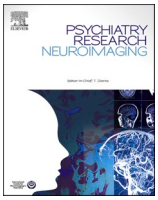
Psychiatry Research: Neuroimaging 334 (2023) 111697

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns



Prefrontal oxygenation varies as a function of response inhibition performance in healthy participants but not in youth with non-suicidal self-injury

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ARTICLE INFO

Keywords:
Self-injury
Adolescent
Response inhibition
Impulsivity
Brain function
Activation
fNIRS
Prefrontal oxygenation

ABSTRACT

Non-suicidal self-injury (NSSI), a highly prevalent symptom in adolescence, has been associated with impulsivity. Behavioral measures of response inhibition in combination with the recording of brain activity potentially improve the understanding of the etiology of the behavior. We therefore investigated prefrontal cortex (PFC) oxygenation during a response inhibition task using functional near-infrared spectroscopy (fNIRS) in $n = 152$ adolescents with NSSI and $n = 47$ healthy controls. We compared groups regarding behavioral performance and PFC oxygenation and tested whether the association between task performance and PFC oxygenation differed between groups. PFC oxygenation was slightly higher in adolescents with NSSI than in controls. Further, there was evidence for a group by performance interaction: In healthy controls, higher oxygenated hemoglobin was associated with better task performance, which was not the case in the NSSI group. We did not find evidence of associations between PFC oxygenation and clinical measures. Our study provides preliminary evidence of altered brain functional correlates of response inhibition in adolescents with NSSI potentially reflecting deficient top-down regulation of limbic regions through prefrontal regions. Due to methodological limitations of the current study, findings must be interpreted with caution and future studies should optimize task designs for fNIRS processing.

1. Introduction

Non-suicidal self-injury (NSSI), which describes the deliberate destruction of one's own body tissue without suicidal intent (American Psychiatric (American Psychiatric Association 2013)) is a common problem among adolescents, with 17.2% of youth from the general population engaging in NSSI once in their lifetime (Swannell et al., 2014). When individuals engage in NSSI on 5 or more days during one year, they fulfill the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criterion A for NSSI disorder, a research diagnosis requiring further investigation (American Psychiatric (American Psychiatric Association 2013)). Prevalence of NSSI disorder has been estimated at 6.7% in the general population and up to 60% in adolescent inpatient samples (Plener et al., 2016; Zetterqvist, 2015). Although per definition without suicidal intent, NSSI is a strong predictor of suicide attempts (Asarnow et al., 2011; Koenig et al., 2017) and suicide (Mars et al., 2019). It has further been associated with borderline personality disorder (BPD) development (Ghinea et al., 2019), and psychopathology in general (Ghinea et al., 2020), suggesting that NSSI is an important transdiagnostic marker of risk and mental distress.

Historically, deliberate self-injury has been suggested to be "a disorder of impulse control" based on the reasoning that NSSI follows an urge or impulse which cannot be resisted. This idea was first supported by research in adolescent psychiatric inpatients showing that a majority of youths did not think about engaging in self-injury before engaging in the behavior or contemplated only a few seconds (Nock and Prinstein, 2005). Several studies have further shown associations between self-ratings of impulsivity and adolescent NSSI (Glenn and Klonsky,

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https://doi.org/10.1016/j.pscychresns.2023.111697
Received 27 January 2023; Received in revised form 24 May 2023; Accepted 27 July 2023
Available online 4 August 2023

2010; Hamza et al., 2012; Janis and Nock, 2009; Koenig et al., 2020; McCloskey et al., 2012). Impulsivity as such is a heterogeneous construct and may entail risk-taking, sensation-seeking, lack of planning, urgency, and rash behaviors in the face of negative emotions (Glenn and Klonsky, 2010). One common way of assessing impulse control – or rather the lack thereof – objectively, is using laboratory-based behavioral measures of response inhibition. Although findings regarding behavioral deficits of inhibition in adolescent NSSI are mixed (Liu et al., 2017; McHugh et al., 2019; Mürner-Lavanchy et al., 2022), these measures allow for the simultaneous recording of brain functional correlates, which might yield further insight into the importance of neurocognitive underpinnings of NSSI.

Striving for a better understanding of the etiology of NSSI, neuroimaging studies have begun to elucidate brain function underlying the behavior. Both task-based and resting-state functional magnetic resonance imaging (rsfMRI) studies have highlighted the role of limbic and prefrontal brain circuits in NSSI (Ando et al., 2018; Dahlgren et al., 2018; Groschwitz et al., 2016; Koenig et al., 2021; Mürner-Lavanchy et al., 2022; Niedtfeld et al., 2010; Plener et al., 2012; Santamarina-Perez et al., 2019; Schär et al., 2022; Vega et al., 2018; Westlund Schreiner et al., 2015). On a phenomenological level, results from these studies suggest negativity bias, hypersensitivity to reward, and hyperarousal, often interpreted as reduced impulse control (Auerbach et al., 2021). However, brain functional correlates of behavioral measures of inhibition, or cognitive control more broadly, have yet to be examined (Kaess et al., 2021). The only study investigating this topic so far found decreased activation in the prefrontal cortex (PFC) and the cingulate cortex during an interference task in young adults with NSSI compared to healthy controls. In the NSSI group, this activity was associated with self-reported impulsivity ($n = 15$) (Dahlgren et al., 2018).

Functional near-infrared spectroscopy (fNIRS) has attracted interest from clinical neuroscientists as an alternative neuroimaging method with advantages due to its ease in application, relatively low cost in comparison with fMRI, high acceptability in patients and consequently the option to recruit larger sample sizes (Lai et al., 2017). fNIRS uses infrared light penetrating the human scalp and skull to measure changes in oxygenated and deoxygenated hemoglobin in the outer cortex. Similar to fMRI, fNIRS relies on the assumption of neurovascular coupling, inferring changes in neuronal activity from changes in infrared light absorbance (Tachtsidis and Scholkmann, 2016). The first study reporting the use of fNIRS in adolescents with NSSI adopted a resting-state approach (Koenig et al., 2021). In this study, we found decreased resting-state PFC oxygenation in adolescents engaging in NSSI and associations between increased PFC connectivity and greater psychopathology across the NSSI and healthy control sample, reflecting changes in PFC oxygenation potentially not specific to NSSI (Koenig et al., 2021).

Using data from the same sample, the objective of the present study was to investigate prefrontal brain activation during response inhibition in adolescent patients engaging in NSSI and healthy controls. The first aim was to examine whether the NSSI vs. healthy control groups differed in prefrontal oxygenation during the inhibition task. The second aim was to investigate how task performance was associated with prefrontal oxygenation and whether this association differed between NSSI and control groups. Finally, we aimed to examine, whether prefrontal oxygenation was associated with clinical measures in patients engaging in NSSI.

2. Methods

2.1. Participants and procedure

Patients with NSSI disorder according to DSM-5 were consecutively recruited at the AtR!Sk (*Ambulanz für Risikoverhaltensweisen und Selbstschädigung*) outpatient clinic for risk-taking and self-harming behavior (Kaess et al., 2017) at the University Hospital of Heidelberg, Germany. The service provides low-threshold initial contact, detailed and comprehensive diagnostic assessment and evidence-based therapeutic intervention for adolescents with risk-taking and self-harming behavior. Within the AtR!Sk cohort study, demographic and clinical data were obtained through a standardized diagnostic assessment at clinic entry. Following participation in the cohort study, patients were invited to take part in the nested AtR!Sk-Bio study, which consisted of neurobiological assessments including the fNIRS measurement of prefrontal cortex oxygenation, a neurocognitive test battery and intelligence assessment. The latter assessment took place within six weeks after the diagnostic assessment in the cohort study. Age-matched healthy controls were recruited via advertisement and underwent a shorter adapted diagnostic assessment. Both studies were approved by the ethical committee of Medical Faculty of the University of Heidelberg (AtR!Sk cohort: S-449/2013; AtR!Sk-Bio: S-514/2015) and comply with the declaration of Helsinki (General Assembly of the World Medical Association 2014). Study inclusion criteria were: 12–17 years of age and participation in the AtR!Sk diagnostic assessment at clinic entry. Patients and healthy controls were excluded for the following reasons: acute psychosis, neurological, endocrinological, or cardiovascular primary diseases, pregnancy, and the lack of fluent German language comprehension and expression. Further, healthy controls were excluded whenever they met criteria for any current psychiatric disorder, or reported prior self-harming behavior, psychological or psychiatric treatment. Before inclusion in the study, all participants and their caregivers provided written informed consent and participants received 40€ for participation in the AtR!Sk-Bio study. As sex was not evenly distributed across patient and control groups, only female patients fulfilling criterion A of the NSSI disorder according to the DSM-5 (i.e., five or more days with NSSI during the last 12 months) were included for the present analyses. Procedures are also described in previously published papers from the same sample (Ando et al., 2018; Flach et al., 2021; Kindler et al., 2022; Koenig et al., 2021; Schär et al., 2022).

2.2. Clinical assessment

Sociodemographic measures obtained during the two study appointments included date of birth, sex, and schooling. Further, body mass index (BMI: weight(kg)/ height(m)^2) and information on smoking, drug use and medication were obtained.

In the first appointment, all patients underwent comprehensive clinical assessment by trained clinical personnel. To assess psychiatric disorders according to DSM-IV and ICD-10 (Sheehan et al., 1998), the Mini-International Neuropsychiatric Interview for Children and Adolescents (M.I.N.I.-KID 6.0), a semi-structured interview was administered. To assess the number of days with NSSI in the last year and in the last month, the German version of the Self-Injurious Thoughts and Behaviors interview (SITBI-G) (Fischer et al., 2014; Nock et al., 2007) was used. The clinician-interviewer further rated the severity of general psychopathology by means of the Clinical Global Impression Scale (CGI-S) (Busner and Targum, 2007) and the patient's global psychological, social and occupational functioning using the Global Assessment of Functioning (GAF) Scale (Moos et al., 2000).

Prior to the study appointment, healthy controls were queried via telephone using screening questions from the SITBI-G to ensure that they had no history of NSSI or suicidal behavior. At the clinic, they then underwent a shortened clinical assessment with a standardized interview to ascertain they did not meet the criteria for any current psychiatric disorder and were not under any psychological or psychopharmacological treatment.

In a second appointment, with both patients and healthy controls, the intelligence quotient (IQ) was assessed using the Hamburg Wechsler Intelligence Scale for Children IV (HAWIK-IV) (Petermann and Petermann, 2007). Finally, patients and healthy controls underwent measurement of prefrontal oxygenation using fNIRS. fNIRS was recorded during a five-minute baseline task immediately *before* the beginning as

well as *during* the administration of a cognitive test battery. The response inhibition task analyzed in the present study was the fourth in a row of eight neurocognitive subtests. A schematic overview of the fNIRS assessment procedure can be found in Figure 4 of the Supplementary Material.

2.3. Baseline task

All participants performed a computerized vanilla baseline task of minimal cognitive effort lasting five minutes (Jennings et al., 1992). Participants were instructed to count colors of a rectangle appearing in the middle of the computer screen. The rectangle changed its color (i.e., red, yellow, blue, green, purple, and white) every few seconds and participants were asked to count the appearance of one specific color. At the end of the five-minutes task, they were instructed to report the number of appearances. This task has consistent within-person and baseline stability and generalizability between sessions (Jennings et al., 1992). Prefrontal oxygenation measured during the baseline task served as a control condition for the measurement of prefrontal oxygenation during the response inhibition task.

2.4. Response inhibition task

Response inhibition was measured via the short form S13 of the Go/Nogo paradigm INHIB from the Cognitive Basic Assessment (COGBAT), a computerized neurocognitive test battery (Aschenbrenner et al., 2012) validated in youths from 12 years (Mürner-Lavanchy et al., 2022). Participants were instructed to respond to one kind of stimuli (triangle) but not to another kind of stimuli (circle) by button press. A visualization of the task is depicted in Fig. 1. Administration time of this task amounts to four minutes. The main variables of interest were: mean reaction time (of correctly answered Go stimuli), standard deviation of the mean reaction time, as a measure of reaction time variability (Kaiser et al., 2017) and number of commission errors (incorrectly answered NoGo stimuli). The latter measure has shown acceptable reliability (Cronbach's α = 0.71) in the S13 version of the task (Aschenbrenner et al., 2012).

2.5. fNIRS recording

fNIRS was recorded with a portable 8-channel continuous-wave system (OctaMon, Artinis, The Netherlands). The device was mounted to participants' head tightly (but without resulting in discomfort or pain) at the beginning of the neurobiological assessment, and recording took place in a seating position. Optodes were placed according to the international 10–20 system for EEG electrodes placement (Jaspers, 1958). The arrangement of the eight transmitters and two receivers is displayed in **Supplementary Figure 1** together with estimated coordinates of optodes according to the Montreal Neurological Institute (MNI) brain template. Inter-optode distance was fixed at 35 mm. When placing the fNIRS headband, the investigator made sure there was no or little hair between optodes and skin to increase signal strength. During recording, time markers were set manually to indicate starting and end of cognitive tasks. The OctaMon emits light at two wavelengths in the near-infrared spectrum, 760 nm and 850 nm. Two positive intrinsic negative diode receivers with ambient light protection record the emitted light. The differential path length factor was set to six centimeters (Scholkmann and Wolf, 2013), according to the general equation for the differential path length factor. A sampling rate of 50 Hz was set for each channel.

2.6. fNIRS data processing

The recorded hemoglobin density values were sent from the device to a laptop via Bluetooth, where the raw data was stored with Oxysoft software (version 3.0.103, (Artinis Medical Systems 2016)). Using markers set manually during the recording, time-series were segmented according to the start and end times of the baseline and inhibition tasks. Raw data was then imported to MATLAB (The Math Works Inc., 2015) using the oxysoft2matlab function, and preprocessed with the HOMER2 toolbox (Huppert et al., 2009). Preprocessing included the following steps: (1) raw optical densities are converted to optical density (hmrIntensity2OD), to detect and correct the data for motion artifacts (Cooper et al., 2012); (2) motion artifact correction in a two-step process: First, wavelet-based motion correction with a probability threshold of α = 0.01 (hmrMotionCorrectWavelet); second, motion artifact correction (hmrMotionArtifact); (3) high-frequency component removal with a low pass filter (removing frequencies greater than 0.5 Hz); (4) channel-wise conversion of optical density rates to hemoglobin concentration changes for oxygenated hemoglobin (HbO_2), deoxygenated hemoglobin (Hb) and total hemoglobin (HbT) (HbT = HbO_2 + Hb), using a modified Beer-Lambert law; and (5) export to Stata/SE software version 16.0 (StataCorp 2019) for further analysis.

2.7. Statistical analyses

For fNIRS data from continuous-wave measurement, it is necessary to contrast two conditions in order to obtain PFC oxygenation attributable to the condition of interest. To obtain brain activity related to response inhibition, fNIRS signal during the baseline task was therefore subtracted from fNIRS signal during the inhibition task, while brain activity was averaged across all trials of the respective task. In line with previous research (Doi et al., 2013; Niu et al., 2013; Pinti et al., 2020), this approach has been chosen, as the neurocognitive tasks were not designed as block design or event-related design. Thus, for each hemoglobin variable (HbO_2, Hb, HbT) mean *delta values* per channel and a grand mean delta value for HbO_2, Hb, and HbT were calculated and used for further analyses.

Data were first analyzed descriptively and explored visually. Variable distributions were checked, and log transformation was applied where necessary (NSSI variables, response inhibition mean reaction

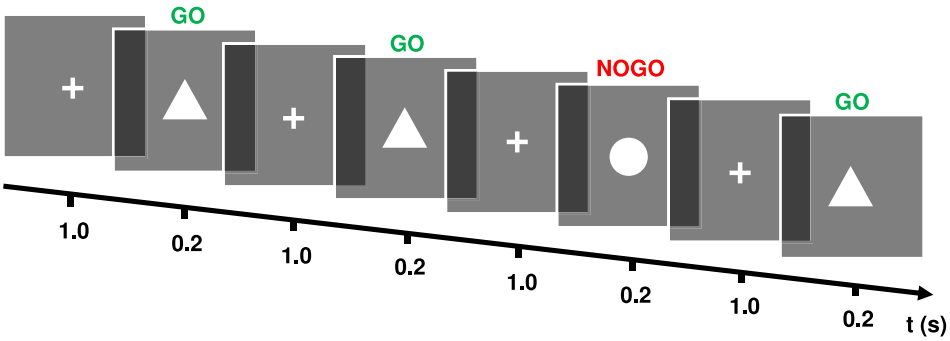

Fig. 1. Experimental paradigm visualization. Schematic illustration of the Go/Nogo task. 101 triangles and 24 circles were shown, stimuli were shown for 200 ms and inter trial interval was 1000 ms. Participants were instructed to press a button when seeing a triangle but not to press when seeing the circle.

time and standard deviation of reaction time). The influence of potential confounding factors (i.e., BMI, handedness, IQ) on PFC oxygenation was tested via t-tests and Pearson product-moment correlations. To examine whether PFC oxygenation differed between NSSI and healthy control groups, regression models with group as predictor and the respective hemoglobin variable of interest as outcome were calculated separately, while controlling for age. Separate regression models were further used to investigate whether there was a group difference in the association between inhibition performance and the hemoglobin variables (each inhibition variable and each hemoglobin variable separately, resulting in 9 models), controlling for age. An interaction term between group and inhibition variable was included in these models. For the above-mentioned regression models, sensitivity analyses were conducted: analyses were repeated including psychotropic medication (yes/no), smoking (yes/no) and drug use (yes/no) as well as those variables shown to be associated with PFC oxygenation as control variables (in addition to age). For the third aim, regression models were used to detect associations between PFC oxygenation and clinical variables (NSSI last year, last month, severity of psychopathology and global functioning; controlling for age and IQ), in the NSSI group only. All statistical analyses were conducted using STATA SE17 and visualized using STATA and R Studio.

3. Results

3.1. Participant characteristics

Of $n = 242$ patients and $n = 49$ healthy controls enrolled in the ATR! Sk-Bio study, $n = 229$ patients and all controls participated in the fNIRS assessment. Of these, $n = 1$ patient withdrew consent to use their data. Further, data from $n = 38$ male patients and $n = 2$ healthy male controls were excluded. Moreover, $n = 34$ patients reported less than 5 days with NSSI incidents in the past year and therefore did not fulfill the NSSI criterion, $n = 3$ had no baseline fNIRS data and $n = 1$ had no fNIRS inhibition data. This resulted in $n = 152$ female patients with NSSI and $n = 47$ healthy female controls included in the present analyses. Participant characteristics are reported in Table 1. Groups were similar with respect to age and BMI. On average, the healthy control group had a higher IQ ($t = 3.30$, $p = .001$) and reported smoking ($\chi^2 = 18.91$, $p < 0.001$), taking psychoactive medication ($\chi^2 = 4.66$, $p = .031$) and drug use ($\chi^2 = 6.12$, $p = .013$) less often. As expected, adolescents engaging in NSSI reported more days with NSSI incidents in the past year and the past month.

3.2. Behavioral response inhibition

Regression analyses controlled for age did not yield evidence for group differences in mean reaction time (coefficient [b], 95% confidence interval [CI] = 0.01 (−0.01, 0.02), standardized beta [β] = 0.07, $p = .315$), standard deviation of reaction time (b (95%CI) = 0.01 (−0.01, 0.03), $\beta = 0.10$, $p = .170$), or the number of errors (b (95%CI) = −0.04 (−1.30, 1.22), $\beta = -0.004$, $p = 0.947$) in the response inhibition task.

3.3. PFC oxygenation

Regression models controlling for age showed higher ΔHbO_2 in adolescents engaging in NSSI than healthy controls (b (95%CI) = 0.33 (0.06, 0.60), $\beta = 0.17$, $p = .016$), but no difference in ΔHb (b (95%CI) = −0.17 (−0.43, 0.09), $\beta = -0.09$, $p = .188$), and ΔHbT (b (95%CI) = 0.16 (−0.25, 0.56), $\beta = 0.055$, $p = .442$). Full regression models are reported in **Supplementary Table 1** and visualization of group averages of PFC oxygenation during response inhibition can be found in **Supplementary Figure 2 and 3**. For the sake of completeness, average values of PFC oxygenation during baseline and response inhibition are reported separately in **Supplementary Table 2**.

While BMI and handedness were not associated with any of the hemodynamic variables, IQ was moderately correlated with ΔHbO_2 ($r = -0.17$, $p = 0.017$), ΔHb ($r = -0.16$, $p = 0.025$), and ΔHbT ($r = -0.22$, $p = 0.002$), and was therefore included as covariate in the sensitivity analyses. Sensitivity analyses including IQ, psychotropic medication, smoking and drug use in addition to age as covariates yielded similar results as the main analyses. PFC oxygenation did not differ between hemispheres in NSSI patients, healthy controls, or the total group.

Table 1
Sample characteristics.

	NSSI ($n = 152$)	Healthy controls ($n = 47$)
Age, *M (SD)*	14.93 (1.50)	14.72 (1.28)
BMI, *M (SD)*	22.46 (4.66)	21.63 (3.46)
IQ, *M (SD)*	100.68 (12.80)	107.40 (10.04)
Psychoactive medication yes, *n (%)*	14 (9%)	0 (0%)
Smoking yes, *n (%)*	52 (34%)	1 (2%)
Drug consumption yes, *n (%)*	18 (12%)	0 (0%)
No. days with NSSI events past year, *M (SD)*	70.93 (74.25)	0 (0)
No. days with NSSI events past month, *M (SD)*	6.72 (8.12)	0 (0)
Severity of psychopathology (CGI-S), *M (SD)*	4.96 (0.73)	–
Global functioning (GAF), *M (SD)*	49.75 (8.44)	–
Inhibition mean RT, *M (SD)*	0.28 (0.05)	0.27 (0.04)
Inhibition SD RT, *M (SD)*	0.10 (0.07)	0.09 (0.05)
Inhibition errors, *M (SD)*	9.10 (4.02)	9.26 (3.63)
Grand mean ΔHbO_2, *(SD)*	0.06 (0.87)	−0.27 (0.57)
Grand mean ΔHb, *(SD)*	0.34 (0.76)	0.51 (0.85)
Grand mean ΔHbT, *(SD)*	0.40 (1.29)	0.24 (0.98)
Diagnoses [a]		
F10-F19, *n (%)*	33 (22%)	
F30-F39, *n (%)*	97 (64%)	
F40-F48, *n (%)*	66 (43%)	
F50-F59, *n (%)*	20 (13%)	
F60-F69, *n (%)*	59 (39%)	
F80-F89, *n (%)*	1 (1%)	
F90-F98, *n (%)*	40 (26%)	

Table 1. NSSI = non-suicidal self-injury, SD = standard deviation, BMI = body mass index, IQ = intelligence quotient, CGI-S = Clinical Global Impression Scale, GAF = Global Assessment of Functioning, RT = reaction time, ΔHbO_2 = delta oxygenated hemoglobin, ΔHb = delta deoxygenated hemoglobin, ΔHbT = delta total hemoglobin. Smoking: on more than five days in the last month. Drug consumption: at least one day of drug consumption during the last month. T-tests were used for continuous, normally distributed variables (age, BMI) and Wilcoxon rank-sum tests were used for non-normal data (medication, smoking, drugs). [a] no F0, F2, or F7 disorders were diagnosed.

3.4. Association between PFC oxygenation and behavioral response inhibition

Regression analyses showed that the association between mean reaction time and ΔHbO_2 differed between the NSSI and the control groups (overall model: $R^2 = 0.054$, $F(4, 194) = 2.77$, $p = .028$; interaction effect: b (95%CI) = 0.34 (0.03, 0.64), $\beta = 0.36$, $p = .031$), full models reported in **Supplementary Table 3**). As visualized in Fig. 2, mean reaction time during the inhibition task was negatively correlated with ΔHbO_2 in healthy controls indicating that better inhibition performance was associated with higher ΔHbO_2. However, no such relationship was found in the NSSI group. Similarly, model results showed a different association between the standard deviation of reaction time and ΔHbO_2 for the NSSI and the control groups (overall model: $R^2 = 0.065$, $F(4, 194) = 3.37$, $p = .011$; interaction effect: b (95%CI) = 0.45 (0.11, 0.79), $\beta = 0.49$, $p = .010$) (Fig. 2). The lower the standard deviation of reaction time, i.e., the better the performance, the higher was ΔHbO_2 in healthy controls, but not in the NSSI group. No interaction effects were found for commission errors as a predictor and ΔHb or ΔHbT as outcomes. Sensitivity analyses including IQ, psychotropic medication, smoking and drug use in addition to age as covariates yielded similar results.

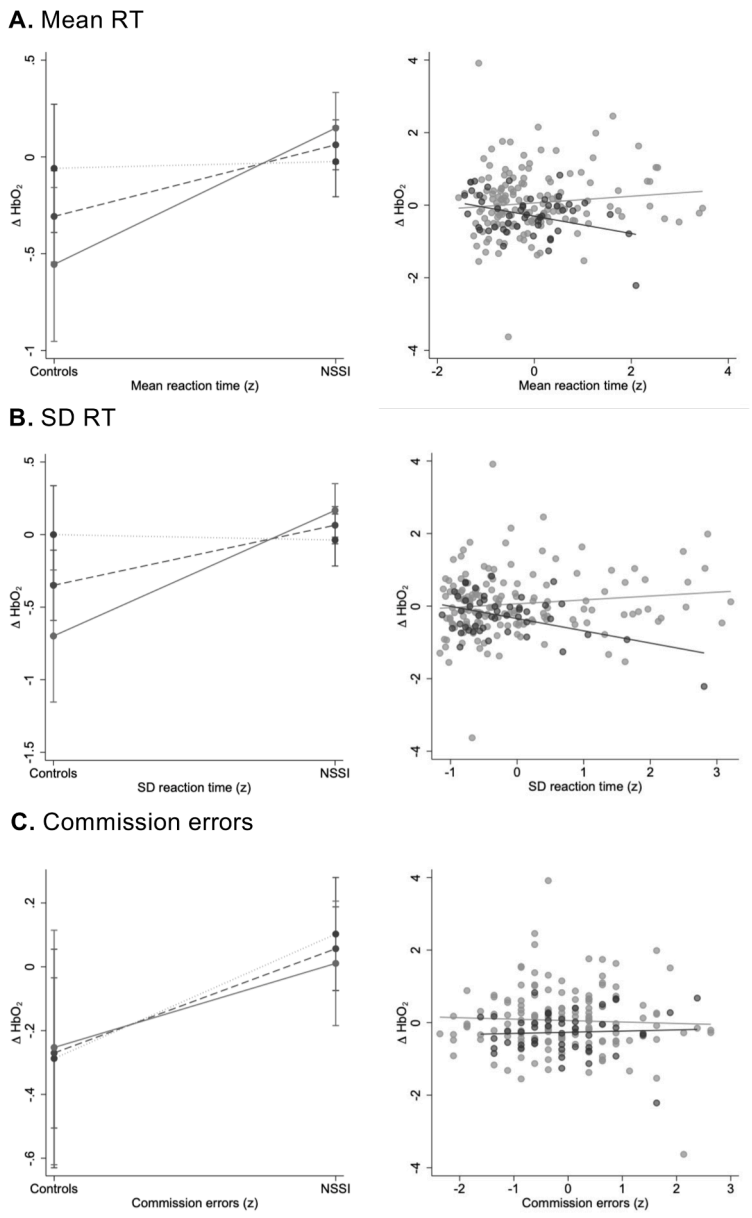

Fig. 2. Associations between response inhibition variables and ΔHbO_2 in NSSI vs. control groups. Left side: predicted margins for group from regression models controlled for age. Blue fit line represents predicted ΔHbO_2 for individuals with −1 SD inhibition performance from the mean; red: mean performance; green +1 SD task performance from the mean. Right side: associations separately for the two groups (NSSI group in light gray, control group in dark gray). RT = reaction time, SD = standard deviation.

3.5. Associations between PFC oxygenation and clinical measures

There was little evidence that PFC oxygenation was associated with the clinical measures assessed in the NSSI group. Only the number of days with NSSI in the last month (b (95%CI) = 0.18 (0.07, 0.29), p = .002) was positively associated with ΔHb, a small sized effect ($\beta = 0.25$). Neither the severity of psychopathology (CGI-S), nor global functioning (C-GAS), nor the number of days with NSSI in the last year were associated with PFC oxygenation and there were no associations between ΔHbO_2, ΔHbT and any of the clinical variables.

4. Discussion

In the present study, we aimed to investigate whether PFC oxygenation during response inhibition measured with fNIRS differed between adolescents engaging in NSSI and healthy controls. We further examined whether task-based fNIRS activity was associated with response inhibition performance and whether patterns of associations differed between the two study groups. Finally, we investigated whether PFC oxygenation was associated with clinical measures in adolescents engaging in NSSI.

While, on average, task performance was similar in both groups, PFC oxygenation during response inhibition was slightly higher in adolescents with NSSI compared to healthy controls. This is in line with previous studies in individuals with NSSI that have found increased activation in the PFC, the orbitofrontal cortex and the anterior cingulate cortex during emotional, social, reward and self-processing (Brown et al., 2017; Groschwitz et al., 2016; Osuch et al., 2014; Plener et al., 2012; Quevedo et al., 2016; Vega et al., 2018). Our results therefore support theories suggesting neurocompensatory mechanisms, according to which higher neural activation is necessary for clinical populations to successfully perform cognitive tasks. One of the very few studies investigating brain activity during cognitive interference – a construct of cognitive control closely related to response inhibition – in young adults engaging in NSSI, found lower dorsolateral PFC (DLPFC) but higher cingulate cortex activation in patients ($n = 15$) than in controls ($n = 15$), while task performance did not differ between groups (Dahlgren et al., 2018). The authors also interpreted their findings in the context of neurocompensation theories, and suggested that brain activation in the cingulate gyrus served to compensate for the lower PFC activation. As

Dahlgren et al. (Dahlgren et al., 2018) used the fMRI Multi Source Interference Task (MSIT) to study cognitive interference, it is difficult to directly compare their findings to the present study. While we were not able to capture activity in the cingulate cortex by fNIRS recording, we cannot rule out that the NSSI group activated brain regions in addition to the PFC, so as to achieve a similar task performance. We previously found lower resting-state PFC oxygenation in the same sample of adolescents reported on in this study, albeit with small effect sizes (Koenig et al., 2021). Comparing results from different neuroimaging methods, behavioral tasks, or between task-based and resting-state approaches, however, makes it challenging to draw definite conclusions.

Examining the associations between response inhibition performance and PFC oxygenation during task, our results yield further evidence that neural mechanisms might differ between adolescents engaging in NSSI and healthy controls. Response inhibition performance, both reflected by mean reaction time and the standard deviation of reaction time, was differently associated with PFC oxygenation in both groups. In the healthy control group, better task performance in response inhibition was associated with higher ΔHbO_2. Our analyses did, however, not yield evidence that PFC oxygenation varied as a function of inhibition performance in the NSSI group. A positive association between prefrontal brain activation measured with fNIRS and inhibition task performance has previously been shown in healthy participants (Herrmann et al., 2005), suggesting that higher brain activation is associated with better task performance. Neuroimaging research provides converging evidence that deficits in emotion processing and regulation implicated in NSSI are accompanied by alterations in fronto-limbic circuitry (Ando et al., 2018; Grant et al., 2007; Westlund Schreiner et al., 2017; Westlund Schreiner et al., 2019) and might indicate a 'dysbalanced' interplay between limbic regions important for emotion processing (such as the amygdala) and frontal brain regions involved in regulatory control (such as the medial or DLPFC and anterior cingulate cortex) (Auerbach et al., 2021; Phillips et al., 2003), as also seen in affective disorders such as depression and bipolar disorder (Chen et al., 2022; Gong et al., 2020). It is therefore possible that our finding reflects deficits in the top-down control processes through prefrontal brain regions in adolescents with NSSI. Given that patients showed similar behavioral response inhibition performance, it is however thinkable, as mentioned previously, that brain activity in other parts of the brain compensates for the potential lack of prefrontal control. Interestingly, self-harming BPD patients who reduced their frequency of self-harm after seven months of dialectical behavior therapy (DBT) showed increases in PFC activity during an fNIRS response inhibition task compared to pre-treatment (Ruocco et al., 2016). Although more research is needed to determine the interplay between different brain regions during cognitive control processes, particularly in longitudinal studies, this finding might indicate that altered patterns of brain circuitry in patients with NSSI are reversible.

Considering the mixed results on deficits of cognitive control processes in adolescents engaging in NSSI raises the question whether response inhibition remains to be an important construct in NSSI research. Only recently, affective measures of inhibition have been investigated in the context of NSSI, showing worse cognitive control in adult NSSI samples in a negative emotional context (Allen et al., 2019; Allen and Hooley, 2019). Whether similar effects occur in adolescents with NSSI, is still to be determined. Interestingly, previous research in young adults has shown increased impulsivity operationalized by behavioral inhibition in 'low-severity NSSI', but not in more severe cases (Fikke et al., 2011). This finding suggests that severe NSSI is thought to rely on deliberate, intentional self-harm and that the construct of impulsivity might be more important for less severe NSSI cases. Finally, self-reported and behavioral impulsivity do not measure the same constructs, which has been shown in meta-analytic research (Cyders & Coskunipar, 2011). While self-report measures target self-perceived general impulsivity, behavioral measures might be more dependent on specific task designs and demands in the laboratory, which may not necessarily represent impulsive behavior in emotional contexts of real life (McCloskey et al., 2012). Therefore, studying brain functional correlates of affective measures of self-control, differentiating between more impulsive and more deliberate NSSI, and combining self-report and behavioral measures using higher temporal resolutions in more ecologically valid real-life situations (e.g., ecological momentary assessment or experience sampling methods via smartphone) may generate a more nuanced picture of the relevance of these processes for NSSI and psychopathology in general.

4.1. Limitations

Some limitations merit comment. As for the present analyses, we included data from female individuals only, we were unable to examine the potential influence of sex on our findings. Further, the inhibition paradigm was not designed as a task optimized for fNIRS, such as a block design or event-related design. On average, the baseline task took place approximately 20 min before the inhibition task. While for fNIRS data from continuous-wave measurement, it is necessary to contrast two conditions in order to obtain PFC oxygenation attributable to the condition of interest (in our case response inhibition), subtracting baseline activity which did not directly precede or follow the inhibition task entails the risk that factors changing across the time-span other than related to task demands, such as a slow signal drift of light sources or detector sensitivity, confound the results (Scholkmann et al., 2014). Further, a block design would have enabled contrasting the different components of the Go/Nogo paradigm, likely to yield a signal more representative of pure response inhibition, e.g. contrasting Go with Nogo blocks (Kaga et al., 2020; Veit et al., 2021).

There is some risk for false positives or false negatives, meaning that the measured signal was not caused by neuronal changes in hemodynamics (oxygenation), but by intracerebral or extracerebral hemodynamics caused by task-related systemic activity (e.g., changes in heart rate (HR) or breathing rate) (Tachtsidis and Scholkmann, 2016). One way to account for this problem is by using short-separation channel recording to measure extracerebral signals and subsequently correct for these confounding components. While we did not use short-separation channels, thanks to our multimodal examination, we were able to conduct post-hoc analyses with HR as a control variable. Including HR as a regressor did not change the patterns of our findings (results not reported), which somewhat alleviates the above-mentioned concerns.

Another limitation to the fNIRS measurement is that our setting included only prefrontal channels. Although fNIRS inhibition tasks have elicited prefrontal activity previously (Kaga et al., 2020; Veit et al., 2021), activation in other brain areas not covered by our recording have been shown (e.g., (Dahlgren et al., 2018)). We have further not focused our analyses on single channels, as we did not have specific hypotheses regarding brain activation to rely on subsections of the PFC. Further, it is still under debate whether the limited spatial resolution of fNIRS allows for such fine-grained localization (Ayaz et al., 2022).

While fNIRS has not widely been used in child and adolescent psychiatry, it has several advantages that make it a promising method: the relative ease of application, and the potential use in naturalistic settings to complement experimental paradigms and enhance ecological validity (e.g. (Pinti et al., 2020)), allowing e.g. for synchronized recording during child-caregiver interactions to measure biobehavioral synchrony (also called fNIRS hyperscanning, (Hoyniak et al., 2021; Nguyen et al., 2021; Reindl et al., 2018)).

4.2. Conclusion

Reporting on PFC oxygenation in a relatively large sample, our study provides some preliminary evidence that brain activity during response inhibition differs in female adolescents engaging in NSSI and healthy controls. However, the effects are small to moderate in size and the lack of previous studies, as well as methodological limitations warrant

cautious interpretation. While fNIRS is a promising method in child mental health, future studies should optimize cognitive/affective tasks for fNIRS processing.

Funding

This work was funded by the Dietmar Hopp Foundation [23011121].

CRediT authorship contribution statement

Ines Mürner-Lavanchy: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Julian Koenig:** Writing – review & editing, Methodology, Investigation. **Nebile Güzel:** Conceptualization, Investigation. **Patrice van der Venne:** Writing – review & editing, Investigation, Data curation. **Saskia Höper:** Writing – review & editing, Investigation, Visualization. **Marialuisa Cavelti:** Writing – review & editing. **Michael Kaess:** Conceptualization, Methodology, Resources, Writing – review & editing, Funding acquisition, Supervision.

Declaration of Competing Interest

None of the authors have any financial disclosures to make nor any conflicts of interest to report.

Acknowledgements

We thank the Dietmar Hopp Foundation that financially supported this study. We thank all participants and their parents for taking part in this study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2023.111697.

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