regression models. These models are robust to the effects of missing data, which occur in our sample due to reduced patient numbers at clinical follow-ups (Molenberghs et al., 1997).

To analyse clinical outcomes across time, mixed-effects regression models were calculated, with time point as a predictor (baseline, FU1, FU2 and FU3), clinical variables as outcome (NSSI incidents, CGI-S scores, GAF scores) and a random intercept for each participant. Separate models were calculated for each of the outcome variables. Age at baseline and psychoactive medication (yes/no) were included as covariates. To control for between-patient differences in the time between the clinical and the MRI baseline assessment, the number of days between these measurements was additionally included as a covariate.

Next, we followed a formal model comparison procedure to examine whether the strength of connectivity between each possible combination of our ROIs at baseline was able to explain variance in changes of clinical outcome above the time point alone (Barr et al., 2013). Model M0 included time point and covariates (i.e., age at baseline, BMI at baseline, psychoactive medication, days between measurements) to predict clinical outcome. Model M1 additionally contained RSFC as a predictor. Model M2 additionally contained the interaction between RSFC and time point as predictor. Each COI was tested and compared in a separate series of models. COIs where one of the models had a singular fit (i.e., variance of the random intercept estimated to be zero) were excluded from further analyses (Lindquist et al., 2012; Müller et al., 2013). We compared models using the Bayes Factor (BF), computed using the Bayesian Information Criterion (BIC) approximation. A BF larger than 3 and below 20 is considered ‘positive evidence’, while a BF above 20 is regarded as ‘strong evidence’

(Raftery, 1995). Models showing a BF above 20 were considered to provide evidence of the influence of RSFC in the present study. A model selection based on Bayesian parameters has several advantages over model selection based solely on P-values (Freedman, 1983; Freedman et al., 1988; Miller, 1990). While Bayesian model selection does not require p-values for statistical comparison, corresponding p-values have been included in the results section for readers more familiar to the conventional frequentist statistical approach. Prompted by a reviewer's comment, we conducted sensitivity analyses by testing for associations between RSFC and clinical outcome including only data from those n = 10 patients who had available data at all time points (complete-data analyses).

Statistical analyses were performed using Stata (Version 15.0; StataCorp LP, College Station, TX, US). Results from Models M1 and M2 were visualized using the margins command in STATA by plotting the predicted clinical outcome for individuals with mean RSFC, - 1 SD from the mean RSFC and plus 1 SD from the mean RSFC. Images of the ROIs were generated in Freeview within FreeSurfer.

Results

Patient characteristics

Of n = 40 patients participating in the cross-sectional neuroimaging study, n = 1 had to be excluded due to a space-consuming lesion, leading to unusable T1 images. Of the n = 39 (n = 2 males, 5.1%) remaining patients, n = 27 (n = 0 males) participated in the baseline assessment of the clinical cohort study.

Therefore, the final sample for the present study comprised n = 27 female patients with a mean age of 15.04 years (SD = 1.26). At FU1, n = 25, at FU2, n = 19 and at FU3, n = 14 patients were included. Patient characteristics for each measurement time point are presented in **Table 1**. Clinical diagnoses met at baseline are detailed in **Supplementary Table 1**. The group average of days passed between baseline measurements of both studies involved was 67.80 days (SD = 656.41).

Table 1. Patient characteristics at each measurement time-point.

Demographic / clinical measures	Baseline (N = 27)	FU1 (N = 25)	FU2 (N = 19)	FU3 (N = 14)	Baseline vs. FU1		FU1 vs. FU2		FU2 vs. FU3	
					p-value	*ES*	*p*-value	*ES*	*p*-value	*ES*
Age, *M (SD)*	15.04 (1.26)	16.12 (1.24)	16.50 (1.04)	17.70 (0.95)	.003	.87	.295	.33	.006	1.19
BMI, *M (SD)*	20.57 (3.01)	20.44 (2.22)	21.11 (2.97)	22.09 (2.92)	.861	-.05	.397	.26	.411	.26
Severity of psychopathology (CGI-S), *M (SD)*	5.08 (0.74)	3.64 (1.63)	3.50 (1.38)	2.70 (1.89)	<.001	.71	.325	.25	.060	.60
Global functioning (GAF), *M (SD)*	47.42 (10.02)	61.20 (16.18)	61.83 (18.13)	74.00 (24.10)	<.001	1.02	.905	.04	.142	.60
NSSI incidents past month, *M (SD)*	7.67 (7.64)	2.60 (4.86)	2.11 (4.28)	0.57 (1.16)	.001	.65	.191	.32	.095	.46
Psychoactive Medication yes, *n (%)*	3 (11.11)	5 (20.0)	8 (42.11)	3 (21.43)	<.001	6.67	.134	2.20	.491	1.38
Alcohol Consumption, *M (SD)*	1.67 (0.71)	2.44 (1.34)	2.81 (1.28)	3.2 (1.56)	.317	.35	.752	.10	.085	-.65
Drug Consumption, *M (SD)*	1.33 (1.00)	1.76 (1.35)	2.06 (1.61)	2.5 (2.01)	1.00	0	.321	-.31	.227	-.43

Note. Paired t-tests were used for paired comparisons of continuous variables of normal data (effect size: Cohen's d, computed as the difference in means divided by the pooled standard deviation of both time points) and Wilcoxon signed-rank test were used for non-normal data (effect size: $Z/\sqrt{(N)}$). For binary variables, McNemar's test was used (effect size: odds ratio). ES = Effect size, BMI = Body Mass Index, BPD = Borderline Personality Disorder, CGI = Clinical Global Impression Scale, GAF = Global Assessment of Functioning. Alcohol consumption: Days of alcohol consumption per year in the past year, 1 = never, 2 = occasional, 3 = at least once a month, 4 = at least once a week, 5 = 2-3 times per week, 6 = almost daily, 7 = daily. Drug consumption: Days of drug consumption per year in the past year: 1 = never, 2 = occasional, 3 = at least once a month, 4 = at least once a week, 5 = 2-3 times per week, 6 = almost daily, 7 = daily. Variables with distributions considered as normal: age, BMI, GAF; non-normal: CGI-S, NSSI incidents, alcohol and drug consumption.

Unadjusted paired comparisons showed differences between baseline and FU1 for age, severity of psychopathology, global functioning, NSSI incidents, and number of patients receiving psychoactive medication. Between FU1 and FU2, no significant differences were observed, while between FU2 and FU3, the sample differed in age. Detailed information on treatment received by patients at FU1, FU2 and FU3 can be found in **Supplementary Table 2**.

Clinical outcome across time-points

Mixed regression models controlling for age at baseline, psychoactive medication, and days between measurements, showed improvements across time points for all clinical outcomes, namely severity of psychopathology, global functioning and NSSI incidents (illustrated in **Figure 1**). Fixed effects estimates of mixed regression models are presented in **Table 2**. The severity of psychopathology decreased across time points (χ^2 = 8016.13, p < .001), with decreases in scores between T0 and T1, between T1 and T2, and between T2 and T3 (all p < .001). Global functioning improved across time points (χ^2 = 7412.08, p < .001), with increases in scores between T0 and T1, between T1 and T2, and between T2 and T3 (all p < .001). Finally, NSSI incidents decreased across time points (χ^2 = 5965.39, p < .001), with decreases between T0 and T1, between T1 and T2, and between T2 and T3 (all p < .001).

The effect of psychoactive medication, which was entered as a covariate, was also associated with clinical improvement over time in all models (severity of psychopathology: z = 38.56, p < .001; global functioning: z = -38.64, p < .001; and NSSI incidents: z = -23.61, p < .001).

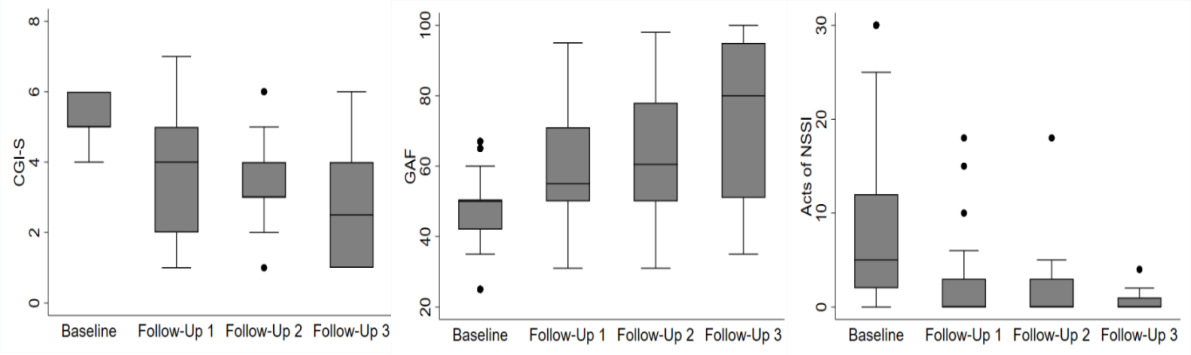

Figure 1. Clinical Outcome across time-points. Illustrated are clinical outcomes across time points in severity of psychopathology (CGI-S), global functioning (GAF) and NSSI incidents. NSSI = non-suicidal self-injury. GAF = Global assessment of Functioning, CGI-S = Clinical Global Impression Scale

Table 2. Fixed effects for the factor time point

	FU1			FU2			FU3		
Outcome	p	Coefficient	95% CI	p	Coefficient	95% CI	p	Coefficient	95% CI
Severity of psychopathology (CGI-S) [a]	<.001	-1.55	-1.60, -1.50	<.001	-2.00	-2.08, -1.94	<.001	-2.57	-2.65, -2.48
Global functioning (GAF) [a]	<.001	15.24	14.69, 15.79	<.001	21.62	20.87, 22.37	<.001	29.55	28.62, 30.48
NSSI incidents [a]	<.001	-3.84	-4.09, -3.60	<.001	-4.81	-5.12, -4.50	<.001	-7.74	-8.08, -7.40

Note. Results from mixed models for each clinical outcome separately. Coefficients indicate differences from baseline to follow-up time points. [a] Additional fixed effect of psychoactive medication use.

RSFC associated with clinical changes at follow-up

Model comparison showed strong evidence (BF > 20) that RSFC between several COIs improved model fits for predicting clinical outcome across time.

Among all COIs, model comparisons for one COI resulted in superior model fit for M2. Model M2 showed an interaction between RSFC and time point in predicting clinical outcome, indicating that RSFC had a predictive value on the *improvement* of clinical outcome across time. In detail, RSFC between left paracentral gyrus and right rostral ACC predicted change in the severity of psychopathology (χ^2 = 152.15, p < .001) as well as global functioning (χ^2 = 150.92, p < .001) (**Figure 2**). Model results are detailed in **Supplementary Table 3**. Lower baseline RSFC in this COI was associated with lower severity of psychopathology (and higher RSFC with higher severity of psychopathology) at FU3 (p < .001). Further, lower baseline RSFC in this COI was associated with higher global functioning (and higher RSFC with lower global functioning) at FU1(p = .037), and at FU3 (p < .001).

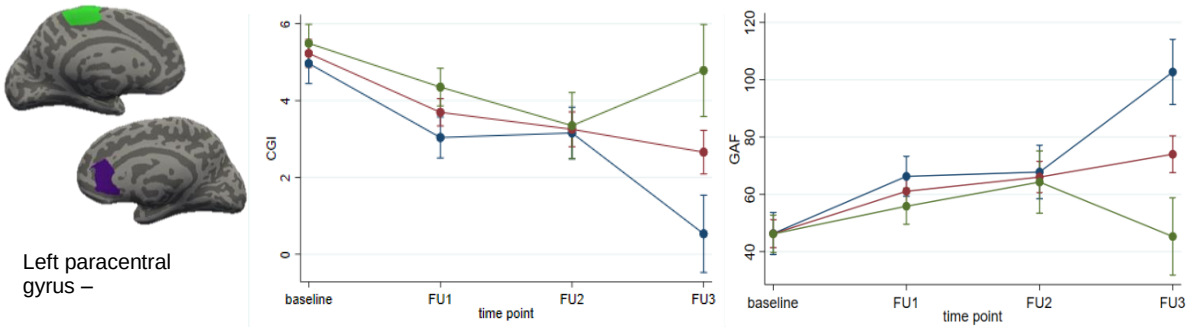

Figure 2. Interaction between left paracentral gyrus and right rostral anterior cingulate gyrus (ACC) resting-state functional connectivity (RSFC) and time point predicting clinical outcome (GAF = global assessment of functioning; CGI = clinical global impression i.e. severity of psychopathology). Blue fit line represents predicted clinical outcome for an individual with -1 standard deviation (SD) RSFC (z-standardized) from the mean; red: mean RSFC; green +1 SD RSFC from mean.

Further model comparisons showed strong evidence that RSFC between several COIs predicted clinical outcome across time (main effect) independent of time (M1). These models indicate that higher or lower baseline RSFC was associated with clinical outcome over time, but not with a change in clinical outcome across time. Results are detailed in **Supplementary Table 4** and visualized in **Supplementary Figure 3.** A summary of results is reported as follows: A higher baseline RSFC between left rostral ACC and left superior frontal gyrus, as well as between left paracentral gyrus and right rostral ACC was associated with higher severity of psychopathology and lower global functioning outcome across time. A higher baseline RSFC between left paracentral gyrus and left caudal middle frontal gyrus was associated with lower global functioning across time points. Further, a higher left hippocampus and right amygdala RSFC were associated with more NSSI incidents across time. In contrast, a lower baseline RSFC between the right rostral ACC and right amygdala was associated with lower global functioning over time. Effects for the different models ranged between an average of 45 to 54 points in the GAF, 4 to 5 points in the CGI-S, and 3.5 NSSI incidents during the past month.

Complete-data analyses including those n = 10 patients with data available at all time points confirmed the association between left paracentral gyrus and right rostral ACC RSFC and the severity of psychopathology as well as global functioning across time (M2). The remaining results were not replicated in the smaller sample. All results are detailed in **Supplementary Table 5**.

Discussion

In the present study, we aimed to investigate whether RSFC measured at baseline was associated with changes in clinical outcome after treatment across three years in a sample of female adolescents engaging in NSSI. This is one of the very few studies assessing brain connectivity predictors of clinical change across time in adolescents with NSSI.

Our sample of adolescents on average showed improvement in clinical outcome as determined by measures of severity of psychopathology, global functioning, and NSSI incidents. With the present study design, clinical improvement cannot solely be attributed to therapy, but might also result from developmental changes across age. The prevalence of NSSI appears to increase continuously until the age of 16, while during later adolescence remission rates are high (Moran et al., 2012; Plener et al., 2015; Reichl and Kaess, 2021). Interestingly, while clinical outcome such as severity of psychopathology and the frequency of NSSI decreased and global functioning increased across time-points, the use of alcohol and drugs increased across follow-up time-points. This secondary finding aligns with existing evidence indicating a potential shift in symptomatology towards more socially accepted behavior occurring during late adolescence and young adulthood (Nakar et al., 2016). In the respective study, a symptom shift was observed in adolescents from the general community showing high-risk trajectories in self-injurious and suicidal behavior as well as substance misuse. As this group reported low levels of participation in therapy, the symptom shift was unlikely attributable to professional help and probably represented a naturalistic course of adolescent self-harm tendencies. Since in the current study, we did not recruit a control group receiving no therapy, we are unable to evaluate whether the symptom shift was associated with therapy or whether it represents a naturalistic trajectory in behavior across adolescence.

To our knowledge, there are only two studies examining RSFC predictors or concomitants of therapy outcome in adolescents with NSSI (Cullen et al., 2020; Santamarina-Perez et al., 2019). Using a seed-based approach Santamarina-Perez et al. (2019) found that stronger amygdala-ACC and amygdala-medial prefrontal connectivity, but weaker amygdala-brainstem connectivity was related to less post-treatment improvement after four months of DBT-A and treatment as usual (n = 24). Examining seed-based RSFC before and after pharmaceutical therapy, Cullen et al. (2020) found that

greater improvements in NSSI were associated with greater increases in RSFC between right amygdala and right frontal pole, and that greater reductions in depression scores were associated with increases in left amygdala - left middle frontal cortex RSFC. In this study, improvement in both NSSI and depression symptoms was further associated with decreased amygdala-supplementary motor area (SMA) connectivity. In a previous report, the same sample of adolescents had greater amygdala - SMA RSFC than healthy controls (Westlund Schreiner et al., 2017). Together, these findings might indicate a 'hyperconnectivity' between limbic regions and the SMA (involved in complex movement planning; part of the SMA is located in the paracentral cortex) in adolescents with NSSI, while the decrease in RSFC after treatment might represent a normalization (Cullen et al., 2020).

Using our exploratory approach including several ROIs which have previously been implicated in the neurobiology of NSSI, our data do not replicate the findings of amygdala - ACC or amygdala - prefrontal connectivity as a concomitant or predictor of treatment outcome. In our sample of n = 27 adolescents, the overall effect of RSFC associations with clinical outcome after treatment was small, with RSFC in only one COI being strongly associated with change in clinical outcome (i.e., an RSFC by time point interaction). Lower resting-state connectivity between left paracentral gyrus and right rostral ACC on average was associated with clinical improvement, in particular from the second to the third follow-up, while higher RSFC in this COI was associated with a worsening in group means of clinical outcome between the second and third follow up.

Several structural MRI studies point to smaller ACC volumes among adolescents engaging in self-injury (Ando et al., 2018; Whittle et al., 2009). The few previous resting-state fMRI studies, despite using the amygdala as seed, have also found the ACC to be implicated in NSSI behavior. Although our findings do not show evidence for amygdala - ACC connectivity, they confirm the role of the ACC for psychopathology in NSSI. Interestingly in our previous RSFC study (Mürner-Lavanchy et al., 2022), we found a lower connectivity in the paracentral gyrus in adolescents with NSSI when compared to healthy controls. This region is known for the motor and sensory control of the legs and has only recently has been shown to be involved in emotion processing (Li et al., 2016). Findings from the present study suggest that a weaker connectivity between ACC and paracentral gyrus – two brain regions affected in adolescents engaging in NSSI – appears to be functional, i.e.,

associated with improved treatment outcome. It is important to note, however, that at the second (n = 19) and third (n = 14) follow up, group sizes were relatively small, resulting in large confidence intervals. Therefore, while the effect of the overall model was considerable, the interaction effect must be interpreted with caution and needs replication with larger samples.

Our findings further point to some influence of RSFC on overall clinical symptomatology and severity independent of time. Higher and/or lower RSFC between several inter- and intrahemispheric cortico-cortical and cortico-subcortical connections was associated with clinical outcome (main effects). This suggests that baseline RSFC was more associated with severity of psychopathology and global functioning in our patients in general, independent of time and likely independent of treatment. However, differences in findings between analyses containing all available data and the sensitivity analyses including patients with complete data at all time-points only, indicate that these associations are less robust and replication in larger samples is therefore warranted. Although preliminary in nature, our data adds to the limited evidence base on neurobiological predictors of treatment outcome in NSSI.

Several limitations merit comment. First, the small sample size constrains the generalizability of our findings. As there was considerable drop-out across time-points, we attempted replication in patients with complete data available at all time-points. These analyses were based on n = 10 patients only, which limits interpretability of the findings and concurrently hampers comparability with the original analyses (already conducted in a relatively small sample). Second, we did not recruit a control group receiving no treatment. Therefore, with our study design, clinical changes across time points cannot (solely) be attributed to treatment. Third, our sample exclusively consisted of female patients. Therefore, we were not able to examine potential sex differences in the association between RSFC and treatment outcome. Fourth, the cross-sectional design of the neuroimaging study did not allow us to investigate whether treatment response was associated with changes in functional connectivity between baseline and the end of treatment. Neural changes are possible and even likely and might interact with change in clinical symptoms or as a function of pharmacological and psychotherapeutic interventions (Cullen et al., 2016; Quidé et al., 2012; Ritchey et al., 2011). Fifth, we have limited our analyses to ROIs previously implicated in adolescent NSSI which were examinable with our

methodological approach. However, RSFC in other brain regions such as the nucleus accumbens, which we did not further examine in the present study (Cullen et al., 2020) might be more strongly associated with outcome after treatment. Further, we only examined RSFC, while other peripheral neurobiological markers, such as autonomic nervous system functioning might be more predictive. For example, pre-treatment resting-state heart rate variability has been found to be associated with clinical outcome after therapy in adolescents with BPD engaging in NSSI (Sigrist et al., 2021; Weise et al., 2021). While the results from our study add to the understanding of the neurobiology of NSSI, they are yet limited in their clinical significance given that our neuroimaging results do not point to a prediction of treatment outcomes. Larger samples, however, including a variety of neuroimaging analyses and allowing complex methods of machine-based learning may detect patterns of brain structure and functioning that allow prediction of treatment response and subsequent risk stratification. In addition, a better understanding of the neurobiological underpinnings of NSSI might in the future help to identify neurobiological treatment targets and thus advance treatment development (Santamarina-Perez et al., 2019).

Despite several limitations, our preliminary findings show some evidence that paracentral - ACC RSFC at baseline was associated with change in clinical outcome following treatment and further evidence that baseline RSFC in several connections of interest is associated with severity of psychopathology independent from time. We thereby add to the very limited evidence-base of neuroimaging predictors of clinical outcome after treatment in adolescents engaging in NSSI. More knowledge on the brain functional concomitants of treatment outcomes in adolescents engaging in NSSI might help to identify targets of neurobiological treatment in the future (Westlund Schreiner et al., 2019).

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Author Statement

Contributors

Ines Mürner-Lavanchy: methodology, formal analysis, visualization, writing - original draft. **Johannes Josi:** formal analysis, writing - review and editing. **Julian Koenig:** writing - review and editing, investigation. **Corinna Reichl:** writing - review and editing, investigation. **Romuald Brunner:** conceptualization, writing - review and editing, funding acquisition. **Michael Kaess:** conceptualization, methodology, writing - review and editing, funding acquisition, supervision.

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Conflict of interest

The authors have no conflict of interest to declare

Highlights

- Adolescent patients with NSSI underwent MRI and three yearly clinical follow-ups
- Patients' clinical outcome improved following treatment across time
- Baseline brain connectivity (RSFC) associated with clinical outcome:
- Lower left paracentral-right anterior cingulate RSFC associated with clinical improvement
- RSFC was more predictive of clinical outcome independent of time and treatment