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Präfrontale Oxygenierung bei Jugendlichen mit Störungen der Emotionsregulation

vorgelegt von
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Zusammenfassung

Erfolgreiche Emotionsregulation (ER) stellt eine wichtige Fähigkeit im Umgang mit Stressoren und kritischen Lebensereignissen dar. Die neurobiologische Basis erfolgreicher ER ist der präfrontale Kortex (PFK), der regulierend auf emotionserzeugende Hirnstrukturen wirkt. Zur ER wenden Personen Strategien an. Eine dysfunktionale ER-Strategie ist nichtsuizidales selbstverletzendes Verhalten (NSSV), welches häufig im Jugendalter auftritt. Viele Betroffene berichten von Schwierigkeiten in der ER. NSSV stellt ein Kriterium der Borderline-Persönlichkeitsstörung (BPS) dar, welche oft im Jugendalter beginnt. Sie ist wesentlich durch eine emotionale Dysregulation gekennzeichnet.

Das Ziel der vorliegenden Arbeit ist es, Befunde aus der neurobiologischen Forschung zur Rolle des PFK an erwachsenen Patient*innen mit BPS bei Jugendlichen mit NSSV über das Spektrum der BPS zu replizieren. Dabei soll das Verständnis der Rolle des PFK bei Jugendlichen mit Störungen in der ER verbessert werden und so die Basis für weitere Forschung und neue (psycho)therapeutische Ansätze gelegt werden. Außerdem soll hiermit das Verständnis neurobiologischer Grundlagen psychischer Erkrankungen, die mit ER-Störungen assoziiert sind, erweitert werden. Dieser Arbeit liegen drei wissenschaftliche Studien zugrunde.

In **Studie I** wird die Aktivität des PFK im Ruhezustand bei einer Gruppe von Jugendlichen mit NSSV im Vergleich zu einer Kontrollgruppe von gesunden Jugendlichen untersucht. Die Ergebnisse legen nahe, dass die Aktivität im PFK im Ruhezustand geringer ist bei Jugendlichen mit NSSV als bei gesunden Jugendlichen. **Studie II** befasst sich mit der Aktivität im PFK während einer Stressaufgabe. Die Ergebnisse deuten bei Jugendlichen mit NSSV auf eine Überaktivierung im PFK während der Exposition mit einem psychosozialen Stressor im Vergleich zur Kontrollgruppe in Abhängigkeit der Schwere der BPS-Symptomatik hin. Eine Option therapeutischer Intervention zur Modulation präfrontaler Aktivität bei Störungen der ER stellt transkutane Vagusnervstimulation (tVNS) dar. Daher wird in **Studie III** die Auswirkung von tVNS auf die Aktivität im PFK bei Jugendlichen ohne affektive Störung untersucht. Dabei zeigt sich, dass die Aktivität im PFK ein Prädiktor für die Veränderungen der Herzratenvariabilität und der Herzrate bei tVNS im Vergleich zu Sham-Stimulation darstellt.

Abstract

Successful emotion regulation (ER) is one of the core competencies to deal with stressors and critical life events. The prefrontal cortex (PFC) regulates emotion-generating brain structures. It serves as neurobiological base for successful ER. For ER, individuals apply different strategies. A dysfunctional ER strategy is non-suicidal self-injury behavior (NSSI), which often occurs in adolescence. Those engaging in NSSI report difficulties in ER. NSSI represents one criterium for Borderline Personality Disorder (BPD) which often emerges during adolescence. Emotional dysregulation substantially marks BPD.

The current work aims to replicate findings from neurobiological research on the role of the PFC in adult patients with BPD in adolescents engaging in NSSI across the spectrum of BPD. It is aimed to improve our knowledge on the role of the PFC in adolescents with difficulties in ER and to provide basic principles for further research and novel (psycho)therapeutic interventions. Furthermore, the current work aims for a better understanding of the neurobiological foundations of psychiatric diseases associated with difficulties in ER. This dissertation is based on three scientific studies.

Study I investigates resting-state activity of the PFC in adolescents engaging in NSSI compared to an adolescent healthy control group. Results indicate an attenuated activity in the PFC during rest among adolescents engaging in NSSI compared to the healthy control group. **Study II** examines prefrontal activity during a stress task. Findings implicate an overactivation of the PFC during the exposition to a psychosocial stressor in adolescents with NSSI in comparison to a healthy control group and in dependence of the severity of BPD symptomatology. One potential therapeutic intervention to modulate prefrontal activity in individuals with difficulties in ER is transcutaneous vagus nerve stimulation (tVNS). Hence, **study III** examines the effect of tVNS on prefrontal activity in adolescents without any affective disorder. The activity of the PFC is shown to be a predictor for changes in heart rate variability and heart rate under tVNS compared to sham stimulation.

Inhaltsverzeichnis

Liste der wissenschaftlichen Veröffentlichungen zur publikationsbasierten Dissertation

I. Studie I

Koenig, J., Höper, S., van der Venne, P., Mürner-Lavanchy, I., Resch, F., & Kaess, M. (2021). Resting state prefrontal cortex oxygenation in adolescent non-suicidal self-injury – A near-infrared spectroscopy study. *NeuroImage: Clinical*, *31*, 102704. doi:10.1016/j.nicl.2021.102704

II. Studie II

Höper, S., Kröller, F., Heinze, A.-L., Bardtke, K. F., Kaess, M., & Koenig, J. (submitted). Prefrontal Cortex Oxygenation under Stress in Adolescent Non-Suicidal Self-Injury and Borderline Personality Disorder – A Functional Near-Infrared Spectroscopy Study. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging.*

III. Studie III

Höper, S., Kaess, M., & Koenig, J. (2022). Prefrontal cortex oxygenation and autonomic nervous system activity under transcutaneous auricular vagus nerve stimulation in adolescents. *Autonomic Neuroscience, 241*, 103008. doi:10.1016/j.autneu.2022.103008

Erklärung zum Eigenanteil der wissenschaftlichen Veröffentlichungen

I. Studie I

S. Höper hat gemeinsam mit J. Koenig die formale Analyse berechnet und den Manuskriptentwurf der Studie verfasst. Sie hat bei der Datenerhebung und -pflege und -aufbereitung erheblich mitgearbeitet und die Visualisierungen erstellt. Sie hat die Überarbeitung des Manuskripts vorgenommen und der finalen Version gemeinsam mit allen Ko-Autoren zugestimmt.

II. Studie II

S. Höper hat die Fragestellung der Studie entworfen, die formale Analyse selbstständig durchgeführt und den Manuskriptentwurf verfasst. Sie hat alle Visualisierungen erstellt und einen Teil der Daten für die formalen Analysen aufbereitet. Gemeinsam mit J. Koenig und M. Kaess hat sie die Überarbeitungen des Entwurfs vorgenommen und der finalen Version gemeinsam mit den Ko-Autoren zugestimmt.

III. Studie III

S. Höper hat die Fragestellung der Studie entworfen und die formale Analyse gemeinsam mit J. Koenig durchgeführt. Sie hat den Manuskriptentwurf verfasst und alle Visualisierungen erstellt. Gemeinsam mit J. Koenig und M. Kaess hat sie die Überarbeitungen des Entwurfs vorgenommen und der finalen Version zugestimmt.

Weitere wissenschaftliche Veröffentlichungen außerhalb der publikationsbasierten Dissertation

van der Venne, P., **Höper, S.**, Koenig, J., & Kaess, M. (submitted) Physiological response to pain in female adolescents with nonsuicidal self-injury as a function of severity. Translational Psychiatry.

Mürner-Lavanchy, I., Koenig, J., Lerch, S., van der Venne, P., **Höper, S.**, Resch, F., & Kaess, M. (2022). Neurocognitive functioning in adolescents with non-suicidal self-injury. *Journal of Affective Disorders*, *311*, 55–62. doi:10.1016/j.jad.2022.05.029

Abkürzungsverzeichnis

BPS	Borderline-Persönlichkeitsstörung
EDA	Elektrodermale Aktivität
ER	Emotionsregulation
fMRT	funktionelle Magnetresonanztomographie
fNIRS	funktionelle Nahinfrarotspektroskopie
HbR	Desoxygeniertes Hämoglobin
HbT	Gesamthämoglobin
HR	Herzrate
HRV	Herzratenvariabilität
NIM	Neuroviszerale Integrationsmodell
NSSV	Nichtsuizidales selbstverletzendes Verhalten
O_2Hb	Oxygeniertes Hämoglobin
PFK	Präfrontaler Kortex
ROI	Region of Interest
sAA	Alpha-Amylase
TSST	Trier Social Stress Test
tVNS	transkutane Vagusnervstimulation

1 Einleitung

Emotionen werden als eine selbstregulatorische Antwort des Organismus definiert, die zu einer effektiven Koordination zielgerichteten Verhaltens führen (Thayer & Lane, 2000). Sie sind durch ihren Gefühlscharakter, einhergehend mit einer Valenz als angenehm oder unangenehm, durch ihre Objektgerichtetheit und durch ihre begrenzte zeitliche Dauer charakterisiert (Eder & Brosch, 2017). Emotionen haben intra- und interpersonale Funktionen (Eder & Brosch, 2017). Intrapersonal lenken sie die Aufmerksamkeit auf Ereignisse und motivieren zu Reaktionen auf diese. So folgt auf eine Bedrohung die emotionale Reaktion Furcht, welche zur Flucht animiert, um sich selbst zu schützen. Interpersonal wirken sie in sozialen Beziehungen, indem sie dem Gegenüber das eigene Befinden vermitteln und emotionale Reaktionen hervorrufen. Die Veränderung von Emotionen in ihrer Art, Stärke oder Dauer wird als Emotionsregulation (ER) bezeichnet (Gross, 1998). Auf neurobiologischer Ebene sind das limbische System, das unter anderem die Amygdala und Teile des präfrontalen Kortex (PFK) umfasst, der anteriore cinguläre Kortex und die Insula an der Entstehung von Emotionen beteiligt (Ahmed, Bittencourt-Hewitt, & Sebastian, 2015; Eder & Brosch, 2017). Während der ER moduliert der PFK die Aktivität von emotionsgenerierenden Strukturen, indem er die Aktivität der Amygdala und des limbischem Systems herauf- oder herabreguliert (Davidson, 2004; Dixon, Thiruchselvam, Todd, & Christoff, 2017; Fusar-Poli et al., 2009; Gross, 2015; Ochsner, Silvers, & Buhle, 2012). Zur erfolgreichen ER wenden Personen unterschiedliche kognitive oder behaviorale Strategien an. Zu den vorrangig funktional bewerteten Strategien zählen *Neubewertung* und *Problemlösen* (Aldao, Nolen-Hoeksema, & Schweizer, 2010). Dem gegenüber stehen dysfunktionale ER-Strategien. Die Verwendung maladaptiver, ungeeigneter, unflexibler oder ineffektiver ER-Strategien wird als emotionale Dysregulation bezeichnet, wodurch eine inadäquate emotionale Reaktion auf eine Situation entstehen kann (Thompson, 2019). Emotionale Dysregulation ist mit dem Auftreten psychischer Störungen assoziiert (Gross & Jazaieri, 2014). Beispielsweise sagen stärkere Schwierigkeiten in der ER bei 11- bis 14-Jährigen vermehrte psychopathologische Auffälligkeiten – in Form von einem höheren Maß an Angst, aggressiven Verhaltensweisen und problematischem Essverhalten – ein halbes Jahr später voraus (McLaughlin, Hatzenbuehler, Mennin, & Nolen-Hoeksema, 2011). Ein Beispiel emotionaler Dysregulation stellt nichtsuizidales selbstverletzendes Verhalten (NSSV) dar. Betroffene berichten häufig, NSSV als Strategie zu verwenden, um ihre eigenen Emotionen zu regulieren (Taylor et al., 2018). NSSV ist ein Kriterium der Borderline-Persönlichkeitsstörung (BPS), welche durch ein hohes Ausmaß emotionaler Dysregulation gekennzeichnet ist (Domes, Schulze, & Herpertz, 2009; Gratz, Moore, & Tull, 2016).

Vor diesem Hintergrund sollen im Rahmen dieser Arbeit sowohl grundsätzliche Unterschiede in der Aktivierung des PFK als auch aufgabenspezifische Anforderungen an den PFK bei Jugendlichen mit Störungen in der ER (NSSV und BPS-Symptomatik) untersucht werden. Zudem sollen therapeutische Möglichkeiten zur Beeinflussung der PFK-Aktivität betrachtet werden. Dazu soll im ersten Teil ein Modell zur ER vorgestellt und in den Kontext jugendlicher emotionaler Dysregulation anhand von NSSV und BPS-Symptomatik integriert werden. Dabei werden die Forschungsfragen dieser Arbeit herausgearbeitet. Im zweiten Teil sollen diese Forschungsfragen mithilfe der durchgeführten Studien beleuchtet und beantwortet werden. Der letzte Teil der Arbeit diskutiert die Befunde, erörtert Stärken und Limitationen der vorliegenden Arbeit und weist Implikationen für zukünftige Forschung und klinische Praxis auf.

2 Theoretischer Hintergrund

ER umfasst die Beeinflussung der Art, des Ausmaßes und des Zeitpunkts von Emotionen sowie deren Erleben und Ausdruck (Gross, 1998). Sie ist als Prozess definiert, bei dem Personen positive und negative Emotionen verstärken, abschwächen oder aufrechterhalten (Gross, 1998). ER kann auf einem Kontinuum betrachtet werden, das von kontrollierter und bewusster Regulation bis hin zu unbewussten und automatischen Prozessen reicht (Braunstein, Gross, & Ochsner, 2017; Gross, 1998; Koole, Webb, & Sheeran, 2015). Beispielsweise kann eine schlechte Leistung in einem Laufwettkampf zu Enttäuschung und Wut führen. Bei einer bewussten und kontrollierten ER führt sich die Person vor Augen, dass die Wettkampfbedingungen an dem Tag schlecht waren. Beispielsweise kann eine bewusste und kontrollierte ER die Enttäuschung und Wut nach einer schlechten Leistung bei einem Laufwettkampf abschwächen, indem die Person die Wettkampfbedingungen bewusst und kontrolliert neu bewertet (z.B. war die Regeneration aus den letzten Trainingseinheiten unzureichend, die Strecke schlecht asphaltiert und das Wetter regnerisch). Ein Beispiel für unbewusste, automatische ER ist das automatische Essen von Schokolade zur Abschwächung von Wut und Enttäuschung nach einem Streit. ER setzt entweder bereits beim Emotionsentstehungsprozess ein (z.B. durch Bewertungen oder Modifikationen der emotionsauslösenden Situation) oder umfasst das Verändern bereits vorhandener Emotionen in ihrer Art oder Intensität. Somit erfolgt ER an einer oder mehreren Stellen im Prozess von der Emotionsentstehung bis zur emotionalen Reaktion (Gross, 1998). Auf neuronaler Ebene stellt erfolgreiche ER mehr als einen Prozess dar, der ausschließlich auf Lernerfahrungen und mentalen Prozessen basiert – einer sogenannten top-down Verarbeitung (Gross, 1998). Vielmehr werden Eindrücke aus dem peripheren Nervensystem zur ER mit einbezogen. Das periphere Nervensystem umfasst den Teil des Nervensystems, der nicht zu Gehirn und Rückenmark gehört. Es liefert Informationen über Sinneseindrücke und Veränderungen von Reizen von Organen, Muskeln oder Haut an das zentrale Nervensystem, welches das Gehirn und Rückenmark umfasst. Bei der ER werden die Informationen aus dem peripheren Nervensystem in regulierenden Hirnregionen wie dem PFK verarbeitet (Thayer & Lane, 2000, 2000). Auf Grundlage der verarbeiteten peripheren Informationen moduliert der PFK die Aktivität emotionsgenerierender Regionen (Davidson, 2004; Dixon, Thiruchselvam, Todd, & Christoff, 2017; Fusar-Poli et al., 2009; Gross, 2015; Ochsner, Silvers, & Buhle, 2012), sodass ER durch ein Zusammenspiel von emotionsgenerierenden Hirnregionen (z.B. limbisches System, Amygdala) zusammen mit regulierenden Hirnregionen (z.B. PFK) gekennzeichnet ist (Steinfurth, Wendt, & Hamm, 2013). Außerdem wird bei der ER die Reaktion auf emotionale Reize beeinflusst

– physiologisch (z.B. durch Veränderungen der Herzrate, Hormonausschüttungen, Schweißproduktion) und psychologisch (z.B. durch das Empfinden der Intensität oder Valenz von Emotionen; Thayer & Lane, 2000).

2.1 Modelle zur Emotionsregulation

Innerhalb der Psychologie wurden zahlreiche Modelle zur Systematisierung und Erklärung von ER und ER-Strategien entworfen. Ein bekanntes Modell ist das Modell adaptiver ER (Berking, 2015), das im Rahmen eines Trainings emotionaler Kompetenzen entworfen wurde. Die vermittelten Kompetenzen sollen die Person befähigen, ihre Emotionen adäquat regulieren zu können. In diesem Modell werden unter *Kompetenzen* sieben Fertigkeiten verstanden: Muskelentspannung, Atementspannung, bewertungsfreie Wahrnehmung, Akzeptieren und Tolerieren, Selbstunterstützung, Analysieren und Regulieren (Berking, 2015, S. 27-31). Diese sollen in dem Training vermittelt werden und die Person dazu befähigen, ihre Emotionen adäquat regulieren zu können. Eine weitere Möglichkeit zur Systematisierung von ER-Strategien ist der deskriptive Ansatz zur Klassifikation von Regulationsstrategien (Parkinson & Totterdell, 1999), der eine Vielzahl kognitiver und behavioraler Strategien umfasst. Über Fragebögen und Interviews wurden n = 162 ER-Strategien erhoben. Diese wurden erfasst und in ein Klassifikationssystem übertragen, das auf drei Ebenen sechs Dimensionen enthält: die Dimension kognitiver und behavioraler Strategien, die Dimension von Strategien der Umlenkung, bei denen Gedanken oder Verhalten von den derzeitigen Emotionen ablenken sollen, und des Engagements, bei denen die derzeitige Emotion im Fokus steht. Die letzte Ebene der Klassifikation umfasst die Dimension der direkten Ablenkung von Emotionen und der aktiven Vermeidung (Parkinson & Totterdell, 1999). Diese beiden Modelle bieten zwar eine Grundlage, um ER-Strategien systematisch einzuordnen, die ER-Strategien von Personen zu identifizieren und auch Personen therapeutisch in ihrem Umgang mit ER zu begleiten. Allerdings bieten sie keine Möglichkeit, ER im Prozess von der Emotionsentstehung bis zur Regulation der bereits vorhandenen Emotion zu betrachten. Das allgemeinpsychologisch wohl bekannteste Modell, das diesen Ansprüchen genügt, ist das Prozessmodell der ER, das 1998 erstmals postuliert und 2015 erweitert wurde (Gross, 1998, 2002, 2015). Es liefert einen organisatorischen Rahmen, um ER in den zeitlichen Prozess von der Entstehung von Emotionen bis zur emotionalen Reaktion einzuordnen (siehe auch Abbildung 1). Dabei unterteilt es ER in antezedenzfokussierte ER, bei der ER während der Entstehung der Emotion und vor der emotionalen Reaktion stattfindet, und reaktionsfokussierte ER, die als ER die Veränderung der emotionalen Reaktion umfasst. Bei der antezedenzfokussierten ER werden die Ebenen *Situation*, *Situationsaspekte* und

Bedeutung unterschieden. Im Laufe des emotionsgenerierenden Prozesses kann durch die Auswahl der Situation, der Modifikation der Situation, der Aufmerksamkeitslenkung auf bestimmte Aspekte der Situation oder der kognitiven Veränderung der Bedeutung der Situation strategisch Einfluss auf die Entstehung der Emotion genommen werden. Nach Entstehung der Emotion erfolgt die Ebene der emotionalen Reaktion. ER erfolgt auf dieser Ebene über Reaktionstendenzen, welche die Modulation der Reaktion im Verhalten (z.B. Weinen unterdrücken), im subjektiven Erleben (z.B. Ekel verstärken durch Nachdenken, welche Krankheiten Schimmel potenziell auslösen kann) und der physiologischen Wirkung (z.B. Furcht verstärken durch schnelles Atmen und Erhöhen der Herzrate) beinhalten. Das Modell postuliert in seiner Ursprungsversion zwei Strategien als vorherrschend: Während antezedenzfokussierter ER erfolgt *Neubewertung* als Strategie, während reaktionsfokussierter ER hingegen *Unterdrückung*. *Neubewertung* findet somit vor der Entstehung der Emotion statt und umfasst die Uminterpretation der Situation, von Situationsaspekten und deren Bedeutung, sodass die daraus resultierende Emotion verändert wird. Zum Beispiel können Psychologiestudierende in der Statistikklausur die persönliche Bedeutung der Note verändern, bevor sie das Ergebnis der Prüfung erhalten, indem sie sich vor Augen führen, dass die Note der Statistikprüfung nur einen geringen Teil der Abschlussnote ausmacht und somit ein Gefühl von Enttäuschung oder Trauer verringern, wenn sie eine schlechte die Note erhalten. *Unterdrückung* bezieht sich auf eine Reaktionsveränderung bereits entstandener Emotionen. Beispielsweise kann die Intensität der Enttäuschung über eine durchgefallene Klausur gemindert werden durch das Zurückhalten starker emotionaler Reaktionen wie Weinen.

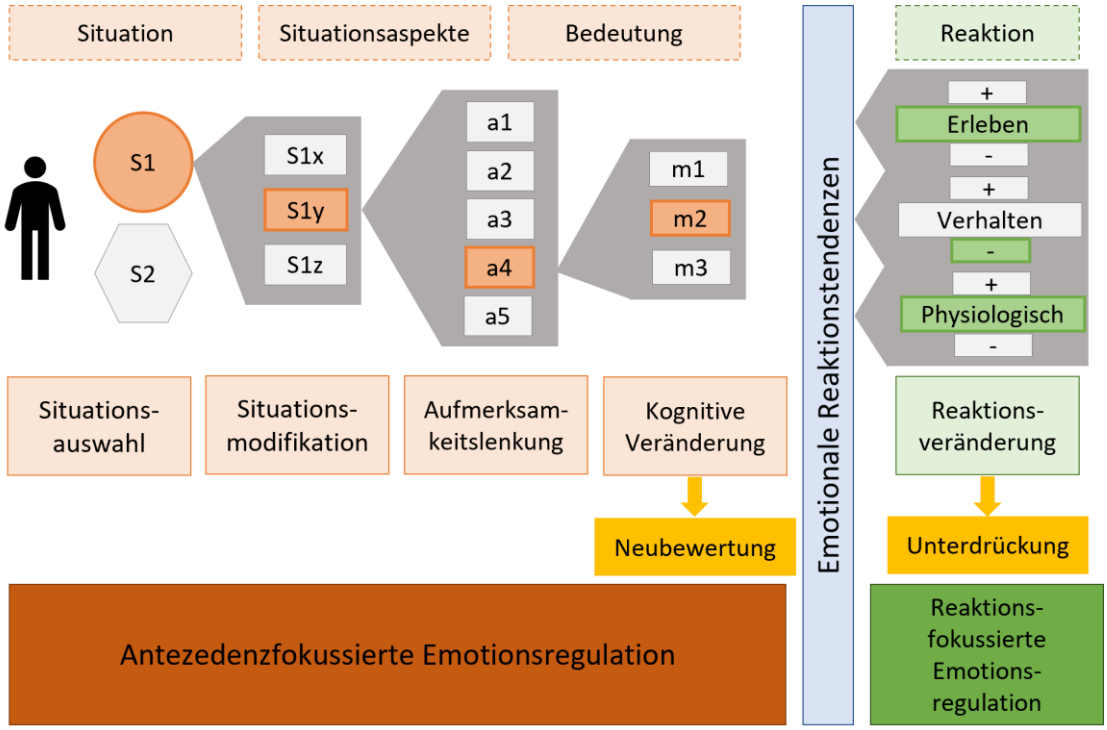

Abbildung 1 Prozessmodell der Emotionsregulation.
Anmerkung. Adaptiert und übersetzt nach Gross (1998).

Durch die Berücksichtigung der zeitlichen Komponente der Emotionsentstehung liefert das Prozessmodell der ER von Gross (1998, 2002, 2015) eine Darstellung der Zeitpunkte, an denen ER stattfinden kann. Es berücksichtigt sowohl emotionsauslösende Komponenten als auch den reaktiven Verlauf der ER, wobei kognitive Faktoren, Umweltfaktoren und die emotionale Wirkung berücksichtigt werden (Hasking, Whitlock, Voon, & Rose, 2017). ER-Strategien lassen sich den einzelnen Ebenen zuordnen. Meta-analytische Befunde deuten darauf hin, dass zur Aufrechterhaltung von psychischem Wohlbefinden die Strategie der *Neubewertung* am erfolgreichsten zu sein scheint (n = 190 Studien mit k = 306 experimentellen Vergleichen von ER-Strategien; Webb, Miles, & Sheeran, 2012), wohingegen die Nutzung von *Unterdrückung* als ER-Strategie als weniger erfolgreich beurteilt wird (John & Gross, 2004; McRae & Gross, 2020).

2.2 Die Rolle des präfrontalen Kortex bei erfolgreicher Emotionsregulation

Die neuronalen Korrelate bei ER wurden vielfach untersucht. Gross postuliert, dass bidirektionale Pfade zwischen dem PFK und tieferliegenden emotionserzeugenden Strukturen existieren, da effektive ER das Feedback überwachender Hirnregionen voraussetze (Gross, 1998). Die Verbindung präfrontaler und limbischer Strukturen bei der ER scheint dabei eine entscheidende Rolle zuzukommen (Linhartová et al., 2019).

Eine dem limbischen System zugehörige Struktur ist die Amygdala, welche entscheidend an der Emotionsgeneration und -regulation beteiligt ist (Ochsner et al., 2012; Steinfurth et al., 2013). Bei der ER steht sie unter dem Einfluss regulatorischer Hirnregionen (Steinfurth et al., 2013). Meta-Analysen (mit bis zu n = 98 Studien) berichten, dass der PFK an der ER beteiligt ist – unabhängig davon, ob Emotionen herauf- oder herabreguliert werden, sowie unabhängig von der Valenz der Emotionen (Buhle et al., 2014; Morawetz, Bode, Derntl, & Heekeren, 2017). Je nach Studienaufbau und Untersuchungsmethode variieren die aktivierten Regionen innerhalb des PFK (Ochsner & Gross, 2008). Buhle und Kollegen interpretieren die Aktivierung von PFK-Regionen während *Neubewertung* als Nutzung kognitiver Kontrollregionen, um semantische Repräsentationen von Eindrücken zu modulieren und so die Aktivität der Amygdala anzupassen (Buhle et al., 2014). Konnektivitätsanalysen untersuchen die zeitgleiche Aktivierung oder zeitlich voneinander abhängige Aktivierung von räumlich getrennt liegenden Hirnregionen (Friston, 1994). Befunde aus Konnektivitätsanalysen unterstreichen die Verbindung zwischen dem PFK und der Amygdala während aktiver ER (Berboth & Morawetz, 2021).

2.3 Emotionale Dysregulation bei psychischen Erkrankungen im Jugendalter am Beispiel nichtsuizidalen selbstverletzenden Verhaltens und Borderline-Persönlichkeitsstörung

Psychische Erkrankungen im Jugendalter stellen ein häufiges Problem dar. Die Punktprävalenz für das derzeitige Vorliegen psychischer Erkrankungen im Jugendalter liegt zwischen 13,3 % und 16,5 % für den amerikanischen und deutschsprachigen Raum (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Costello et al., 2003; Philipp et al., 2018, 2018; Ravens-Sieberer et al., 2008, 2008). Sie sind ein Prädiktor für das Vorliegen psychischer Erkrankungen im Erwachsenenalter (Copeland et al., 2013, 2013; Copeland, Shanahan, Costello, & Angold, 2009; Copeland et al., 2009) und mit Schwierigkeiten in der Lebensführung assoziiert (z.B. Schulabbruch, niedriges Einkommen, höhere Kriminalität, geringere Arbeitsfähigkeit; Gibb, Fergusson, & Horwood, 2010; Stoep et al., 2000). Der Erforschung psychischer Störungen im Jugendalter kommt daher eine große Bedeutung zu. Im Zusammenhang mit ER stellt NSSV eine dysfunktionale ER-Strategie dar, die insbesondere im Jugendalter auftritt (Plener, Schumacher, Munz, & Groschwitz, 2015; Plener et al., 2015). NSSV umfasst die absichtliche Schädigung von Körpergewebe ohne suizidale Absicht (International Society for the Study of Self-injury, 2018). Die Prävalenz für einmaliges NSSV liegt bei 17,2 % bis 22,1 % (Lim et al., 2019; Swannell, Martin, Page, Hasking, & John, 2014). In

klinischen Stichproben liegt die Lebenszeitprävalenz unter jungen Menschen bei bis zu 50 % (Plener et al., 2018). NSSV ist auf zwei Arten mit ER assoziiert: zum einen kann es als ER-Strategie betrachtet werden (Bentley, Nock, & Barlow, 2014; Bentley et al., 2014), zum anderen nutzen Personen mit NSSV mehr dysfunktionale Strategien (Andrews, Martin, Hasking, & Page, 2013; Andrews et al., 2013) oder sind bei der Anwendung funktionaler Strategien weniger erfolgreich (Hasking, Momeni, Swannell, & Chia, 2008). Betroffene berichten, dass sie sich selbst verletzen, um mit starken Emotionen und Verzweiflung umzugehen (Taylor et al., 2018; Zetterqvist, Lundh, Dahlström, & Svedin, 2013). Außerdem wird NSSV mit Schwierigkeiten in der ER assoziiert (Haid-Stecher & Sevecke, 2019; In-Albon et al., 2008; Wolff et al., 2019) und eine stärkere Ausprägung von NSSV – im Sinne von einer größeren Vielfalt an verwendeten Methoden zur Selbstschädigung und der Häufigkeit des NSSV – hängt mit stärkerer emotionaler Dysregulation bei jungen Menschen zusammen (Gratz, Dixon-Gordon, Chapman, & Tull, 2015; Midkiff, Lindsey, & Meadows, 2018). Zwar werden Defizite in der ER als eines der Hauptmerkmale von NSSV beschrieben (McKenzie & Gross, 2014). Dennoch ist nicht eindeutig, inwiefern Schwierigkeiten in der ER NSSV vorausgehen oder ER ein Bestandteil von NSSV ist. Bei der Nutzung von ER-Strategien berichten Jugendliche mit NSSV, die vermehrt *Neubewertung* als ER-Strategie einsetzten, weniger starke Verläufe von NSSV (weniger tiefes NSSV, weniger medizinische Vorstellungen aufgrund von NSSV) in einem Drei-Jahres-Untersuchungszeitraum verglichen mit Jugendlichen mit NSSV, die andere ER-Strategien nutzten (Voon, Hasking, & Martin, 2014). NSSV stellt keine eigenständige Diagnose dar und tritt selten isoliert auf (Turner et al., 2015). Im DSM-5 ist es erstmals als Forschungsentität aufgegriffen (American Psychiatric Association, 2013). Neben der Klassifikation als Forschungsentität stellt regelmäßiges NSSV ein diagnostisches Kriterium der BPS dar. Insbesondere in der Adoleszenz ist der Beginn einer BPS auch mit NSSV assoziiert (Kaess, Brunner, & Chanen, 2014). Der Leidensdruck derjenigen, bei denen BPS und gleichzeitig NSSV vorliegen, ist größer als bei denjenigen, die NSSV ohne weitere psychische Erkrankung aufweisen (Auerbach et al., 2014; Kaess, Fischer-Waldschmidt, Resch, & Koenig, 2017; Santangelo et al., 2017; Turner et al., 2015). Im Jugendalter stellt regelmäßiges NSSV einen Prädiktor für das Auftreten einer BPS-Diagnose ein Jahr später dar (Ghinea et al., 2019). Es liegt also ein enger Zusammenhang zwischen NSSV und BPS vor (Nitkowski & Petermann, 2011), sodass beides auf einem Kontinuum betrachtet werden kann, das den Schweregrad der BPS-Symptomatik der einzelnen Person abbildet. Auf diesem Kontinuum steht NSSV als alleiniges Symptom der BPS an einem Ende und das Vorliegen des Vollbilds der BPS am anderen Ende. BPS ist durch wiederkehrende Impulsivität sowie durch emotionale

und interpersonale Instabilität charakterisiert. Die Kriterien umfassen Ängste vor dem Verlassenwerden, instabile und intensive Beziehungsmuster, Identitätsstörungen, impulsives Verhalten, wiederkehrende suizidale und selbstverletzende Verhaltensweisen, affektive Instabilität, chronische Gefühle innerer Leere, unangemessene Wutausbrüche und stressbezogene paranoide Vorstellungen oder ernsthafte dissoziative Symptome (American Psychiatric Association, 2013). BPS ist gekennzeichnet durch Störungen in der ER und geht häufig mit extremen Stimmungsschwankungen und Schwierigkeiten im emotionalen Umgang mit Mitmenschen einher (Domes et al., 2009; Gratz et al., 2016). Die Prävalenzen für das Vorliegen einer BPS liegen zwischen 0,9 bis 3,2 % unter Jugendlichen und jungen Erwachsenen in den USA (Johnson, Cohen, Kasen, Skodol, & Oldham, 2008). Bei der Wahl von ER-Strategien greifen Personen mit BPS häufig zu Strategien wie *Grübeln* oder *Unterdrückung* von Gedanken und negativen Gefühlen (Baer, Peters, Eisenlohr-Moul, Geiger, & Sauer, 2012). Sie tendieren zu einer unzureichenden Interpretation und Evaluation von Gefühlszuständen (Baer et al., 2012). Diese von Personen mit BPS genutzten Strategien zur ER werden von Gross in seiner Erweiterung des Prozessmodells zur ER als ungünstig eingestuft (Gross, 2015).

Zur Klärung der Entwicklung von Schwierigkeiten in der ER über das Kontinuum von NSSV und BPS sollten Veränderungen in der Hirnaktivität bei Betroffenen mitberücksichtigt werden. Bei Erwachsenen mit BPS konnten dysfunktionale Aktivierungsmuster im PFK bei Inhibitionsaufgaben gefunden werden (Sebastian et al., 2014), sowie Veränderungen in der Aktivität im frontolimbischen System, insbesondere auch bei der ER (Chanen & Kaess, 2012; Dudas et al., 2017; Ruocco, Amirthavasagam, Choi-Kain, & McMain, 2013; Schulze, Schmahl, & Niedtfeld, 2016). Die Studienlage zur Untersuchung neuronaler Korrelate von NSSV ist gering. Dahlgren und Kollegen (2018) untersuchten die Aktivierung emotionsassoziierter Hirnregionen während der ER bei jungen Erwachsenen mit NSSV und einer Kontrollgruppe während einer Interferenzaufgabe. Interferenzaufgaben erfordern die bewusste Unterdrückung von automatischem Antwortverhalten und die aktive Regulation der aufgabenspezifischen Antwort. Dabei spielt der PFK eine zentrale Rolle bei der Regulation der Antwort (Dahlgren et al., 2018). Außerdem fanden sie eine geringere Aktivität im PFK und dem cingulären Kortex in der NSSV Gruppe. Es fanden sich jedoch keine signifikanten Unterschiede bei der Leistung der Interferenzaufgabe zwischen den Gruppen. Dies legt den Schluss nahe, dass eine stärkere neuronale Deaktivierung in der NSSV-Gruppe notwendig ist, um Defizite in der ER zu kompensieren (Dahlgren et al., 2018). Die verringerte Aktivität im dorsolateralen PFK war bei Personen mit NSSV zusätzlich mit einer geringeren Fähigkeit Emotionen adäquat zu regulieren – im Sinne von

selbstberichteter Impulsivität und emotionaler Reaktivität – assoziiert. Diese Assoziation zeigte sich jedoch nicht bei Personen der gesunden Kontrollgruppe (Dahlgren et al., 2018).

Zusammenfassend gibt es wenig Forschung zur Untersuchung von emotionsregulatorischen Gehirnstrukturen über das Kontinuum von NSSV und BPS im Jugendalter. Beide Störungsbilder sind mit Schwierigkeiten in der ER assoziiert. Aufgrund der zeitlichen Verläufe im Jugendalter und der Rolle von NSSV als Prädiktor für BPS (Ghinea et al., 2019) können beide auf einem Kontinuum betrachtet werden. Bildgebende Forschung bei erwachsenen Personen mit BPS findet funktionale Veränderungen in Hirnregionen, die mit ER assoziiert sind. Ob diese Abweichungen eine Ursache für die Entstehung einer BPS sind oder das Ergebnis langjähriger Krankheitsverläufe oder Medikamenteneinnahmen, lässt sich meist nicht beantworten. Studien im Jugendalter sowie bildgebende Untersuchungsverfahren bei NSSV sind selten. Die wenigen vorliegenden Studien erheben NSSV entweder als Merkmal in einer BPS-Stichprobe oder untersuchen die Aktivität bestimmter Hirnregionen bei sehr aufgabenspezifischen Fähigkeiten. Es fehlen bildgebende Studien bei Jugendlichen mit beginnender BPS und bei Jugendlichen mit NSSV, die sowohl grundlegende Veränderungen in der Gehirnaktivität sowie darauf aufbauend – aufgabenspezifische Aktivierungen – untersuchen und die diese Ergebnisse, mit denen von gesunden Jugendlichen vergleichen.

2.4 Funktionelle Nahinfrarotspektroskopie

Die Darstellung der neuronalen Aktivierung mentaler Prozesse mithilfe nicht-invasiver Bildgebungsverfahren basiert zumeist auf zwei Prinzipien: der Darstellung der elektrischen Aktivierung während mentaler Prozesse (z.B. Elektroenzephalographie) oder der Darstellung der aus elektrischer Aktivierung resultierenden Veränderungen physiologischer Prozesse (Matthews & Jezzard, 2004). Funktionelle Magnetresonanztomographie (fMRT) basiert auf dem zweiten Prinzip (Matthews & Jezzard, 2004). Es nutzt die magnetischen Eigenschaften des oxygenierten (O_2Hb) und deoxygenierten Hämoglobins (HbR) der venösen Blutgefäße im Gehirn, um Veränderungen in der Aktivität von Hirnregionen darzustellen (Matthews & Jezzard, 2004). Die Erhebung der neuronalen Aktivität mittels fMRT ist aufwändig in der Datenaufbereitung und kostenintensiv in der Durchführung (Scarapicchia, Brown, Mayo, & Gawryluk, 2017; Scarapicchia et al., 2017). Eine alternative Methode zur Erhebung von Unterschieden in der Oxygenierung der Blutgefäße während neuronaler Aktivität ist die funktionelle Nahinfrarotspektroskopie (fNIRS). Während fMRT die magnetischen Eigenschaften des Hämoglobins nutzt (Matthews & Jezzard, 2004, 2004), beruht die

Funktionsweise von fNIRS auf den Reflexions- und Absorptionseigenschaften von O_2Hb und HbR auf Licht aus dem Nahinfrarotbereich – den spezifischen Eigenschaften von O_2Hb und HbR zur Spiegelung und Aufnahme von Lichtwellen aus dem Nahinfrarotspektrum (Ferrari & Quaresima, 2012). fNIRS-Geräte bestehen aus Lichtquellen und Lichtaufnahmeoptoden. Sie werden auf der Stirn mithilfe eines Stirnbands befestigt. Die Lichtquellen geben Licht aus dem Nahinfrarotbereich in zwei Wellenlängen ab. Dieses durchdringt die Haut, den Schädelknochen und die Cerebrospinalflüssigkeit und trifft so auf das O_2Hb und HbR der venösen Blutgefäße im Gehirn (Ferrari & Quaresima, 2012). Beide haben eigene Reflexions- und Absorptionseigenschaften in Reaktion auf Licht aus dem Nahinfrarotspektrum (Ferrari & Quaresima, 2012, 2012). Die zwei Wellenlängen des fNIRS-Geräts sind so ausgewählt, dass sie jeweils vom O_2Hb oder HbR reflektiert werden. Aufgrund dieser Funktionsweise können Veränderungen in der Oxygenierung an der Kortexoberfläche, der direkt unterhalb der Schädeldecke liegenden Region des Gehirns, wenige Zentimeter tief gemessen werden (Ferrari & Quaresima, 2012, 2012). Im Vergleich zu fMRT ist die räumliche Auflösung von fNIRS geringer (Scarapicchia et al., 2017). Solange neuronale Prozesse an der Kortexoberfläche ohne Fokus auf der exakten temporalen oder strukturellen Auflösung untersucht werden, zeigen fMRT und fNIRS vergleichbare Aktivierungsmuster (Alderliesten et al., 2014, 2014; Bulgarelli et al., 2018, 2018; Quaresima & Ferrari, 2016, 2016). Aufgrund der einfachen und kostengünstigen Anwendungsweise und seiner hohen Akzeptanz bei Jugendlichen im Vergleich zur fMRT-Messung wurde in den nachfolgenden Studien ein tragbares acht-Kanal fNIRS-Gerät verwendet, das die Veränderung der Oxygenierung im Bereich des PFK misst (Octamon, Artinis, Niederlande, NL). Es nutzt Licht mit den Wellenlängen $\lambda = 760$ nm und $\lambda = 850$ nm.

3 Ziele und Forschungsfragen

Aus den Vorkapiteln lässt sich zusammenfassen: ER kann sowohl vor als auch nach der Entstehung von Emotionen stattfinden. Der PFK spielt dabei eine wichtige Rolle durch seine regulierende Wirkung auf emotionsgenerierende Hirnregionen. Der PFK verarbeitet zur ER Informationen aus dem peripheren Nervensystem. NSSV stellt eine dysfunktionale ER-Strategie dar, die eine hohe Prävalenz unter Jugendlichen hat. Gleichzeitig weisen Personen, die sich selbst verletzen, emotionale Dysregulation auf. NSSV tritt selten isoliert auf und kann auf einem Kontinuum betrachtet werden, an dessen anderem Ende das Vollbild der BPS steht. Die Forschungslage zur Untersuchung des PFK bei NSSV über die BPS-Symptomatik hinweg ist spärlich. Derartige Erkenntnisse können bei der Entwicklung maßgeschneiderter therapeutischer Interventionen helfen. Die Prävalenz von BPS im Jugendalter liegt deutlich niedriger als die von NSSV. Jedoch ist ein früher Krankheitsbeginn mit schwereren Verläufen im Erwachsenenalter und Einschränkungen an der gesellschaftlichen Teilhabe assoziiert (Bozzatello, Bellino, Bosia, & Rocca, 2019; Hastrup, Jennum, Ibsen, Kjellberg, & Simonsen, 2022). Insbesondere bei der BPS sind strukturelle und funktionelle Abweichungen im PFK sowie im limbischen System gefunden worden (Chanen & Kaess, 2012; Dudas et al., 2017; Ruocco et al., 2013; Schulze et al., 2016; Sebastian et al., 2014). Leider beschränken sich diese Befunde auf den Erwachsenenbereich und die wenigen existierenden Studien verfügen über kleine Stichproben, sodass deren Aussagekraft eingeschränkt ist. Daher sollen in der vorliegenden Arbeit die Rolle des PFK bei Jugendlichen mit NSSV über das Spektrum der BPS-Symptomatik hinweg systematisch untersucht werden: Aufgrund der Tatsache, dass Befunde zur neuronalen Aktivität im PFK als einer der zentralen mit ER assoziierten Hirnregionen bei Jugendlichen mit NSSV unter Berücksichtigung der BPS-Symptomatik fehlen, sollen in einer ersten Studie die Aktivierung des PFK im Ruhezustand bei Jugendlichen mit NSSV im Vergleich zu einer jugendlichen Kontrollgruppe untersucht werden. Veränderungen in der Aktivität im Ruhezustand könnten hierbei Hinweise auf frühe Veränderungen im PFK geben. Darauf aufbauend untersucht die zweite Studie die Aktivierung des PFK während einer emotionsauslösenden Stressaufgabe. Aktive Stressverarbeitung lässt sich im Prozessmodell zur ER von Gross (1998, 2002, 2015) abbilden und die einzelnen Ebenen der ER auf die Stressaufgabe assoziieren. Untersucht werden Jugendliche mit regelmäßigem NSSV. Gleichzeitig wird BPS als dimensionales Konstrukt erfasst. Die dritte Studie umfasst die aktive Manipulation der Aktivität des PFK durch transkutane Vagusnervstimulation (tVNS) bei Jugendlichen, um mögliche therapeutische Optionen zur Modulation der PFK-Aktivität aufzuzeigen. Dabei sollen vornehmlich drei Forschungsfragen durch diese Arbeit beantwortet werden: (1) Liegen bei Jugendlichen

mit regelmäßigem NSSV grundlegende Veränderungen (= im Ruhezustand messbare Unterschiede) in für erfolgreiche ER relevanten Hirnregionen nach dem Prozessmodell der ER vor (Studie 1)? (2) Liegt darüber hinaus eine aufgabenspezifische Reaktivität in der Verarbeitung emotionsauslösender Situationen (z.B. Stress) in Hirnregionen vor, die für die ER relevant sind (Studie 2)? (3) Kann die Aktivität dieser mit ER assoziierten Hirnregionen bei gesunden Jugendlichen moduliert werden und welche Auswirkungen könnte dies auf eine erfolgreiche ER haben (Studie 3)?

4 Studien

Die im Folgenden vorgestellten Studien sollen die aufgestellten Forschungsfragen beantworten. Die genannten Studien stammen aus drei Forschungsprojekten. Die erste Studie basiert auf Daten aus dem durch die Dietmar-Hopp-Stiftung finanzierten Forschungsprojekt „Ambulanz für Risikoverhaltensweisen und Selbstschädigung (AtR!Sk)“ (S-449/2013; Kaess, Ghinea, Fischer-Waldschmidt, & Resch, 2017) mit der Projekterweiterung „Neurobiogenetische Prädiktoren der Entwicklung und des Verlaufs Selbstschädigender und Riskanter Verhaltensweisen bei Jugendlichen“ (S-514/2015). Es hat das Ziel, neurobiologische Korrelate zu NSSV im Querschnitt und im Längsschnitt zu erfassen. Die zweite Studie „Neurobiologische Korrelate der Emotionserkennung unter Stress bei Jugendlichen mit Borderline-Persönlichkeitsstörung“ (S-449/2013) hat das Ziel, den Einfluss von akutem Stress auf die Emotionserkennung bei Jugendlichen mit NSSV im Vergleich zu einer gesunden Kontrollgruppe zu untersuchen. Beiden Studien ist gemein, dass sie NSSV unter Berücksichtigung von Symptomen der BPS auf einem Kontinuum erfassen und so Rückschlüsse auf die Dimensionalität zwischen NSSV und BPS zulassen. Zuletzt basiert die dritte Studie auf Daten aus dem Projekt „Transcutaneous Vagus-Nerve Stimulation for the Treatment of Adolescent Depression – An Experimental Proof of Concept [Transkutane Vagusnervstimulation zur Behandlung von Depression im Jugendalter – eine experimentelle Beweisführung]“ (S-365/2017). Das Projekt verfolgt das Ziel, den Einsatz von tVNS bei Jugendlichen zu untersuchen und Zusammenhänge von psychophysiologischen Variablen mit dem PFK herzustellen.

4.1 Studie I – Resting state prefrontal cortex oxygenation in adolescent non-suicidal self-injury – A near-infrared spectroscopy study

Koenig, J., Höper, S., van der Venne, P., Mürner-Lavanchy, I., Resch, F., & Kaess, M. (2021). Resting state prefrontal cortex oxygenation in adolescent non-suicidal self-injury – A near-infrared spectroscopy study. NeuroImage: Clinical, 31, 102704. doi:10.1016/j.nicl.2021.102704

Die meisten Studien untersuchen vorrangig BPS, selten NSSV als eigenständige Entität. Erfolgreiche ER wird meist mit dem PFK und damit einer erfolgreichen Inhibitionskontrolle emotionaler Prozesse in Verbindung gebracht (Fusar-Poli et al., 2009; Golkar et al., 2012; Kim, Cornwell, & Kim, 2012; Kober et al., 2008; Ochsner, Bunge, Gross, & Gabrieli, 2002). Die Ergebnisse bezüglich der Untersuchung des PFK sind gemischt. Während einige Studien zur BPS eine aufgabenspezifische stärkere

präfrontale Oxygenierung fanden (Groschwitz, Plener, Groen, Bonenberger, & Abler, 2016; Ruocco, Medaglia, Tinker, et al., 2010), fanden andere eine im Ruhezustand abweichende Konnektivitäten mit der Amygdala (Westlund Schreiner et al., 2017), eine niedrigere präfrontale Oxygenierung in Teilen des PFK bei einer *verbal fluency*[1] Aufgabe (Husain, Tang, et al., 2020; Husain, Yu, et al., 2020) oder einen reduzierten Anstieg in der Oxygenierung linker präfrontaler Areale bei der Betrachtung emotionaler Bilder (Ehlis, Schneider, Dresler, & Fallgatter, 2014; Ruocco, Medaglia, Ayaz, & Chute, 2010). Zur Abgrenzung von NSSV als eigenständige Entität und NSSV im Rahmen der BPS sowie der Frage nach grundlegenden aufgabenunabhängigen Veränderungen in der Funktionsweise des PFK ist eine Untersuchung des PFK im Ruhezustand von großer Bedeutung. Grundsätzliche Unterschiede in der präfrontalen Oxygenierung könnten zu einem besseren Verständnis der maladaptiven ER bei Jugendlichen mit NSSV beitragen.

Das Ziel dieser Studie war es zu untersuchen, ob sich die Aktivität im PFK bei Jugendlichen mit regelmäßigem NSSV im Ruhezustand von gesunden Jugendlichen unterscheidet. Befunde aus dem Erwachsenenbereich, insbesondere bei Personen mit BPS, deuten auf eine geringere Aktivität hin. Für den Rahmen dieser Dissertation legt diese Studie die Grundlage und soll die Frage beantworten, ob es bereits im Jugendalter signifikante Veränderungen in der Oxygenierung im PFK gibt, die unabhängig von aufgabenspezifischen Anforderungen existieren und somit auf strukturelle Veränderungen oder grundlegende Unterschiede in der Funktionalität des PFK hindeuten könnten.

Jugendliche zwischen 12 und 17 Jahren mit regelmäßigem NSSV (n = 170) und gematchte jugendliche Kontrollpersonen (n = 43) wurden in einem ersten Termin einem ausführlichen diagnostischen Interview unterzogen. Hier wurden bei den Jugendlichen mit NSSV die Häufigkeit selbstverletzenden Verhaltens, Suizidgedanken, -pläne und -versuche, die Anzahl erfüllter BPS-Kriterien, Achse-I-Störungen, das allgemeine Funktionsniveau und die Symptomschwere untersucht. In Selbstauskunftsfragebögen wurden bei allen Jugendlichen im Selbstbericht die depressive Symptomatik, gesundheitsbezogene Lebensqualität, negative Kindheitserlebnisse und die Symptomschwere erfasst. An einem zweiten Termin fand eine neurobiologische Testung statt. Während des Termins wurde die präfrontale Oxygenierung mittels fNIRS gemessen. Grundlage dieser Studie war die Bearbeitung einer fünfminütigen Vanilla-

[1] Die Personen in dieser Studie wurden gebeten innerhalb von jeweils 20 Sekunden so viele Wörter zu nennen, die entweder mit A, F oder S beginnen. Die Leistung dieser Aufgabe war die Anzahl unterschiedlicher genannter Wörter.

Baseline-Aufgabe. Hierbei saßen die Jugendlichen vor einem Computerbildschirm. Auf dem Bildschirm wurde mittig ein farbiges Rechteck präsentiert (rot, grün, gelb, blau, violett, weiß), welches alle paar Sekunden die Farbe wechselte. Die Jugendlichen wurden gebeten, die Auftretenshäufigkeit einer Farbe während der fünf Minuten zu zählen. Vanilla-Aufgaben sind so konzipiert, dass sie nur minimale kognitive Anforderungen stellen (Jennings, Kamarck, Stewart, Eddy, & Johnson, 1992). Gemessen wurden Veränderungen im O_2Hb und HbR, sowie im Gesamthämoglobin (HbT).

Zuerst wurden in gepaarten t-Tests Mittelwertsunterschiede zwischen den Gruppen im O_2Hb, HbR oder HbT im PFK untersucht. Gruppenunterschiede zeigten sich nur beim O_2Hb (t = -2.33; p = .021). Hier war das mittlere O_2Hb bei Jugendlichen mit NSSV niedriger als bei den jugendlichen Kontrollen. Für HbR und HbT zeigten sich auch nach Berücksichtigung von Alter und Intelligenz als mögliche Kovariaten keine Gruppenunterschiede. In einem zweiten Schritt wurde anhand von Korrelationen untersucht, inwieweit die Symptomatik aus den Selbstauskunftsfragebögen und die Anzahl erfüllter BPS-Kriterien mit dem mittleren O_2Hb während der Vanilla-Baseline-Aufgabe zusammenhängt. Hier zeigte sich eine positive Korrelation mit der gesundheitsbezogenen Lebensqualität, sodass eine höhere Oxygenierung mit einer höheren selbstberichteten gesundheitsbezogenen Lebensqualität einherging ($r_{(162)}$ = 0.154; p = .049). Des Weiteren ergab sich eine negative Korrelation mit negativen Kindheitserlebnissen ($r_{(187)}$ = -0.155; p = .034). Weniger negative Kindheitserlebnisse hingen mit einer stärkeren Oxygenierung im PFK zusammen. Für die weiteren Variablen aus den Selbstauskunftsfragebögen und für die Anzahl erfüllter BPS-Kriterien ergab sich kein signifikanter Zusammenhang mit der Oxygenierung im PFK. Für die Untersuchung, welche Regionen des PFK in ihrer Aktivität zusammenhingen, wurden Konnektivitätsanalysen über die Kanäle des fNIRS durchgeführt. Da HbR und HbT keine signifikanten Gruppenunterschiede in der ersten Analyse aufwiesen, wurde die Konnektivität lediglich für das O_2Hb bestimmt. Zur Berechnung der Konnektivität wurden Kreuzkorrelationen zwischen den Kanälen für beide Gruppen berechnet und miteinander verglichen. Dabei zeigten sich keine signifikanten Unterschiede in der Konnektivität zwischen den Gruppen. Allerdings wiesen fast alle Kanäle signifikante Konnektivitätswerte bei der Betrachtung innerhalb der Gruppen auf. Beide Gruppen zeigten insbesondere bei den Kanälen eine hohe Konnektivität, die die orbitofrontalen Gebiete des PFK abdecken. In einem letzten Schritt wurden die Zusammenhänge zwischen der Konnektivität und der Ausprägung klinischer Symptomatik untersucht. Hierbei war eine stärkere Konnektivität einiger Kanäle mit mehr BPS-Kriterien, mehr depressiven Symptomen, einer höheren generellen psychologischen Belastung, mehr

negativen Kindheitserlebnissen und schlechterer gesundheitsbezogener Lebensqualität assoziiert.

Das Ziel dieser Studie war es zu untersuchen, inwieweit grundsätzliche Unterschiede in der Oxygenierung im PFK während einer Ruhemessung auftreten beim Vergleich einer großen Gruppe Jugendlicher mit regelmäßigem NSSV mit einer Gruppe Jugendlicher, die sich noch nie selbst verletzt haben. Die bisherige Studienlage hierzu ist limitiert. Einige Studien fanden eine erhöhte aufgabenspezifische Oxygenierung im PFK (Dudas et al., 2017; Malejko et al., 2019; Vega et al., 2017), während meta-analytische Befunde, sowie eine Studie mit jüngeren Erwachsenen eine geringere Oxygenierung im PFK während Interferenzaufgaben berichten (Dahlgren et al., 2018; Schulze et al., 2016). Die Befunde dieser Studie gliedern sich hier ein und könnten darauf hindeuten, dass eine Unteraktivierung im PFK bei Jugendlichen mit NSSV eine Art Entwicklungseffekt illustriert, bei dem eine Unteraktivierung im Jugendalter im Laufe der Entwicklung und Länge beziehungsweise Chronifizierung von Krankheitsverläufen zu einer kompensatorischen Überaktivierung im Erwachsenenalter führen. Es ist anzumerken, dass bei den vorherigen Studien im Vergleich zur vorliegenden deutliche Unterschiede in den Stichproben aufweisen, in Bezug auf Stichprobengröße (kleinere Stichproben in vorherigen Studien) und der untersuchten Personengruppe (Fokus in vorherigen Studien eher auf BPS als auf NSSV).

Vor dem Hintergrund, dass die präfrontale Oxygenierung bei Jugendlichen mit NSSV gemessen mit fNIRS geringer ist als bei jugendlichen Kontrollen, erscheint es sinnvoll, auch Befunde zu strukturellen Veränderungen im präfrontalen Kortex bei Menschen mit NSSV und/oder BPS zu betrachten. Strukturelle Veränderungen könnten die in dieser Studie gefundene geringere präfrontale Oxygenierung im Ruhezustand bei Jugendlichen mit NSSV erklären. Bisherige Befunde berichten von Verlusten der grauen Substanz bilateral im dorsolateralen PFK und dem Orbitofrontalkortex (Brunner et al., 2010; Chanen et al., 2008). Des Weiteren wurden in einer meta-analytischen Untersuchung Verluste der grauen Substanz im rechten inferioren frontalen Gyrus bei Personen mit BPS gefunden, die mit steigendem Alter stärker ausgeprägt waren (Schulze et al., 2016). Bei Jugendlichen mit NSSV wurden Verkleinerungen in der Insula und dem anterioren cingulären Kortex gefunden, nicht jedoch im Volumen des PFK (Ando et al., 2018). Bei Untersuchungen tieferliegender Strukturen wurden unter anderem ein geringeres Volumen der Hypophyse und eine geringere Aktivierung des limbischen Systems bei jugendlichen und erwachsenen Personen mit BPS im Vergleich zu Kontrollpersonen gefunden (Chanen & Kaess, 2012; Dudas et al., 2017; Groschwitz & Plener, 2012; Jovev et al., 2012; Ruocco et al., 2013; Whittle et al., 2009). In dieser Studie lässt sich aufgrund

der Messmethode nicht sagen, warum bei Jugendlichen mit NSSV im Ruhezustand eine geringere Aktivierung des PFK gegenüber jugendlichen Kontrollpersonen festzustellen ist. Strukturelle Veränderungen der grauen Substanz könnten ein Auslöser sein, sowohl für eine niedrigere präfrontale Aktivierung im Ruhezustand als auch für eine erhöhte Aktivierung bei der Bearbeitung aufgabenspezifischer Anforderungen im Sinne einer Überkompensation von strukturellen Defiziten. Dementsprechend sollte der Zusammenhang funktioneller und struktureller Veränderungen im PFK im Ruhezustand und bei Aufgaben, die den PFK involvieren, in nachfolgenden Studien Berücksichtigung finden.

Zusammengenommen erweitert diese Studie den Wissensstand zu adoleszenter Selbstverletzung und ist die erste, die eine verringerte präfrontale Oxygenierung im Ruhezustand in einer großen Stichprobe von Jugendlichen mit NSSV zeigen konnte. Dieser Befund bietet eine Basis, um darauf aufbauend in der zweiten Studie aufgabenspezifische Veränderungen in der präfrontalen Oxygenierung zu untersuchen.

4.2 Studie II – Prefrontal cortex oxygenation under stress in adolescent non-suicidal self-injury and borderline personality disorder – A functional near-infrared spectroscopy study

Höper, S., Kröller, F., Heinze, A.-L., Bardtke, K. F., Kaess, M., & Koenig, J. (submitted). Prefrontal Cortex Oxygenation under Stress in Adolescent Non-Suicidal Self-Injury and Borderline Personality Disorder – A Functional Near-Infrared Spectroscopy Study. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging.*

Jugendliche mit regelmäßigem NSSV berichten häufig, dieses Verhalten zur ER einzusetzen (Zetterqvist et al., 2013). Dabei stehen vor allem intrapersonale Faktoren zur eigenen ER im Vordergrund und beinhalten das Beenden unerwünschter und das Herbeiführen gewünschter emotionaler Zustände (Taylor et al., 2018). Erwachsene Personen mit BPS berichten, dass sie stärker unter Stress und ihrer emotionalen Reaktion auf alltägliche Stressoren leiden als gesunde Kontrollpersonen, aber auch stärker als Personen mit psychotischen Störungen (Glaser, Os, Mengelers, & Myin-Germeys, 2008). Personen mit BPS berichten mehr negative Emotionen nach Stressexpositionen im Vergleich zu gesunden Kontrollpersonen, aber auch im Vergleich zu Personen mit anderen Persönlichkeitsstörungen (Deckers et al., 2015). Im Vergleich zu Kontrollpersonen lassen sich bei Personen mit BPS weniger physiologische

Reaktionen auf Stress finden (Deckers et al., 2015), wie eine herabgesetzte Stressreaktion im Speichelkortisol und eine verringerte Herzrate (Aleknaviciute et al., 2016). Das Einschneiden der Haut führt bei Personen mit BPS zu einer Verringerung der Amygdala-Aktivität (Reitz et al., 2015). Zur Stressreaktivität bei BPS im Jugendalter existieren bislang wenige Untersuchungen. Eine Studie zeigte, dass bei Jugendlichen mit BPS die Herzrate während eines psychosozialen Stressors herabgesetzt ist (Kaess, Parzer, Koenig, Resch, & Brunner, 2016). Bislang gibt es keine (mir bekannten) Studien, die auf neuronaler Ebene die Stressreaktion bei Personen mit NSSV untersucht haben, auch wenn Befunde darauf hindeuten, dass Betroffene auf physiologischer Ebene ähnliche Reaktionsmuster zeigen wie Personen mit BPS. So zeigen Personen mit NSSV ebenfalls eine erniedrigte Kortisolantwort auf einen akuten Stressor (Kaess et al., 2012; Klimes-Dougan et al., 2019). Da sowohl Personen mit BPS als auch mit NSSV von Schwierigkeiten im Umgang mit Stress berichten, soll in dieser Studie die präfrontale Oxygenierung des PFK bei Personen mit NSSV über das Spektrum der BPS-Symptomatik hinweg bei Stress untersucht werden.

Das Ziel dieser Studie war die Erweiterung der Befunde aus Studie I. Während Studie I die präfrontale Oxygenierung während einer Ruheaufgabe untersuchte, wurde in dieser Studie die präfrontale Oxygenierung während einer psychosozialen Stressaufgabe gemessen und zwischen Jugendlichen mit regelmäßigem NSSV und einer gesunden Kontrollgruppe verglichen. Dazu wurde angenommen, dass Jugendliche mit NSSV im Vergleich zur Kontrollgruppe eine erhöhte präfrontale Oxygenierung während der Stressaufgabe aufweisen, um die in Studie I gefundene herabgesetzte Oxygenierung während der Ruhemessung zu kompensieren. Weiterhin wurde angenommen, dass diese Erhöhung im O_2Hb mit der Stärke der BPS-Symptomatik zusammenhängt.

In die Studie wurden weibliche Jugendliche zwischen 13 und 17 Jahren aufgenommen. Patientinnen mit regelmäßigem NSSV (NSSV an mindestens fünf verschiedenen Tagen während der letzten zwölf Monate) wurden in der Spezialambulanz für Risikoverhaltensweisen und Selbstschädigung (AtR!Sk) rekrutiert (n = 30). Gesunde weibliche Jugendliche für die Kontrollgruppe wurden über Werbung rekrutiert und nach Alter gematcht (n = 29). An einem ersten Termin fand ein ausführliches diagnostisches Interview statt, bei dem Suizidalität und NSSV sowie Achse-I- & Achse-II-Störungen erhoben wurden. In zusätzlichen Selbstauskunftsfragebögen wurden BPS-Symptomatik, traumatische Kindheitserfahrungen und BPS-Symptomschwere erfasst. Während eines zweiten Termins bearbeiteten alle Teilnehmerinnen dieselbe Vanilla-Baseline-Aufgabe wie in Studie I beschrieben. Im Anschluss daran wurde eine für Jugendliche modifizierte Version des Trier Social Stress Test (TSST) durchgeführt (Kirschbaum, Pirke, &

Hellhammer, 1993). Der TSST wurde in drei Blöcke geteilt. In Block eins wurden die Teilnehmerinnen gebeten, sich auf ein Bewerbungsgespräch bei ihrer Traumschule vorzubereiten. Im zweiten Block sollten sich die Teilnehmerinnen fünf Minuten lang vor einer zweiköpfigen Jury in einem freien Vortrag selbst präsentieren, warum sie die perfekte Kandidatin für die Traumschule wären. Im dritten und letzten Teil des TSST wurden sie gebeten, im Kopf zu subtrahieren. Bei einem Fehler mussten sie neu starten. Vor und nach dem TSST wurden die Teilnehmerinnen zusätzlich nach ihrem Dissoziationserleben sowie positivem und negativem Affekt befragt. Während des gesamten Termins wurden Veränderungen in der präfrontalen Oxygenierung mittels fNIRS gemessen. Für die Auswertung wurden die durchschnittlichen Veränderungen des O_2Hb im PFK für jeden einzelnen Zeitblock je fNIRS-Kanal (CDT, Vorbereitung TSST, freier Vortrag TSST, arithmetische Aufgabe TSST) in linearen gemischten Modellen berechnet. Außerdem wurde die BPS Dimensionalität (im Selbstbericht und anhand klinischer Interviews) in die linearen gemischten Modelle mit aufgenommen und mithilfe von Marginsplots dargestellt.

Die beiden in der Studie untersuchten Gruppen unterschieden sich nicht in Alter oder Schulbildung. Lediglich der Body Mass Index war in der NSSV-Gruppe höher als in der Kontrollgruppe. Der Wert lag jedoch weiter im Normalbereich. Die Gruppe der Jugendlichen mit NSSV berichtete in allen klinischen Variablen eine signifikant größere Symptomausprägung als die Jugendlichen der Kontrollgruppe. Ähnlich wie in Studie I war das O_2Hb während des CDT in der Gruppe der Jugendlichen mit NSSV erniedrigt im Vergleich zu den Jugendlichen aus der Kontrollgruppe, war jedoch nicht statistisch signifikant (t = -1.839; p = .071). In linearen gemischten Modellen mit O_2Hb als abhängiger Variable zeigte sich ein Haupteffekt über die Zeit (CDT, Vorbereitung TSST, freier Vortrag TSST, arithmetische Aufgabe TSST; $\chi^2(3) = 9.34$; p = .025), kein Haupteffekt für die Gruppenzugehörigkeit ($\chi^2(1) = 0.43$; p = .512), und eine signifikante Zeit-Gruppen-Interaktion ($\chi^2(3) = 14.33$; p = .003). Beim Betrachten aufeinanderfolgender Kontraste der Zeitblöcke wurde deutlich, dass die Oxygenierung im PFK in der Kontrollgruppe nach dem CDT und mit Beginn der Stressaufgabe absank, während sie in der Gruppe der Jugendlichen mit NSSV anstieg ($\chi^2(1) = 8.30$; p = .004). Danach blieb das mittlere O_2Hb in beiden Gruppen auf dem gleichen erniedrigten – beziehungsweise erhöhten – Niveau und veränderte sich im Verlauf der Stressaufgabe kaum. Die Schwere der BPS-Symptomatik konnte als signifikanter Prädiktor für Veränderungen im O_2Hb über die Zeit mit aufgenommen werden (Selbstbericht: $\chi^2(3) = 14.03$; p = .003; Interview: $\chi^2(3) = 17.25$; p = .001). Eine stärker ausgeprägte BPS-Symptomatik war mit einer geringeren Oxygenierung im PFK während der Baseline-Aufgabe und einer stärkeren Oxygenierung im PFK während der Stressaufgabe

assoziiert. Die Hinzunahme von selbstberichtetem Dissoziationserleben, Stress, positivem und negativem Affekt verbesserte den Model-fit nicht. Exploratorische Konnektivitätsanalysen zeigten eine signifikante Konnektivität zwischen Kanälen, die den linken PFK abdecken, wenn die Schwere der BPS-Symptomatik als Prädiktor mit aufgenommen wurde.

Diese Studie betont und erweitert Studie I. Während in Studie I gezeigt werden konnte, dass es grundsätzliche Unterschiede in der Oxygenierung im PFK im Ruhezustand zwischen Jugendlichen mit regelmäßigem NSSV und Jugendlichen ohne NSSV gibt, beleuchtet diese Studie Veränderungen im O_2Hb während einer psychosozialen Stressaufgabe. Es fällt auf, dass weibliche Jugendliche mit NSSV im Vergleich zu Jugendlichen der Kontrollgruppe eine gegensätzliche Reaktion auf Stress im präfrontalen O_2Hb zeigen. Bei ihnen steigt das mittlere O_2Hb leicht an, während es in der Kontrollgruppe deutlich absinkt. Es kann an dieser Stelle nur spekuliert werden, dass strukturelle Unterschiede (z.B. geringere graue Substanz in Bereichen des PFK) die geringere Oxygenierung während der Ruhemessung auslösen. Geringere graue Substanz war bei älteren Personen mit einem reduzierten Blutfluss während einer Ruhemessung assoziiert (Vaidya, Paradiso, Boles Ponto, McCormick, & Robinson, 2007). Bei Personen mit NSSV und BPS konnten Verluste in der grauen Substanz im PFK und verringerte Aktivität im PFK gefunden werden (Brunner et al., 2010; Chanen et al., 2008; Schulze et al., 2016). Darüber hinaus waren bei älteren Personen bei Aufgaben, die die Integration mehrerer Informationen beinhalteten im Vergleich zu einfachen Aufgaben, Verluste in der grauen Substanz im PFK mit einem stärkeren Anstieg der präfrontalen Aktivität assoziiert (Wagshul, Lucas, Ye, Izzetoglu, & Holtzer, 2019). In Läsionsstudien wurden zudem geschlechtsabhängige Veränderungen in der Stressantwort bei Personen mit Läsionen im PFK gefunden (Buchanan et al., 2010). Auf diese Weise könnte eine reduzierte PFK-Aktivität während einer Ruhemessung und eine Überkompensation während Anforderungen (in diesem Falle bei Stressregulation) mit strukturellen Defiziten bei Jugendlichen mit NSSV zusammenhängen und so eine adäquate Adaption auf Stress zu erzielen. Es sollte jedoch beachtet werden, dass diese Studie keine strukturellen Unterschiede im PFK gemessen hat und diese Argumentation daher einen hypothetischen Charakter hat.

Die Gruppe der sich selbst verletzenden Jugendlichen in dieser Studie bildet ein breites Spektrum der BPS-Dimensionalität ab. Nur ein kleiner Teil (n = 7) erfüllte das Vollbild der BPS. Im Schnitt wurden zwischen drei und vier Kriterien nach DSM-5 erfüllt. Damit ist die hier untersuchte Stichprobe deutlich belastet. Zusätzlich zu der Einschätzung durch einen Interviewer mithilfe des SKID-II wurde die BPS-Symptomatik dimensional

anhand von Selbstauskunftsfragebögen ermittelt. Bei der Betrachtung der Veränderung im O_2Hb zwischen der Baseline-Aufgabe und den einzelnen Aufgaben des TSST zeigte sich, dass eine stärkere BPS-Symptomatik mit einem stärkeren Anstieg im O_2Hb über die Stressaufgabe hinweg zusammenhing. Bei Erwachsenen mit BPS waren Verluste in der grauen Substanz des PFK mit mehr selbstberichteten BPS-Symptomen assoziiert (Nenadić, Voss, Besteher, Langbein, & Gaser, 2020). Die Ergebnisse deuten darauf hin, dass mit BPS assoziierte neuronale Veränderungen bereits im Jugendalter bei Jugendlichen mit NSSV gefunden werden können. Inwiefern die Aktivität im PFK mit weiteren psychophysiologischen Variablen zusammenhängt und ob diese moduliert werden können, untersucht Studie III.

4.3 Studie III – Prefrontal cortex oxygenation and autonomic nervous system activity under transcutaneous auricular vagus nerve stimulation in adolescents

Höper, S., Kaess, M., & Koenig, J. (2022). Prefrontal cortex oxygenation and autonomic nervous system activity under transcutaneous auricular vagus nerve stimulation in adolescents. Autonomic Neuroscience, 241, 103008. doi:10.1016/j.autneu.2022.103008

Während die ersten beiden Studien sich mit grundlegenden Veränderungen in der Aktivierung des PFK im Ruhezustand und mit reaktiven Veränderungen in der Oxygenierung des PFK bei akutem Stress beschäftigen, liegt der Fokus der dritten Studie auf der Modulation der Oxygenierung des PFK bei gesunden Jugendlichen. Hintergrund sind die Annahmen des Neuroviszeralen Integrationsmodells (NIM; Thayer & Lane, 2000). Das NIM erklärt das Zusammenspiel viszeraler und neuronaler Strukturen. Es geht von einem neuronalen Netzwerk aus, das zielbezogene Handlungsweisen, Anpassungsfähigkeit und Gesundheit steuert. Das NIM betont die Integration peripherer, körperbezogener Informationen aus dem autonomen Nervensystem ins zentralautonome Nervensystem (Thayer, Hansen, Saus-Rose, & Johnsen, 2009). Das vom Modell postulierte neuronale Netzwerk basiert auf bidirektionalen Feedbackschleifen, die Informationen vom Körper integrieren, prozessieren und regulieren. An der Schnittstelle zwischen zentralem Nervensystem und autonomem Nervensystem spielt der Vagusnerv eine zentrale Rolle. Er besteht aus einer Vielzahl unterschiedlicher Nervenfasern, welche afferente und efferente Informationen transportieren (Berthoud & Neuhuber, 2000; Yuan & Silberstein, 2016). Afferente Nervenfasern transportieren Informationen vom Körper zum Gehirn, während efferente

Nervenfasern Informationen vom Gehirn an den Körper transportieren. Die Abzweigungen des Vagusnervs innervieren Organe und Drüsen im Körper (Berthoud & Neuhuber, 2000; Yuan & Silberstein, 2016). Schätzungsweise 80 % seiner Äste sind afferent (Bonaz, Bazin, & Pellissier, 2018; Yuan & Silberstein, 2016). Auf diese Weise versorgt der Vagusnerv höhere Hirnstrukturen, wie den PFK, mit Informationen aus dem Körper, sodass diese integriert und verarbeitet werden können und top-down Regulationsprozesse angeregt werden. Mithilfe tieferliegender Strukturen, wie der Amygdala, werden inhibitorische Signale über das autonome Nervensystem koordiniert (Thayer & Lane, 2009). Die Veränderbarkeit der Zeit zwischen zwei Herzschlägen, Herzratenvariabilität (HRV) genannt, wird durch den Vagusnerv inhibitorisch beeinflusst und stellt einen Indikator für eine erfolgreiche Integration zentral-peripherer neuraler Feedbackschleifen dar (Laborde, Mosley, & Thayer, 2017; Malik et al., 1996; Thayer et al., 2009). Die HRV kann dabei als transdiagnostischer Biomarker für Psychopathologie verstanden werden (Beauchaine & Thayer, 2015). Meta-analytische Befunde unterstreichen die enge Verbindung von HRV und neuronaler Aktivität. Sie legen nahe, dass die HRV ein Indikator für die erfolgreiche Integration von Informationen in der neuronalen Schleife zwischen dem ventromedialen PFK und dem Hirnstamm sowie deren Austausch mit peripheren physiologischen Prozessen darstellt (Thayer, Åhs, Fredrikson, Sollers, & Wager, 2012). Dies unterstützt die Annahme des NIM, dass Informationsverarbeitung aus der Peripherie mithilfe neuronaler Schleifen verläuft. Die Aktivität des Vagusnervs kann durch Stimulation bestimmter Teile der Ohrmuschel moduliert werden, da Äste des Vagusnervs Teile der Ohrmuschel innervieren. Die Stimulation erfolgt transkutan – über die Haut. tVNS löst, im Gegensatz zu Sham-Stimulation als Kontroll-Stimulation, an Körperstellen, die nicht vom Vagusnerv innerviert werden, Aktivierung im Sinne des NIM in präfrontalen Hirnregionen, dem limbischen System und dem Hirnstamm aus (Badran et al., 2018; Frangos, Ellrich, & Komisaruk, 2015; Kraus et al., 2007; Yakunina, Kim, & Nam, 2017). Aufgrund der Tatsache, dass die HRV durch den Vagusnerv beeinflusst wird, liegt die Annahme nahe, dass die HRV auch mittels tVNS verändert werden kann. Studien, die die präfrontale Aktivierung sowie Maße des autonomen Nervensystems während aktiver Stimulation des Vagusnervs untersuchen, sind selten. Condy und Kollegen haben während einer Inhibitionsaufgabe anstelle von tVNS die Aktivität des PFK und die HRV mithilfe von fNIRS untersucht und so versucht, die vom NIM postulierten Feedbackschleifen darzustellen (Condy, Friedman, & Gandjbakhche, 2020).

Das Ziel dieser Studie war es, die Annahmen des NIM im Jugendalter zu prüfen und Veränderungen parasympathischer (HRV) und sympathischer Variablen (Hautleitfähigkeit (EDA), Alpha-Amylase (sAA)) und solchen gemischten Ursprungs

(Herzrate (HR)) während tVNS und Sham-Stimulation zu untersuchen. Außerdem sollte untersucht werden, inwiefern sich die Aktivierung im PFK durch tVNS verändert und ob dies mit den Veränderungen der physiologischen Variablen zusammenhängt.

In die Studie wurden n = 30 Jugendliche ohne aktuelle affektive Störung mit Spannungskopfschmerzen im Alter von 14 - 17 Jahren eingeschlossen. Die Studie bestand aus zwei Terminen. Beim ersten Termin fand ein diagnostisches Interview statt, in dem Daten zu Demographie, Achse-I-Störungen, Persönlichkeitsstörungen, Suizidalität und NSSV, negativen Kindheitserlebnissen sowie ER erhoben wurden. Beim zweiten Termin bearbeiteten die Jugendlichen in einem *within-subject cross-randomized Design* eine Vanilla-Baseline-Aufgabe, gefolgt von einer 15-minütigen Phase mit aurikularer tVNS oder Sham-Stimulation (aufgeteilt in drei Zeitblöcke á fünf Minuten), sodass alle Teilnehmenden zwei Mal die Baseline-Aufgabe bearbeiteten und jeweils eine tVNS-Stimulation und eine Sham-Stimulation erhielten. Während der gesamten Zeit wurde die Veränderung der Oxygenierung im PFK mithilfe von fNIRS gemessen. Des Weiteren wurden für denselben Zeitraum HR, HRV, sAA und EDA erhoben. Für die Auswertung wurden gemischte lineare Modelle berechnet für Veränderungen in HR, HRV, sAA, EDA und O_2Hb mit der Zeit (Baseline vs. 5 Minuten vs. 10 Minuten vs. 15 Minuten) und Stimulationsart (tVNS vs. Sham-Stimulation) als *fixed effects* und der ID der Teilnehmenden als *random effect*. Bei signifikantem Modell fit wurden zusätzlich geplante Kontraste berechnet, um den Zusammenhang von der Stimulationsart über die Zeit zu untersuchen. Zur Auswertung des Zusammenwirkens präfrontaler Aktivität mit physiologischen Variablen wurden gemischte lineare Modelle mit O_2Hb als zusätzlichem Prädiktor berechnet. In exploratorischen Analysen wurde die Konnektivität betrachtet.

Die gemischten linearen Modelle für die HR und die HRV waren beide signifikant mit signifikanten Haupteffekten für Zeit (Baseline vs. 5 Minuten vs. 10 Minuten vs. 15 Minuten) und die Stimulationsart (tVNS vs. Sham) (**HR**: *Wald* $\chi^2(7) = 55.91$; $p < .0001$; ZEIT: $\chi^2(3) = 24.94$; $p < .0001$; STIMULATION $\chi^2(1) = 28.84$; $p < .0001$; ZEIT x STIMULATION: $\chi^2(3) = 2.13$; $p = .547$; **HRV**: *Wald* $\chi^2(7) = 51.90$; $p < .001$; ZEIT: $\chi^2(3) = 14.11$; $p = .003$; STIMULATION $\chi^2(1) = 34.96$; $p < .0001$). Außerdem waren die geplanten Kontraste bei HR und bei HRV zwischen den Stimulationsarten signifikant für alle Zeitblöcke außer dem letzten (15 Minuten Prästimulation) (**HR**: base: $\chi^2 = 9.46$; $p = .002$; ES: -.29; 5 min: $\chi^2 = 12.33$; $p < .001$; ES: -.37; 10 min: $\chi^2 = 6.77$; $p = .009$; ES: -.28; 15 min: $\chi^2 = 2.41$; $p = .121$; ES: -.27; **HRV**: base: $\chi^2 = 13.85$; $p < .001$; ES: .45; 5 min: $\chi^2 = 14.77$; $p < .001$; ES: .44; 10 min: $\chi^2 = 5.49$; $p = .019$; ES: .27; 15 min: $\chi^2 = 3.68$; $p = .055$). Trotz des *within-subject cross-randomized Designs* unterschieden sich HR und HRV zum Zeitpunkt der Baseline-Aufgabe zwischen den Stimulationsarten. Deswegen

wurden die Analysen unter Herausrechnen der Baseline-Aufgabe wiederholt. Die vorherigen Unterschiede zwischen den Stimulationsarten wurden dabei bestätigt und der Kontrast für den letzten Zeitblock (15 Minuten) wurde für die HRV signifikant. Die Modelle für sAA und EDA waren nicht signifikant (**EDA**: *Wald* $\chi^2(7) = 9.97$; $p = .190$; sAA: *Wald* $\chi^2(3) = 3.56$; $p = .313$). Das Modell für Veränderungen in der globalen Oxygenierung im PFK wurde signifikant. Es zeigte sich ein Haupteffekt für die Stimulationsart, aber nicht für die Zeit (*Wald* $\chi^2(7) = 17.99$; $p = .012$; ZEIT: $\chi^2(3) = 4.71$, $p = .195$; STIMULATION ($\chi^2(1) = 9.76$, $p = .002$; ZEIT x STIMULATION: $\chi^2(3) = 3.52$; $p = .318$). Kontrastanalysen ergaben, dass die Kontraste der Stimulationsart über die Zeitblöcke nur bei 10 und 15 Minuten signifikant wurden (base: $\chi^2 = 0.00$; $p = .964$; ES: .01; 5 min: $\chi^2 = 2.34$; $p = .126$; ES: .38; 10 min: $\chi^2 = 5.06$; $p = .025$; ES: .53; 15 min: $\chi^2 = 5.88$; $p = .015$; ES: .57). Die Hinzunahme der Veränderungen in den einzelnen fNIRS-Kanälen als *region of interest* (ROI) bestätigt die Ergebnisse und die größer werdenden Unterschiede zwischen den Stimulationsarten über die Dauer der Prästimulation. Darüber hinaus war O_2Hb ein signifikanter Prädiktor für die Veränderungen in der HR und der HRV. Eine stärkere Zunahme von O_2Hb unter tVNS über die Zeit war assoziiert mit einer Abnahme der HR und einer Zunahme der HRV. Für Veränderungen in der EDA war O_2Hb kein signifikanter Prädiktor. Zuletzt zeigten explorative Analysen der Konnektivität über die fNIRS-Kanäle über den PFK hinweg, dass die Konnektivität zwischen einzelnen Kanälen signifikant unterschiedlich zwischen den Stimulationsarten war.

Die Ergebnisse deuten darauf hin, dass tVNS vorrangig auf den Parasympathikus wirkt. Veränderungen zeigten sich nur bei Variablen mit parasympathischem Ursprung (HRV) oder gemischten Ursprungs (HR), aber nicht bei Variablen sympathischen Ursprungs wie EDA und sAA. In früheren Untersuchungen wurde die Veränderung der HRV während tVNS als Wechsel von einer überwiegend sympathischen Erregung hin zu einer überwiegend parasympathischen Erregung interpretiert (Ylikoski et al., 2017). Unsere Befunde unterstützen diese Interpretation und deuten auf eine Aktivierung parasympathischer Äste des autonomen Nervensystems, während keine Effekte für sympathische Veränderungen durch tVNS gefunden werden konnten. Die durch tVNS hervorgerufenen Veränderungen bei kardiovaskulären Variablen, HR und HRV, sind vor allem zu Beginn der Stimulation zu beobachten und werden über die Zeit geringer. Die Reaktion erfolgt ohne Zeitverzögerung, ist aber von kurzer Dauer. Dem gegenüber steht die Aktivierung des PFK. Diese nimmt über die Zeit zu. Die Ergebnisse der Konnektivitätsanalysen deuten darauf hin, dass diese Zunahme in der Aktivierung des PFK an einigen Stellen stärker ist als an anderen. Weitere Studien fanden eine Aktivierung tieferliegender Hirnstrukturen durch tVNS, wie dem cingulären Kortex, Amygdala oder Nucleus accumbens (Fang et al., 2016; Frangos et al., 2015; Kosel,

Brockmann, Frick, Zobel, & Schlaepfer, 2011; Kraus et al., 2013; Tu et al., 2018; Wang et al., 2018). Zusammengenommen unterstützen diese und unsere Befunde die Annahme des NIM von Vagus-innervierten Feedbackschleifen zur Regulation parasympathischer Prozesse. Dies wird auch durch die Ergebnisse gestützt, dass eine höhere Aktivierung des PFK während tVNS zu einer stärkeren Abnahme der HR und einer größeren Zunahme der HRV führte. Diese Studie zeigt deutlich, dass durch tVNS auch bei Jugendlichen Veränderungen in der Oxygenierung des PFK hervorgerufen werden und der Parasympathikus aktiviert wird. Im Erwachsenenalter wird der Effekt von tVNS auf das ANS bereits bei Menschen mit depressiven Erkrankungen oder Tinnitus therapeutisch genutzt. Die hier bei psychisch gesunden Jugendlichen gefundenen Effekte deuten auf parasympathisch innervierte Variablen des ANS hin. Präfrontale Veränderungen könnten auf bottom-up und top-down Prozesse hinweisen, die auch bei der Emotionsverarbeitung eine Rolle spielen. Diesen Zusammenhang kann die derzeitige Studie nicht aufzeigen, sondern sollte in nachfolgenden Studien untersucht werden. Dies könnte therapeutische Implikationen von tVNS zur ER aufzeigen.

5 Übergreifende Diskussion

Das Ziel dieser Arbeit war es, eingangs beschriebene Forschungslücken zu schließen und den aktuellen Forschungsstand zur Untersuchung präfrontaler Aktivität bei Jugendlichen mit NSSV über das Spektrum der BPS-Symptomatik zu erweitern. Dabei standen drei Forschungsfragen im Fokus:

(1) Liegen bei Jugendlichen mit regelmäßigem NSSV grundlegende Veränderungen in für erfolgreiche ER relevanten Hirnregionen nach dem Prozessmodell der ER vor?
(2) Liegen darüber hinaus aufgabenspezifische Veränderungen in der Verarbeitung emotionsauslösender Situationen (z.B. Stress) in Hirnregionen vor, die für die ER relevant sind?
(3) Kann die Aktivität dieser mit ER assoziierten Hirnregionen bei gesunden Jugendlichen modifiziert werden und welche Auswirkungen könnte dies auf eine erfolgreiche ER haben?

Die erste Forschungsfrage kann anhand der Studien I und II beantwortet werden. Während die Ergebnisse in Studie II deskriptiv eine Verringerung der PFK-Aktivität in Ruhe bei Jugendlichen mit NSSV zeigten, fand sich in Studie I eine signifikant verringerte präfrontale Aktivität im Ruhezustand im Vergleich zur Kontrollgruppe. Studie I untersuchte zudem den Zusammenhang verringerter PFK-Aktivität mit weiteren klinischen Variablen. Die Effektgröße zwischen den gefundenen Zusammenhängen von verringerter PFK-Aktivität mit mehr negativen Kindheitserlebnissen und einer geringeren gesundheitsbezogenen Lebensqualität waren klein. Zusätzlich werden diese Effekte durch die fehlende Korrektur für multiples Testen limitiert. Während eine vermehrte Anzahl an negativen Kindheitserfahrungen mit der späteren Entwicklung einer BPS in Zusammenhang gebracht wird (Carvalho Fernando et al., 2014), deutet die niedrigere gesundheitsbezogene Lebensqualität auf einen allgemeinen Psychopathologie-Faktor hin. Durch eine veränderte statistische Analyse in Studie II (siehe Kapitel 4.2) konnte eine geringere präfrontale Oxygenierung im Ruhezustand mit einer stärker ausgeprägten BPS-Symptomatik im Selbst- und Fremdurteil in Zusammenhang gebracht werden. Es bleibt an dieser Stelle unklar, ob eine stärkere Verringerung im O_2Hb im Ruhezustand einem allgemeinen Psychopathologie-Faktor zugeschrieben werden kann oder mit einer stärker ausgeprägten BPS-Symptomatik zusammenhängt. Aus den Daten lässt sich nicht beantworten, ob es sich bei diesen Unterschieden in der PFK-Aktivität während Ruhemessung um eine genetische Disposition im Sinne eines Vulnerabilitätsfaktors handelt oder diese Unterschiede Resultat der Nutzung von NSSV als ER sind. Längsschnittliche Untersuchungen und genetische Untersuchungen

könnten hier Hinweise liefern. Beispielsweise untersucht das Projekt STAR Neuro eine Stichprobe von Jugendlichen mit NSSV und berücksichtigt hierbei auch genetische Analysen (Ergebnisse noch ausstehend; „Star-Projekt“, o. J.). In Bezug auf das Prozessmodell zur ER nach Gross (1998, 2002, 2015) bedeutet die Beantwortung der ersten Forschungsfrage, dass bei Jugendlichen mit NSSV grundlegende neuronale Unterschiede vorliegen, die zu veränderten Voraussetzungen beim Eintritt in das Prozessmodell nach Gross (1998, 2002, 2015) führen, was zu einem allgemein erschwerten Umgang mit der ER zu jedem Zeitpunkt des Prozessmodells führen kann. Das Modell führt als erste Möglichkeit zur ER an, dass die Situationsauswahl angepasst werden kann. Wenn jedoch bereits im Ruhezustand die neuronalen Zustände unterschiedlich sind, kann es für Jugendliche mit NSSV mit Schwierigkeiten verbunden sein, Strategien im Sinne adäquater ER auszuwählen. Insbesondere im Rahmen von BPS ist bekannt, dass Betroffene eine erhöhte Sensitivität für emotionale (negative) Gesichtsausdrücke aufweisen (Domes et al., 2009).

Zusammenfassend kann die erste Forschungsfrage anhand der Studien I und II beantwortet werden. Jugendliche mit NSSV wiesen in beiden Studien eine verringerte Aktivität im PFK im Ruhezustand auf. Damit schließen die beiden Studien eine Forschungslücke, bei der es bislang keine Untersuchungen zur PFK-Aktivität bei Jugendlichen mit NSSV in Ruhe gab und zeigen, dass Unterschiede in der präfrontalen Aktivität auch unabhängig von aufgabenspezifischen Anforderungen in dieser Stichprobe existieren.

Zur Beantwortung der zweiten Forschungsfrage wurde Studie II durchgeführt. Hier zeigte sich eine in Abhängigkeit der Schwere der BPS-Symptomatik stärkere PFK-Aktivität während einer Stressaufgabe, während die Aktivität im PFK in der Kontrollgruppe absank. Wir interpretierten den Anstieg der präfrontalen Oxygenierung im PFK als mögliche Überkompensation zur ER, um potenzielle strukturelle Defizite auszugleichen (siehe Kapitel 4.2). Zukünftige Forschung sollte daher strukturelle und funktionale Bildgebungstechniken verwenden, um diese These zu prüfen. Befunde zur Aktivität im PFK bei gesunden Erwachsenen bei der Stressregulation sind unterschiedlich. So wird während Stress sowohl eine erniedrigte (Ossewaarde et al., 2011) als auch eine erhöhte Aktivität (Hänsel & von Känel, 2008) berichtet. Weitere Studien zeigen, dass die PFK-Aktivität bei gesunden Personen von der im PFK untersuchten Region sowie von der Stärke des selbstberichteten Stresserlebens abhängig ist (Orem et al., 2019, 2019). In Bezug auf das Prozessmodell der ER von Gross (1998, 2002, 2015) lässt sich an dieser Stelle feststellen, dass durch das standardisierte Vorgehen des Studienablaufs die Stressaufgabe vorgegeben war und die Jugendlichen keine Möglichkeit hatten, durch

die Wahl der Situation oder der Modifikation von Aspekten der Situation ihre Emotionen zu regulieren. Inwiefern die Jugendlichen Strategien durch Aufmerksamkeitslenkung oder kognitive Veränderungen (z.B. Neubewertung der Situation: „es ist eine Studie, es geht um nichts“) vorgenommen haben, lässt sich an dieser Stelle nicht sagen. In Bezug auf die reaktionsfokussierte ER lässt sich erkennen, dass Jugendliche mit NSSV auf physiologischer Ebene mit einer erhöhten PFK-Aktivität im Vergleich zu Jugendlichen in der Kontrollgruppe reagierten. Weiterführende Ergebnisse aus Studie II zeigen, dass die Leistungen im Erkennen von emotionalen Gesichtern bei Jugendlichen mit NSSV und der Kontrollgruppe nach der Stressexposition gleichbleibt. Gleichzeitig bewertet die Gruppe der Jugendlichen mit NSSV die Stressaufgabe als deutlich stressiger und berichtet einen höheren negativen Affekt (Koenig et al., 2022), sodass sich die Leistung trotz Unterschieden auf neuronaler Ebene und dem Erleben der Stresssituation zwischen den Gruppen nicht unterscheidet und somit ER im Sinne von Unterdrückung der emotionalen Reaktion stattfindet.

Somit kann Forschungsfrage 2 durch Studie II beantwortet werden. Die gefundenen Unterschiede tragen zum aktuellen Forschungsstand bei, der aufgabenspezifische Unterschiede in der präfrontalen Oxygenierung bei Personen mit NSSV und BPS berichtet. Allerdings scheinen diese Unterschiede stark von der Art und den Anforderungen der Aufgabe abhängig zu sein.

Die letzte Forschungsfrage kann durch Studie III beantwortet werden. In dieser konnte gezeigt werden, dass die Aktivität im PFK bei Jugendlichen ohne aktuelle affektive Erkrankung durch tVNS hinaufreguliert werden kann. Dieser Anstieg in der Oxygenierung im PFK geschah im Vergleich zu Variablen parasympathischen Ursprungs langsamer. Unter Berücksichtigung der Ergebnisse zur Forschungsfrage 1, kann die These aufgestellt werden, dass tVNS bei Jugendlichen mit NSSV dazu führen könnte, die Unterschiede im Vergleich zu gesunden Jugendlichen in der präfrontalen Aktivität bei Ruhemessung zu verringern oder sogar auszugleichen. In Bezug auf das Prozessmodell zur ER nach Gross (1998, 2002, 2015) kann dies bedeuten, dass Jugendliche mit NSSV nicht mit einem Bias (also einer verringerten neuronalen Aktivität bei Ruhe) in eine emotionsauslösende Situation gehen. Potenziell könnte dies zu einer Reduktion emotionaler Dysregulation bei Jugendlichen mit NSSV führen. In Bezug auf die Ergebnisse zur Beantwortung der Forschungsfrage 2 würde dies bedeuten, dass eine Überkompensation präfrontaler Aktivität zur Erreichung derselben Leistung (wie gesunde Jugendliche) in emotionalen Situationen nicht mehr notwendig wäre. So könnte das Stresserleben und die Abnahme des positiven Affekts infolge der emotionalen Situation im Sinne erfolgreicher reaktionsfokussierter ER nach dem Prozessmodell

erfolgen. Befunde zur Anwendung von tVNS im Erwachsenenbereich bei Depressionen zeigen, dass eine wiederholte Anwendung tVNS längerfristig zu einer Verbesserung parasympathischer Variablen führt (Fang et al., 2017). Eine Übertragung der Ergebnisse auf den Jugendbereich und auf Personen mit NSSV bei tVNS sollte Bestandteil zukünftiger Forschung sein und hat eine hohe klinische Implikation.

5.1 Limitationen

Die vorliegenden Ergebnisse der Studien replizieren zum großen Teil Befunde aus dem Erwachsenenalter und deuten darauf hin, dass funktionelle und strukturelle Veränderungen, die mit BPS einhergehen, kein Produkt jahrzehntelanger Krankheitsverläufe sind, sondern bereits im Jugendalter zu finden sind – auch bei NSSV. Dennoch erklärt dies nicht die Entstehung oder die Rolle von Plastizität bei der Entwicklung von NSSV und/oder BPS. Hierfür wären groß angelegte Studien im Längsschnittdesign hilfreich, um die Entwicklung des Gehirns parallel zur Entwicklung von NSSV und BPS zu beobachten. Des Weiteren fehlen in allen drei Studien eine hinreichend große Zahl männlicher Teilnehmer, um Geschlechtsunterschiede zu untersuchen. Die vorliegenden Ergebnisse basieren auf einer vorwiegend weiblichen Stichprobe. Darüber hinaus ist anzumerken, dass männliche Jugendliche sich eher durch Schlagen und Verbrennen selbst verletzen, während weibliche Jugendliche sich eher durch Schneiden oder Ritzen selbst verletzen (Andover, Primack, Gibb, & Pepper, 2010). Auch bei der Ausprägung von BPS wird von geschlechtsspezifischen Unterschieden berichtet (Silberschmidt, Lee, Zanarini, & Schulz, 2015). Zur Untersuchung des Zusammenspiels von Hirnregionen bei NSSV und/oder BPS wäre die Untersuchung tieferliegender Hirnregionen zur Emotionsentstehung, wie des limbischen Systems, von Interesse. Somit bieten die hier vorgestellten Studien zur Rolle des PFK eine Basis für weiterführende Forschung auch unter Berücksichtigung weiterer bildgebender Verfahren. Außerdem sollte darauf hingewiesen werden, dass der jugendliche PFK starker Veränderung und Entwicklung unterworfen ist (Caballero, Granberg, & Tseng, 2016), sodass auch die Rolle des Alters Jugendlicher stärker berücksichtigt werden sollte. Zuletzt liegt allen drei Studien die Messung der präfrontalen Aktivität mithilfe fNIRS zugrunde. Dies hat den Vorteil, dass die Studien innerhalb dieser Arbeit in ihrer Methodik miteinander vergleichbar sind. Insbesondere bei aufgabenspezifischen Anforderungen an den PFK unterscheiden sich die Regionen des PFK in ihrer Aktivität (Orem et al., 2019). Aufgrund der Einschränkungen von fNIRS bei der räumlichen Abgrenzung einzelner Regionen konnten derartige Unterschiede an dieser Stelle nicht berücksichtigt werden. Andere Bildgebungsverfahren mit einer

besseren räumlichen Auflösung könnten an dieser Stelle in zukünftigen Studien Abhilfe schaffen.

5.2 Implikationen für die klinische Praxis

Die hier beschriebenen Studien erweitern den Wissensstand zu Unterschieden in der Oxygenierung des PFK bei Störungen in der ER – an dieser Stelle NSSV über das Spektrum der BPS. Therapeutische Interventionen mit Jugendlichen mit NSSV sollten auch darauf abzielen, den in Studie I gefundenen Nachteil beim Eintreten in das Prozessmodell der ER auszugleichen. Bereits bestehende therapeutische Programme im deutschsprachigen Raum zur Verbesserung der ER, wie dem Training emotionaler Kompetenzen (Berking, 2015), der Dialektisch-Behavioralen Therapie für Adoleszente mit BPS-Symptomatik (Fleischhaker et al., 2011; Fleischhaker, Böhme, Sixt, & Schulz, 2005) oder dem an der Dialektisch-Behavioralen Therapie angelegten „Cutting-Down"-Programm zur Behandlung von Jugendlichen mit NSSV (Kaess et al., 2020) üben explizit den Umgang mit Emotionen und emotionsgeladenen Situationen. Die Erforschung der Aktivierung im PFK vor und nach derartigen Therapieprogrammen sollte in zukünftigen Studien evaluiert werden. Erkenntnisse hieraus würden wertvolle Informationen über die Plastizität der neuralen Aktivierung geben und die Ergebnisse ließen sich auf das Prozessmodell der ER übertragen. Aus Studie II ergibt sich, dass aufgabenspezifische Unterschiede in der präfrontalen Aktivierung vorliegen. Diese könnte die Betroffenen im Prozessmodell der ER nach Gross (1998, 2002, 2015) daran hindern, adäquate antezendenzfokussierte ER vorzunehmen. Therapie könnte an dieser Stelle ansetzen und die aktuelle präfrontale Aktivität während ER beobachten und im Sinne von Neurofeedback – Anpassen physiologischer Reaktionen durch Strategien und Rückmeldung über die Veränderung dieser Reaktionen – einüben. Dabei sollte beachtet werden, dass Unterschiede in der PFK-Aktivität aufgabenspezifisch zu sein scheinen. Aus Studie III ergibt sich für die klinische Praxis, dass tVNS als potenziell geeignete therapeutische Intervention die Aktivität im PFK anhebt. Langfristige tVNS ist bei Depressionen bereits vielfach erforscht und könnte auch bei der Therapie von Menschen mit Schwierigkeiten in der ER Einsatz finden.

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Wissenschaftliche Publikationen im Original: Studie I

Resting State Prefrontal Cortex Oxygenation in Adolescent Non-Suicidal Self-Injury– A Near-Infrared Spectroscopy Study

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Highlights

- Resting prefrontal cortex (PFC) oxygenation is decreased in adolescents with non-suicidal self-injury (NSSI) compared to healthy controls
- Lower PFC oxygenation (full sample) is associated with greater adverse childhood experiences and less health-related quality of life (HRQoL)
- On the group-level, patients show no alterations of resting state functional connectivity within the PFC
- Among other clinical variables, increased PFC connectivity (full sample) is associated with greater borderline personality pathology

Abbreviations

BMI – body mass index

BOLD - blood oxygenation level dependent

BPD – Borderline Personality Disorder

(dl)PFC – (dorsolateral) prefrontal cortex

(f)NIRS – (functional) Near-infrared spectroscopy

fMRI - functional magnetic resonance imaging

HbR – deoxygenated hemoglobin

HbT – total hemoglobin

HC – healthy controls

HRQoL – health related quality of life

NSSI – non-suicidal self-injury

O_2Hb – oxygenated hemoglobin

PIN diode – positive intrinsic negative diode

Abstract

Introduction: Neural alterations in limbic and prefrontal circuits in association with self-injurious behavior have been studied primarily in adult borderline personality disorder (BPD). In adolescent patients, research is still sparse. Here, we used resting functional near-infrared spectroscopy (NIRS) to examine oxygenation of the prefrontal cortex (PFC) and its association with symptom severity in adolescents engaging in non-suicidal self-injury (NSSI) and matched healthy controls (HC).

Methods: Adolescents (12-17 years) with recurrent episodes of NSSI (*n* = 170) and healthy controls (*n* = 43) performed a low-demanding resting-state vanilla baseline task. Mean oxygenation of the PFC and functional connectivity within the PFC, were measured using an 8-channel functional NIRS system (Octamon, Artinis, The Netherlands). Various clinical variables derived from diagnostic interviews and self-reports were included in statistical analyses to explore potential associations with PFC oxygenation and connectivity.

Results: Adolescents with NSSI showed significantly decreased PFC oxygenation compared to HC, as indexed by oxygenated hemoglobin. Lower PFC oxygenation was associated with greater adverse childhood experiences and less health-related quality of life (HRQoL). While there was no evidence for alterations in PFC connectivity in adolescents engaging in NSSI compared to HC, increased PFC connectivity in the full sample was associated with greater adverse childhood experience, a greater BPD pathology, greater depression severity and psychological burden in general, as well as lower HRQoL.

Conclusion: This study is the first to examine PFC oxygenation using NIRS technology in adolescents engaging in NSSI. Overall, results indicate small effects not specific to NSSI. Clinical implications of these findings and recommendations for further research are discussed.

Introduction

Non-suicidal self-injury (NSSI) is defined by the *International Society for the Study of Self-Injury* as the deliberate physical damage of own body tissue without suicidal intent (International Society for the Study of Self-injury, 2018). It excludes culturally or spiritually accepted behavior. Most commonly, adolescents injure themselves to regulate intense emotions or to cope with distress (Taylor et al., 2018). NSSI has been associated with greater emotion dysregulation (Haid-Stecher & Sevecke, 2019; In-Albon et al., 2008; Wolff et al., 2019) as well as with higher impulsiveness (Glenn & Klonsky, 2010; Hamza & Willoughby, 2019; Hamza, Willoughby, & Heffer, 2015; You, Deng, Lin, & Leung, 2016). The prevalence of NSSI in clinical samples is reported as high as 50% (Plener et al., 2018). Meta-analytic research on non-clinical samples revealed lifetime prevalence rates for single events of NSSI of 17.2%-22.1% in adolescents, 13.4% for young adults, and 5.5% for adults (Lim et al., 2019; Swannell, Martin, Page, Hasking, & John, 2014). The high prevalence of NSSI even in nonclinical populations has made the behavior a major public health concern. In the DSM-5, NSSI has been included as a condition that requires further study and is therefore acknowledged as an entity worth consideration in clinical practice and research (American Psychiatric Association, 2013). Albeit concepts considering NSSI as stand-alone diagnostic entity (also see (Ghinea et al., 2020), recurrent NSSI is one of the diagnostic criteria for borderline personality disorder (BPD) in the DSM-5 (American Psychiatric Association, 2013) and the presence, severity and duration of NSSI are important predictors for BPD development (Ghinea et al., 2019; Groschwitz et al., 2015). BPD itself is characterized by instability in affect, identity, and interpersonal relationships as alongside increased impulsivity and a tendency for risk-taking and self-harm behavior (American Psychiatric Association, 2013). The onset of BPD is frequently reported in early adolescence with prevalence rates ranging from 0.9% in 14-year old adolescents to 3.2% in 22-year old young adults among the U.S. population (Johnson, Cohen, Kasen, Skodol, & Oldham, 2008). BPD has been associated with a host of comorbid psychiatric disorders such as mood, anxiety, or

substance use disorders (Grant et al., 2008; Kaess, Fischer-Waldschmidt, Resch, & Koenig, 2017; Lenzenweger, Lane, Loranger, & Kessler, 2007), a lower health-related quality of life (HRQoL), and higher distress as a function of the severity of personality pathology (Kaess, Fischer-Waldschmidt, et al., 2017). In most cases, emerging BPD during adolescence is strongly associated with NSSI (Kaess, Brunner, Chanen, 2014). Taken together, while NSSI is one of the major symptoms of BPD, in particular in adolescents, there is ongoing debate whether NSSI disorder should be considered as an independent phenomenon and diagnostic entity, requiring further investigation.

Neurobiological mechanisms underlying various psychiatric entities and phenotypes have been under extensive investigation for the past decade, in the hope that the respective studies may contribute to a better understanding of predictors of treatment outcome, improved diagnostics, and the development of tailored interventions (Ehlis, Schneider, Dresler, & Fallgatter, 2014; Oldehinkel, Francx, Beckmann, Buitelaar, & Mennes, 2013). While the neurobiological underpinnings of NSSI have not been extensively investigated, more research has been conducted on the neurobiology of BPD. In a review of existing neuroimaging findings, prefrontal dysfunctions during impulse control tasks in adult BPD patients have been mainly found in the orbitofrontal cortex, the dorsomedial PFC, and the dorsolateral prefrontal cortex (dlPFC) (Sebastian et al., 2014). During emotion regulation, alterations of limbic brain activity in adult BPD have been reported in the amygdala, the ventral striatum, the hippocampus and the posterior cingulate cortex. While the literature is consistent regarding the frontolimbic regions involved, there is mixed evidence regarding increases and decreases of brain activation (Dudas et al., 2017; Schulze, Schmahl, & Niedtfeld, 2016). Generally speaking, abnormalities in frontolimbic networks have been found to be characteristic of BPD in *adult* patients (Chanen & Kaess, 2012; Ruocco, Amirthavasagam, Choi-Kain, & McMain, 2013). Considering that BPD is associated with high comorbidity and burden, neuroimaging studies in BPD yield limited insight into NSSI per se and neglect a developmental perspective by exclusively focusing on adults. As neuroimaging research

in NSSI is sparse, studies on BPD patients still serve as a helpful proxy and direction sign for studies on NSSI in adolescents.

The few existing studies, which examined brain activation in individuals engaging in NSSI, primarily focused on task-dependent alterations in neural activity. For example, one study addressing NSSI specifically found that decreased activation in the PFC and the cingulate cortex of young adults with NSSI (n = 15) during an interference task was associated with poorer emotion regulation abilities and increased impulsivity (Dahlgren et al., 2018). Alongside difficulties in emotion regulation and impulse control, alterations in pain sensitivity in patients engaging in NSSI are well documented (Koenig, Thayer, & Kaess, 2016). Further research showed that, pain sensation was associated with brain activation in the posterior insula in participants with NSSI and healthy controls (HC), but only HC showed greater neural activity as a function of increasing pain intensity. However, out of n = 14 participants of the NSSI group, only n = 6 reported actual incidents of NSSI during the past 12 months (Bonenberger, Plener, Groschwitz, Grön, & Abler, 2015). Hence, it might be questionable whether these findings are specifically related to NSSI or are driven by other factors. As emphasized in the definition of the *International Society for the Study of Self-Injury* (International Society for the Study of Self-injury, 2018), NSSI is often related to interpersonal difficulties. In line with this, adolescents with NSSI showed increased activation of the PFC compared to HC and depressed adolescents in a social exclusion paradigm (Groschwitz, Plener, Groen, Bonenberger, & Abler, 2016). Finally, aberrant amygdala connectivity with various cortical regions was found during resting state and an emotion task (n = 24 females with NSSI and n = 20 HC) (Westlund Schreiner et al., 2017). On a brain structural level, volumetric abnormalities of the insula and the inferior frontal gyrus in female adolescent NSSI patients have been reported to be similar to those observed in adult BPD patients (Beauchaine, Sauder, Derbidge, & Uyeji, 2019). Taken together, neuroimaging studies focusing on NSSI only showed neural alterations in association with impulse control, pain sensation, and social exclusion. Unfortunately, it is unknown whether patterns of altered

brain activation are due to task-specific demands or exist during rest. The finding of volumetric abnormalities might implicate that activation patterns at rest might differ between NSSI patients and HC.

Unfortunately, the majority of neuroimaging studies in adolescents engaging in NSSI lack statistically sufficient sample sizes. One alternative method with the potential to overcome difficulties associated with sample size due to its high acceptability in patients and relative ease in application, is near-infrared spectroscopy (NIRS). NIRS recordings are based on light within the near-infrared spectrum (650-950 nm). Human scalp and skull are penetrable for light at this wavelength (Ferrari & Quaresima, 2012) and the greatest light absorbing structure in this area is the hemoglobin in the venous vessels of the cortex. Functional NIRS (fNIRS) devices measure changes of oxygenated (O_2Hb) and deoxygenated (HbR) hemoglobin over time. In comparison with (f)MRI, fNIRS is conducted with smaller devices and tolerates body movement to a greater degree, which results in a high acceptance among patients undergoing respective recordings (Lai, Ho, Lim, & Ho, 2017) – especially in adolescents. Additionally, fNIRS has superior time resolution, although struggling with exact spatial resolution and measuring only changes in activation on the cortical surface (Koike, Nishimura, Takizawa, Yahata, & Kasai, 2013). During simultaneous fMRI and fNIRS assessment, it has been shown that fNIRS measurement correlates with blood oxygenation level dependent (BOLD) signals in fMRI, suggesting equivalence of both methods when examining activation on the cortical surface (Alderliesten et al., 2014; Bulgarelli et al., 2018).

To our knowledge, there are no previous studies investigating adolescent NSSI patients using NIRS technology. Even research on BPD using NIRS is sparse. In one of the few studies, adult BPD patients (n = 10) showed increased oxygenation in the left medial PFC during a social exclusion paradigm, related to ratings of rejection and fear of abandonment (Ruocco, Medaglia, Tinker, et al., 2010). A recent study reported hemodynamic alterations (i.e. decreased O_2Hb compared to HC during a verbal fluency

task) in the frontal, parietal, and temporal cortices of adult (mean age = 32 years) BPD patients (Husain et al., 2020). Young BPD patients (n = 9) with a mean age of 20 years showed a reduced slope in oxygenation of left prefrontal channels when viewing emotional (sad) pictures (Ehlis et al., 2014; Ruocco, Medaglia, Ayaz, & Chute, 2010). As BPD emerges during adolescence, investigating young patients seems crucial to disentangle effects of chronicity and long-term illness. To our knowledge, PFC oxygenation has not been investigated in adolescents explicitly engaging in NSSI only.

Unfortunately, current evidence on NSSI is barely existent and research on fMRI in NSSI reports mainly task-dependent alterations in the PFC. When extending the focus to BPD, the reported studies above present mixed findings regarding the question whether activity and/or oxygenation levels in the PFC in BPD patients are decreased or increased compared to HC. While findings on brain functional correlates of BPD from task-based studies yielded somewhat inconsistent results due to the different tasks used, the investigation of alterations in intrinsic brain activation during resting state seems important. Further, to detect cortical changes occurring already during the early course of BPD, it is important to examine adolescents engaging in NSSI across the spectrum of BPD pathology. As pointed out in the DSM-5 (American Psychiatric Association, 2013), NSSI is an entity which should be scrutinized in present research. Hence, this study focuses on brain alterations occurring in adolescents engaging in NSSI. In addition to that, the symptom severity of BPD should also be considered to control for effects solely relying on BPD. The aim of the present study therefore was to investigate resting state oxygenation of the PFC in adolescent NSSI patients compared to HC using NIRS. We hypothesized that (1) the mean oxygenation and deoxygenation is lower in patients compared to HC during a resting-state task and that (2) the relative decrease of oxygenation would be correlated with BPD symptom severity. Furthermore, we aimed to investigate differences in connectivity strength between patients and HC in exploratory analyses.

Methods

2.1 Participants

Participants were recruited from the outpatient clinic for risk-taking and self-harming behavior (AtR!Sk; *Ambulanz für Risikoverhaltensweisen und Selbstschädigung* (Kaess, Ghinea, Fischer-Waldschmidt, & Resch, 2017). The specialized outpatient clinic is part of the Clinic for Child and Adolescent Psychiatry at the Center for Psychosocial Medicine at the University of Heidelberg, Germany. The study was approved by the ethical committee of the University of Heidelberg (study ID S-449/2013; study ID S-514/2015) and consisted of two appointments, a diagnostic interview and a neurobiological assessment, at baseline. Adolescents and their caregivers provided written informed consent before inclusion in the study. The recruitment period for baseline assessments started in August 2016 and ended in January 2020. The general inclusion criteria were (1) presentation at our outpatient clinic, (2) written informed consent of the adolescents and their caregivers, (3) age between 12 and 17 years and (4) fluent German language skills. General exclusion criteria for study participation were: (1) acute psychosis, (2) pregnancy, and (3) neurological, endocrinological, or cardiovascular primary diseases, potentially interfering with the neurobiological assessments. For the present analyses, only patients reporting incidents of NSSI on at least five or more days during the past 12 months were included in the analyses. NSSI incidents were defined according to the definition of the *International Society for the Study of Self-Injury* (International Society for the Study of Self-injury, 2018) and included the intentional damage of own body tissue (e.g., via cutting, biting, hitting, burning).

HC were recruited via advertisement and matched to the patient sample according to age and sex. Exclusion criteria for HC were the same as for the patient group. Further exclusion criteria for the HC group only were: lifetime self-harming behavior, lifetime psychological or psychiatric treatment, or any current psychiatric disorder. After completing the study, all participants received an allowance of 40€ for study participation.

2.2 Procedures

In a first appointment, participants completed an extensive diagnostic assessment. The presence of NSSI, suicidal thoughts and behavior were assessed using the German version of the *Self-Injurious Thoughts and Behaviors interview* (SITBI-G; (Fischer et al., 2014; Nock, Holmberg, Photos, & Michel, 2007). To assess BPD the respective sections of the *Structured Clinical Interview for DSM-IV Personality Disorders* were queried (SCID-II; (Wittchen, Zaudig, & Fydrich, 1997). Additionally, in patients, common axis-I disorders were assessed using the semi-structured *Mini International Neuropsychiatric Interview for Children and Adolescents* (M.I.N.I.-KID; (Sheehan et al., 1998). The interview ended with the investigator´s rating of the patient´s global functioning by means of the *Global Assessment of Functioning* (GAF; (Saß, Wittchen, Zaudig, & Houben, 2003) and rating of the severity of psychiatric symptoms on the basis of the *Clinical Global Impression Scale* (CGI-S; (Busner & Targum, 2007).

HC underwent a shortened clinical interview to make sure they did not meet the criteria for any current mental disorders and were not under psychological or pharmacological treatment. In a first interview via telephone, screening questions from the SITBI-G (Fischer et al., 2014) were used to ensure that there was no history of NSSI or suicidal behavior. The *Structured Clinical Interview (non-patient edition)* (SCID-N/P) was used to check whether there was any evidence for the presence of any axis-I disorder (First, Spitzer, Gibbon, & Williams, 2002). Whenever HC reported any symptoms indicative of the presence of a psychiatric disorder, the M.I.N.I.-KID was used as an additional diagnostic tool. Those participants meeting the criteria for any psychiatric disorder were compensated for their participation in the diagnostic assessment and excluded from further study appointments.

Furthermore, patients and controls answered questionnaires addressing depressive symptoms using the German version of the *Depression Inventory for Children and Adolescents* (DIKJ; (Stiensmeier-Pelster, Schürmann, & Duda, 1991). HRQoL was

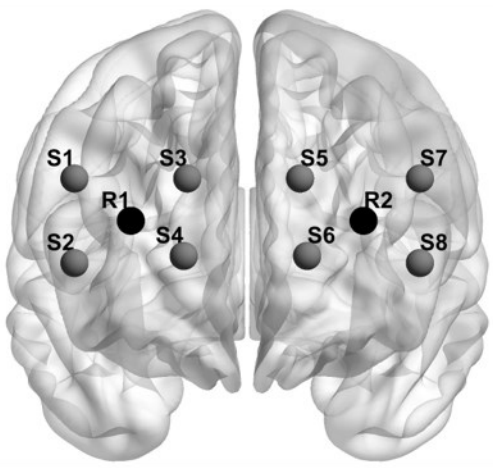
assessed with the *KIDSCREEN-52* (The KIDSCREEN Group Europe, 2006). Adverse childhood experiences (ACE) were assessed with the *Childhood Experiences of Care and Abuse* questionnaire (CECA-Q3; (Kaess et al., 2011). Lastly, general psychological burden was measured using the Symptom Checklist 90-Revised (SCL-90-R; (Franke, 1995).

The second part of the study was designed to investigate a host of neurobiological variables as well as the participants´ intelligence. All participants were invited for a second appointment within six weeks after their diagnostic assessment. In the beginning of the second appointment, participants´ weight and height were measured to calculate the body mass index (BMI). In addition, information about handedness, allergies, and diseases during the past three months were collected. Subsequently, the intelligence quotient (IQ) was assessed using the *Hamburg Wechsler Intelligence Scale for Children IV* (HAWIK-IV) (Petermann & Petermann, 2007). Afterwards, prefrontal resting oxygenation in patients and HC was assessed using NIRS technology. For this purpose, a NIRS device was attached to the participants´ forehead. During a five-minute baseline task, prefrontal resting oxygenation was recorded. A detailed description of the measurement is provided below.

2.3 NIRS Measurement

PFC oxygenation was assessed using a portable 8-channel continuous-wave NIRS-system (OctaMon, Artinis, The Netherlands). NIRS is an optical neuroimaging tool consisting of light sources and receivers which are attached to the forehead of the participants with a headband. The light sources emit light in the near-infrared spectrum. The near-infrared light passes the skull cap and the cerebrospinal fluid before encountering the brain. The different tissues have unique light scattering and absorbing properties. The attenuation of light intensity is described by the modified Beer-Lambert law which calculates the absorption of light by different tissues and substances. As oxygenated hemoglobin best absorbs light with a wavelength greater than 800nm and

deoxygenated hemoglobin has its highest sensitivity to light at a wavelength smaller than 800nm, the eight transmitters of the OctaMon emit light at two wavelengths, 760nm and 850nm, to detect both oxygenated and deoxygenated hemoglobin. The emitted light is recorded by two positive intrinsic negative (PIN) diode receivers with ambient light protection. The arrangement of receivers and transmitters (summarized by the term optodes) on the forehead is displayed in *Figure 1*. Inter-optode distance was fixed at 35mm. Optodes were placed onto the forehead of the participants according to the international 10-20 system for EEG electrodes placement (Jaspers, 1958). Estimated coordinates of optodes according to the Montreal Neurological Institute brain template are provided in *Figure 1*. When placing the NIRS headband, the investigator made sure that no hair was between optodes and skin impairing signal strength. The data acquisition values for signal strength should be between 3 and 97% of the intensity of the emitted light. If the percentage is close to 0%, light absorption in the tissue is so high that almost no signal reaches the receiver. A percentage close to 100% indicates that environmental light was received and measured. According to the general equation for the differential path length factor and in regard to current study protocols, the differential path length factor was set to six centimeters (Scholkmann & Wolf, 2013). A sampling rate of 50 Hz was set for each channel. The penetration depth of the NIRS light is around 17 millimeters. All participants were seated in front of a computer screen and performed a five-minute vanilla baseline task. Vanilla tasks are designed to be minimally demanding and have been shown to have consistent within- and baseline stability as well as generalizability between sessions (Jennings, Kamarck, Stewart, Eddy, & Johnson, 1992). The task in our study consisted of a colored rectangle which is presented in the middle of the screen. The rectangle contained one of the following colors: red, green, yellow, blue, purple, white. Every few seconds, it changed its color. Participants were asked to count the incidents of one specific color. After five minutes, they had to report the number of incidents.



	MNI coordinates		
	x	*y*	*z*
Receiver 1	33	61	20
Receiver 2	-35	57	22
Transmitter 1	49	45	32
Transmitter 2	49	53	8
Transmitter 3	17	69	32
Transmitter 4	18	78	10
Transmitter 5	-15	67	32
Transmitter 6	-17	77	10
Transmitter 7	-49	37	36
Transmitter 8	-57	45	8

Figure 1 Optode placement on the forehead; *Note*. R = receiver, S = source.

2.4 NIRS Data Preprocessing

Hemoglobin density values were recorded by the NIRS device and sent to a laptop via Bluetooth. There, the raw optical density measures were stored with the Oxysoft software version 3.0.103 (Artinis Medical Systems, 2016). NIRS data were segmented according to the start and end times of the color detection task. For analysis, they were imported to MATLAB (The Math Works Inc., 2015) using the oxysoft2matlab function and preprocessed with the HOMER2 toolbox (Huppert, Diamond, Franceschini, & Boas, 2009). During preprocessing, the raw optical densities were first converted to optical density (hmrIntensity2OD), which is recommended to detect and correct the data for motion artifacts (Cooper et al., 2012). Next, motion artifacts were rectified in a two-step process. First, wavelet-based motion correction with a probability threshold of $\alpha = .01$ was applied (hmrMotionCorrectWavelet). In a second step motion artifacts were corrected (hmrMotionArtifact). Additionally, high-frequent noise was removed with a Bandpass filter which removed frequencies greater than 0.5 Hz. As a final step, optical density rates were converted to hemoglobin concentration for O_2Hb, HbR and HbT (HbT = O_2Hb + HbR) and exported to Stata/SE software version 16.0 (StataCorp, 2019).

2.5 Statistical Analysis

All statistical analyses were conducted either in Stata/SE software version 16.0 (StataCorp, 2019) or in MATLAB (The Math Works Inc., 2015). In line with previous research (Alderliesten et al., 2014; Artemenko, Soltanlou, Ehlis, Nuerk, & Dresler, 2018; Niu et al., 2013, 2011; Pinti et al., 2018; Seidel, Carius, Kenville, & Ragert, 2017; Shi, Sakatani, Okamoto, Yamaguchi, & Zuo, 2014), we assessed the mean of O_2Hb, HbR and HbT across the standardized CDT, instead of applying event-related analyses of NIRS data. For each hemoglobin variable (O_2Hb, HbR, HbT) mean values per channel and a grand mean value for oxygenated (O_2Hb), deoxygenated (HbR), and total hemoglobin (HbT) were calculated. For hypothesis one, t-tests were calculated for each hemoglobin variable to test for general differences between the groups. In a second step, the influence of potential confounding factors on PFC oxygenation was tested via t-tests (handedness, sex) and Pearson product-moment correlations (age, BMI, IQ). In a final step, regression models were calculated with group as predictor for differences in the hemoglobin variables of interest, while adjusting for those factors that showed significant influence on the variable of interest in step two. For hypothesis two, Pearson product-moment correlations were used to detect associations between PFC oxygenation and clinical variables, in case a respective hemoglobin variable showed significant group differences. First, correlations for variables of interest, assessed in both groups (number of BPD criteria, SCL-90-R, KIDSCREEN-52, CECA-Q3, DIKJ), were calculated in the full-sample. Second, analyses were repeated in the NSSI sample only – to avoid inflation of correlation coefficients - further including variables only assessed in patients (e.g. NSSI frequency, number of suicide attempts, CGI-S, GAF). For the exploratory analysis on connectivity within the PFC across all participants, cross-correlations between the n = 8 channels over the time of the CDT were generated with the FC-NIRS toolbox in MATLAB (Xu et al., 2015). Correlation coefficients from connectivity analyses for both groups were compared using Fisher´s z-transformation. In line with mean oxygenation parameters, associations between cross-correlation coefficients and clinical variables

were assessed, following the approach outlined above. For all analyses, a significance level of p = .05 was applied. For visualization of the data, channel locations were provided as MNI coordinates and projected to a brain template using the BrainNet toolbox (see *Figure 1*) (Xia, Wang, & He, 2013). For visualization of results, differences in mean activation were assigned to the corresponding channels. A nifti-data format was generated in xjview (*XjView Toolbox*, 2019) and visualized using the software SurfIce (*Surf Ice*, 2019) and BrainNet (Xia et al., 2013). Visualization of the heat maps for the connectivity analyses was done within the FC-NIRS toolbox.

Results

3.1 Sample Characteristics

For the NSSI group, written informed consent was provided by *n* = 257 consecutive patients. Of these, *n* = 242 (94.16%) participated in the baseline assessment. *N* = 227 (88.33%) completed the NIRS assessment. *N* = 195 (75.88%) reported five or more events of NSSI during the past twelve months. *N* = 25 (9.73%) had to be excluded from the present analyses due to problems during the NIRS assessment (e.g. signal loss), resulting in a patient group of *n* = 170 (66.15%) participants. *N* = 58 adolescents provided written informed consent for the HC group. Of these *n* = 49 (84.48%) completed the baseline assessment. Reasons for not completing the baseline assessment were withdrawal of interest in study participation (*n* = 7; 12.07%), lifetime history of NSSI (*n* = 1; 1.72%), and present psychiatric disorder (*n* = 1; 1.72%). *N* = 6 (10.34%) adolescents from the HC group were excluded from data analyses due to problems during the NIRS assessment resulting in a HC group of *n* = 43 (74.14%) adolescents. Eventually, the final study sample consisted of *n* = 170 NSSI patients and *n* = 43 HC. For a detailed description of sociodemographic and clinical characteristics of the current sample see *Table 1*. Groups differed on IQ ($t_{(211)} = 2.491$; $p = .014$), with lower IQ in the patient group, and sex ($\chi^2(1) = 5.524$; $p = .019$) due to the fact that the present sample only consisted of a sub sample (only those patients engaging in NSSI) and due to data loss during NIRS assessment. No significant group differences were found for age, school type, handedness, nor BMI.

Table 1 Sociodemographic and clinical characteristics by group

		NSSI	HC	*P*
N (% female)		170 (84.12)	43 (95.55)	.019
Age (SD)		15.04 (1.47)	14.74 (1.31)	.228
School type, *n* (%)				.086
	Hauptschule	19 (11.18)	1 (2.33)	
	Realschule	63 (37.06)	14 (32.56)	
	Gymnasium	61 (35.88)	27 (62.79)	
	Other	27 (15.88)	1 (2.33)	
IQ (SD)		100.83 (1.07)	106.56 (1.78)	.014
Right-handedness, *n* (%)		154 (90.59)	40 (93.02)	.617
BMI (SD)		21.58 (0.34)	20.34 (0.51)	.096
DIKJ (SD)		28.41 (9.94)	6.21 (4.03)	<.001
KIDSCREEN-52 (SD)		34.95 (6.93)	56.07 (8.43)	<.001
CECA-Q3 (SD)		0.35 (0.30)	0.02 (0.07)	<.001
SCL-90-R (SD)		1.55 (0.74)	0.21 (0.17)	<.001
CGI-S (SD)		4.96 (0.76)	-	
GAF (SD)		49.76 (8.97)	-	
Comorbidity (ICD-10), *n* (%)				
	F0X	0	-	
	F1X	40 (23.53)	-	
	F2X	0	-	
	F3X	99 (58.24)	-	
	F4X	69 (40.59)	-	
	F5X	18 (10.59)	-	
	F6X	60 (35.29)	-	
	F7X	0	-	
	F8X	2 (1.18)	-	
	F9X	54 (31.76)	-	
Number of suicide attempts (SD)				
	lifetime	10.81 (58.57)	-	
	past 12 months	1.60 (8.37)	-	
	past 6 months	1.71 (4.74)	-	
Number of NSSI events (SD)				
	past 12 months	75.56 (92.84)	-	
	past 6 months	38.37 (40.21)	-	

Note. NSSI = non-suicidal self-injury, HC = healthy controls, SD = standard deviation, IQ = intelligence quotient, BMI = body mass index, DIKJ = Depression Inventory for Children and Adolescents, KIDSCREEN-52 = Health-related quality of life questionnaire, CECA-Q3 = Childhood Experiences of Care and Abuse questionnaire, SCL-90-R = Symptom Checklist 90-Revised, CGI-S = Clinical Global Impression Scale, GAF = Global Assessment of Functioning.

N = 46 (27.06%) patients fulfilled criteria for BPD diagnosis (≥ 5 criteria). On average, NSSI patients met 3.14 (SD = 2.11) BPD criteria. Mostly, they met the criterion on recurrent suicidality and NSSI behavior (74.7%), followed by emotional instability (54.82%) and chronic feelings of emptiness (33.73%). The mean age of onset of NSSI was 12.81 years (SD = 0.13). *N* = 73 (42.94%) patients reported at least one suicide attempt. Number of suicide attempts and events of NSSI are also provided in *Table 1*. NSSI patients and HC differed significantly on all clinical measures of interest (including number of BPD criteria, depression symptoms, ACE, and HRQoL), indicating greater burden of psychopathology in adolescents engaging in NSSI (see *Table 1*).

3.2 PFC Activation

First, paired t-tests were calculated to investigate general group differences in PFC oxygenation. The NSSI group showed significantly decreased O_2Hb ($t_{(211)}$ = 2.333; p = *.021*) compared with HC. No significant group differences were found for HbR ($t_{(211)}$ = -0.654; p = *.514*) nor HbT ($t_{(211)}$ = 1.281; p = *.201*), see also (*SM Table 1*). In a second step, we aimed to investigate potential confounders of PFC oxygenation (handedness, sex, age, BMI, IQ). None of the tested variables was significantly related to O_2Hb (see *SM Table 2, SM Table 3,* and *SM Table 4*). Age and IQ were significantly correlated with HbR (age: $r_{(208)}$ = -.137, p = *.048*; IQ: $r_{(211)}$ = .141, p = *.040*) while IQ was also correlated with HbT ($r_{(211)}$ = .168, p = *.014*). None of the remaining variables (handedness, BMI, sex) was significantly related to PFC oxygenation. In a third step, regression models were calculated with group as predictor. Results from model one provided evidence that O_2Hb differed between groups ($F_{(1,211)}$ = 5.45, p = *.021*; NSSI: β = -0.353, $t_{(212)}$ = -2.33, p = .021). Model two yielded no evidence that HbR differed between groups, while adjusting for age and IQ ($F_{(3,204)}$ = 2.90, p = .036; NSSI: β = 0.144, $t_{(207)}$ = -1.21, p = *.227*; age: β = -0.063, $t_{(207)}$ = -1.91, p = .058; IQ: β = 0.007, $t_{(207)}$ = 1.97, p = .051). Finally, model three did not provide evidence of group differences in HbT, when adjusting for IQ ($F_{(2,209)}$ = 3.40, p = *.035*; NSSI: β = -0.182, $t_{(211)}$ = -0.84, p = *.400*; IQ: β = 0.015, $t_{(211)}$ =

2.29, *p* = *.023*). Further model characteristics are presented in SM Table 5. Mean PFC oxygenation and group differences for all hemoglobin variables are displayed in *Figure 2*.

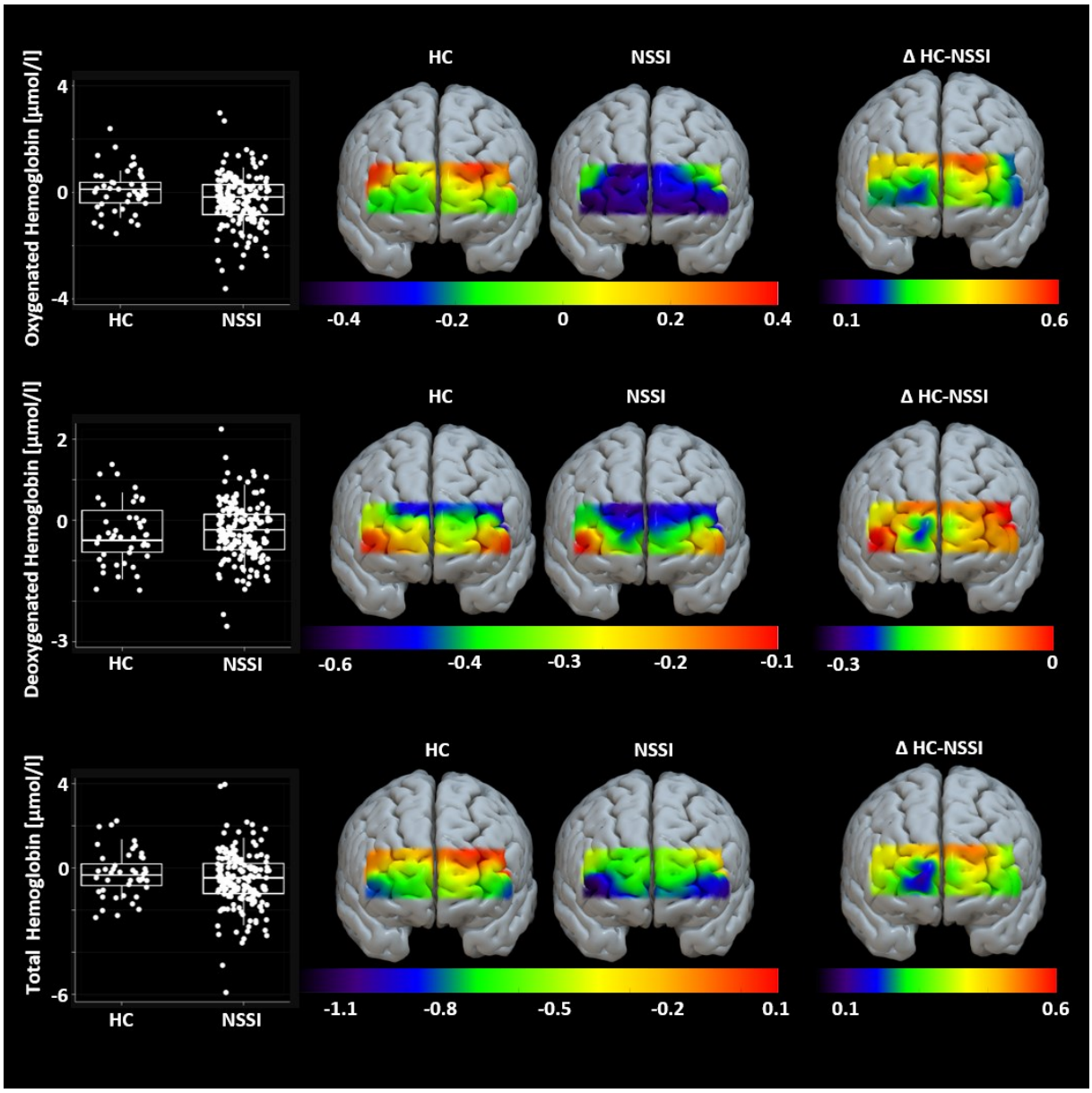


Figure 2 Differences in prefrontal brain activation across groups; *Note*. Hemoglobin unit = µmol/l, HC = healthy controls, NSSI = non-suicidal self-injury group, ΔHC-NSSI = difference in hemoglobin concentration between HC and NSSI group.

3.3 Association between PFC Oxygenation and Symptom Severity

First, Pearson product-moment correlations between O_2Hb and clinical variables that were assessed in both groups were calculated. Here, significant correlations were found

between O_2Hb and ACE (CECA-Q3: $r_{(187)}$ = -.155; p = *.034*) and between O_2Hb and HRQoL ($r_{(162)}$ = .154; p = *.049*; see also *Figure 3*). No significant correlations were found between O_2Hb and the number of BPD criteria met ($r_{(207)}$ = -.105; p = *.129*), general symptom severity (SCL-90-R; $r_{(188)}$ = -0.100; p = *.169*), or depression severity (DIKJ; $r_{(186)}$ = -.100; p = *.175*). In subsequent calculations, only the patient group was included. In addition to the correlations above, the number of incidents of NSSI during the past 12 months and during the past six months, number of suicide attempts (lifetime), clinical global impression (CGI-S), and level of functioning (GAF) were included to the analysis. None of the Pearson product-moment correlations revealed a significant relationship to O_2Hb in the PFC (number of NSSI events during the past 12 months: $r_{(168)}$ = .062; p = *.420*; number of NSSI events during the past six months: $r_{(148)}$ = .050; p = *.544*; number of suicide attempts during lifetime: $r_{(70)}$ = .065; p = *.589*; clinical global impression: $r_{(160)}$ = -.113; p = *.154*; GAF: $r_{(160)}$ = .118; p = *.135*; number of BPD criteria: $r_{(164)}$ = -.022; p = *.783*; depression severity: $r_{(143)}$ = .030; p = *.719*; general symptom severity: $r_{(146)}$ = .014; p = *.870*; trauma severity: $r_{(145)}$ = -.109; p = *.189*; HRQoL: $r_{(122)}$ = .024; p = *.794*).

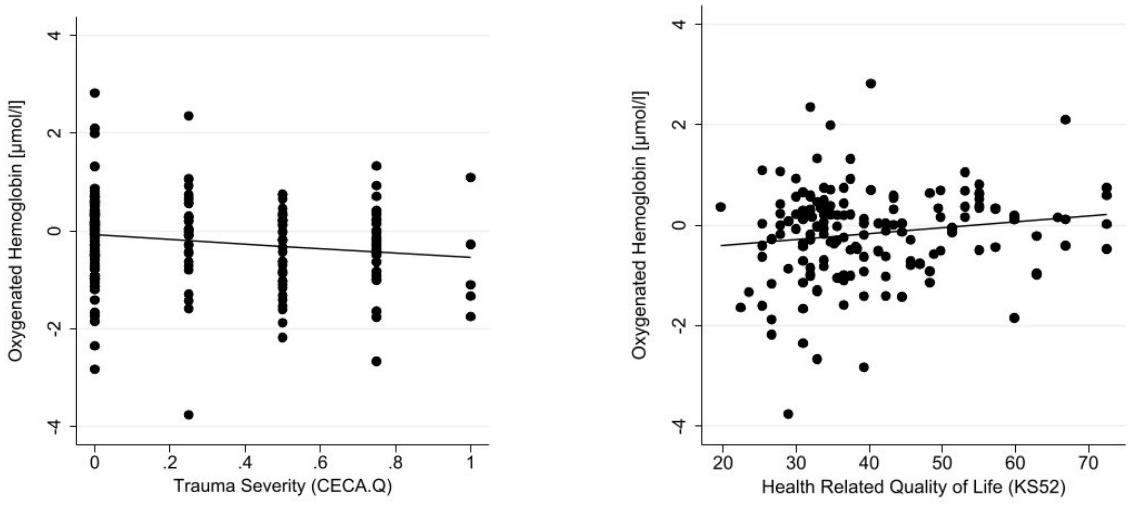


Figure 3 Significant correlation between O_2Hb and Adverse Childhood Experiences and Health-Related Quality of Life; *Note*. CECA = Childhood Experiences of Care and Abuse questionnaire, KIDSCREEN-52 = Health-related quality of life questionnaire.

3.4 Analysis of Functional Connectivity

Due to technical problems, *n* = 2 NSSI patients had to be excluded from the connectivity analyses resulting in *n* = 168 patients and *n* = 43 HC that were subject to the analysis. Connectivity analyses within the PFC were calculated only for O_2Hb, as this measure differentiated the NSSI and HC group in the preceding analyses. Cross-correlation coefficients were determined between all channels for each group (see *SM Table 6* and *SM Table 7*). Subsequently, Fisher´s z-transformation was conducted, and PFC connectivity values were compared between groups. Whereas almost all channels revealed a significant connectivity between channels on the within-group level (see *Figure* 4), no differences between groups were found (see *SM Table* 8). As illustrated in *Figure* 4, connectivity measures were descriptively higher in NSSI patients (range: $r_{(166)}$ = .488 – $r_{(166)}$ = .680; all $p<.0001$) compared to HC (range: $r_{(41)}$ = .285 – $r_{(41)}$ = .613; p = *.064 – p < .001*). Both groups showed especially high connectivity between channels covering the orbitofrontal cortex area and slightly lower connectivity in the dorsolateral cortex areas.

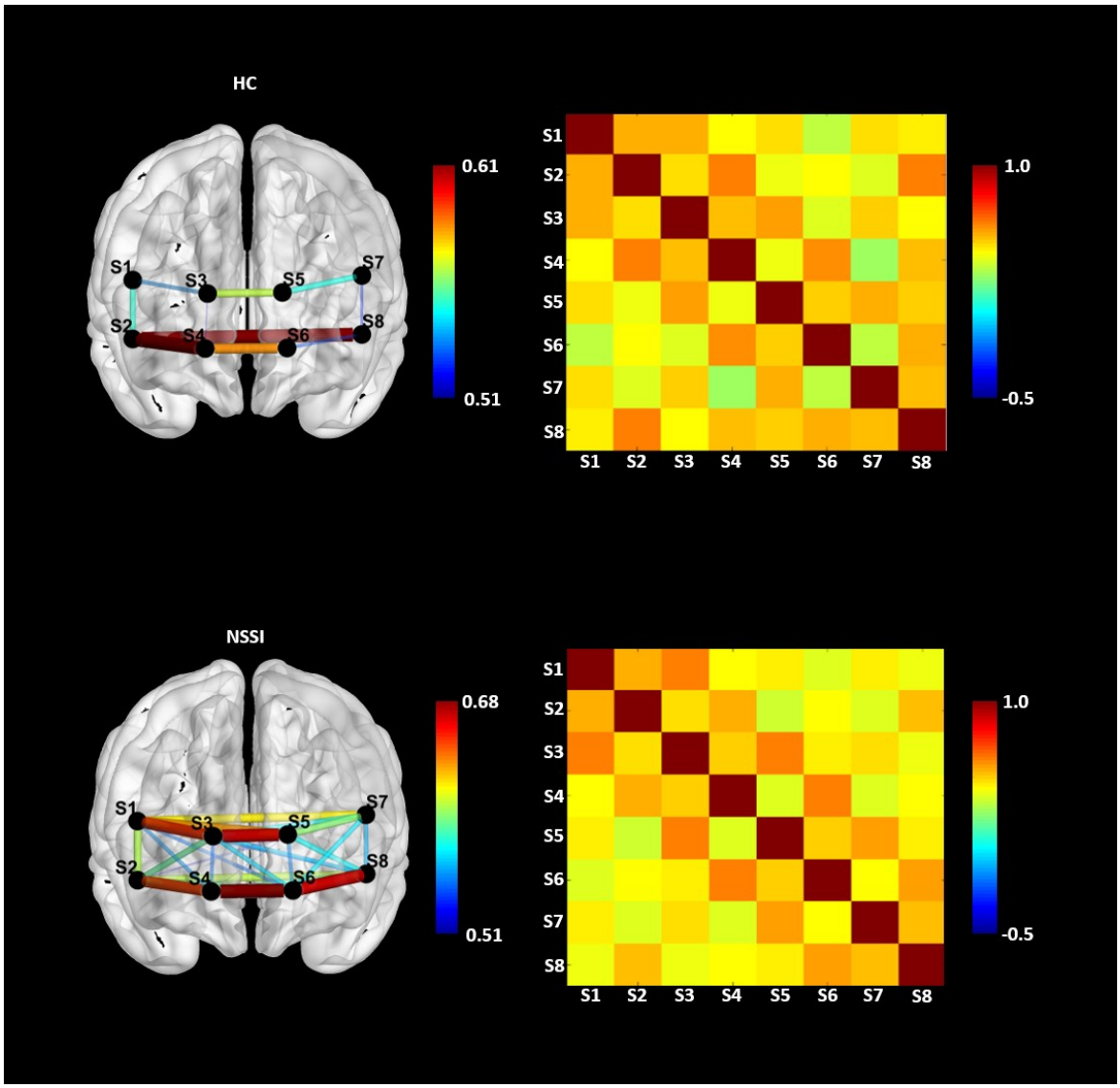


Figure 4 Brain connectivity pattern of cross correlations between HC and NSSI patients; *Note*. In the left only the topmost correlations with correlation coefficients greater than r = .50 are displayed.

When examining associations between PFC connectivity and clinical variables across all participants, positive correlations were found between the number of BPD criteria and O_2Hb connectivity in n = 6 inter- and intrahemispheric channel pairs (range: $r_{(205)}$ = .138, p = *.047* – $r_{(205)}$ = .177, p = *.011*), depressive symptoms and connectivity in n = 3 mostly left hemispheric channel pairs (range: $r_{(184)}$ = .148, p = *.045* – $r_{(184)}$ = .179), general psychological burden (SCL-90-R) and connectivity in n = 3 channel pairs (range: $r_{(187)}$ = .154, p = *.035* – $r_{(187)}$ = .166, p = *.023*), and ACE (CECA-Q3) in n = 4 channel pairs (range: $r_{(186)}$ = .155, p = *.034* – $r_{(186)}$ = .184, p = *.012*). Negative correlations were found between

HRQoL (KIDSCREEN-52) and connectivity between n = 8 channel pairs (range: $r_{(161)}$ = -.157, p = *.046* – $r_{(161)}$ = -.228, p = *.004*). We did not find evidence of associations between global clinical impression (CGI-S) and PFC connectivity. Associations are illustrated for the number of BPD criteria, ACE and HRQoL in *Figure* 5. All correlations are provided in the *Supplemental Material* (*SM Table* 9 to *SM Table* 14).

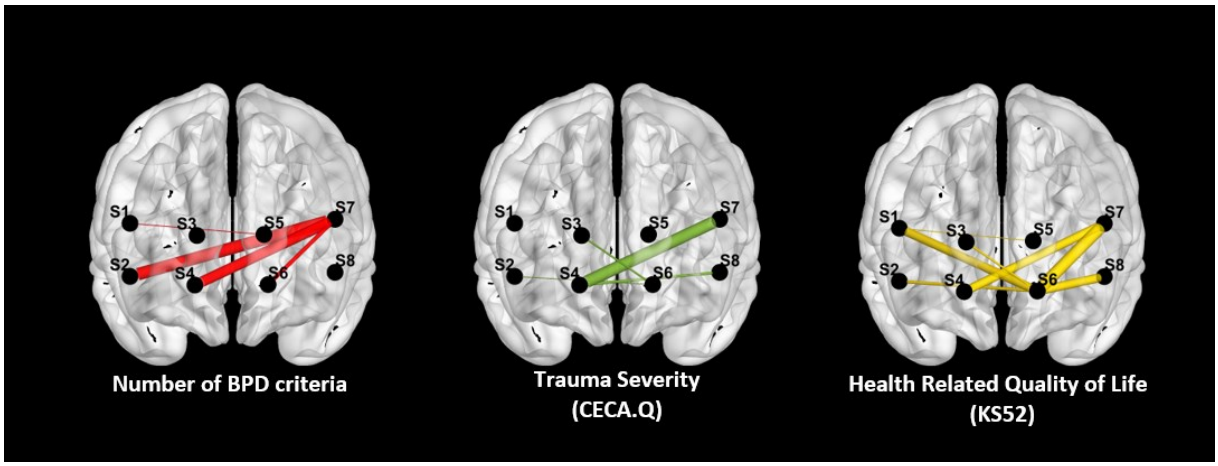


Figure 5 Significant correlations between Connectivity Measures and Clinical Measures; *Note*. Only significant correlations with p < .50 are displayed. Positive correlations between number of BPD criteria and adverse childhood experience and negative correlations between health-related quality of life with prefrontal cortex connectivity.

Discussion

To our knowledge, this is the first study to investigate resting-state PFC oxygenation in adolescents with NSSI. Analyses revealed significantly decreased O_2Hb concentration in the PFC in the NSSI group compared to HC. No group differences were found for HbR and HbT. Thus, hypothesis one was partially confirmed. For hypothesis two, we found decreased O_2Hb concentrations associated with ACE as well as lower HRQoL. Unlike hypothesized, there was no association with BPD pathology. Exploratory analyses on PFC connectivity revealed no significant group differences. However, correlations of the connectivity measures with clinical variables revealed that stronger connectivity was associated with greater BPD pathology, more depressive symptoms, higher general psychological burden and ACE as well as a lower HRQoL.

Our finding of reduced PFC oxygenation in adolescents engaging in NSSI adds some clarity to previous findings on brain functional correlates of NSSI and BPD that were somewhat inconsistent. Several studies using task-based fMRI found *increased* activation of different parts of the PFC, including dlPFC (Dudas et al., 2017), orbitofrontal PFC (Vega et al., 2018), and dmPFC (Malejko et al., 2019) in adults with NSSI and/or BPD. In contrast, meta-analytic research in BPD patients (Schulze et al., 2016) as well as one of the few studies in younger patients with NSSI (n = 15) found *decreased* activation of the PFC during an interference task (Dahlgren et al., 2018). Our finding is in line with the sparse existing literature in adolescents and potentially illustrates a developmental effect; we suggest that activity of the PFC might switch from under- (adolescence) to over- (adult) activation as a function of age and development. Importantly, however, most of the existing studies – in adults and adolescents - have been conducted in relatively small samples, did not carefully distinguish NSSI and BPD, and group differences in brain activation have been found in task-based designs only. Our study is one of the first to show decreased resting-state PFC oxygenation in a relatively large sample of well-characterized adolescents engaging in NSSI.

As our study examined differences in resting-state prefrontal activation and not of task-dependent alterations, a comparison to findings on structural changes in the PFC seems warranted. For example, studies using structural MRI to characterize brain alterations in patients with NSSI and BPD have shown reduced grey matter volume of the bilateral dlPFC as well as the left orbitofrontal cortex (Brunner et al., 2010) and the right orbitofrontal cortex (Chanen et al., 2008). In the same vein, a meta-analysis found reduced grey matter volume of the right inferior frontal gyrus in BPD patients, with greater alterations in older samples (Schulze et al., 2016). A recent study in adolescents with NSSI, however, found decreased brain volume of the insula and the anterior cingulate cortex but no differences in PFC volume compared to healthy adolescents (Ando et al., 2018). Finally, while not caption by our current investigation using NIRS, alterations of deeper brain structures, indexed e.g. by a decreased volume of the pituitary gland or decreased activity of the limbic system, were shown in adolescent and adult BPD patients (Chanen & Kaess, 2012; Dudas et al., 2017; Groschwitz & Plener, 2012; Jovev et al., 2012; Ruocco et al., 2013; Whittle et al., 2009). Taken together, research consistently shows grey matter volume losses in patients with NSSI and/or BPD. These structural differences might contribute to decreased PFC oxygenation during a rest. Furthermore, it might explain prefrontal overaction during specific tasks, as described in the studies above, to compensate structural deficits. However, further research, integrating structural and functional measures, is needed to support these assumptions.

We have shown that NSSI patients and HC differed significantly on mean O_2Hb only. Most studies that investigated alterations in activation using NIRS focused on O_2Hb only and did not report values for the other two hemoglobin variables or only in the respective supplemental material (Husain, Tang, et al., 2020; Ruocco, Medaglia, Ayaz, et al., 2010; Ruocco, Medaglia, Tinker, et al., 2010; Ruocco et al., 2016). Generally speaking, differences between groups are easier to detect when focusing on O_2Hb (Ferreri, Bigand, Perrey, & Bugaïska, 2014). This phenomenon is routed in the physiology of brain activity and reactivity. NIRS technology measures O_2Hb and HbR concentration changes in the

venous vessels. After O_2Hb has arrived in the cells through arterial vessels, the oxygen is partially consumed by the cells resulting in O_2Hb and HbR in the venous vessels. Whenever more oxygen is demanded, the cells are overflooded with O_2Hb. As the consumption of O_2Hb rises, the amount of HbR in the venous vessels rises simultaneously. But because of the overflow of O_2Hb, the ratio of O_2Hb in the venous vessels increases even more (Obrig, Rossi, Telkemeyer, & Wartenburger, 2010). Hence, it is important to report both O_2Hb and HbR and related to this its sum, HbT. But as differences in O_2Hb are bigger than in HbR, it is easier to detect significant results. Hence, the reported group differences in O_2Hb – also of small effect size - support the assumption that PFC activation is decreased in NSSI patients compared to HC during resting-state. Surprisingly, we did not find evidence of associations between PFC oxygenation and specific NSSI behavior. However, there was some evidence that decreased oxygenation was associated with ACE and HRQoL. Longitudinal treatment studies are warranted, assessing the clinical relevance of these associations. In a very first study, the influence of psychotherapy on cortical activation in BPD patients was examined (Ruocco et al., 2016). An increase in cortical activation in patients (n = 18) that reduced their self-harming behavior the most over the course of dialectical behavioral therapy was found. This finding indicates that changes in prefrontal oxygenation may help to monitor treatment progress and outcome.

Recent efforts in neuroimaging research, aimed at elucidating neural concomitants of psychiatric symptomatology, have been directed at studying not only regional brain activation, but rather the interplay between different regions, i.e., brain connectivity. While we found no group differences in PFC connectivity comparing NSSI and HC, O_2Hb connectivity was associated with a range of clinical measures, indicating higher connectivity in case of worse outcome - a seemingly counterintuitive finding. However, the only study examining resting-state connectivity in NSSI, has found greater connectivity between amygdala and the supplementary motor area as well as dorsal anterior cingulate to be associated with NSSI (compared to HC) (Westlund Schreiner

2017). Associations between connectivity and other clinical variables have not been investigated, limiting the integration of the present findings. Potentially, higher connectivity between prefrontal regions might act as a compensatory mechanism in those patients with greater psychopathology in order to counteract overactivation of the limbic system (Niedtfeld et al., 2010; Plener, Kapusta, Kölch, Kaess, & Brunner, 2012), a speculative hypothesis that remains to be tested in future fMRI studies in NSSI and adolescent BPD.

Albeit the known advantages of NIRS technology, including high feasibility and acceptance by patients, facilitating recruitment of larger samples, this method is limited to the study of cortical brain oxygenation - in the present study even limited to PFC brain oxygenation. While the literature mentioned in the present report, as well as the data, speak for the relevance of the PFC for neurobiological research on NSSI and BPD, findings from MRI studies have also emphasized the importance of limbic structures. In fact, the interplay between the limbic and frontal regions has been demonstrated to be crucial for emotion regulation (e.g.,Etkin, Büchel, & Gross, 2015) and as such might be a promising target when investigating neurobiological mechanisms underlying NSSI. Therefore, more research on brain connectivity including prefrontal and limbic regions underlying NSSI as a precursor of BPD, is needed.

Studying resting-state PFC oxygenation may provide insights in basic physiological structures that may determine the phenotype of NSSI and BPD. The current study provides evidence that resting-state NIRS technology is able to differentiate between healthy and psychiatric samples. A critical question in resting state analysis is the required length of the paradigm to be sure that activity levels have stabilized. Research using NIRS technology has shown that signal stabilization occurs within the first minute of application, readily captured by our five minute paradigm (Geng, Liu, Biswal, & Niu, 2017). Further, research has illustrated the general suitability of NIRS devices to index resting-state activation (Niu et al., 2011). Traditionally, connectivity analyses are based

on MRI technology or electroencephalogram. When comparing BPD patients either during resting-state or during tasks, altered connectivity was found with fMRI (Das, Calhoun, & Malhi, 2014; Zhu et al., 2017). Further, lateral asymmetries were illustrated using electroencephalogram (Beeney, Levy, Gatzke-Kopp, & Hallquist, 2014; LeBoeuf, Guilé, Labelle, & Luck, 2016). In the present study, no significant differences in connectivity between the two groups were found. However, it should be emphasized that this sample did not consist of BPD patients solely but of adolescents engaging in NSSI, across the spectrum of BPD pathology. This might explain why no significant differences were detected although patterns of connectivity differed.

As most research on PFC alterations in association with self-injurious behavior is limited to adult BPD patients, the present research extends our understanding of adolescent NSSI. It shows that findings from adult BPD samples are comparable to adolescent NSSI samples. In both groups, alterations in the PFC were found with decreased activation in patients compared to HC regardless of the imaging modality (MRI or NIRS) (Brunner et al., 2010; Chanen et al., 2008; Dudas et al., 2017; Husain, Tang, et al., 2020; Ruocco, Medaglia, Ayaz, et al., 2010; Ruocco, Medaglia, Tinker, et al., 2010; Ruocco et al., 2016; Schulze et al., 2016). Hence, we suggest that decreased PFC activation is a potential feature of NSSI, independent of BPD. As these alterations are readily evident in adolescents, it can be assumed that prefrontal hypoactivation is not a consequence of the long-term course of comorbid psychopathology (such as BPD) or psychotropic medication intake for years - although an increase of functional aberrations in limbic systems in BPD patients has been found with older age (Schulze et al., 2016). One core feature of BPD and NSSI are difficulties in emotion regulation (Carpenter & Trull, 2012; Dixon-Gordon et al., 2015; Glenn & Klonsky, 2009). Successful emotion regulation requires increased activity of the PFC (Fusar-Poli et al., 2009; Golkar et al., 2012; Kim, Cornwell, & Kim, 2012; Kober et al., 2008; Ochsner, Bunge, Gross, & Gabrieli, 2002). Our finding of reduced PFC oxygenation at rest might be one contributing factor underlying these deficits in executive function. However, difficulties in emotion regulation

have been shown in various psychiatric disorders, including depression, anxiety, substance use and eating disorders (Sloan et al., 2017). For example, adult depressive patients showed lower integral values over the course of a verbal fluency task compared to controls (Husain et al., 2020). Studies including clinical controls and explicit measures of emotion regulation are warranted to address the specificity versus generalizability of findings. Hence, the hypoactivation of the PFC found in this study might not represent a specific feature of BPD but supports the assumption that impaired emotion regulation plays a crucial role in NSSI as well as general psychopathology. The finding that self-perceived HRQoL decreased with a decline of PFC activation emphasizes that there might be a relationship between general well-being and prefrontal oxygenation. Further research is required to investigate the relationship between well-being, symptomatology and brain activation in detail utilizing longitudinal designs.

The present study has several limitations that should be considered when interpreting the results. First, although NIRS devices have a great spatial resolution, exact optode placement could only be estimated as we were not able to determine exact positioning with a 3D digitizer. Therefore, exact interpretation of region of interests for connectivity analysis was not possible. Second, as previously mentioned, the focus of this study relied on the PFC surface only. The PFC is known as the neural control center for integrating information from different brain regions. Hence, connectivity and activity analyses covering different regions of interest would be very informative and should be considered in future studies examining BPD and NSSI in adolescents. Furthermore, activation patterns and connectivity analyses could have revealed more distinctive results when using a fNIRS device with a higher density of channels covering the PFC, such as those used in other studies with up to 48 channels covering prefrontal areas (Zhang et al., 2020). Additionally, long-term effects of therapeutic interventions will help to provide more knowledge on the relationship of certain symptoms with neural alterations as well as the durability of these improvements. A further limiting factor of the study sample is that it mainly consisted of female, help-seeking adolescents. Hence, sex differences in

PFC oxygenation could not be examined. When considering previous research on sex differences in brain activation, it becomes clear that differences may be related to certain tasks. For example, sex differences in brain activation have been found for working memory tasks (Li, Luo, & Gong, 2010; Schmidt et al., 2009), for the processing of emotional stimuli (Stevens & Hamann, 2012) as well as for visuo-spatial, memory and emotion tasks (Al Ryalat, 2017). Therefore, it would have been interesting to investigate sex differences in adolescent NSSI patients, especially as self-harming behavior often differs between sexes (Andover, Primack, Gibb, & Pepper, 2010). Lastly, the study sample consisted of a NSSI group and a HC group only. To disentangle whether hypoactivation of the PFC in the NSSI group is specifically related to NSSI or general psychopathology, future studies in the field should include an additional clinical control group.

Conclusion

In conclusion, the present results emphasize the importance to investigate neural alterations in young patients with NSSI and provide some insight on underlying etiological factors that may contribute to impaired emotion regulation, associated with NSSI, comorbid psychopathology, and decreased health related quality of life. Future studies are needed to investigate the specificity of the reported neural alterations in patients with NSSI, including samples of clinical controls, and their long-term clinical trajectories in association with comorbid psychiatric diagnoses.

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Supplemental Material

SM Table 1 T-tests of the prefrontal oxygenation between groups

	NSSI		HC				
	M	SD	M	SD	t-statistic	df	p
Oxygenated hemoglobin	-0.290	0.940	0.064	0.625	2.333	211	.021
Deoxygenated hemoglobin	-0.273	0.699	-0.350	0.663	-0.654	211	.514
Total hemoglobin	-0.562	1.344	-0.287	0.852	1.281	211	.201

Note. Hemoglobin in µmol/l, M = mean, SD = standard deviation, df = degrees of freedom.

SM Table 2 T-test of the prefrontal oxygenation for handedness of participants

Handedness	right		left				
	M	SD	M	SD	t-statistic	df	p
Oxygenated hemoglobin	-0.221	0.878	-0.193	1.089	0.128	211	.899
Deoxygenated hemoglobin	-0.288	0.681	-0.299	0.803	-0.067	211	.947
Total hemoglobin	-0.508	1.219	-0.492	1.695	0.054	211	.957

Note. Hemoglobin in µmol/l, M = mean, SD = standard deviation, df = degrees of freedom.

SM Table 3 T-test of the prefrontal oxygenation for the sex of participants

Sex	female		male				
	M	SD	M	SD	t-statistic	df	p
Oxygenated hemoglobin	-0.188	0.897	-0.420	0.874	1.284	211	.201
Deoxygenated hemoglobin	-0.263	0.704	-0.455	0.578	1.368	211	.173
Total hemoglobin	-0.451	1.273	-0.875	1.151	1.662	211	.098

Note. Hemoglobin in µmol/l, M = mean, SD = standard deviation, df = degrees of freedom.

SM Table 4 Pearson product-moment correlation between prefrontal oxygenation and age, BMI, and intelligence

	Age			BMI			IQ		
	Obs.	r	p	Obs.	r	p	Obs.	r	p
Oxygenated hemoglobin	209	-0.013	.854	210	-0.128	.064	212	0.128	.064
Deoxygenated hemoglobin	209	-0.137	.048	210	0.089	.201	212	0.141	.040
Total hemoglobin	209	-0.084	.228	210	-0.043	.540	212	0.168	.014

Note. Hemoglobin in µmol/l, Obs. = number of observations, M = mean, SD = standard deviation, df = degrees of freedom, BMI = body mass index, IQ = intelligence quotient.

SM Table 5 Regression models of the prefrontal oxygenation

	Sum of Squares	df	Mean Square	F	R^2	RMSE	Coefficient	Standard Error	t	p
Oxygenated hemoglobin										
Model	4.278	1	4.278	5.45	0.025	0.886				.021
Residual	165.737	211	0.785							
Group (NSSI)							-0.353	0.151	-2.33	.021
Deoxygenated hemoglobin										
Model	4.044	3	1.348	2.9	0.041	0.682				.036
Residual	94.851	204	0.465							
Group (NSSI)							0.144	0.119	1.21	.227
Age							-0.063	0.033	-1.91	.058
IQ							0.007	0.004	1.97	.051
Total hemoglobin										
Model	10.577	2	5.289	3.4	0.035	0.032				.035
Residual	324.93	209	1.555							
Group (NSSI)							-0.182	0.216	-0.84	.400
IQ							0.015	0.007	2.29	.023

Note. df = degrees of freedom, F = F-statistic, RMSE = root mean square error, t = t-statistic, IQ = intelligence quotient.

SM Table 6 Mean values and cross correlation coefficients for O_2Hb between channels in NSSI patients

Channel	M	SD	df	1	2	3	4	5	6	7	8
1	0.345	1.376	166	1.000							
				-							
2	-0.155	1.411	166	.603	1.000						
				< .00001	-						
3	-0.011	1.902	166	.651	.588	1.000					
				< .00001		-					
4	-0.191	1.127	166	.553	.649	.545	1.000				
				< .00001	*< .00001*	*< .00001*	-				
5	0.380	1.759	166	.631	.517	.668	.511	1.000			
				< .00001	*< .00001*	*< .00001*	*< .00001*	-			
6	0.042	1.767	166	.548	.591	.564	.680	.550	1.000		
				< .00001	*< .00001*	*< .00001*	*< .00001*	*< .00001*	-		
7	0.250	1.584	166	.619	.521	.570	.488	.596	.567	1.000	
				< .00001	*< .00001*	*< .00001*	*< .00001*	*< .00001*	*< .00001*	-	
8	-0.151	1.281	166	.548	.605	.562	.589	.573	.670	.560	1.000
				< .00001	*< .00001*	*< .00001*	*< .00001*	*< .00001*	*< .00001*	*< .00001*	-

Note. Italic values indicate p-values. M = mean value; SD = standard deviation; df = degrees of freedom.

SM Table 7 Mean values and cross correlation coefficients for O_2Hb between channels in HC

Channel	M	SD	df	1	2	3	4	5	6	7	8
1	-0.106	1.516	41	1.000							
				-							
2	-0.424	0.974	41	.554	1.000						
				.000	-						
3	-0.459	1.297	41	.539	.483	1.000					
				.000	*.001*	-					
4	-0.348	0.622	41	.429	.613	.517	1.000				
				.004	*.000*	*.000*	-				
5	-0.205	1.551	41	.466	.395	.569	.399	1.000			
				.002	*.009*	*.000*	*.008*	-			
6	-0.390	1.176	41	.338	.416	.385	.586	.491	1.000		
				.027	*.006*	*.011*	*.000*	*.001*	-		
7	0.000	1.144	41	.467	.372	.499	.285	.553	.344	1.000	
				.002	*.014*	*.001*	*.064*	*.000*	*.024*	-	
8	-0.382	0.813	41	.454	.613	.436	.513	.490	.532	.528	1.000
				.002	*.000*	*.003*	*.000*	*.001*	*.000*	*.000*	-

Note. Italic values indicate p-values. M = mean value; SD = standard deviation; df = degrees of freedom.

SM Table 8 Z-values for cross correlation coefficients in O_2Hb between NSSI patients and HC

Channel	1	2	3	4	5	6	7	8
1	-							
	-							
2	0.420	-						
	.675	-						
3	0.990	0.840	-					
	.322	*.401*	-					
4	0.930	0.340	0.220	-				
	.352	*.734*	*.826*	-				
5	1.350	0.880	0.910	0.800	-			
	.177	*.379*	*.363*	*.424*	-			
6	1.500	1.340	1.320	0.890	0.460	-		
	.134	*.180*	*.187*	*.374*	*.646*	-		
7	1.230	1.060	0.560	1.360	0.360	1.610	-	
	.219	*.289*	*.576*	*.174*	*.719*	*.107*	-	
8	0.710	1.330	0.960	0.620	0.660	1.240	0.260	-
	.478	*.184*	*.337*	*.535*	*.509*	*.215*	*.795*	-

Note. Italic values indicate p-values; degrees of freedom = 207.

SM Table 9 Pearson correlation coefficients between prefrontal connectivity for O_2Hb and number of BPD criteria

Channel	1	2	3	4	5	6	7	8
1	1.000							
2	0.031	1.000						
	.655							
3	0.051	0.098	1.000					
	.463	*.162*						
4	0.067	-0.001	0.006	1.000				
	.335	*.994*	*.933*					
5	0.138	0.007	0.038	-0.019	1.000			
	.047	*.924*	*.584*	*.787*				
6	0.080	0.112	0.038	0.094	-0.047	1.000		
	.254	*.109*	*.592*	*.178*	*.506*			
7	0.091	0.177	0.077	0.171	0.091	0.149	1.000	
	.193	*.011*	*.273*	*.014*	*.193*	*.033*		
8	0.069	0.036	0.042	0.072	-0.022	0.020	0.015	1.000
	.326	*.606*	*.551*	*.303*	*.757*	*.774*	*.826*	

Note. Italic values indicate p-values; degrees of freedom = 205.

SM Table 10 Pearson correlation coefficients between prefrontal connectivity for O_2Hb and Clinical Global Impression Scale (CGI-S)

Channel	1	2	3	4	5	6	7	8
1	1.000							
2	-0.031	1.000						
	.696							
3	-0.007	0.052	1.000					
	.927	*.514*						
4	-0.043	-0.122	0.046	1.000				
	.590	*.124*	*.566*					
5	0.017	-0.108	0.007	-0.031	1.000			
	.831	*.173*	*.932*	*.700*				
6	0.043	0.035	0.018	0.040	0.104	1.000		
	.586	*.664*	*.827*	*.614*	*.190*			
7	-0.016	-0.014	0.039	-0.099	0.010	0.022	1.000	
	.839	*.858*	*.623*	*.214*	*.904*	*.785*		
8	0.021	-0.028	-0.008	-0.035	0.005	0.058	0.059	1.000
	.795	*.725*	*.924*	*.665*	*.954*	*.466*	*.461*	

Note. Italic values indicate p-values; degrees of freedom = 158.

SM Table 11 Pearson correlation coefficients between prefrontal connectivity for O_2Hb and depression ratings (DIKJ)

Channel	1	2	3	4	5	6	7	8
1	1.000							
2	0.019	1.000						
	.796							
3	0.115	0.013	1.000					
	.118	*.858*						
4	-0.008	-0.079	0.030	1.000				
	.918	*.283*	*.686*					
5	0.102	0.044	0.093	0.020	1.000			
	.166	*.551*	*.209*	*.792*				
6	0.118	0.131	0.108	0.090	-0.011	1.000		
	.109	*.075*	*.141*	*.223*	*.879*			
7	0.093	0.086	0.100	0.148	0.030	0.165	1.000	
	.205	*.243*	*.176*	*.045*	*.689*	*.024*		
8	0.013	-0.021	0.085	0.115	0.002	0.179	0.017	1.000
	.858	*.773*	*.248*	*.119*	*.983*	*.014*	*.820*	

Note. Italic values indicate p-values; degrees of freedom = 184.

SM Table 12 Pearson correlation coefficients between prefrontal connectivity for O_2Hb and Symptom Checklist 90 Revised (SCL-90-R)

Channel	1	2	3	4	5	6	7	8
1	1.000							
2	0.039	1.000						
	.597							
3	0.076	-0.003	1.000					
	.302	*.963*						
4	0.018	-0.038	0.030	1.000				
	.812	*.602*	*.680*					
5	0.101	0.047	0.023	-0.012	1.000			
	.167	*.523*	*.753*	*.866*				
6	0.154	0.166	0.127	0.059	-0.028	1.000		
	.035	*.023*	*.083*	*.417*	*.705*			
7	0.072	0.099	0.074	0.086	0.061	0.162	1.000	
	.328	*.176*	*.313*	*.241*	*.408*	*.026*		
8	-0.003	-0.031	0.040	0.037	-0.075	0.127	-0.006	1.000
	.963	*.671*	*.584*	*.616*	*.303*	*.083*	*.934*	

Note. Italic values indicate p-values; degrees of freedom = 187.

SM Table 13 Pearson correlation coefficients between prefrontal connectivity for O_2Hb and trauma severity (CECA.Q)

Channel	1	2	3	4	5	6	7	8
1	1.000							
2	-0.075	1.000						
	.307							
3	0.073	0.075	1.000					
	.322	*.306*						
4	-0.031	-0.085	0.043	1.000				
	.678	*.244*	*.558*					
5	0.094	-0.016	0.041	0.066	1.000			
	.200	*.824*	*.573*	*.367*				
6	0.122	0.155	0.158	0.086	0.041	1.000		
	.097	*.034*	*.031*	*.241*	*.573*			
7	0.057	-0.011	0.122	0.184	0.052	0.090	1.000	
	.441	*.877*	*.095*	*.012*	*.476*	*.222*		
8	0.075	0.031	0.138	0.160	0.059	0.098	-0.055	1.000
	.306	*.676*	*.059*	*.028*	*.436*	*.180*	*.457*	

Note. Italic values indicate p-values; degrees of freedom = 186.

SM Table 14 Pearson correlation coefficients between prefrontal connectivity for O_2Hb and health-related quality of life (KIDSCREEN-52)

Channel	1	2	3	4	5	6	7	8
1	1.000							
2	-0.056	1.000						
	.474							
3	-0.124	-0.077	1.000					
	.114	*.331*						
4	-0.076	0.047	-0.043	1.000				
	.338	*.553*	*.584*					
5	-0.161	-0.110	-0.109	-0.092	1.000			
	.040	*.164*	*.167*	*.245*				
6	-0.208	-0.175	-0.169	-0.067	-0.051	1.000		
	.008	*.026*	*.031*	*.396*	*.522*			
7	-0.116	-0.129	-0.046	-0.207	-0.044	-0.228	1.000	
	.142	*.101*	*.559*	*.008*	*.574*	*.004*		
8	-0.077	-0.013	-0.157	-0.141	-0.025	-0.208	-0.016	1.000
	.331	*.865*	*.046*	*.073*	*.756*	*.008*	*.839*	

Note. Italic values indicate p-values; degrees of freedom = 161.

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Prefrontal Cortex Oxygenation under Stress in Adolescent Non-Suicidal Self-Injury and Borderline Personality Disorder – A Functional Near-Infrared Spectroscopy Study

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Highlights

- Prefrontal cortex (PFC) oxygenation is increased under stress in adolescents with non-suicidal self-injury (NSSI) compared to healthy controls
- In the NSSI group, greater increases in PFC oxygenation during the stress task were associated with greater Borderline Personality Disorder (BPD) pathology
- Exploratory analyses revealed overall stronger connectivity within the left PFC associated with greater BPD pathology

Abstract

Introduction: Neuroimaging studies suggest alterations in prefrontal cortex (PFC) activity in healthy adults under stress. Adolescents with non-suicidal self-injury (NSSI) report difficulties in stress and emotion regulation, which may be elevated depending on their level of borderline personality disorder (BPD). Systematic research on PFC activity during stress in adolescent with NSSI/BPD is scarce.

Methods: Adolescents (12-17 years) engaging in non-suicidal self-injury (*n*=30) and matched healthy controls (*n*=29) performed a low-demanding resting-state vanilla baseline task and the Trier Social Stress Test (TSST). Mean PFC oxygenation and functional connectivity across the PFC were measured using an 8-channel NIRS system. Alongside self-reports on affect, dissociation, and stress, BPD pathology was assessed via clinical interviews.

Results: Mixed linear-effects models revealed a significant effect of time on PFC oxygenation and a significant time by group interaction, indicating increased PFC activity in patients with NSSI at the beginning of the TSST compared to healthy controls. Greater BPD symptomatology overall was associated with an increase in PFC oxygenation during stress. In exploratory analyses, mixed models addressing changes in PFC connectivity over time as a function of BPD symptoms were significant only for the left PFC.

Conclusion: Results indicate differences in the neural stress response in adolescents with NSSI in line with classic neuroimaging findings in adults with BPD. The link between PFC oxygenation and measures of BPD symptomatology emphasizes the need to further investigate adolescent risk-taking and self-harm across the whole spectrum of BPD and maybe overall personality pathology, and might provide implications for tailored therapeutic interventions.

Introduction [2]

Non-suicidal self-injury (NSSI) is defined as the intentional, self-directed damage of own body tissue without suicidal intent and for purposes not culturally or socially sanctioned Given that NSSI is commonly associated with high psychological strain and large range of comorbid mental disorders (1), NSSI is nowadays regarded as a transdiagnostic marker of risk, in particular for the presence of disorders that are related to severe emotion dysregulation such as depression or borderline personality disorder (BPD). The diagnosis of BPD is nowadays widely accepted as reliable and valid for adolescents (2,3) with prevalence rates ranging from 0.9% to 3.2% among adolescents and young adults in the U.S. (4). Compared with other patient groups, patients with BPD commonly report high levels of psychopathological distress and lower health-related quality of life as well as psychosocial functioning (5,6). BPD is associated with altered emotion regulation and increased stress vulnerability (7–9). Research suggests altered stress-reactivity in patients with NSSI and/or BPD. Adult BPD patients often report a higher burden from stress and greater emotional reactivity to daily stressors compared to healthy controls (HC) but also compared to patients with psychotic disorders (10). Altered stress reactivity in adult BPD patients is characterized by increased negative emotions after stress (11) as well as an attenuated cortisol response (12). The stress-reducing effect of self-injury is described by a decrease of amygdala activation after incisions in adult BPD (13).

Research on stress responses in adolescent BPD patients is sparse. For example, adolescent BPD patients showed an attenuated heart rate response during a dual-task under stress (14). In addition, attenuated cortisol response to stress was also found in

[2] **Abbreviations:** BOLD – blood oxygenation level dependent; BPD – Borderline Personality Disorder; CDT – Color Detection Task; dlPFC – dorsolateral prefrontal cortex; DSM-5 – Diagnostic and Statistical Manual-5; EEG – Electroencephalography; fMRI – functional magnetic resonance imaging; fNIRS – functional near-infrared spectroscopy; HbR – deoxygenated hemoglobin; HC – healthy controls; NSSI – non-suicidal self-injury; O_2Hb – oxygenated hemoglobin; OFC – orbitofrontal cortex; PFC – prefrontal cortex; TSST – Trier Social Stress Test

adolescents with NSSI (15,16). To our knowledge, there are no existing studies examining neural responses to acute stress in adolescents with NSSI or BPD.

General findings from functional MRI (fMRI), electroencephalography (EEG), and functional near-infrared spectroscopy (fNIRS) studies suggest alterations in prefrontal brain activation in response to stress. In healthy participants, stress affects the dorsolateral and ventral right prefrontal cortex (PFC) (17–19), and the orbitofrontal cortex (OFC) (17,18).

Due to its narrowness and functionality, in-scanner stress tasks pose considerable challenges to the research methodology. Some reliable paradigms for stress induction cannot be performed in the scanner without compromising their external validity. Others need extensive modification to be scanner-compatible. fNIRS represents a valuable alternative to study neural response during stress induction paradigms, and is highly correlated with the assessment of blood oxygenation level dependent (BOLD) signals from fMRI, when focusing on the cortical surface (20,21). The main principle of fNIRS is light in the near-infrared spectrum. Through light attenuation due to absorption and scattering, it detects changes in the concentration of oxygenated (O_2Hb) and deoxygenated (HbR) hemoglobin in the surface areas of the brain in real-time (22).

Most research on participants engaging in NSSI focuses on adult BPD patients. To account for developmental aspects and the interlink between NSSI and BPD in adolescents, studies on NSSI across the spectrum of BPD pathology in adolescent samples are needed. In the present study, we aimed to investigate the neural responses of adolescents with NSSI to an acute stressor while i) comparing with a HC group and ii) investigating the stress response as a function of BPD severity. We hypothesized that (1) adolescent NSSI patients would show an increased PFC activation in response to an acute stress task compared to matched HC. We further expected that (2) the severity of BPD pathology would be positively correlated with the increase in PFC activation in the

NSSI group. In exploratory analyses, we aimed to examine PFC connectivity under stress and in association with BPD pathology.

Methods

2.1 Participants

Patients were recruited from the specialized outpatient clinic for risk-taking and self-harming behavior (*AtR!Sk; Ambulanz für Risikoverhaltensweisen und Selbstschädigung* (23) at the Clinic for Child and Adolescent Psychiatry at the Center for Psychosocial Medicine at the University of Heidelberg, Germany). HC were recruited via advertisement and matched to the patient group according to age and sex. The study was approved by the ethical committee of the University of Heidelberg (Study ID: S-685/2015). Previous data from the study, focusing on behavioral and psychophysiological outcomes, were published earlier (24). Details on recruitment procedures and general assessments are provided in *Supplement 1*. The study comprised two appointments. The first appointment included an extensive clinical characterization of subjects via interviews and self-reports. Appointment two comprised the actual stress-induction experiment. Written informed consent was provided by participants and their caregivers before inclusion in the study.

2.2 Procedures

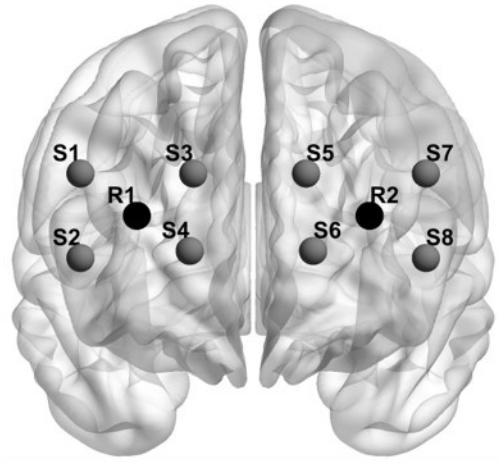
At the first appointment, patients completed a diagnostic interview and answered self-report questionnaires. In the following, diagnostic tools which are relevant for the present manuscript are presented. Further instruments are reported elsewhere (24). For all diagnostic tools, a validated German translation was used. During the interview, demographic data (e.g., school form, age, height, weight) were queried. Suicidality and NSSI behavior were assessed using the *Self-Injurious Thoughts and Behaviors Interview* (SITBI-G) (25), BPD criteria were assessed using the *Structured Clinical Interview* for the DSM-IV (SCID-II) (26). The semi-structured *Mini-International Neuropsychiatric Interview for children and adolescents* (M.I.N.I.-Kid) (27) was conducted with all participants to check for common axis-I disorders. In self-report questionnaires, dimensional characteristics of BPD criteria were determined with the *Borderline Symptom List Short Form* (BSL-23) (28). Moreover, traumatic childhood experiences

were determined with the *Childhood Trauma Questionnaire* (CTQ) (29). In addition to the diagnostic interview, possible influencing factors of the physiological stress reaction were assessed. Therefore, somatization, depression, and anxiety were assessed using the Brief Symptom Inventory (BSI-18) (30). HC also underwent a diagnostic interview and questionnaires which included a demographic assessment, SITBI-G, BSL-23, BSI-18, and CTQ. To make sure that HC participants did not fulfill criteria for any psychiatric disorder the SCID-II Non-Patient (SCID-N/P) (31) was conducted. All interviews and questionnaires were digitized using *LimeSurvey*.

The second appointment comprised the actual experiment including the stress induction paradigm. The detailed procedures are described elsewhere (24). As stress task the Trier Social Stress Test (TSST) for stress induction in children and adolescents was used (32). The TSST consisted of a preparation phase and two stress tasks. During the preparation phase, participants had five minutes to prepare themselves for an interview for their dream school. During phase one of the TSST, they were asked to present themselves in front of two interviewers. They were asked to elaborate on why they were the perfect candidate for a new school. Participants believed that their speech was videotaped. The interviewers did not show any reaction to the participants´ speech and did not answer any questions. After five minutes they interrupted the participant and continued with a mental arithmetic test during which the participant had to subtract mentally. Every time the participant made a mistake, she had to start subtracting from the beginning. Before and after the stress task the participants answered two short questionnaires regarding their momentary mental state (Positive and Negative Affect Schedule, PANAS (33); Dissociation-Tension Scale, DSS-4 (34)) and rated their stress levels on a visual analogue scale ranging from 0 to 100. At the end, all participants were debriefed.

2.3 NIRS Measurement

An eight-channel continuous-wave fNIRS system was used for continuous recordings of PFC oxygenation (OctaMon, Artinis Medical Systems, The Netherlands). It is an optical neuroimaging device that contains eight LED light sources and two PIN diode receivers which are placed with a headband onto the forehead of the participant. The light sources emit light in the near-infrared spectrum which passes the skull cap and is absorbed by the O_2Hb and the HbR. The attenuation of light by different tissues is described by the modified Beer-Lambert-Law. As O_2Hb absorbs light with a wavelength greater than 800nm and HbR absorbs light with a wavelength smaller than 800nm, the OctaMon device emits light in two wavelengths, 760nm and 850nm. Receivers and transmitters are summed up as *optodes*. The inter-optode distance is 35mm which results in an estimated cortical penetration depth of 17mm. The optodes were placed onto the forehead according to the international 10-20 system for EEG electrodes placement (35). The optode configuration and their estimated coordinates according to the Montreal Neurological Institute brain template are displayed in *Figure 1*. When placing the headband to the forehead, the instructor made sure that there was no hair between optodes and skin and that the received light was between 3% and 97% of the emitted light. Values close to 0% indicate that almost no light reaches the receiver whereas values close to 100% indicate that environmental light is also received. According to the general equation for the differential path length factor and in regard to current study protocols, the differential path length factor was set to six centimeters (36). The sampling rate was set to 50 hertz per channel.



	MNI coordinates		
	x	*y*	*z*
Receiver 1	33	61	20
Receiver 2	-35	57	22
Transmitter 1	49	45	32
Transmitter 2	49	53	8
Transmitter 3	17	69	32
Transmitter 4	18	78	10
Transmitter 5	-15	67	32
Transmitter 6	-17	77	10
Transmitter 7	-49	37	36
Transmitter 8	-57	45	8

Figure 1 Optode placement on the forehead (49).

Note. R = receiver; S = source; MNI = Montreal Neurological Institute.

2.4 NIRS Data Preprocessing

Raw hemoglobin density values (O_2Hb and HbR) were recorded by the fNIRS device and sent to a laptop via Bluetooth where it was stored as *.oxy3-data using the Oxysoft software version 3.0.103 (37). All fNIRS data were segmented according to the start and end times of the different blocks during the study. In preparation for the preprocessing of the data, they were imported to MATLAB (38) with the *oxysoft2matlab* function provided by Artinis Medical Systems (The Netherlands). Preprocessing was conducted using the HOMER2 toolbox (39). First, the raw optical density measures were converted to optical density values (*hmrIntensity2OD*). Next, we corrected for motion artefacts as recommended (40). We applied a two-step correction process. The first step was the application of a wavelet-based motion correction with a probability threshold of α=.01 (*hmrMotionCorrectWavelet*). In the second step, we corrected for motion artifacts using the *hmrMotionArtifact* function. This function removes signal changes where the standard deviation exceeds the factor 20 (*SDThresh*) or where the peak-to-peak amplitude exceeded 0.5 (*AMPThresh*) within 0.5 seconds (*tMotion*). High-frequent noise was removed using a 3rd order Butterwoth filter (*LowFrequencyPass*) which only allowed

frequencies lower than 0.5 Hz so that high-frequency physiological noise (e.g., cardiac) was removed. Finally, optical density rates were converted to hemoglobin concentrations in µmol/l (10^{-6} mol/l) for O_2Hb, HbR and total hemoglobin ($HbT=O_2Hb$ +HbR) and were exported for segmentation and further analyses to Stata/SE software version 16.0 (41). After preparing the NIRS data for analysis, recordings from channel five of one HC were removed from the analysis during the CDT and the preparation of the TSST as the recorded values were unrealistically high suggesting that external light was absorbed. Visualizations were prepared using BrainNet Viewer (42).

2.5 Statistical Analysis

All statistical analyses were conducted in STATA/SE software version 16.0 (41). In line with previous research (20,43–47), we calculated mean values and standard deviations for O_2Hb for all relevant time blocks (four time blocks: CDT; Preparation TSST; TSST, divided into the free speech and the mental arithmetic test). For O_2Hb, mean values per channel and a grand mean value per block were calculated. First, to check for differences between groups on demographical data and on the clinical interviews, t-tests (continuous variables) and χ^2-tests (categorical variables) were calculated. Second, a linear mixed-effects model was calculated for O_2Hb to test hypothesis 1. Predictors were TIME (CDT, preparation TSST, free speech, arithmetic task) and GROUP (patients versus HC) as well as their interaction included as fixed effects. The participants´ ID was addressed as random effect. Where applicable, planned contrasts were used to investigate effects of GROUP at single events of TIME to address when effects emerged and how long they lasted. To account for the severity of BPD symptomatology and to test hypothesis 2, models were repeated using a dimensional approach of BPD severity based on BSL-23 and the number of BPD criteria (SCID-II). The interaction of TIME by SYMPTOMATOLOGY was addressed. Consistency between the two measurement modalities (BSL-23 and SCID-II) was inspected. For consistent interactions between the modalities, margin plots at fixed levels of BPD symptomatology (BSL-23: 0 | 1 | 2 | 3 | 4;

BPD criteria: 0 | 3 | 6 | 9) were composed. Next, effects of self-reported levels of dissociation, stress, and positive as well as negative affect on PFC oxygenation were addressed. Each measure was included separately as a predictor to the mixed linear-effects model on O_2Hb and it was checked whether the inclusion of self-reports improved the overall model fit. Group differences on self-reports in response to stress are reported elsewhere (24). Lastly, connectivity between fNIRS channels across the PFC was analyzed; cross correlation coefficients were determined for each time block and analyzed in mixed effects models with TIME and GROUP as predictors. Contrast analyses were used to address changes in connectivity strength by TIME and GROUP. Furthermore, BPD dimensionality (BSL-23 and SCID-II) was also included in additional mixed-linear effects models as indicated above. Due to technical issues, n = 1 HC had to be excluded from the connectivity analysis. Hence, the sample resulted in *n* = 30 NSSI patients and *n* = 28 HC participants. For simplicity and in line with previous research, only O_2Hb was included in all analyses as it is the most informative hemoglobin variable and changes in hemoglobin are easier to detect (48,49).

Results

3.1 Sample Characteristics

For a detailed description of sociodemographic and clinical characteristics of the sample, see *Table 1*. As illustrated in *Table 1*, groups differed on BMI as well as on measures of psychopathological distress.

Table 1 Sociodemographic and clinical characteristics by group

	NSSI group	HC group	*P*
N (% female)	30 (100.00)	29 (100.00)	
Age (SD)	15.733 (0.19)	15.759 (0.24)	*.934*
School, *n* (%)			*.236*
Hauptschule	1 (3.33)	0 (0)	
Realschule	7 (23.33)	5 (17.86)	
Gymnasium	20 (66.67)	22 (78.57)	
Other	2 (6.67)	2 (7.14)	
BMI (SD)	22.127 (0.62)	19.802 (0.35)	*.002*
BSI-GSI	1.535	.243	*<.0001*
BSL-23	1.826	.142	*<.0001*
BSL overall personal state	38.33 (1.64)	80.00 (1.25)	*<.0001*
CTQ	43.87 (1.36)	28.28 (0.40)	*<.0001*
BPD, full diagnosis	7 (23.33)	0 (0.00)	*.004*
BPD fulfilled criteria, n (%)			
Frantic efforts to avoid abandonment	4 (13.33)	0 (0.00)	*<.0001*
Pattern of unstable/intense relationships	16 (53.33)	0 (0.00)	*<.0001*
Identity disturbance	9 (30.00)	0 (0.00)	*<.0001*
Impulsivity	6 (20.00)	0 (0.00)	*<.0001*
Recurrent suicidal/self-injurious behavior	28 (93.33)	0 (0.00)	*<.0001*
Affective instability	21 (70.00)	0 (0.00)	*<.0001*
Chronic feelings of emptiness	10 (33.33)	0 (0.00)	*<.0001*
Inappropriate, intense anger	9 (30.00)	0 (0.00)	*<.0001*
Paranoid ideation/severe dissociative symptoms	9 (30.00)	0 (0.00)	*<.0001*
Comorbidity (ICD-10), *n* (%)			
F0X	0 (0.00)	0 (0.00)	
F1X	3 (10.00)	0 (0.00)	*<.0001*
F2X	0 (0.00)	0 (0.00)	
F3X	17 (56.67)	0 (0.00)	*<.0001*
F4X	14 (46.67)	0 (0.00)	*<.0001*
F5X	1 (3.33)	0 (0.00)	*.321*
F6X	6 (20.00)	0 (0.00)	*.011*
F7X	0 (0.00)	0 (0.00)	
F8X	1 (3.33)	0 (0.00)	*.321*
F9X	3 (10.00)	0 (0.00)	*.080*
Number of suicide attempts (SD)			
lifetime	2.545 (1.92)	0 (0.00)	
past 12 months	1.200 (1.61)	0 (0.00)	
past 6 months	0.545 (0.93)	0 (0.00)	
Number of NSSI events (SD)			
past 12 months	89.033 (144.90)	0 (0.00)	
past 6 months	39.720 (49.79)	0 (0.00)	

*Table 1 N*ote. All values are means with standard deviations (SD) in brackets if not otherwise classified. NSSI = adolescents with five or more events of non-suicidal self-injury; HC = healthy control group; BMI = body mass index; BSI-GSI = Brief Symptom

Inventory - Global Severity Index; BSL-23 = Borderline Symptom List; CTQ = Childhood Trauma Questionnaire; BPD = Borderline Personality Disorder.

On average, participants of the NSSI group fulfilled 3.53 (*SD*=1.85) BPD criteria. Predominantly, they reported the criterion of NSSI and/or suicidality (*n*=28; 93.33%), followed by emotional instability (*n*=21; 70.00%) and unstable and intense relationships (*n*=16; 53.33%). The mean age of NSSI onset was 12 years (*SD*=0.436).

3.2 PFC Activation

General PFC activation over time is visualized in *Figure 2*. The model on O_2Hb was significant (Wald $\chi^2(7)=23.63$; $p=.001$). Main effects were found for TIME ($\chi^2(3)=9.34$; $p=.025$), not for GROUP ($\chi^2(1)=0.43$; $p=.512$). The interaction between TIME and GROUP was significant ($\chi^2(3)=14.33$; $p=.003$). Adjacent contrast for TIME revealed a significant contrast between CDT and preparation of the TSST ($\chi^2(1)=8.30$; $p=.004$), but not for TIME blocks later on (preparation TSST vs. free speech: $\chi^2(1)=1.18$; $p=.277$; free speech vs arithmetic task: $\chi^2(1)=1.00$; $p=.317$). Whilst the O_2Hb in the NSSI group remained unchanged from baseline (CDT) to the preparation phase of the TSST and increased slowly during the course of the TSST, the level of O_2Hb in HC decreased between CDT and preparation phase and slowly increased again during the free speech and the arithmetic task (see *Figure 2*). When comparing O_2Hb between groups during the CDT, baseline O_2Hb in the NSSI group is descriptively lower compared to HC. The difference just failed to reach statistical significance ($t=-1.839$; $p=.071$). Results of the exploratory connectivity analyses are provided in *Supplement 2*.

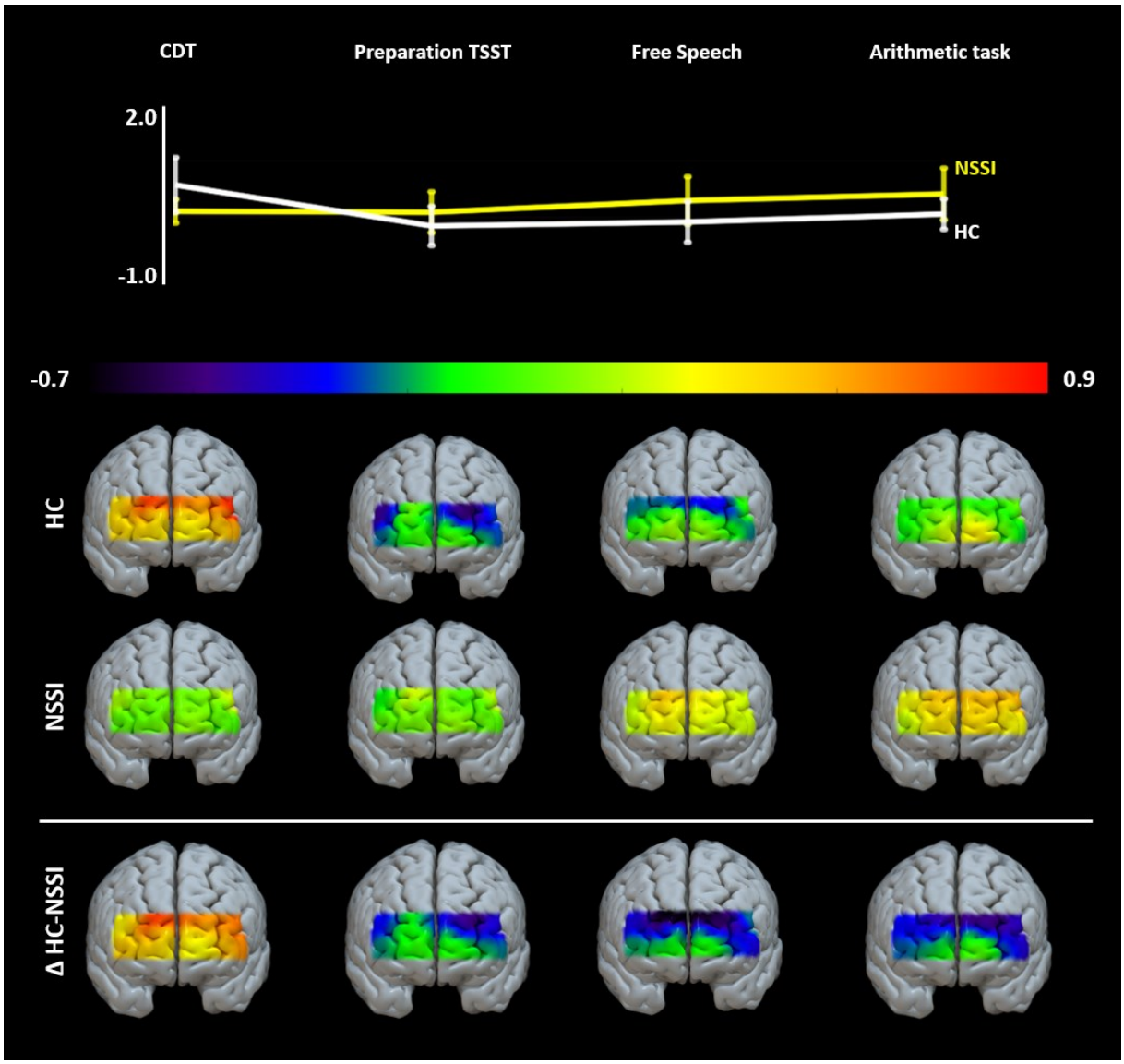


Figure 2 Prefrontal oxygenation over the course of time

Note. Displayed is the prefrontal oxygenation in µmol/l over the course of the CDT (Color Detection Task) and the TSST (Trier Social Stress Test, divided into preparation phase, free speech task, arithmetic task); HC = healthy control group; NSSI = Adolescents with non-suicidal self-injury; Δ HC-NSSI = difference between HC and NSSI group.

3.3 BPD Symptomatology and Changes in PFC Activation

Both continuous models on BPD severity showed significant model fit for O_2Hb (BSL-23: Wald $\chi^2(7)=23.05$; $p=.002$; BPD criteria: Wald $\chi^2(7)=28.08$; $p < .001$). There was a significant TIME by SEVERITY interaction for BPD severity in predicting changes in O_2Hb for BSL-23 ($\chi^2(3)=14.03$; $p=.003$) as well as for the number of BPD criteria ($\chi^2(3)=17.25$; $p=.001$). The respective findings are illustrated in *Figure 3*. As illustrated, higher self-reported BPD pathology (BSL-23) as well as a greater number of BPD criteria (SCID-II) were associated with lower O_2Hb during baseline and higher O_2Hb during the preparation of the TSST and during the TSST itself.

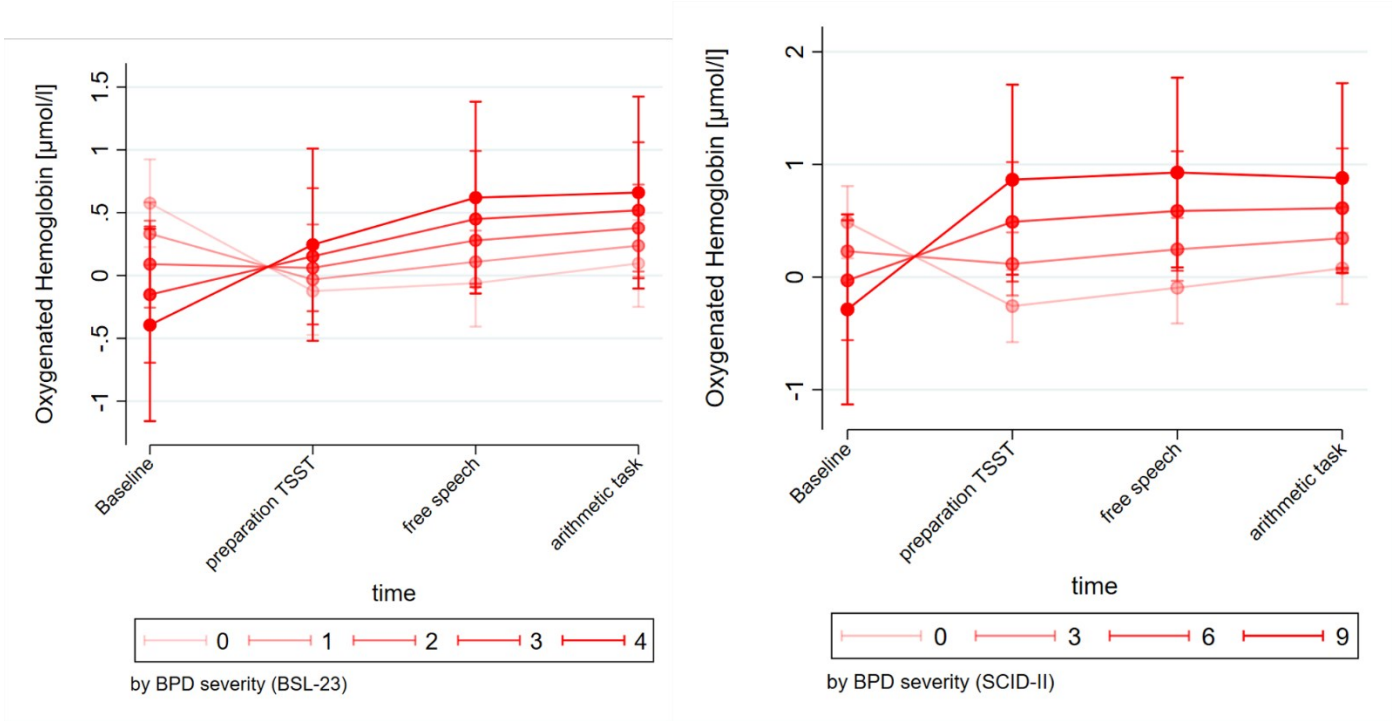


Figure 3 Margins plots between Borderline Personality Disorder symptomatology and prefrontal oxygenated hemoglobin over time.

3.4 Self-Reported Dissociation, Stress and Mood and Changes in PFC Activation

To investigate the influence of self-reports (i.e., dissociation, stress, and negative and positive affect), each measure was included separately as predictor to the linear-mixed effects model on O_2Hb. Adding self-reported dissociation as a predictor did not improve

the respective model fit (Wald $\chi^2(11)=23.15$; $p=.017$). Furthermore, no significant main effect of dissociation on the course of O_2Hb occurred (Coef.=0.022; $p=.836$). In the same vein, self-perceived stress rating as predictor on O_2Hb did not improve the model fit (Wald $\chi^2(11)=28.42$; $p=.003$) and no significant main effect of stress on the course of O_2Hb was found (Coef.=-0.003; $p=.655$). For the inclusion of negative affect as a predictor to the model on O_2Hb the model fit remained significant but did not improve (Wald $\chi^2(11)=27.31$; $p=.004$). The main effect of negative affect was not significant (Coef.=0.004; $p=.948$). Lastly, positive affect was included as a predictor to the linear mixed-effects model on O_2Hb. Again, the model fit did not improve (Wald $\chi^2(11)=37.13$; $p=.0001$) and the main effect for positive affect on the course of O_2Hb was not significant (Coef.=0.051; $p=.180$).

Discussion

To our knowledge, this is the first study investigating neural response indicated by PFC oxygenation to stress in adolescents engaging in NSSI across the spectrum of BPD pathology. We examined PFC activation before and during the TSST. While PFC oxygenation during baseline was descriptively lower in patients engaging in NSSI, it slightly increased in response to stress. In contrast, PFC oxygenation in HC decreased under stress. This result partially supports hypothesis one, expecting greater PFC oxygenation in response to stress among adolescents with NSSI. We found evidence for such group difference, however, unlike expected, resulting mainly from a decrease in PFC activation in HC. . Interestingly, the anticipation of the stressor (preparation of the TSST) was sufficient to cause the decrease in HC. In a former study, we found significant differences in PFC oxygenation at rest (49). Here, in a much smaller sample, the difference at baseline just missed statistical significance, but replicating the finding of lower resting PFC oxygenation in patients with NSSI in principle.

We can speculate, that structural differences, e.g., lower grey matter volume in PFC areas, might cause lower PFC oxygenation during resting-state in patients with NSSI. Decreased grey matter volume in the anterior cingulate cortex of older adults has been related to lower blood flow during resting state (50). Research on BPD and NSSI patients show volume losses in PFC areas (51,52), and decreased activation in the dorsolateral PFC (53). Hence, potential volume losses occurring in association with BPD and/or NSSI pathology might account for PFC hypoactivation during rest in NSSI patients. It has been shown that reduced prefrontal grey matter volume in older adults is associated with a greater increase in PFC activation during dual-task walking compared to single-task walking (54). In addition, lesion studies found altered stress response in people with lesion in the medial PFC (55). This line of reasoning links reduced PFC activation during rest, and overcompensation during demand (e.g., task-based activity) with structural deficits in BPD and NSSI patients that might compromise their capacity to adequately adapt to psychosocial stress.

Concerning hypothesis two, we expected that greater BPD pathology would be related to greater PFC oxygenation. Here, we found that greater BPD pathology (self-report and clinical interview) was associated with decreased PFC oxygenation at baseline and increased PFC oxygenation during the task on a dimensional level. Hence, hypothesis two was supported. In adults with BPD, a negative correlation between grey matter volume loss in PFC and temporal areas and self-reported BPD symptoms was found at rest using MRI (56). Together with results from the present study, these findings support the assumption of linear alterations of neurobiological systems as a function of BPD severity. As BPD-specific changes in PFC oxygenation seem to be prevalent even in adolescents with NSSI, the need for early detection and therapeutic interventions is emphasized.

In exploratory analyses, connectivity across the PFC over time was investigated using mixed linear-effects models. Results revealed significant model fit mainly concerning connectivity between channels covering the left PFC when accounting for BPD symptom severity over time. The left PFC seems to play a crucial role in stress compensation, especially for those reporting greater BPD pathology. Prior research indicates a higher vulnerability of the left PFC to higher cortisol levels and chronic stress compared to the right hemisphere (57). Studies on frontal asymmetry found that left individual frontal activity predicted greater cortisol increases during stress (58). Decreased activity in the orbitofrontal PFC seems to be related to an increased cortisol secretion after stress (17). Interestingly, cortisol response is reported to be attenuated after stress in adolescent NSSI (15).

As reported elsewhere (24), cortisol secretion of the present sample increased after the stress task in both groups. However, compared to controls, NSSI patients´ cortisol increase after stress was attenuated and greater BPD pathology (self-report and clinical interview) was associated with a more attenuated increase in cortisol secretion after stress (24). These results on the cortisol response are in line with prior findings and add

to the overall picture. In the control group, prefrontal oxygenation decreased under stress and cortisol secretion increased, in line with findings from studies in healthy adults (19,59). This finding suggests a maladaptive interplay between the PFC and the hypothalamus–pituitary–adrenal axis in NSSI. Findings from this study extended by the results from Koenig et al. (2022) (24) implicate that that neural mechanisms as a function of BPD severity are associated with the observed attenuation in physiological stress reactivity (i.e., blunted cortisol response) in NSSI. This blunted cortisol response in adolescents with NSSI has been previously described and replicated in independent studies (15,16) and might present a physiological marker for difficulties in emotion regulation in NSSI. Here, we provide evidence on a potential neural mechanism associated with this phenomenon, related to alterations in PFC oxygenation and its connectivity. Importantly, this pattern seems to manifest on a continuum as a function of BPD severity. Prior research found that greater connectivity between prefrontal and limbic areas in healthy adolescents during rest was associated with greater cortisol reactivity to an acute stressor whereas this relationship was only weak or inversed in depressed adolescents with and without NSSI (60). In a sample of patients at ultra-high-risk for psychosis reduced grey matter volume in the PFC was associated with a blunted response of the hypothalamus–pituitary–adrenal axis (61). Taken together, structural deficits of the PFC resulting in altered activation patterns in adolescent NSSI may compromise the capacity to regulate emotions and stress, both, on a psychological and physiological level and seem to be related to BPD severity. Future research should assess real-time prefrontal reactivity to stress in relation to physiological reactivity in NSSI to disentangle the temporal associations between cortex activation and physiological response – also in consideration of neural feedback loops.

This study comes with several limitations. First, only female adolescents were investigated. For neural activation, sex differences are often reported (e.g., (62–64)). Hence, the findings from this study are not readily transferable to male adolescents with NSSI and further research is needed. Second, sample size was a limiting factor when

investigating the influence of BPD pathology Lastly, connectivity measures implemented in the present study are limited because of the limited spatial resolution of NIRS measurement in comparison to other neuroimaging techniques. Other neuroimaging modalities such as fMRI have a greater spatial resolution and even provide insight into the connectivity with deeper subcortical brain structures such as the limbic system which is known to be relevant in emotion regulation and BPD.

Conclusion

Taken together, this study shows differences in the neural response of the PFC to a psychosocial stress task comparing adolescents with and without NSSI. Whereas PFC oxygenation decreased in HC, PFC oxygenation slightly increased in adolescents with NSSI. The trajectory of PFC oxygenation from rest to stress was overall associated with the severity of BPD pathology. To our knowledge, this is the first study to investigate PFC oxygenation during stress in a sample of adolescents with and without NSSI across the spectrum of BPD pathology. Further research is needed to replicate and extend on these findings. The finding that the severity of BPD pathology is related to alterations in the PFC activation during stress emphasizes that not only patients with full-blown BPD might benefit from tailored therapeutic interventions in stress regulation, but also patients with NSSI only partially fulfilling BPD criteria.

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Supplemental Material

Supplement 1: Detailed recruitment procedures and assessments

The recruitment period lasted from July 2016 until May 2018. Inclusion criteria for the patient group were at least five incidents of NSSI during the past 12 months, age between 13 and 17 years, and female sex. Inclusion criteria for the HC group were age between 13 and 17 years and female sex. General exclusion criteria were deficient language skills or clinically relevant impairments in intelligence, glucocorticoid medication intake, pregnancy, any underlying neurological or endocrinological diseases, acute psychosis, acute suicidality, substance dependency, a body mass index (BMI) below 17.5 kg/m^2 or above 30 kg/m^2. Additional exclusion criteria for the patient group was current BPD drug treatment. A further exclusion criterion for participants of the control group was any current and former psychiatric disorder or lifetime NSSI. After completion of the study, every participant received an allowance of 40€ for study participation.

For the NSSI group *n* = 180 (100%) adolescents were screened. *N* = 37 (20.56%) were included in the study. Reasons for study exclusion are provided in the *Supplemental Material* (see Supplement 1). During study participation, *n* = 7 participants of the NSSI group dropped out of the study: *n* = 1 (0.56%) had acute headaches, *n* = 2 (1.11%) showed dissociative symptoms that required interruption of experimental procedures, *n* = 3 (1.67%) did not show up for the second appointment, *n* = 1 (0.56%) due to further reasons not documented in detail). This resulted in a final sample of *n* = 30 (16.67%) for the NSSI group. *N* = 66 (100%) female adolescents were screened as HC for study participation. Of those *n* = 31 (46.97%) were included in the study. *N* = 1 (1.52%) refused to participate in the stress task and hence dropped out of the study. Finally, *n* = 1 (1.52%) had to be excluded from NIRS analyses due to technical issues during the assessment. This resulted in a sample of *n* = 29 HC (43.94%).

Supplemental Table 1 Reasons for study exclusion

	NSSI group	HC group
Age (18 and older)	16	0
Missing study informed consent	16	0
Acute substance use disorder	16	0
Male sex	15	0
BMI lower 17.5 or greater 30	9	2
Study withdrawal	9	8
Diagnostic assessment older than 3 months	8	0
Medical treatment for BPD	7	0
Acute psychotic disorder	3	0
Neuroendocrinological diseases	3	2
Not showing up for appointment	3	1
Unsuccessful contact attempts	2	3
Acute suicidality	1	0
Inpatient treatment	1	0
Glucocorticoid drug intake	1	2
Pregnancy	1	0
Neurological diseases	1	0
Participation in former similar studies	0	2
Antihistamine intake	0	1
Further reasons	3	0
NSSI only: Less than five events of NSSI	28	-
HC only: Current or former psychiatric treatment	-	5
HC only: Lifetime events of NSSI or suicidality	-	4

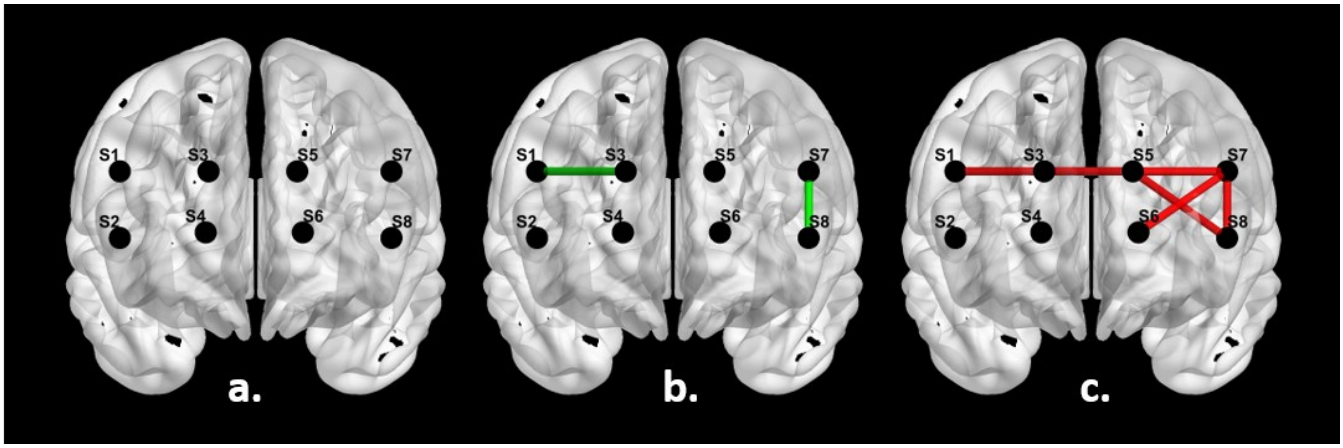
Note Supplemental Table 1. NSSI = non-suicidal self-injury; HC = healthy control; BMI = body mass index; BPD = borderline personality disorder.

Supplement 2: Results form Exploratory Connectivity Analyses

Cross-correlation coefficients for each time block (CDT, preparation TSST, free speech TSST, arithmetic task TSST) were calculated between all channels for each group. Results on connectivity are comprehensively summarized in Supplemental Figure 1. These cross-correlation coefficients were included in a linear mixed-effects model for each channel pair with time block and group as predictors. None of the models reaches statistical significance (see Supplemental Figure 1*,* brain template *a.*). Continuous models on BPD severity operationalized by the BSL-23 (see Supplemental Figure 1, brain template *b.*) showed significant model fit for the connectivity of channel #S1 to

channel #S3 with a significant TIME by SEVERITY interaction (Wald $\chi^2(7) = 14.57$; $p = .042$; BSL-23: $\chi^2(3) = 9.89$; $p = .020$), as well as for channel #S7 to #S8 but with no significant TIME by SEVERITY interaction (Wald $\chi^2(7) = 17.28$; $p = .016$; BSL-23: $\chi^2(3) = 1.02$; $p = .795$). In addition, continuous models on BPD severity operationalized by the number of BPD criteria (SCID-II; see Supplemental Figure 1, brain template *c.*) showed significant model fit predicting the connectivity of channel #S1 to channel #S5 with no significant TIME by SEVERITY interaction (Wald $\chi^2(7) = 14.26$; $p = .047$; number of BPD criteria: $\chi^2(3) = 6.82$; $p = .078$). Furthermore, channel #S5 showed a significant model fit to channel #S7 with a significant TIME by SEVERITY interaction (Wald $\chi^2(7) = 15.61$; $p = .029$; number of BPD criteria: $\chi^2(3) = 11.07$; $p = .011$), to #S8 with no significant TIME by SEVERITY interaction (Wald $\chi^2(7) = 14.77$; $p = .039$; number of BPD criteria: $\chi^2(3) = 4.91$; $p = .178$), and from channel #S7 to #S6 with a significant TIME by SEVERITY interaction (Wald $\chi^2(7) = 17.10$; $p = .017$; number of BPD criteria: $\chi^2(3) = 11.95$; $p = .008$), and to #S8 with no significant TIME by SEVERITY interaction (Wald $\chi^2(7) = 16.75$; $p = .019$; number of BPD criteria: $\chi^2(3) = 1.14$; $p = .767$).

Supplemental Figure 1: Significant mixed models for connectivity analyses on O2Hb and with Borderline Personality Disorder dimensionality



Note Supplemental Figure 1. a. – mixed model on O2Hb; b. – mixed model on O2Hb with the number of Borderline Personality Disorder criteria as predictor; c. – mixed model on O2Hb with the score of the Borderline Symptom Checklist (BSL-23) Score as predictor; displayed are p-values < .05.

Prefrontal Cortex Oxygenation and Autonomic Nervous System Activity under Transcutaneous Auricular Vagus Nerve Stimulation in Adolescents

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Introduction[3]

Human behavior is the result of a complex interplay of various factors. Environmental influences encounter biological predispositions on a neural and peripheral level. The result of this individual ensemble is the foundation of our cognitive, affective, behavioral, and physiological responses (Thayer & Lane, 2000). In daily life, well-developed emotion regulation and inhibitory skills seem crucial to adhere with societal norms. In turn, difficulties in emotion regulation are often associated with the development and maintenance of psychiatric disorders (Compas et al., 2017). Thayer and Lane have proposed the *Neurovisceral Integration Model* (NIM) to explain the complex interplay of visceral and neural structures that result in adaptive and maladaptive responses to changing environmental demands (Thayer & Lane, 2000). On a functional level, this model outlines a neural network constituting the internal regulatory system for goal-directed behavior, adaptability, and health (Thayer, Hansen, Saus-Rose, & Johnsen, 2009). On a structural level, the model explains the integration of peripheral information by the autonomic nervous system (ANS) in the central autonomic network (CAN) which represents functional units of the central nervous system (CNS) (Thayer et al., 2009). The promoted network consists of higher-order bidirectional feedback loops and pathways in the brain, serving as information processor. It includes structures such as the prefrontal cortex (PFC), cingulate cortex, insula, amygdala, hypothalamus, and nuclei in the brainstem, namely the nucleus of the solitary tract, the nucleus ambiguous,

[3]**Abbreviations:** ANS – autonomic nervous system; BDI-II – Beck Depression Inventory; CAN – Central autonomous nervous system; CDRS-R – Children´s Depression Rating Scale – Revised; CDT – Color Detection Task; CECA.Q – Childhood Experiences of Care and Abuse questionnaire; C-GAS – Children´s Global Assessment Scale; CNS – central nervous system; DERS – Difficulties in Emotion Regulation Scale; (dl)PFC – (dorsolateral) prefrontal cortex; ECG – electrocardiography; EDA – electrodermal activity; (f)NIRS – (functional) near-infrared spectroscopy; HR(V) – heart rate (variability); IBI – inter-beat interval; iSCR – integrated skin conductance response; mPFC – medial prefrontal cortex; NVM – neurovisceral integration model; PIN – positive intrinsic negative; rMSSD – root Mean Square of Successive Differences; ROI – region of interest; sAA – saliva alpha-amylase; SCID-II – Structured Clinical Interview for DSM-IV Personality Disorders; SITBI-G - Self-Injurious Thoughts and Behaviors interview; TTH – Tension type headache; (t)VNS – (transcutaneous) vagus nerve stimulation

and the dorsal vagal motor nucleus (Thayer et al., 2009). Structures of the CAN process information of the ANS and, in turn, the ANS is regulated by the CAN. The ANS can be divided into two structures: the sympathetic and parasympathetic branch. Whereas the sympathetic branch is associated with the activation and up-regulation of glands, unstriated muscles, and blood vessels, the parasympathetic branch is predominantly associated with inhibitory processes.

At the transition from the CAN to the ANS, the vagus nerve serves a central role. Anatomically, the vagus nerve consists of different types of fibers, which carry afferent and/or efferent information respectively (Berthoud & Neuhuber, 2000; Yuan & Silberstein, 2016). Most fibers transmit afferent information from visceral organs to the brain (up to 80 %) (Bonaz, Bazin, & Pellissier, 2018; Yuan & Silberstein, 2016). The afferent fibers terminate in the area postrema, the spinal nucleus of the trigeminal nerve, and the nucleus of solitary tract. In contrast, the efferent fibers, emerge from the nucleus ambiguous and the dorsal motor nucleus which are the root of preganglionic parasympathetic fibers (Yuan & Silberstein, 2016). The outlet of the vagus nerve to the peripheral system is the jugular foramen. Most afferent cell bodies lie in the jugular (superior) ganglion and the nodose (inferior) ganglion (Berthoud & Neuhuber, 2000; Yuan & Silberstein, 2016). After passing these ganglia, the vagus nerve branches into the auricular branch, the meningeal branch, the sympathetic branch, the pharyngeal branch, and the laryngeal branch (Berthoud & Neuhuber, 2000; Yuan & Silberstein, 2016). That way, the vagus nerve provides higher brain structures, as the PFC, with feedback from the body, to integrate the information, and exhibit inhibitory control over the ANS, especially via the amygdala (Thayer & Lane, 2009). One of these variables controlled by inhibitory feedback loops is cardiac vagal activity which can be indexed by vagally-mediated heart rate variability (HRV) - representing the variation in the length between successive heart beats (Laborde, Mosley, & Thayer, 2017; Malik et al., 1996). HRV serves as an indicator of central-peripheral neural feedback and successful CNS-ANS integration (Thayer et al., 2009). If these integration mechanisms are working

insufficiently and HRV is reduced, somatic and psychological well-being is compromised. The interconnection between HRV and neural activation is supported by meta-analytic findings from neuroimaging studies suggesting that HRV may serve as an index of the successful integration of information in the neural loop between the ventromedial PFC and brainstem, in communication and exchange with peripheral physiological processes (Thayer, Åhs, Fredrikson, Sollers, & Wager, 2012). In line with this finding, emotion regulation may rely on the association between HRV, the medial PFC, and amygdala activity (Sakaki et al., 2016). Hence, higher HRV has been shown to be associated with a stronger medial PFC-amygdala connectivity (Sakaki et al., 2016). Ventrolateral PFC-amygdala connectivity was associated with higher HRV only in younger adults, not in older ones (Sakaki et al., 2016). These findings support the core assumptions by the NIM, highlighting a neural feedback loop in response to peripheral information. They also emphasize that the ANS and neural activation cannot be considered as independent systems but illustrates their well-balanced interplay.

Based on the close relationship between HRV and PFC activation, it seems reasonable to assume that HRV and PFC activation can be modulated via transcutaneous vagus nerve stimulation (tVNS). Active tVNS stimulation has been shown to activate the neural loops proposed by the NIM with activation in PFC regions, limbic regions, and the brainstem which represent central vagal projections (Badran et al., 2018; Frangos, Ellrich, & Komisaruk, 2015; Kraus et al., 2007; Yakunina, Kim, & Nam, 2017), whereas sham stimulation differed in its activation patterns. As the neural projections of tVNS activate those regions that are involved in inhibition and emotion regulation, and given that HRV represents an index of vagal activity, it seems plausible to assume that HRV is also affected by tVNS (Murray, Atkinson, Mahadi, Deuchars, & Deuchars, 2016). Research indicates that the effect of tVNS on HRV might be more complex than initially expected. For example, in one study short term tVNS revealed increased HRV only on selected indices of HRV, but not on others, and long-term tVNS was more effective in influencing HRV in female participants compared to males (De Couck et al., 2017). Other

studies have found no effect of tVNS on HRV (Burger, Van der Does, Thayer, Brosschot, & Verkuil, 2019; Burger, Van Diest, et al., 2019), in line with a recent meta-analysis (Wolf, Kühnel, Teckentrup, Koenig, & Kroemer, 2021). However, different studies applied different stimulation parameters and used different stimulation sites, potentially explaining discrepancies and inconsistencies in study findings.

Studies combining measures of PFC activity, ANS function and active manipulation using tVNS are still sparse. Condy and colleagues investigated PFC activation and HRV during an inhibition task using functional near-infrared spectroscopy (fNIRS) (Condy, Friedman, & Gandjbakhche, 2020). Instead of activating neural feedback loops via tVNS, they used an inhibition task to activate endogenous inhibitory control processes in the PFC. Their results supported the NIM partially as prefrontal activation at rest was associated with HRV. During the inhibition task, however, no such association was observed (Condy et al., 2020).

To our knowledge, there has been no study investigating PFC activation using fNIRS and HRV under active manipulation using tVNS. Hence, the aim of the present study was to further investigate the assumptions made by the NIM and to disentangle the role of the vagus nerve, linking PFC activation and peripheral physiological processes. Hence, we aimed to study changes in parasympathetic measures (HRV), sympathetic measures (electrodermal activity (EDA), saliva alpha-amylase (sAA), and those of mixed origin (heart rate (HR)) under tVNS compared to sham stimulation and their relation to PFC activation. We hypothesized that (1) tVNS compared to sham stimulation would result in an increase of parasympathetic activity (HRV) and a decrease in sympathetic activity (EDA, sAA) as further reflected by a decrease in measure of mixed influence (HR). We further hypothesized that (2) tVNS compared to sham stimulation would be associated with an increase in PFC activation and that (3) the relative increase in PFC activation would be associated with the relative increase in parasympathetic activity and the relative decrease in sympathetic activity. In exploratory analyses, we examined

different regions of interest (ROI) of PFC activity as well as their connectivity, in association with the aforementioned changes in ANS activity.

Methods

2.1 General procedures

Data for the present, secondary analyses were taken from a previously published study (Koenig, Parzer, et al., 2021). The study was approved by the ethics committee of the Medical Faculty, Heidelberg University (Study ID: S-365/2017) and registered at the German Clinical Trial Register (Study ID: DRKS00011112) and the World Health Organization (Universal Trial Number: U1111-1188-0829). Only data from non-depressed controls (14-17 years) with tension-type headache (TTH) were used for the present analyses. As the use of the respective tVNS device under medical device regulations does not allow the application of tVNS in a fully healthy non-clinical sample, adolescents with TTH were recruited. Participants were recruited between October 2017 and January 2018 via public advertisement. All participants and their caregivers provided written informed consent and participants received an allowance of 50€ for study participation. Hence, inclusion criteria were age between 14-17, TTH as assessed through a screening interview, and written informed consent provided by the participants and their caregivers. Exclusion criteria were poor German language skills, regular intake of glucocorticoid medication, pregnancy, neurological or endocrinological diseases, cardiovascular diseases, acute suicidality, and present affective mood disorders as well as current psychotherapeutic treatment. A formal sample size calculation (i.e., power analysis) was not conducted a priori. The sample size in the present study is comparable to studies using tVNS (e.g., Burger et al., 2019: n = 29 adults per group; De Couck et al., 2017: n = 30 adults) as well as studies using fNIRS (e.g., Condy et al., 2021: n = 38 adults).

2.2 Clinical assessments and self-reports

In a first appointment, participants underwent a diagnostic interview which took about two hours. Alongside general information (such as school type, height, weight), psychopathology was determined. All interviews and questionnaires were used in their

German version. Details on the respective assessments are reported elsewhere (Koenig, Parzer, et al., 2021). In brief, depression and depression severity were measured using the *Children's Depression Rating Scale – Revised* (CDRS-R; Poznanski, Freeman, & Mokros, 1985). Common axis-I disorders were assessed using the semi-structured *Mini International Neuropsychiatric Interview for Children and Adolescents* (M.I.N.I.-KID; Sheehan et al., 1998). Personality disorders were assessed, using the respective sections of the *Structured Clinical Interview for DSM-IV Personality Disorders* (SCID-II; Wittchen, Zaudig, & Fydrich, 1997). Suicidal ideation and non-suicidal self-injury were assessed using the *Self-Injurious Thoughts and Behaviors interview* (SITBI-G; Fischer et al., 2014; Nock, Holmberg, Photos, & Michel, 2007). Lastly, the interviewer rated the severity of psychiatric symptoms based on the *Children´s Global Assessment Scale* (C-GAS; Schaffer et al., 1983). Additionally, participants answered self-report questionnaires including the *Childhood Experiences of Care and Abuse* questionnaire (CECA.Q; Kaess et al., 2011), the *Difficulties in Emotion Regulation Scale* (DERS; Gratz & Roemer, 2004), and the *Beck Depression Inventory II* (BDI-II; Beck, Steer, & Brown, 1996). After the first appointment, participants were asked to attend to a second appointment, which included the tVNS stimulation and a neurobiological assessment.

2.3 Stimulation Experiment

The second appointment took about two hours. To control for circadian patterns, all appointments were scheduled in the afternoon after 1 pm. However, unlike implemented by other trials, participants were not informed to avoid caffeine and strenuous exercise 12 hours before the appointment. After arrival at the laboratory, participants completed the *State-Trait Anxiety Inventory* (STAI; Spielberger, Gorsuch, & Lushene, 1983), a self-report questionnaire to assess state and trait anxiety. Following this, participants were instructed to put on the electrocardiographic (ECG) device and the NIRS device was attached to their forehead (for detailed information see respective sections below). The study design was a within-subject cross-randomized design. Hence, participants were

randomized to the tVNS or sham condition for block one. During block two they received sham or tVNS, respectively. At the beginning of each block a baseline measurement of ECG and NIRS took place during a five minute color detection task (CDT; Jennings, Kamarck, Stewart, Eddy, & Johnson, 1992). Here, participants were asked to sit in front of a computer screen on which a colored rectangle was displayed. Every few seconds, the rectangle changed its color (red, green, blue, yellow, purple, white). The participants were instructed to count the number of appearances of one color. After the CDT, the 15 minutes pre-stimulation phase started. During this phase, participants received tVNS or sham stimulation while they were watching a non-arousing movie. Following the pre-stimulation phase, a series of emotion recognition tasks were administered. Detailed information concerning these tasks can be found elsewhere (Koenig, Parzer, et al., 2021). Data on the respective tasks are not reported in the present manuscript. For a better overview of the study design see also *Figure 1.*

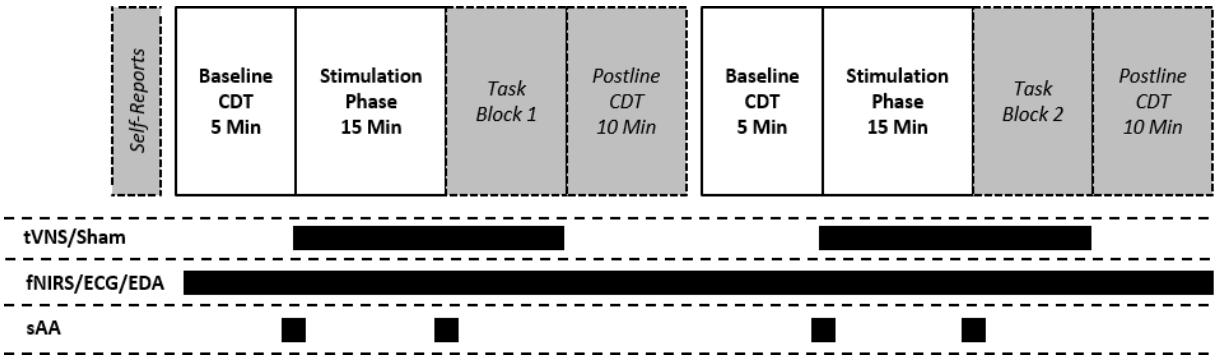


Figure 1 Study Design; *Note*. In the present analyses, only measurements from bold printed blocks (baseline and stimulation phase) are included. Results from tasks in grey-colored blocks with dashed lines are reported elsewhere (Koenig et al., 2019).

2.4 tVNS/Sham Stimulation

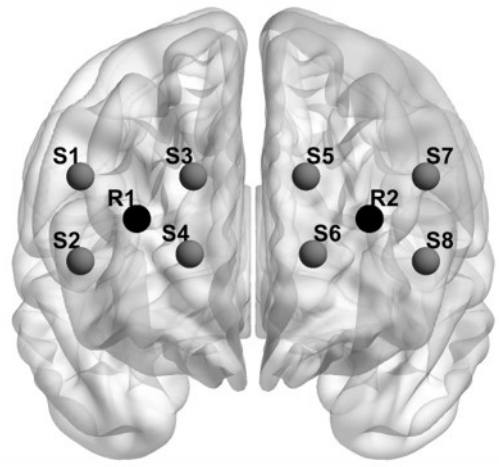
Reporting of tVNS stimulation, adheres to recent recommendations (Farmer et al., 2021). For tVNS and sham stimulation, the VITOS® tVNS device was used (tVNS Technologies GmbH, Erlangen, Germany). It is a battery-operated handheld device for auricular vagus

nerve stimulation with electrodes that are attached to the concha. It has a CE marking for the treatment of depression and pain, meaning that health, safety and environmental protection standards are compliant with EU regulations. The concha is known to be innervated by the auricular branch of the vagus nerve (also termed Arnold´s nerve) and stimulation of the cymba conchae provokes a strong activation of the vagus nerve (Yakunina et al., 2017). The stimulator applies an impulse frequency of 1 Hz with a pulse width of 250 µs. For this study, the stimulation was applied unilateral to the left ear and cycled with 30s on and 30s off with a stimulation intensity of 0.5 mA. In preparation for the stimulation, the left concha of the participants was cleaned with alcohol swipes. The technical settings remained the same for sham stimulation. For sham stimulation the electrode was placed at the left ear lobe of participants, not innervated by the vagus nerve (also see Koenig et al., 2021).

2.5 Physiological Measurement

Changes in PFC oxygenation were measured using an eight-channel continuous-wave NIRS device (Octamon, Artinis, The Netherlands). It is an optical neuroimaging device that consists of light transmitters and receivers and is attached with a headband to the participants´ forehead. The eight light transmitters emit light within the near-infrared spectrum. This light penetrates the skull and the cerebrospinal fluid before it encounters the PFC. All these tissues have unique light absorbing and scattering properties. The attenuation of light is calculated with the modified Beer-Lambert law which calculates the absorption of light within different tissues. The oxygenated hemoglobin of the PFC best absorbs light with a wavelength greater than 800 nm whereas deoxygenated hemoglobin best absorbs light with a wavelength smaller than 800 nm. Hence the light transmitters of the NIRS device emit light with two wavelengths (760 nm and 850 nm) to ensure to measure changes in the concentration of oxygenated hemoglobin as well as of deoxygenated hemoglobin. The emitted and scattered light is recorded by two positive intrinsic negative (PIN) diode receivers with ambient light protection. Hence, eight

channels are formed. The positioning of transmitters and receivers (summarized as optodes) on the participants´ forehead is displayed in *Figure 2.* The inter-optode distance was 35 mm and optodes were placed onto the forehead according to the international 10-20 system for EEG electrodes placement (Jaspers, 1958). The estimated positioning of the optodes according to the Montreal Neurological Institute template is reported in *Figure 2*. When placing the headband, the investigators made sure that there was no hair between the headband and the skin as hair impairs the light absorption exceedingly. The signal strength should be between 3% and 97%. Values close to 0% indicate that the absorption of the tissue is so high that almost no light is received by the PIN diodes whereas values close to 100% indicate that external light was received and measured. According to general recommendations (Scholkmann & Wolf, 2013), the differential path length factor was set to six centimeters. The sampling rate was set to 50 Hz. Due to the inter-optode distance of 35 mm the penetration depth of light was around 17 mm.



Montreal Neurological Institute coordinates			
	x	*y*	*z*
Receiver 1	33	61	20
Receiver 2	-35	57	22
Transmitter 1	49	45	32
Transmitter 2	49	53	8
Transmitter 3	17	69	32
Transmitter 4	18	78	10
Transmitter 5	-15	67	32
Transmitter 6	-17	77	10
Transmitter 7	-49	37	36
Transmitter 8	-57	45	8

Figure 2 Optode Placement of the functional near-infrared device on the forehead (Koenig, Höper, et al., 2021); *Note*. S = Source; R = Receiver.

HR and HRV were assessed using an electrocardiographic device (ECG Move3 Sensor, Movisens, Karlsruhe, Germany). The device was attached with a belt to the chest of the

participants at the lower end of the sternum and recorded inter-beat intervals (IBI) between adjacent heart beats with a sampling rate of 1024 Hz. For the assessment of EDA, participants wore an edaMove sensor (movisens GmbH, Karlsruhe, Germany) which was attached to their left wrist. In preparation for the assessment, the wrist was degreased using an alcoholic wipe. The edaMove sensor consists of two Ag/AgCl electrodes with a diameter of 10 mm which are filled with an electrode gel (containing ≤ 0.5% chloride salt). The electrodes were attached to the left palm onto the thenar and hypothenar hand muscles using adhesive rings. Data were continuously sample at a frequency of 32 Hz. Saliva samples were taken after the CDT and after each of the stimulation phases to determine sAA (see *Figure 1*). Saliva samples were collected using cotton rolls in a collection tube (Salivette®, Sarstedt, Nümbrecht, Germany). Participants were asked to carefully chew on the cotton roll for 60 seconds and place the saliva-moist roll back into the tube. The samples were stored in the freezer at -20° Celsius until analysis. For a better overview of the measurement of physiological variables throughout the study see also *Figure 1.*

2.6 Physiological Data Preprocessing

The NIRS device recorded hemoglobin density values which were saved as raw optical density values using Oxysoft software (Artinis Medical Systems, 2016). The data were segmented according to the different time points of the study protocol and imported to MATLAB (The Math Works Inc., 2015). Preprocessing in MATLAB was conducted using the HOMER2 toolbox (Huppert, Diamond, Franceschini, & Boas, 2009). Next, the data were converted to optical density measures which is recommended to detect motion artifacts (Cooper et al., 2012). Motion correction was performed with a probability threshold of $\alpha = .01$. Subsequently, motion artifacts were removed. A Bandpass-filter removed frequencies greater than 0.5 Hz. In a final step, optical density measures were converted to hemoglobin concentration for oxygenated hemoglobin (O_2Hb),

deoxygenated hemoglobin (HbR), and total hemoglobin (HbT) (O_2Hb + HbR = HbT). All data were exported to STATA/SE Software version 16.0 (StataCorp, 2019).

Recordings of the heartbeat throughout the study were saved using movisens Sensor Manager software version 1.14.4 (movisens GmbH, Karlsruhe, Germany). Data processing was conducted with Kubios HRV Premium Software version 3.1.0 (Tarvainen, Niskanen, Lipponen, Ranta-aho, & Karjalainen, 2014). R-peaks were marked manually and artifacts removed. For IBI, smoothing priors were applied as detrending method ($\lambda = 500$) and the output file was saved for HRV analysis in R (García Martínez et al., 2017). IBIs corresponding to a mean HR < 30 or > 200 bpm were discarded. The Root Mean Square of Successive Differences (RMSSD) was saved for analyses as index of vagally-mediated HRV. Similar to NIRS data, RMSSD and IBI were segmented according to the various time points of the study and exported to STATA/SE Software version 16.0 (StataCorp, 2019). EDA data were converted to a .txt-file using Ledalab version 3.4.9 (Benedek & Kaernbach, 2010). For each participant, the integrated skin conductance response (iSCR) was calculated. The analysis of sAA was carried out at the Department Biopsychology of the Technical University of Dresden, Germany. First, salivettes were centrifuged at 3000 rpm for five minutes to gain the saliva in a supernatant clear form of low viscosity from the cotton wool. Cortisol concentrations were assessed using a highly sensitive luminescence immunoassay (IBL International, Hamburg, Germany). Values for sAA ranged between 4.257 to 690.161 nmol/l.

2.6 Statistical Analyses

For statistical analyses, either STATA/SE software version 16.0 (StataCorp, 2019) or MATLAB (The Math Works Inc., 2015) were used. The statistical significance level was set to $\alpha = .05$. In a first step, the 15 minutes stimulation phase was subdivided into three five-minute blocks so that each block had a corresponding length to the CDT baseline task without any stimulation. Hence, the continuous measurements of the NIRS, the EDA, and the ECG device were segmented according to the blocks. For each block a

mean value was generated for RMSSD, HR, EDA, and O_2Hb in each NIRS channel, as well as global O_2Hb across all channels.

Linear mixed-effects models were calculated predicting changes in parasympathetic activity (HRV) and sympathetic activity (EDA, sAA) and the respective measure of mixed influence (HR) by the fixed effects of TIME (base, 5 min, 10 min, 15 min) and STIMULATION (tVNS versus sham) as well as their interaction using the participants' ID as random effect. Similar, mixed models predicting sAA were calculated, however, here the fixed effect of TIME was limited to pre and post assessments. In case of a significant model fit and significant main effects of TIME and STIMULATION, we used planned contrasts to investigate effects of STIMULATION at single segments of TIME, providing a detailed understanding on when effects of stimulation occurred and how long the respective effects lasted. Specifically, planned contrasts were derived to investigate effects of STIMULATION at each block of TIME. The later contrasts were chosen, assuming that effects of STIMULATION might emerge after a certain time of stimulation only and thus not result in an overall significant interaction effect. We further calculated posthoc t-test for contrasts of interest to derive an estimate of the effect size (ES) using *Cohen's d*. To provide an in depth analyses of global O_2Hb, O_2Hb was additionally analyzed by ROI. For this purpose, ROI was also included as a random effect. In a next step, to examine the additional effect of changes in O_2Hb on physiological variables of interest, mixed models were calculated predicting RMSSD, HR, and EDA again by STIMULATION, and TIME, adding O_2Hb, as additional predictor. sAA was not included in the later analyses as sAA was only sampled directly before and after the 15 min stimulation phase. Hence, time blocks did not align to the segmented data of the respective NIRS assessment. Lastly, connectivity between NIRS channels was investigated exploratory. First, cross correlation coefficients between channels were calculated for all TIME segments by STIMULATION. In a second step, the cross correlation coefficients were subjected to mixed models as outlined above. For simplicity,

all analyses include O_2Hb-values only as O_2Hb is the most informative variable from NIRS analyses (Condy et al., 2020).

Results

3.1 Sample Characteristics

For the study *n* = 62 adolescents were contacted. Of those, *n* = 30 (48.39 %) participants completed the study. Reasons for exclusion from study participation are provided in *Figure 3*. Of those participating (*n* = 30), *n* = 24 were female, the mean age was 15.73 years (*SD* = 0.98). A detailed description of sociodemographic and clinical characteristics of participants is provided in *Table 1* and has also been provided elsewhere (Koenig, Parzer, et al., 2021).

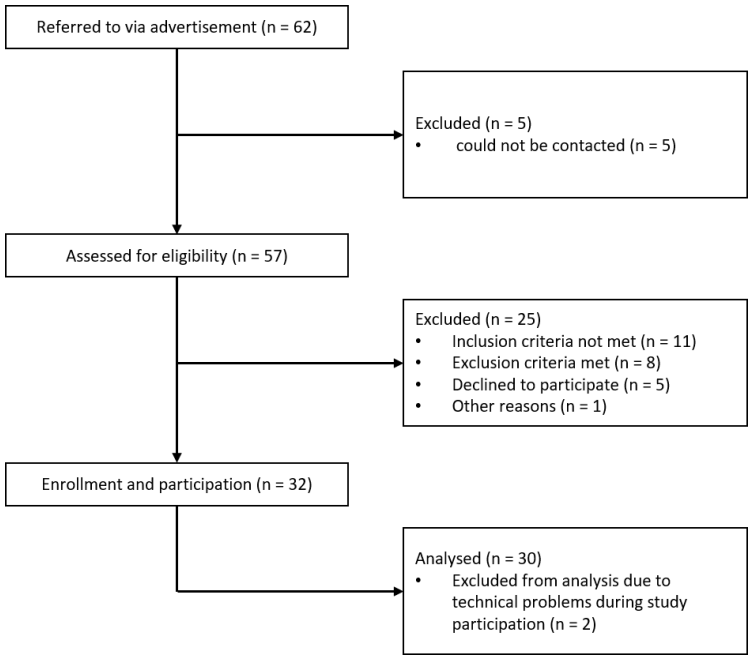


Figure 3: Participant Flow Chart

Table 1 Sociodemographic and Clinical Characteristics of Participants

Variable	
N (female %)	30 (80.00)
Age, years (SD)	15.73 (0.98)
Height, cm (SD)	167.83 (8.95)
Weight, kg (SD)	59.40 (7.76)
BMI (SD)	21.13 (2.64)
School type, *n* (%)	
Hauptschule	0 (0.00)
Realschule	8 (26.67)
Gymnasium	19 (63.33)
Other	3 (10.00)
Medication, *n* (%)	1 (3.33)
CDRS (SD)	19.93 (10.59)
BDI (SD)	4.67 (4.57)
DERS (SD)	61.57 (12.39)
Adverse childhood experiences, *n* (%)	5 (16.67)
STAI-state (SD)	32.27 (6.03)
STAI-trait (SD)	33.07 (8.24)
C-GAS (SD)	93.23 (6.79)

Note. Depicted are mean and standard deviations (SD) values if not otherwise indicated; BMI = body mass index; school, after 4 years of elementary school the German school system branches into three types of secondary schools. The so-called Hauptschule (Secondary General School which takes 5 years after Primary School) prepares pupils for vocational training, whereas the Realschule (Intermediate Secondary School) concludes with a general certificate of secondary education after 6 years. Eight years of Gymnasium provide pupils with a general university entrance qualification; Medication: one participant reported daily intake of painkillers; CDRS = Children's Depression Rating Scale – Revised; BDI = Beck Depression Inventory II; DERS = Difficulties in Emotion Regulation Scale; STAI = State-Trait Anxiety Inventory; C-GAS = Children´s Global Assessment Scale; *past depressive disorder. Further information on demographics of this sample can be found in Koenig et al., 2021.

3.2 Hypothesis 1: Effects of tVNS/Sham Stimulation on Physiological Outcomes

The model predicting HR was significant (*Wald* $\chi^2(7) = 55.91$; $p < .0001$). Main effects were found for TIME ($\chi^2(3) = 24.94$; $p < .0001$) and STIMULATION ($\chi^2(1) = 28.84$; $p < .0001$). No significant TIME x STIMULATION interaction was found ($\chi^2(3) = 2.13$; $p = .547$). Contrast analyses revealed a significant effect of STIMULATION for all blocks of TIME (base: $\chi^2 = 9.46$; $p = .002$; ES: -.29; 5 min: $\chi^2 = 12.33$; $p < .001$; ES: -.37; 10 min:

χ^2 = 6.77; p = .009; ES: -.28) with the exception of 15 min (χ^2 = 2.41; p = .121; ES: -.27). As illustrated in *Figure 4*, HR initially decreased under tVNS compared to sham and slightly increased again over the course of time. After 15 minutes of stimulation the effect of stimulation was no longer significant. Similar, the model predicting RMSSD was significant (*Wald* $\chi^2(7) = 51.90$; $p < .001$) with main effects for TIME ($\chi^2(3) = 14.11$; p = .003) and STIMULATION ($\chi^2(1) = 34.96$; $p < .0001$). No significant TIME x STIMULATION interaction was found ($\chi^2(3) = 2.83$; p = .419). Contrasts for STIMULATION were again significant for all blocks of TIME (base: χ^2 = 13.85; $p < .001$; ES: .45; 5 min: χ^2 = 14.77; $p < .001$; ES: .44; 10 min: χ^2 = 5.49; p = .019; ES: .27) with the exception of 15 min (χ^2 = 3.68; p = .055). The course of HR and RMSSD over TIME by STIMULATION is displayed in *Figure 4*.

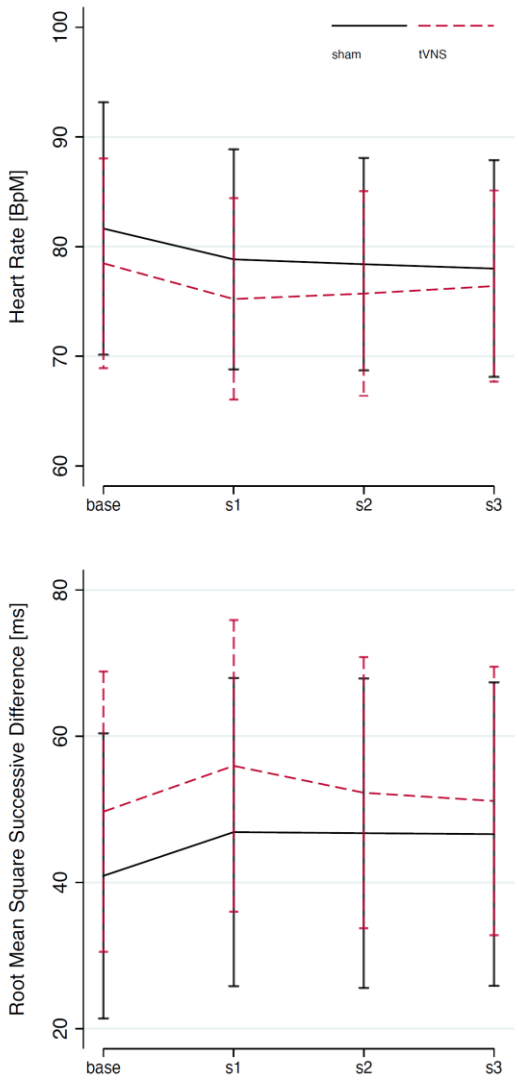


Figure 4: Heart Rate and Root Mean Square of Successive Differences by Stimulation Condition Over Time; *Note*. sham = sham stimulation; tVNS = transcutaneous vagus nerve stimulation; base = baseline task; s1 = 5 minutes of stimulation; s2 = 10 minutes of stimulation; s3 = 15 minutes of stimulation; post = post stimulation phase; depicted are mean values +/- their standard deviations.

As illustrated in *Figure 4*, the effects for HR and HRV already emerged during baseline, when no stimulation was applied. Although our within-subject cross-randomized design and strategy of analyses (ID as random factor) accounted for potential baseline differences, we calculated additional analyses to rule out baseline influence. Excluding the baseline segment confirmed prior findings with main effects of STIMULATION on HR (Model fit: *Wald* $\chi^2(5) = 26.62$; $p = .0001$; main effect STIMULATION: $\chi^2(1) = 24.17$; $p <$

.0001) and HRV (Model fit: *Wald* $\chi^2(5) = 27.67$; $p < .0001$; main effect STIMULATION: $\chi^2(1) = 22.89$; $p < .0001$). Additionally, for HRV only, the 15 min contrast was significant ($\chi^2 = 3.84$; $p = .049$). Under tVNS stimulation, participants showed increased RMSSD compared to sham up to 15 min of stimulation. The respective model predicting EDA was not significant (*Wald* $\chi^2(7) = 9.97$; $p = .190$). Similar, the model predicting sAA was not significant (*Wald* $\chi^2(3) = 3.56$; $p = .313$). *Figure 5* illustrates that EDA and sAA did not change over TIME nor as a function of STIMULATION.

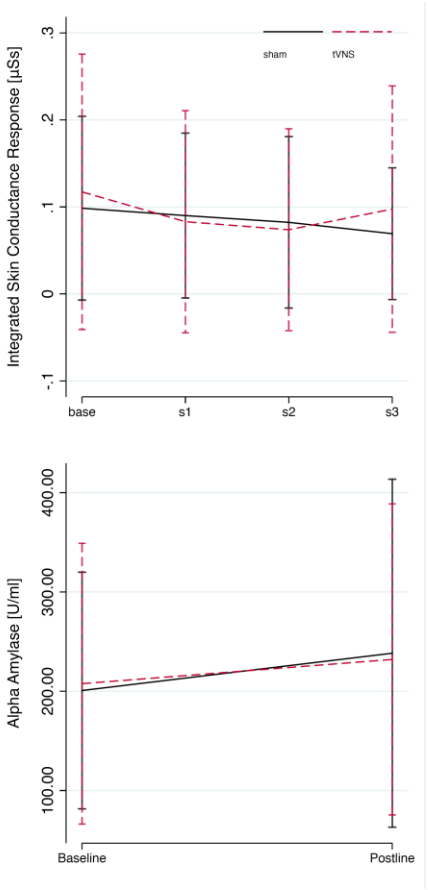


Figure 5: Integrated Skin Conductance Responses and Alpha Amylase by Stimulation Condition Over Time; *Note*. sham = sham stimulation; tVNS = transcutaneous vagus nerve stimulation; base = baseline task; s1 = 5 minutes of stimulation; s2 = 10 minutes of stimulation; s3 = 15 minutes of stimulation; post = post stimulation phase; depicted are mean values +/- their standard deviations.

3.3 Hypothesis 2: Effects of tVNS/Sham Stimulation on Changes in PFC Oxygenation

The mixed linear model addressing effects of TIME and STIMULATION on global O_2Hb (independent of ROI) was significant (*Wald* $\chi^2(7) = 17.99$; $p = .012$). There was a significant main effect of STIMULATION ($\chi^2(1) = 9.76$, $p = .002$) but not TIME ($\chi^2(3) = 4.71$, $p = .195$) or a TIME x STIMULATION interaction ($\chi^2(3) = 3.52$; $p = .318$). Contrasts of STIMULATION by block of TIME illustrated no significant differences in early phases of stimulation (base: $\chi^2 = 0.00$; $p = .964$; ES: .01; 5 min: $\chi^2 = 2.34$; $p = .126$; ES: .38) but effects emerged after 10 and 15 min (10 min: $\chi^2 = 5.06$; $p = .025$; ES: .53; 15 min: $\chi^2 = 5.88$; $p = .015$; ES: .57). The course of global O_2Hb over TIME by STIMULATION is illustrated in *Figure 6*, showing steady increases in O_2Hb under tVNS over the course of stimulation.

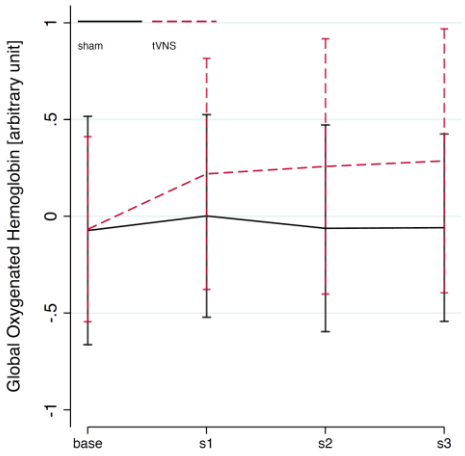


Figure 6: Global Prefrontal Cortex Oxygenation (independent of Region of Interest) by Stimulation Condition Over Time; *Note*. sham = sham stimulation; tVNS = transcutaneous vagus nerve stimulation; base = baseline task; s1 = 5 minutes of stimulation; s2 = 10 minutes of stimulation; s3 = 15 minutes of stimulation; post = post stimulation phase; depicted are mean values +/- their standard deviations.

In depth analyses, considering the different ROI as additional factor confirmed the analyses. Overall model fit improved (*Wald* $\chi^2(7) = 52.31$; $p < .0001$) with significant main effects for TIME ($\chi^2(3) = 13.68$; $p = .003$), STIMULATION ($\chi^2(1) = 28.35$; $p < .0001$) and

a significant TIME x STIMULATION interaction ($\chi^2(3) = 10.22$; $p = .017$). Contrasts of STIMULATION by block of TIME illustrated absence of effects during baseline ($\chi^2 = 0.01$; $p = .938$; ES: .01), but increasing effects with ongoing duration of stimulation (5 min: $\chi^2 = 6.79$; $p = .009$; ES: .39; 10 min: $\chi^2 = 14.69$; $p < .001$; ES: .53; 15 min: $\chi^2 = 17.09$; $p < .0001$; ES: .58), as further illustrated in *Figure 7*.

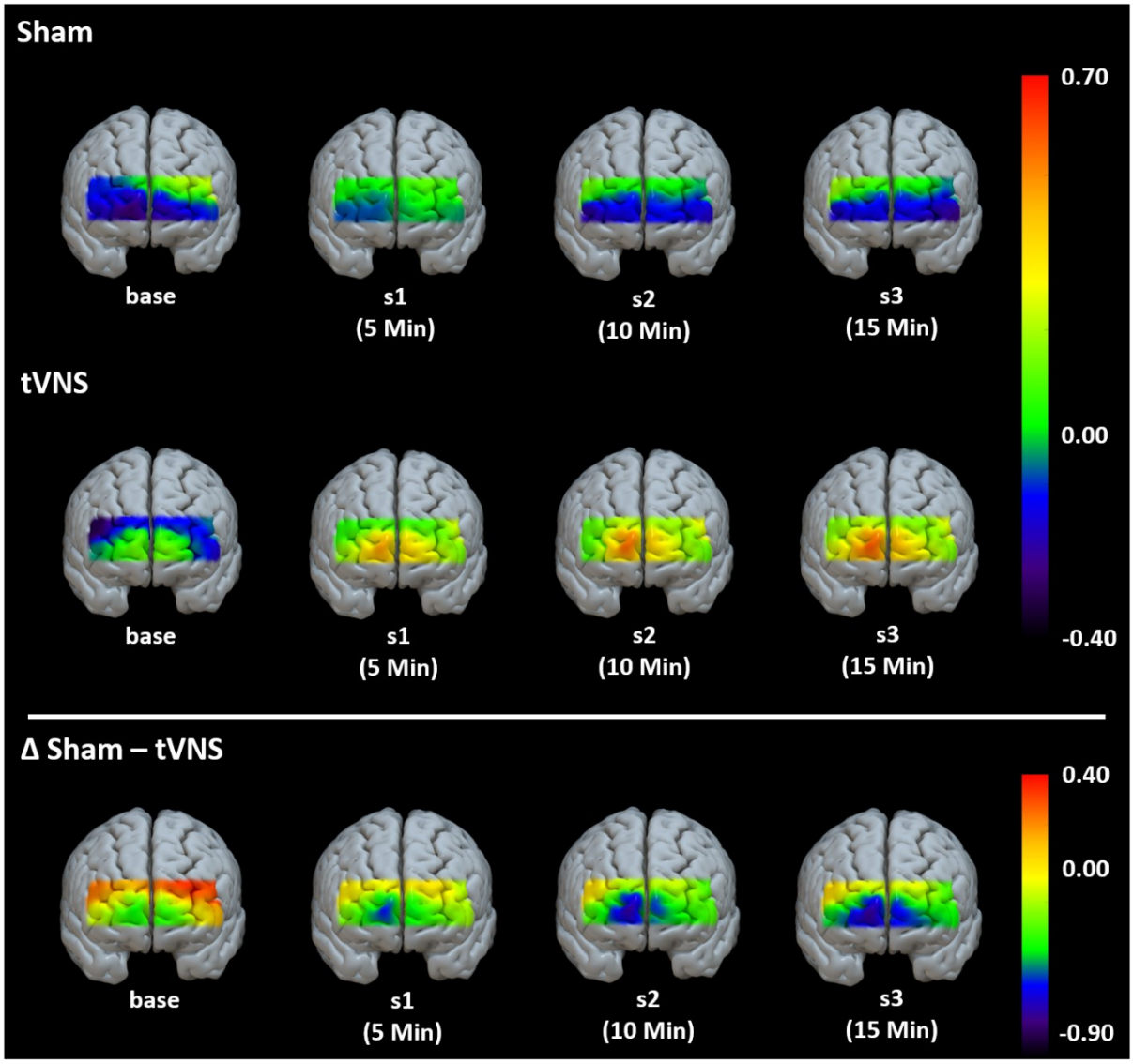


Figure 7 Region of Interest dependent Prefrontal Cortex Oxygenation by Stimulation Condition Over Time; *Note*. sham = sham stimulation; tVNS = transcutaneous vagus nerve stimulation; Δ Sham – tVNS = difference in mean oxygenated hemoglobin in transcutaneous vagus nerve stimulation compared to sham stimulation; base = baseline task; s1 = 5 minutes of stimulation; s2 = 10 minutes of stimulation; s3 = 15 minutes of stimulation. Displayed are mean measures of changes in the oxygenated hemoglobin for each time block.

3.4 Hypothesis 3: Changes in PFC Oxygenation as Predictor of Physiological Changes during tVNS/Sham Stimulation

To address hypothesis 3, O_2Hb was included as a predictor to the linear mixed-effects models on HR and RMSSD that showed significant effects of STIMULATION. Adding global O_2Hb (independent of ROI) as predictor of HR improved the respective model fit (*Wald* $\chi^2(8) = 118.52$; $p < .0001$) and showed a significant main effect of O_2Hb on the course of HR (Coef. = -3.158, $p < .0001$). Greater increases in O_2Hb under tVNS were associated with a decrease in HR. Similar effects were evident for RMSSD. Model fit improved when adding global O_2Hb (independent of ROI) as predictor (*Wald* $\chi^2(8) = 60.89$; $p < .0001$) and a significant main effect of O_2Hb on the course of RMSSD was found (Coef. = 3.007, $p = .007$). Greater increases in O_2Hb under tVNS were associated with greater increases in RMSSD. For EDA, no such effect was found. Adding global O_2Hb still resulted in non-significant model fit (*Wald* $\chi^2(8) = 10.45$; $p = .235$). Findings for HR and RMSSD were robust in respective model investigating O_2Hb by ROI.

3.5 Exploratory Analyses: Connectivity Analyses

Exploratory analyses of functional connectivity changes within the PFC across fNIRS channels, illustrated several hubs with significant main effects of STIMULATION. In particular, channel #S4 showed increased connectivity #S2 ($\chi^2 = 5.21$; $p = .022$), #S3 ($\chi^2 = 7.47$; $p = .006$), #S5 ($\chi^2 = 4.85$; $p = .028$), #S7 ($\chi^2 = 13.60$; $p < .001$), and #S8 ($\chi^2 = 8.37$; $p = .004$) under tVNS compared to sham. Further hubs included channel #S7, that showed increased connectivity to #S1 ($\chi^2 = 11.62$; $p = .001$), #S2 ($\chi^2 = 9.00$; $p = .003$), #S5 ($\chi^2 = 16.83$; $p < .0001$), and #S8 ($\chi^2 = 8.66$; $p = .003$). In a similar fashion, channel #S8 showed increased connectivity to #S1 ($\chi^2 = 12.12$; $p < .001$), #S2 ($\chi^2 = 5.11$; $p = .024$), #S3 ($\chi^2 = 6.75$; $p = .009$) and #S5 ($\chi^2 = 12.50$; $p < .001$). Beyond these, channel #S1 showed increased connectivity to #S3 ($\chi^2 = 9.47$; $p = .002$), #S5 ($\chi^2 = 5.79$; $p = .016$), and #S6 ($\chi^2 = 5.01$; $p = .025$). For better clarity, findings are visualized in *Figure 8*.

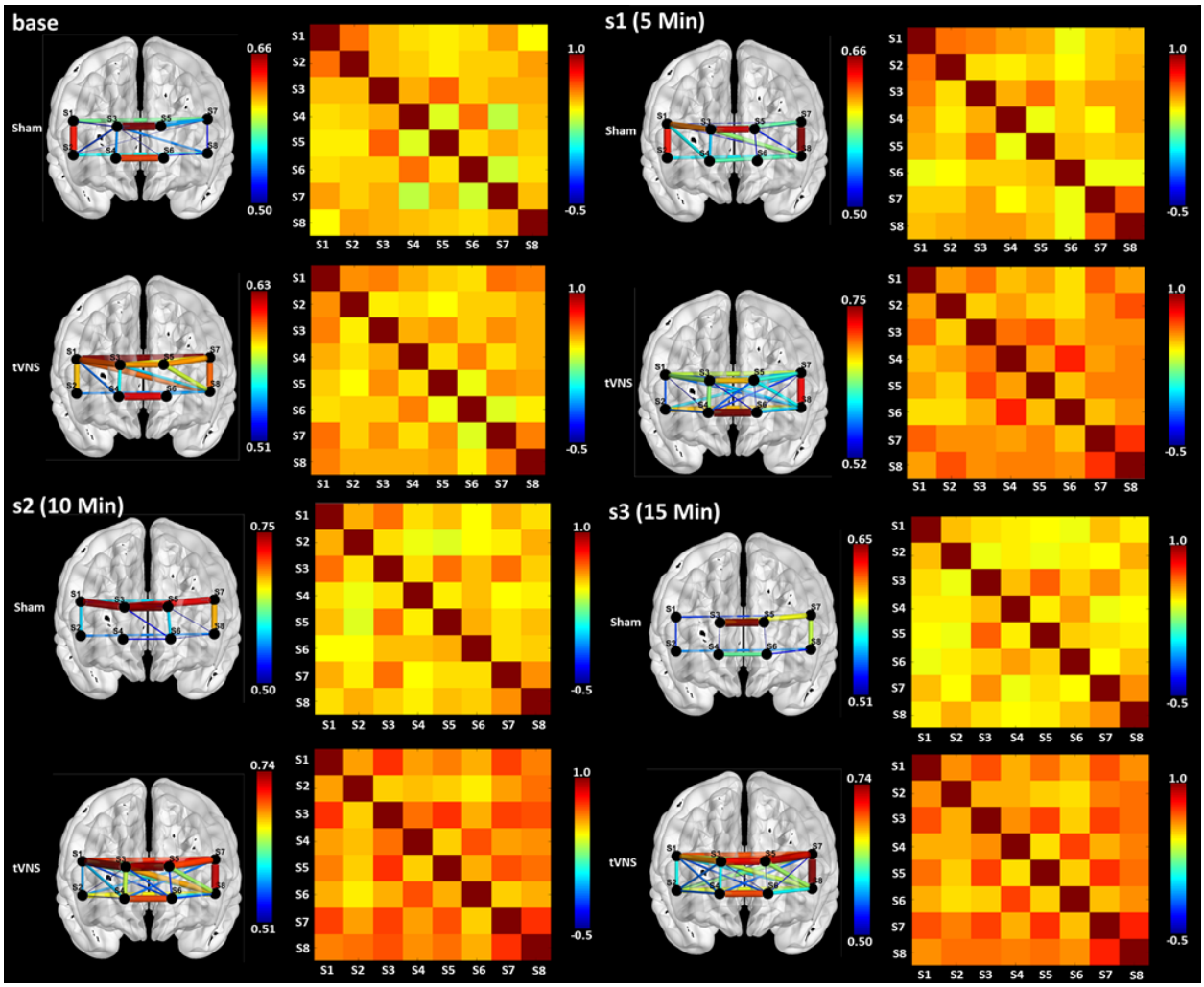


Figure 8 Prefrontal Cortex Connectivity by Stimulation Condition Over Time*;* Displayed are mean values across participants; sham = sham stimulation; tVNS = transcutaneous vagus nerve stimulation; base = baseline task; s1 = 5 minutes of stimulation; s2 = 10 minutes of stimulation; s3 = 15 minutes of stimulation. On the brain surfaces cross correlation coefficients between channels of the functional near-infrared device are presented. Only correlations greater r > .50 are displayed. The heat maps illustrate all cross correlation coefficients between channels.

Discussion

To our knowledge, this is the first study to investigate prefrontal cortex oxygenation using fNIRS in association with changes in ANS activity under tVNS in a sample of adolescents. Analyses revealed increased RMSSD and decreased HR in response to tVNS stimulation compared to sham. Interestingly, changes in cardiovascular ANS activity were only observed in the first 10 min, and were potentially driven by baseline effects. Controlling for such influence, leaving out the respective baseline segment, confirmed the findings in principle, but showed longer lasting effects on RMSSD under tVNS. Analyses of the trajectory of HR and RMSSD over time revealed that greatest differences between both stimulation modalities occurred early during stimulation and subsequently vanished over time.

4.1 tVNS Effects on Autonomic Nervous System Activity

For EDA and sAA we found no effects of tVNS, suggesting that the parasympathetic branch of the ANS is predominantly affected by tVNS. Hence, hypothesis one was partially supported as we were able to observe an increase in parasympathetic activity under tVNS. Previous studies showing a decrease in HRV in tinnitus patients after tVNS, interpreted this as shift from a sympathetic to a parasympathetic predominance of the ANS (Ylikoski et al., 2017). Also others have found that an increase in HRV led to a decrease in sympathetic nerve activity (Clancy et al., 2014) or that tVNS reduced HR in healthy participants (Tobaldini et al., 2019). Our findings confirm effects on the parasympathetic branch of the ANS in the absence of changes in sympathetic activity. In contrast to our finding, Warren and colleagues found an increase in sAA during tVNS, but not during sham stimulation (Warren et al., 2019). Also for other measures, mixed findings have been reported. For example, tVNS has been found to not influence neither HRV nor HR (Gauthey et al., 2020). Taken together, results from tVNS studies examining biomarkers of sympathetic and parasympathetic activation are mixed. One explanation might be that experimental settings, statistical analyses, and even the use of different

indices of HRV (RMSSD or high frequency HRV) differ widely. Standards in experimental assessments might help to overcome this problem and might contribute to a clearer picture of the effects of tVNS on peripheral markers of ANS activity (Burger, D'Agostini, Verkuil, & Diest, 2020).

4.2 tVNS Effects on Prefrontal Cortex Oxygenation

Second, we found an increase in O_2Hb under tVNS that emerged over time, confirming our second hypothesis. This effect was observed in global O_2Hb (independent of ROI) and in ROI specific analyses. Findings from our exploratory analyses on functional connectivity further indicate that there might be specific hubs within the PFC sensitive to tVNS that warrant further investigation using different neuroimaging modalities with better spatial resolution. What seems interesting are differences in the temporal dynamics comparing changes in peripheral measures of ANS function and those observed for PFC oxygenation. Whereas HR and HRV showed immediate but shorter-lived responses to tVNS, the opposite was observed for O_2Hb. Here effects were not present during early phases of the stimulation but emerged with continuing stimulation. Interestingly, Hulsey and colleagues found that varying pulse frequency of tVNS affected the timing, but not the total amount of activation in the locus coeruleus as this might explain the later response of O_2Hb in the PFC found in the present study (Hulsey et al., 2017). Various neuroimaging studies, mainly focusing on depressed patients, found an increase in blood flow or oxygenation in the PFC as well as a greater functional connectivity of the PFC and deeper brain structures such as the precuneus or the nucleus accumbens, or the anterior cingulate cortex (Fang et al., 2016; Kosel, Brockmann, Frick, Zobel, & Schlaepfer, 2011; Tu et al., 2018; Wang et al., 2018). More generally, tVNS has been found to evoke activation in areas innervated by the vagus nerve in the nucleus tractus solitarii (Frangos et al., 2015; Thomas Kraus et al., 2013). Taking these findings and considering the increase of O_2Hb in the PFC following tVNS found in the present study, the assumptions of neural circuits as proposed by the NIM is

supported. The only other study, using fNIRS as neuroimaging modality to investigate vagally innervated feedback loops and the NIM, was conducted by Condy and colleagues. They aimed to confirm the NIM by investigating changes in O_2Hb of the PFC via fNIRS during an inhibition task (Condy et al., 2020). They found an increase of O_2Hb during the inhibition task compared to a baseline task, but they found no relation between HRV and PFC activation during the inhibition task. A gap that the present study was able to close.

4.3 Brain-Body Associations

Finally, we were able to show, that changes in PFC oxygenation were associated to changes in ANS activity. Again, only models predicting cardiovascular variables of interest (HR and HRV) showed the respective effect, partially confirming hypothesis three. Greater changes in oxygenation of the PFC under tVNS were associated with a greater decrease in HR and a greater increase in HRV, supporting the neural circuitry outlined by the NIM. Although our analyses prohibit any conclusion regarding the causality of observed associations, the different time course of effects observed for measures of ANS activity and PFC oxygenation allow some speculation. Previous studies have found strong connectivity measures between the PFC and deeper brain structures supporting the proposed feedback loops of the NIM. The medial PFC can be divided into functional subdivisions serving different cognitive and inhibitory requirements (Amodio & Frith, 2006). Hence, connectivity patterns within the PFC and with deeper brain structures might change in dependence with the requirements of the given autonomic and visceral information which is conveyed via the vagus nerve. Here we relied on an assessment of PFC activity only, not covering sub-cortical brain structures and their influence on timing of PFC activation. The NIM proposes the neural system as an integrative instance which processes information from perceptual, motor, interoceptive, and memory systems Thayer et al., 2012). As a result of this integration, adaptive responses will be initiated (Thayer et al., 2012). This idea might serve as an

explanation why cardiovascular measures (i.e., HR and RMSSD) showed stronger effects of tVNS in the very beginning of the stimulation period. With the integration of this change in the neural network, adaptive processes might have been initiated requiring stronger prefrontal activation. To provide evidence for the exact time course underlying this assumption, extensive research is necessary using whole-brain functional neuroimaging techniques and ideally measuring various physiological outcomes simultaneously.

4.4 Limitations and Outlook

When examining neural activation on the cortical surface, fNIRS yields some advantages over fMRI and offers a cost-effective alternative to fMRI. On the one hand, it has a superior time resolution (Koike, Nishimura, Takizawa, Yahata, & Kasai, 2013) which might be crucial to investigate associations between stimulus presentation, HRV, and neural activation. On the other hand, it is a small device, tolerating body movement to greater degree. This characteristic makes the application of fNIRS also possible for children, adolescents, or people with fear of narrowness (i.e., in the fMRI scanner). A disadvantage of fNIRS is its lower spatial resolution compared to fMRI (Koike et al., 2013) – hence our ROI specific analyses and analyses addressing functional connectivity should be viewed with caution. Nonetheless, simultaneous fMRI and fNIRS assessment showed that the measurement of O_2Hb correlates with blood oxygenation level dependent measures in fMRI (Alderliesten et al., 2014; Bulgarelli et al., 2018). These findings suggest the equivalence of both methods when focusing on activation on the cortical surface.

Our finding of increased parasympathetic activity under tVNS in association with greater changes in PFC oxygenation emphasizes the therapeutic potential of tVNS in a variety of disorders that have been associated with altered ANS and/or PFC functioning (see Farmer et al. (2021) for a review of therapeutic applications). A limiting factor of this study is its focus on female adolescents only. In a larger sample, potential sex dependent

effects of the stimulation should be addressed, as ANS activity has been shown to differ between the sexes (e.g. Koenig & Thayer 2016). Studies on long-term tVNS are warranted to address lasting trajectories in ANS and PFC activity over time. Further, the present study was limited by a relative small sample size used for secondary analyses and findings should be confirmed in larger prospective studies.

Conclusion

Overall, this study supports the assumptions of the NIM, illustrating that under tVNS, increases in PFC oxygenation are associated with greater increase in HRV and decreases in HR, respectively.

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