Longitudinal Analysis of the Brain and Hypothalamic-Pituitary-Adrenal Axis Stress Systems and Risk for Non-Suicidal Self-Injury

A Dissertation

SUBMITTED TO THE FACULTY OF THE UNIVERSITY OF MINNESOTA, TWIN CITIES

BY

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IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

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May 2024

Acknowledgments

I would like to thank my mentors and colleagues in the Research on Adolescent Depression Lab, particularly Bonnie Klimes-Dougan, and Katie Cullen, for their professional and personal support throughout my time in graduate school. I am grateful for their support and facilitation of me pursuing projects about which I am passionate. I am also particularly grateful to Caroline Ostrand, Tori Papke, Marvin Yan, and Andrea Wiglesworth, who all dedicated their time and talent to helping me make my dissertation project a reality. I am honored to have been deemed worthy of your valuable time and enjoyed working with you all immensely.

I would also like to thank my committee members, Monica Luciana, Bonnie Klimes-Dougan, Katie Cullen, and Katerina Marcoulides, for making time to serve on my final exam committee. I would also like to thank Shmuel Lissek, who supported me throughout earlier graduate school milestones.

I am indebted to the incredible women who have mentored, supervised, and supported me on the journey of getting into and through graduate school. These include Caroline Hoyniak, Alex Silver, Allison Papadakis, Bonnie Klimes-Dougan, Katie Cullen, Aimee Murray, Kristina Reigstad, Mindy Westlund-Schreiner, Michelle Thai, Sylia Wilson, Cheryl Olman, and Pat Frazier, among many others.

I am grateful for the friends I have made during my higher education journey, particularly Andrea, Caroline, Jess, Marvin, Mike, Poojah, Rylee, Sarah, Talia, Tori, Victor (in alphabetical order, lest anyone thinks I have picked favorites), and the CSPR graduate student community. Your companionship, commiseration, and co-conspiracy have been life-sustaining for me while navigating some of the most challenging years of my life.

I am forever in awe of the incredible community built around the NextGen Psych Scholars Program. I am so grateful to everyone, near and far, who has dedicated effort to lifting up our mentees and creating lasting change in our field. I am particularly grateful for Meriah DeJoseph, Ekom Eyoh, and Holley Lochlear, who have all gone above and beyond to support our common goals.

Those who know me are aware of how beholden I am to my four-legged loved ones; I am grateful to Rocky B. Carosella for showing me the power of being hard-headed, for Margherita P. Carosella, whose constant need for attention and supervision has provided much-needed diversion throughout the writing process, and for Mozzarella C. Carosella, for only rarely objecting to my affection.

Thank you to my extended Carosella family who made musings about the biological basis of psychopathology the topic of quotidian dinnertime conversations, modeled what it means to be a good clinician, and inspired my path. Thank you to my extended Blank family, who facilitated and supported my education. Thank you to the Petronack family for welcoming me and helping make Minnesota home for these past four years. Thank you to my immediate family for unceasingly supporting me throughout my life and loving me despite my incessant whining about the Minnesota winters.

Finally, I am incredibly grateful for the unwavering support of my husband, Austin Petronack, who has been my cheerleader, copyeditor, confidant, physics tutor, personal comedian, caretaker, taste tester, co-dog-wrangler, partner in all things, and best friend since 2015.

Dedication

This dissertation is dedicated to the participants of the following studies, who have given us their time, energy, and trust to make this work possible.

Abstract

Background: Non-suicidal self-injury (NSSI) is the harming of oneself without the intent to die and is reported by about 18% of adolescents. The brain and hypothalamic-pituitary-adrenal (HPA) axis stress systems undergo widespread changes during adolescence. There is evidence that alterations in these systems are related to NSSI engagement. Indeed, prior literature has identified some reliable alterations in frontal regulatory control of the amygdala as well as in HPA axis reactivity in adolescents who engage in NSSI compared to those who do not. This work has predominantly used variable-centered analyses. Emerging work using variable-centered and person-centered analyses has identified some meaningful heterogeneity among adolescents who do engage in NSSI. Despite these advances, little work has been done to characterize how these biological processes unfold across development for those who engage in NSSI. The following multi-level, longitudinal studies aim to identify patterns in the development of the brain and HPA axis using variable-centered analyses in conjunction with person-centered analyses. **Study 1 Methods:** This study employs a large, community-representative sample of adolescents to examine neurodevelopmental patterns in the amygdala and superior frontal reactivity to emotional stimuli and fronto-limbic resting state functional connectivity. **Study 1 Results:** Person-centered analyses identified five neurodevelopmental trajectories. Participants in a person-centered derived group with a normative developmental profile first reported engaging in NSSI later than a profile typified by dynamic change across study time points. Variable-centered analyses found that decreased frontal reactivity to emotional stimuli at baseline and decreased slope of change of fronto-limbic resting state functional connectivity were associated with increased risk for NSSI. **Study 2 Methods:** This study includes a sample of adolescents at high risk for NSSI with HPA axis metrics in addition to measures of the brain's stress system (including the amygdala and medial prefrontal cortex reactivity to emotional stimuli and fronto-limbic resting state functional connectivity). **Study 2 Results:** Person-centered analyses identified six developmental trajectories of the brain and HPA axis. Two person-centered profiles in which participants, in part, demonstrated a pattern of blunted frontal regulatory control were found to differ in severity of NSSI. Variable-centered analyses found that decreased baseline fronto-limbic resting state functional connectivity was associated with increased risk of NSSI, increased severity of NSSI, and higher number of episodes of NSSI. Decreased baseline HPA axis reactivity was associated with increased risk of NSSI and increased severity of NSSI, while a more positive slope of change in HPA axis reactivity was associated with increased severity of NSSI. **Discussion:** The person-centered analyses provide novel insights into within-group heterogeneity among adolescents who engage in NSSI. The variable-centered analyses replicate and extend past work by providing longitudinal evidence of biological signatures associated with NSSI. These findings provide new insights into developmental alterations in the brain and HPA axis which are related to NSSI which may have implications for intervention efforts with this population.

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1. Introduction to Non-Suicidal Self-Injury and Underlying Alterations in the Brain and Body's Stress Systems

Non-suicidal self-injury (NSSI) is a transdiagnostic maladaptive emotion regulation strategy that involves the deliberate harming of oneself without the intent to die (Plener et al., 2015). Though engagement in NSSI is intended to manage distress (Klonsky, 2007), it is associated with a significant risk of harm due to the behaviors themselves (e.g., cutting, burning, hitting) as well as the heightened risk for future suicidal thoughts and behaviors (Franklin et al., 2016). NSSI is remarkably prevalent among adolescents, with about 18% of 12-18 year-olds reporting engaging at some point in their lives as of 2015 (Monto et al., 2018), though there is emerging evidence that this proportion increased to 28-40% following the onset of the COVID-19 pandemic (Tang et al., 2021; Zetterqvist et al., 2021). Despite the alarmingly high rate of incidence, the biological processes that underlie this maladaptive behavior and the role of development are yet to be fully characterized. Work thus far has implicated dysfunction in the stress processing and response systems of the brain and hypothalamic-pituitary-adrenal (HPA) axis. Specifically, there is growing evidence implicating alterations in the brain's ability to apply higher-order filtering to stress responses (Başgöze, Mirza, et al., 2021; Santamarina-Perez et al., 2019; Westlund Schreiner et al., 2017) and the HPA axis' ability to muster the appropriate alarm signal for the rest of the body (Kaess et al., 2012; Klimes-Dougan et al., 2019; Plener et al., 2017). The stress processing conducted in the brain is iterative and integrative, and, as such, there are many points in intra-brain processing at which errors may occur. The brain informs the degree to which the HPA axis responds to stressors, and thus, the interplay between the brain and the HPA axis is also critical to producing stress responses. The following studies hope to identify patterns of alterations in the development of these systems that underlie risk for NSSI. To do so, traditional variable-centered analyses will be conducted in conjunction with more novel person-centered analyses to facilitate a greater understanding of developmental changes in biological stress systems. The first study will use a large, community-representative sample of adolescents who are being measured longitudinally (Adolescent Brain and Cognitive Development [ABCD] Study; Barch et al., 2018; Casey et al., 2018). Presently, neuroimaging and psychopathology metrics are available for ages 9-14 years, allowing for the investigation of developmental trajectories in the early stages of the adolescent period. The second study will use a high-risk sample with rich biological (brain and HPA axis metrics) and more nuanced measures of NSSI at

three time points during adolescence (Brain Imaging Development of Girl's Emotion and Self [BRIDGES] Study; R01MH107394-01). Participants in this study ranged in age from 12-17 years old at the first time point, allowing for the investigation of trajectories across the entire span of adolescence. Together, these studies aim to leverage the unique strengths of both data sets to advance the understanding of the biological underpinnings of NSSI.

2. Longitudinal Analysis of Stress System Development and NSSI in a Large Community Sample

Introduction

Overview

Adolescence is marked by significant physical and social changes, chief among them is widespread re-organization and plasticity in the brain, which has been associated with heightened vulnerability for psychopathology (Giedd et al., 1999, 2009; Paus et al., 2008; Somerville et al., 2010). Indeed, one form of maladaptive response to stressors, non-suicidal self-injury (NSSI), the injury of oneself without the intent to die (Nock et al., 2007a), frequently onsets between the ages of 12 and 14 years (Cipriano et al., 2017). It is estimated that about 18% of adolescents have engaged in NSSI at least once (Monto et al., 2018). The investigation of NSSI is important not only due to the injuries incurred by the behaviors themselves but also because of the association with a heightened risk of suicidality in the future (Monto et al., 2018). Earlier onset of NSSI has been associated with greater frequency and severity of NSSI behaviors (Ammerman et al., 2018; Muehlenkamp et al., 2019) and greater future risk of suicide attempt (Muehlenkamp et al., 2019). NSSI frequently co-occurs with depression, anxiety, and suicidal thoughts and behaviors, though the unique underlying biological processes are yet to be fully characterized (Başgöze, Wiglesworth, et al., 2021; Klonsky, 2007). Understanding the patterns of neurodevelopmental changes that occur across adolescence in relation to NSSI could illuminate pathways of risk and points for intervention, including avenues for tailoring interventions (Carosella, Wiglesworth, Başgöze, et al., 2023; Westlund Schreiner et al., 2023).

The brain's stress system, crucial to the processing and formulating responses to stressors, has been implicated in the etiology of NSSI. This system works closely with the autonomic nervous system to modulate responses based on the frequency and intensity of stressors (for review: McEwen, 2007). The brain serves as a higher-order filter for stress responses by combining and analyzing input from sensory systems to identify appropriate behavioral responses (McEwen, 2007). Failures within this processing can result in maladaptive responses, both insufficient and excessive, which results in the use of maladaptive emotion regulation techniques, such as NSSI (Faravelli et al., 2012; van Oort et al., 2017).

The Brain's Stress System and NSSI

Background

One proposed explanatory mechanism for the increase in psychopathology and maladaptive behavior during adolescence is an imbalance between heightened sensitivity in limbic regions and immature frontal regulatory control (Casey et al., 2011). The brain's stress system employs both limbic and frontal regions to conduct integrative and iterative processing of stress stimuli (for review: LeDoux, 2003). Though many steps in this processing could be vulnerable to error, clinical conditions such as NSSI have been repeatedly linked to failures in frontal regulatory control of the amygdala (for review: Brañas et al., 2021).

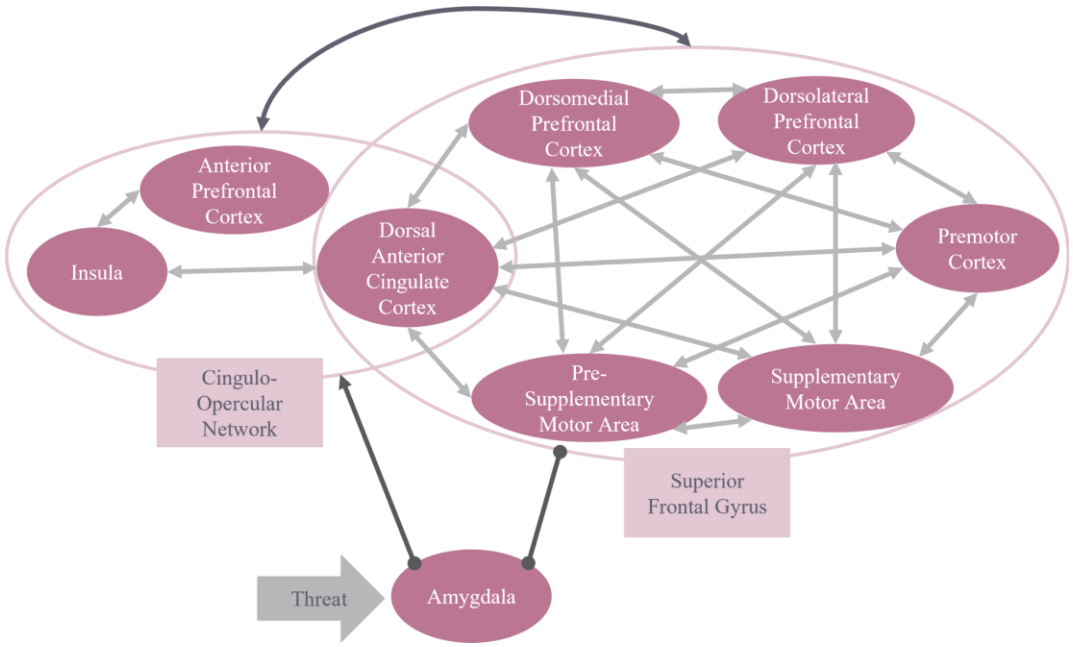
The amygdala is a crucial component of the threat system, combining information about stimuli in the environment, memory, and arousal (LeDoux, 2003; Ulrich-Lai & Herman, 2009). The amygdala uses this information to identify potentially salient stimuli and initiate signals to muster responses from other stress system components, including the medial prefrontal cortex (mPFC), locus coeruleus, and hippocampus (Winklewski et al., 2017).

The mPFC is part of the larger superior frontal (SF) region, which is similarly involved in aspects of cognitive control, including modulation of the stress responses by modulating responses to stressors (Hu et al., 2016). The SF is made up of Brodmann areas (BA) 6 (only rostral and dorsal portions), 8, 9, and 32 (Garey, 2006; Li et al., 2013). The subareas of BA 6 represent the supplementary motor area (SMA) and premotor cortex, which govern the organization and planning of behaviors (Mihailoff & Haines, 2018) and have been implicated in habitual behaviors such as NSSI (Cullen et al., 2020; Westlund Schreiner et al., 2017). BA 8 represents the pre-SMA and has been shown to act in the context of uncertainty to assist in decision-making (Volz et al., 2005). The portion of BA 9 that is included in SF represents the medial portions of the dorsolateral prefrontal cortex (dlPFC) and the dorsomedial prefrontal cortex (dmPFC; Garey, 2006). The dlPFC is integral in supporting the regulation of behaviors and control of responses to stressful stimuli (Wood & Grafman, 2003), while the dmPFC exerts top-down control over motor behavior and is engaged in self-referential thinking and responses to social stimuli (Ferrari et al., 2016; Gusnard et al., 2001; Narayanan & Laubach, 2006). Finally, BA 32 is the dorsal anterior cingulate cortex (dACC), which governs the representation of context-specific stimuli and is active in top-down control of decision-making and behaviors (Stevens et al., 2011). Though these regions of the SF have discrete functional roles, they work

together to guide adaptive responses under stress through modulation of the emotional and behavioral responses.

While measuring amygdala and SF functioning in response to stressors can provide some insight into how frontal regions may exert control over the amygdala, it cannot directly assess the degree to which frontal regions are functionally interconnected with the amygdala. Directly interrogating fronto-limbic resting state functional connectivity (RSFC) provides further measures of the degree to which such control is engaged. Cingulo-opercular-amygdala (CO-A) RSFC is used to index the link between frontal regulatory regions and the amygdala (Brieant et al., 2021; Thijssen et al., 2022). The cingulo-opercular (CO) network is made up of frontal (anterior prefrontal cortex [aPFC] and dACC) and limbic regions (insula) and is heavily implicated in the regulation of emotional states and executive control of behaviors (Dosenbach et al., 2007; Gordon et al., 2016). The aPFC is involved in decision-making, facilitating movement towards long-term goals over immediate impulses (Koechlin & Hyafil, 2007). The dACC acts as a bridge between the cognitive and emotional processing systems (Stevens et al., 2011). The insula modulates attention based on the salience of stimuli and the allocation of downstream resources for processing and response (Krause-Utz et al., 2017; Menon & Uddin, 2010). The CO network exerts inhibitory control over the amygdala, thus impacting the degree of response to stressors (Sylvester et al., 2020). Measuring the degree of functional connectivity at rest between the CO network and the amygdala may give insight into the degree of frontal regulatory control exerted on the amygdala. See Figure 1 for a depiction of the interrelated network.

Figure 1. The Brain's Stress System Model for the ABCD Study



Note. Lines ending in arrows indicate excitatory relationships, while lines ending in blocks indicate inhibitory relationships. Based on Garey, 2006 and Gordon et al., 2016.

Normative Developmental Changes in the Brain's Stress Processing System

The recalibration and reorganization that occur in the frontal regions during adolescent development are of particular interest in relation to NSSI. There is an increase in prefrontal cortex (PFC) activation in response to stressful stimuli (Yurgelun-Todd & Killgore, 2006). Simultaneously, there is a maturation of the connections between the frontal lobe, including the regions of the SF and the limbic system, facilitating increased frontal regulatory control over the brain's stress response (Cunningham et al., 2002; Gee, Gabard-Durnam, et al., 2013; Perlman & Pelphrey, 2011; Silvers et al., 2015; Swartz et al., 2014). The CO network has been shown to have increasing within-network connectivity across neurodevelopment (Fair et al., 2009), while preliminary evidence from early adolescence indicates that CO-Amygdala RSFC may decrease as puberty progresses, though it is unclear if this finding is confounded by other factors that impact puberty (Thijssen et al., 2022). It may be inferred that as these regions become more integrated, the regulation of emotions becomes more effective.

Variable-Centered Findings of Alteration in the Brain's Stress System Associated with NSSI

Amygdala activation in response to stressors in participants with a history of NSSI has been investigated repeatedly, yielding mixed results (for review: Brañas et al., 2021). When

comparing amygdala activation in response to emotional faces or fear-inducing photographs in those with and without a history of NSSI engagement, heightened activation in female adolescents (Plener et al., 2012), no difference between groups of female adolescents (Mayo et al., 2021; Westlund Schreiner et al., 2017), and blunted activation in female adults who have engaged in NSSI (Hooley et al., 2020). One study showed that there may be heterogeneity among participants who engage in NSSI, as those with moderate, but not severe, NSSI showed heightened amygdala activation compared to participants with mild or no history of NSSI (Başgöze, Mirza, et al., 2021). Given that the amygdala is integral in facilitating stress processing, understanding the nuances in amygdala activation in response to evocative stimuli may be critical to understanding the biological signatures associated with NSSI.

While direct interrogation of the whole CO network as a singular unit in the context of NSSI has not been undertaken, work examining the regional components of this network has identified some intriguing alterations. Hooley et al. (2020) demonstrated that aPFC activation in response to emotionally evocative stimuli (both positive and negative) was heightened in those with a history of NSSI compared to those without a history of NSSI. Plener et al. (2012) found increased anterior cingulate cortex (ACC) activation in the context of emotionally evocative stimuli in those with a history of NSSI compared to healthy controls. Perini et al. (2019) found no difference in activity in dACC and insula between those with a history of NSSI and healthy controls. Mayo et al. (2021) found a positive association between insula reactivity to negative affective pictures and heightened physiological reactivity to emotional stimuli in adolescents with a history of NSSI compared to healthy controls. Finally, Westlund Schreiner et al. (2017) found a novel relationship between amygdala-SMA RSFC and the history of NSSI.

Fronto-limbic RSFC is consistently lower in those who engage in NSSI compared to those who do not (Başgöze, Mirza, et al., 2021; Santamarina-Perez et al., 2019; Westlund Schreiner et al., 2017). These findings theoretically correspond with decreased inhibitory signals from frontal regulatory regions to the amygdala and, thus, decreased executive control over stress responses (Dahlgren et al., 2018). Though work has yet to be conducted examining the relationship between alterations in CO-Amygdala RSFC and NSSI, a similar pattern would be expected. This pattern of decreased fronto-limbic RSFC holds promise as a broad biomarker for the risk of NSSI and maladaptive emotion regulation. Thus far, only a subset of work examining the biological patterns associated with NSSI has employed multi-modal imaging metrics. Taken

from the same sample, Başgöze, Mirza, et al. (2021) and Carosella, Mirza, et al. (2023) both examined amygdala reactivity to stressful stimuli in conjunction with amygdala-mPFC RSFC. Carosella, Mirza, et al. (2023) found that adolescents who continued engaging in NSSI after the onset of the COVID-19 pandemic showed greater amygdala reactivity with no difference in amygdala-mPFC RSFC compared to peers who desisted from NSSI or never engaged. As noted previously, Başgöze, Mirza, et al. (2021) found that adolescents with severe NSSI demonstrated more negative amygdala-mPFC RSFC, while those with moderate NSSI showed higher amygdala reactivity compared to each other and the group with a history of mild or no NSSI engagement. These studies represent only the beginning of work considering multiple metrics of the brain's stress systems in conjunction. Additionally, they point to the possibility of meaningful heterogeneity within groups of adolescents with a history of NSSI.

Person-Centered Analyses

Much of the work investigating the neural underpinnings of NSSI has used variable-centered analyses (i.e., comparing groups of individuals with and without a history of NSSI), which pre-suppose homogeneity within these groups. These methods have yielded some reliable patterns (e.g., decreased fronto-limbic RSFC; Başgöze, Mirza, et al., 2021; Santamarina-Perez et al., 2019; Westlund Schreiner et al., 2017) but have also shown some null or mixed findings regarding some metrics that should be theoretically involved in instantiating NSSI (e.g., amygdala reactivity; Hooley et al., 2020; Mayo et al., 2021; Plener et al., 2012; Westlund Schreiner et al., 2017). Person-centered analytic techniques should be employed to facilitate the identification of participant groups based on threat response patterns. This approach may promote data-driven discoveries of patterns that would otherwise be obscured due to the assumptions inherent in variable-centered analyses.

The Adolescent Brain and Cognitive Development (ABCD) Study (Barch et al., 2018; Casey et al., 2018) is ideal for person-centered examinations of neurodevelopment due to its large, representative sample and the longitudinal nature of the imaging data. Indeed, some work using this sample has employed person-centered analyses (ex: Brislin et al., 2021; Conley et al., 2023; Huffman & Oshri, 2022; Lichenstein et al., 2022; Pollmann et al., 2024; Zhuo et al., 2022), though none have included the full scope of available longitudinal data or examined risk for NSSI. Some person-centered work has been conducted in other samples that were at heightened risk of NSSI but have focused on patterns in self-reported experience of stress, observer-reported

expressions of stress, and endocrine response to stressors rather than brain metrics. When investigating stress response patterns in adolescents with and without major depressive disorder (MDD), Bendezú et al. (2022) found that those with heightened discordance in their responses had a heightened risk for engagement in NSSI. When examining adolescent females oversampled for a history of NSSI, Carosella, Wiglesworth, Bendezú, et al. (2023) again found that discordant response group membership was associated with heightened risk for a history of NSSI, though no significant findings emerged relating these stress response groups to amygdala or mPFC reactivity to emotional faces or amygdala-mPFC RSFC. Wiglesworth, Butts, et al. (2023) used the same sample to assess which patterns were associated with greater resilience from NSSI and depressive symptoms and found that the discordant group demonstrated the least clinical improvement. While information is accumulating implicating the power of person-centered analyses, no research to date has used neural indexes to identify groups relevant to NSSI, nor has any work used both person-centered and variable-centered analytic techniques to explore neurodevelopmental patterns across adolescence. When employed in tandem, person-centered and variable-centered approaches may offer novel insights into previously unobserved neurodevelopmental patterns not accessible through variable-centered analyses alone.

Aims

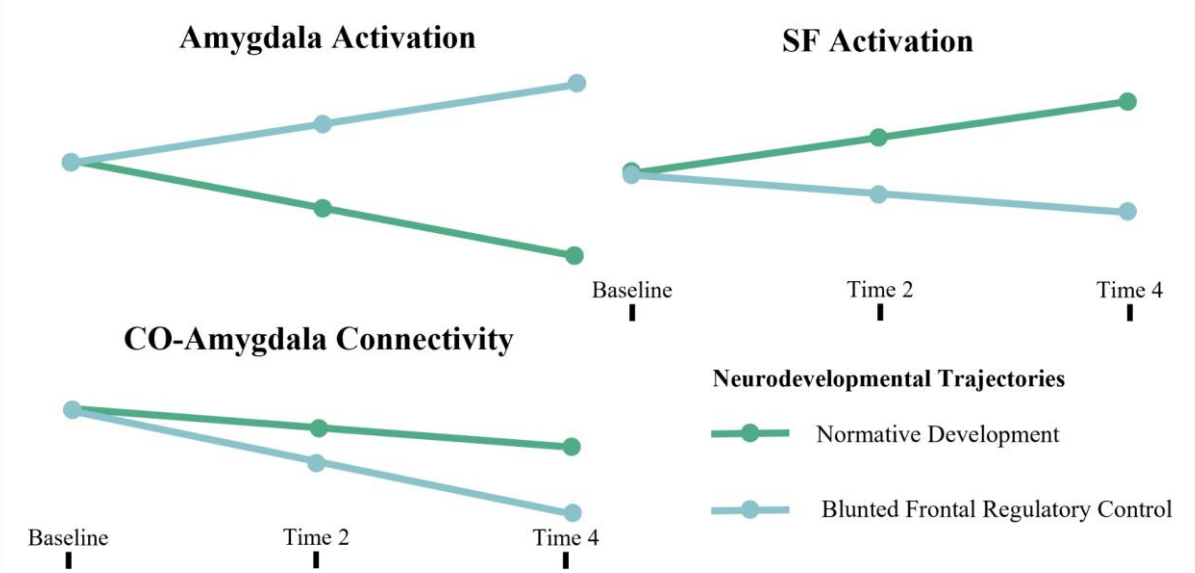
This study leverages the large, epidemiologically informed sample of the ABCD study, which recruited families with children 9-10 years old from across the United States (see Garavan et al., 2018 for recruitment information). Neuroimaging, including activation in response to emotionally evocative stimuli and RSFC (Casey et al., 2018), was collected every other year, and interviews/surveys regarding psychopathology were collected yearly (Barch et al., 2018). The study described below includes data from Baseline (9-10 years old), Time 1 (10-11 years old), Time 2 (11-12 years old), Time 3 (12-13 years old), and all presently available data for Time 4 (13-14 years old). This study broadly attempts to characterize the neural developmental patterns that relate to engagement in NSSI using both person-centered and variable-centered analyses.

Aim 1

To use person-centered analytic approaches to identify distinct trajectories of neurodevelopment in the brain's stress system captured by the reactivity of the amygdala and SF gyrus in response to emotionally evocative stimuli and CO-amygdala RSFC. There are no predictions for the number of groups; however, it is hypothesized among the empirically derived

trajectories will be one that represents a Normative Development trajectory group and is typified by decreasing amygdala reactivity, increasing SF reactivity to evocative stimuli, and increasingly negative CO-amygdala connectivity. Another hypothesized group is a Blunted Frontal Regulatory Control trajectory, composed of participants with increasing amygdala reactivity, decreased or stable SF activation, and more increasingly negative CO-amygdala RSFC. Hypothesized groups are shown in Figure 2.

Figure 2. Diagram of Hypothesized Neurodevelopmental Trajectories for the ABCD Study



Note: SF=Superior Frontal; CO=Cingulo Opercular

Aim 2

To assess whether these neurodevelopmental trajectories are related to a history of engagement in NSSI and the age at which NSSI engagement is first reported. Given the high rates of comorbidity between NSSI and depression, follow-up sensitivity analyses will be conducted in which depression symptom severity is included as a covariate to determine if any observed patterns are uniquely associated with NSSI. It is hypothesized that those in the Blunted Frontal Regulatory Control trajectory group will be at the highest risk for engagement in NSSI. Analyses exploring the age at the first report of NSSI are exploratory as no prior work has been conducted examining neural signatures and this attribute of NSSI.

Aim 3

To employ variable-centered analyses to assess if changes in amygdala reactivity, SF reactivity, and CO-amygdala RSFC are related to a history of NSSI engagement and the age at which NSSI is first reported. Given that the particular person-centered analytic approach to be employed can account for both the Baseline and slope of change of brain metrics, both the Baseline and slope (change over time) of these metrics will be examined in relation to NSSI engagement and age at the first report of NSSI. Follow-up sensitivity analyses will be conducted in which depression symptom severity is included as a covariate to determine if any observed patterns are uniquely associated with NSSI.

Baseline. It is hypothesized that lower Baseline SF reactivity and more negative Baseline CO-Amygdala RSFC will be associated with a greater risk of engaging in NSSI. Analyses exploring the age at the first report of NSSI are exploratory as no prior work has been conducted examining neural signatures and this metric. Analyses assessing amygdala reactivity are exploratory given the mixed findings in the literature on NSSI, however prior work in similar populations (e.g., those with depression) has indicated that higher reactivity is associated with more significant emotion regulation difficulties (Klimes-Dougan et al., 2014).

Slope. It is hypothesized that decreasing or stable SF reactivity and increasingly more negative CO-Amygdala RSFC will be associated with a greater risk of engaging in NSSI. Analyses exploring the age at the first report of NSSI are exploratory as no prior work has been conducted examining neural signatures and this metric. Analyses assessing amygdala reactivity are exploratory given the mixed findings in the literature on NSSI, however prior work in similar

populations (e.g., those with depression) has indicated that higher reactivity is associated with more significant emotion regulation difficulties (Klimes-Dougan et al., 2014).

Significance

This study could provide novel evidence of neurodevelopmental trajectories through person-centered analyses related to risk for NSSI. In addition, it could add to the extant body of literature exploring the biological underpinnings of NSSI via variable-centered analyses and potentially support the robustness of these findings. This study leverages the large, epidemiologically informed, longitudinal sample that captures rich multilevel metrics of neural functioning and psychopathology across a critical development period and uses novel analytic approaches to replicate and extend the extant literature on the biological basis of NSSI in a framework.

Methods

Sample

The original ABCD sample includes 11,877 participants at Baseline who provided brain data (Baseline, Time 2, and partial data for Time 4) and self-report and parent/guardian-report metrics of NSSI and depressive symptoms at each time point. Brain data was filtered using the pre-tabulated MRI quality control variables (Hagler et al., 2019). Participants missing more than 50% of brain data points across the three time points (due to attrition, scanner failure, poor MRI scan quality, etc.) were excluded, resulting in a sample of 5,563 participants. The sample selection process is such that participants with missing data for Time 4 and/or low-quality data are more likely to be excluded from the subsample. See Table 1 for demographic information and Table A1 for an overview of the reported patterns of NSSI across time points.

Measures

Demographic Information:

Demographic variables were reported by a parent or guardian at each time point and are used to examine differences between groups. These data included participant age in months, participant sex assigned at birth (male =”1”, female=”2”), participant race and ethnicity, total family income, site ID, and scanner platform. For this study, Baseline demographic data was used for all metrics besides age (which was included for each time point). Additionally, participants and parents/guardians were asked to report on the participant's gender identity and transgender status at each time point as a part of the psychodiagnostic interview (Kiddie

Schedule for Affective Disorders and Schizophrenia for School-Age Children-Computerized Version; Barch et al., 2018; Kaufman et al., 1997, 2021). Most recently reported gender identity was used. Discrepancies between the participant and parent/guardian reported gender identity were resolved using the participant report. Endorsement of transgender status by either the parent/guardian or participant at any time was coded as "1"; no endorsement across all Time points was coded as "0".

Functional Neural Activation to Emotionally Evocative Stimuli:

Tabulated metrics of the amygdala and SF regional activation during the emotional N-Back task were used. This task was administered while participants underwent functional magnetic resonance imaging (fMRI), which has been shown to engage processes related to memory and emotion regulation (Barch et al., 2013). The task consists of two types of blocks (0-back [low memory load] and 2-back [high memory load]), each with four types of photograph stimuli: happy, fearful, and neutral faces (Conley et al., 2018; Tottenham et al., 2009) and places. The cognitive processing of these stimuli reliably activates the fronto-limbic circuitry involved in emotion reactivity and regulation (Gee, Gabard-Durnam, et al., 2013; Hare et al., 2008). Data were collected during two 5-minute fMRI runs, each with four 0-back and 2-back blocks each. Runs included 362 whole-brain volumes after discarded acquisition (Rosenberg et al., 2020). The SF regional parcellation was defined using the Desikan-Killany cortical atlas (Desikan et al., 2006), while the amygdala parcellation was defined using the FreeSurfer Aseg atlas (Fischl et al., 2002). Contrasts in regional activation to neutral faces to the happy and fearful faces allow for an assessment of the specificity of activation to emotionally evocative stimuli. A description of the processing of task-based neuroimaging and the parcellation methodology can be found in Hagler et al. (2019). The pre-tabulated mean beta weight for nBack emotion versus neutral face contrast for the amygdala and SF parcellations were used. The means of the two hemispheric values were computed to represent the bilateral activation in each region because there are no a priori hypotheses about hemispheric-specific differences. Pre-tabulated task MRI quality control recommendations for inclusion/exclusion were used to determine if each participant's scan at each time point met the inclusion criteria (Hagler et al., 2019).

Resting State Functional Connectivity:

Tabulated metrics of CO-amygdala RSFC were captured while participants were in the scanner with their eyes open, passively viewing a crosshair for 5 minutes across four different

scanning segments (Casey et al., 2018). A description of the processing and parcellation of this data can be found in (Hagler et al., 2019). The CO network was defined using the Gordon atlas (Gordon et al., 2016), and the amygdala was parcellated using the FreeSurfer Aseg atlas (Fischl et al., 2002). Means of the two hemispheric values represented the RSFC between the bilateral CO network and bilateral amygdalae, as there are no apriori hypotheses about hemispheric-specific differences. Pre-tabulated resting state MRI quality control recommendations for inclusion/exclusion were used to determine if each participant's scan at each time point met the inclusion criteria (Hagler et al., 2019).

NSSI Engagement:

Participant self-reported and parent/guardian-reported responses on the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Computerized Version (Barch et al., 2018; Kaufman et al., 1997, 2021) were used to measure NSSI engagement. Participants and their parents/guardians were asked, "Sometimes when kids get upset or feel numb, they may do things to hurt themselves, like scratching, cutting, or burning themselves. In the past two weeks, how often [have you/has your child] done any of these things or other things to try to hurt [yourself/themselves]?" to assess for present NSSI engagement and "Was there ever a time in the past when [you/your child] did things to hurt [yourself/themselves] on purpose because [you/they] were upset, like cut, scratch or burn yourself?" to assess past instances of NSSI. Affirmative responses by the parent/guardian or the participant at each time point were coded as "1," while negative responses by both parent/guardian and participant were coded as "0" for that time point. Affirmative responses at any time point resulted in NSSI engagement history being coded as "1," and negative responses across all time points, NSSI history was coded as "0".

Age at First Report of NSSI:

The participant's age (in months) at the visit at which NSSI was first endorsed was found. The age of onset of NSSI could not be determined based on the information gathered, but it is hoped that the age at the first report is a useful approximation.

Depressive Symptoms:

Participants' parents or guardians completed the Child Behavior Checklist (CBCL; Achenbach & Ruffle, 2000) at each time point. The CBCL assesses various externalizing and internalizing problems in children and adolescents. The Depression DSM-5 Scale questions

about apathy, anhedonia, crying, loss of/increase in appetite, difficulty sleeping, fatigue, and sadness. The pre-calculated Depression DSM-5 Scale t-score (Achenbach, 2013) was used to index the severity of depressive symptoms, with higher scores indicating heightened depressive symptom severity.

Analytic Plan

The same metrics will be used across person-centered and variable-centered analyses, though the different analytic methods frame questions slightly differently. Person-centered analyses (Aims 1 and 2) can simultaneously examine all time points for all metrics, allowing for the direct investigation of interplay across time. Variable-centered analyses (Aim 3) can examine the individual metrics separately within the same model and can only examine one time point (i.e., Baseline) or a composite measurement formed from data across time points (i.e., slope).

Aim 1:

Multi-Trajectory Modeling (Nagin et al., 2018) was conducted using the "gbmt" package (Magrini, 2022) in R (R Core Team, 2023a). The model variables were amygdala reactivity, SF reactivity, and CO-amygdala RSFC from Baseline, Time 2, and Time 4. The number of derived groups was determined based on model fit statistics (including AIC, BIC, and posterior probability) and parsimony, as described in Nagin (2005). Once the appropriate number of groups was identified, the number of polynomial degrees was determined using the same iterative process based on the same model fit statistics. The resulting groups represent neurodevelopmental trajectory groups.

Demographic attributes were compared between groups. Chi-squared tests were conducted to assess for differences between groups in relation to categorical variables (race, ethnicity, family income, sex at birth, gender identity, scanner platform, and site ID). One-way ANOVAs were conducted to assess for group differences in age at each time point. Chi-squared and ANOVAs were conducted using the "stats" package in R (R Core Team, 2023b).

Aim 2:

NSSI Engagement: Multilevel binomial regressions were conducted using the "lme4" package in R (Bates et al., 2015) to assess whether any neurodevelopmental trajectory groups are associated with more individuals endorsing a history of NSSI engagement. Covariates included sex at birth, age at Baseline, age at Time 2, age at Time 4, scanner platform, and family ID nested in the site ID. Follow-up sensitivity analyses were conducted using the mean CBCL

Depression score as a covariate. Follow-up group comparisons were conducted using pairwise t-tests with a Bonferroni correction using the "stats" package in R (R Core Team, 2023b).

Age at First Report of NSSI: Multilevel linear regressions were conducted using the "lme4" package in R (Bates et al., 2015) to assess whether any neurodevelopmental trajectory groups are associated with an earlier age at which NSSI was reported. Covariates included sex at birth, age at Baseline, age at Time 2, age at Time 4, scanner platform, and family ID nested in the site ID. Follow-up sensitivity analyses were conducted using the mean CBCL Depression score as a covariate. Follow-up group comparisons were conducted using pairwise t-tests with a Bonferroni correction using the "stats" package in R (R Core Team, 2023b).

Aim 3:

Baseline: Correlations between Baseline brain metrics, age at Baseline, sex at birth, NSSI engagement, age of first report of NSSI, and Baseline CBCL Depression score were conducted using the "Hmisc" package in R (Harrell, 2023). To compare Baseline brain metrics (amygdala reactivity, SF reactivity, and CO-amygdala RSFC) between participants with and without a history of NSSI, multilevel binomial regressions were conducted using the "lme4" package in R (Bates et al., 2015). To assess the relationship between Baseline brain metrics and the age at which NSSI was first reported, multilevel linear regressions were conducted in R using the "lme4" package (Bates et al., 2015). Covariates included sex at birth, age, scanner platform, and family ID nested within site ID. Follow-up sensitivity analyses were conducted using the Baseline CBCL Depression DSM-5 t-score as a covariate.

Slope: To compare the change in brain metrics over time, the slope of change in each metric was found for each participant by calculating the difference between the most recently available data and the earliest available data and dividing the difference by the change in age (in months) between the two time points. To compare the slope of change of brain metrics (amygdala reactivity, SF reactivity, and CO-amygdala RSFC) between participants with and without a history of NSSI, multilevel binomial regressions were conducted using the "lme4" package in R (Bates et al., 2015). To assess the relationship between Baseline brain metrics and the age at which NSSI was first reported, multilevel linear regressions were conducted in R using the "lme4" package (Bates et al., 2015). Covariates included sex at birth, age, scanner platform, and family ID nested within site ID. Follow-up sensitivity analyses were conducted using the mean CBCL Depression score as a covariate.

Results

Sample Characteristics

Of the 5,563 participants included in this study, 1,261 (22.7%) reported engaging in NSSI at some point by Time 4. A significant proportion of this group reported engagement at the Baseline time point (n=485, 38.5% of the total group reporting NSSI). Participants assigned female sex at birth (AFAB) accounted for 54.2% of the group reporting NSSI across time points (n=684). When examined longitudinally, the number of participants assigned male sex at birth (AMAB) reporting NSSI for the first time decreased across the time points while the number of participants AFAB increased over time. See Table 1 for participant demographic information and Table A1 for greater detail on NSSI reporting across time points and by sex at birth.

Table 1. Demographic Characteristics of Subsample for the ABCD Study

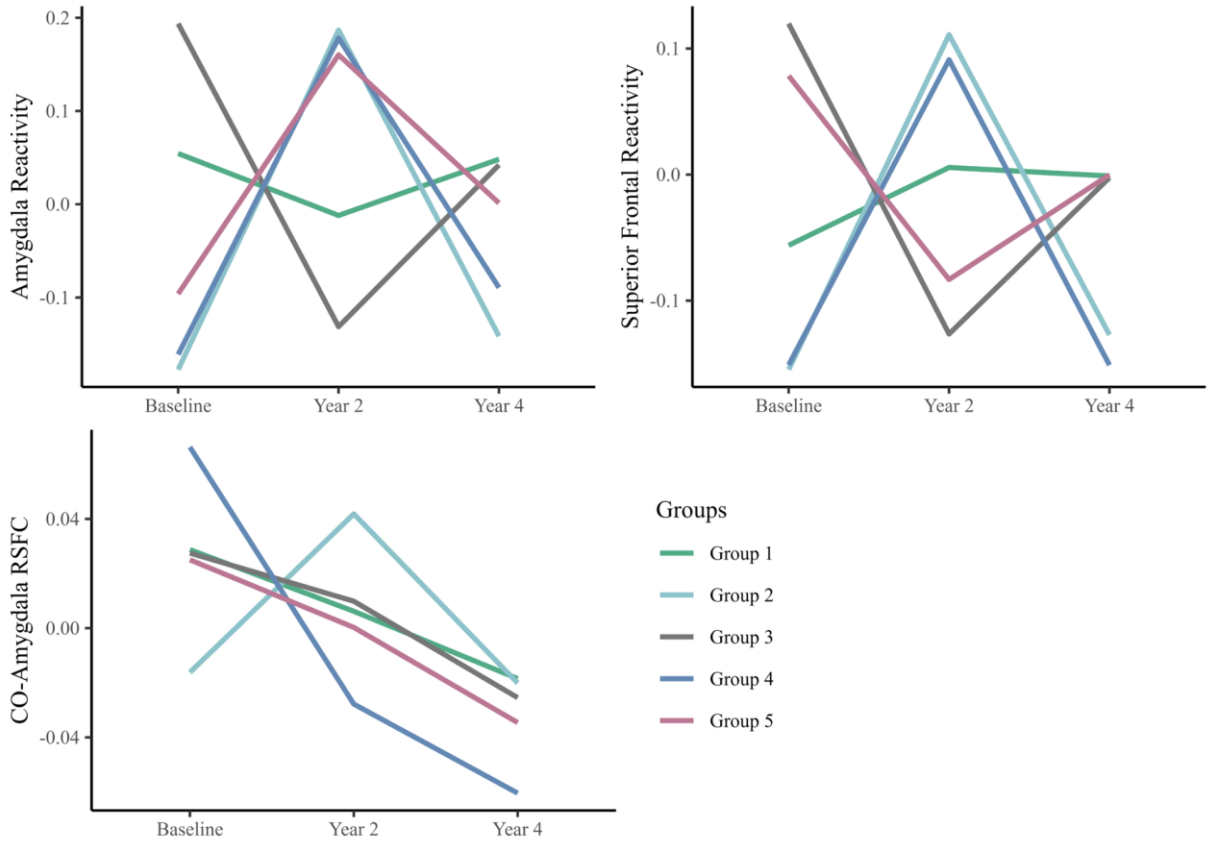
Age At Each Time Point Mean (SD)	
Baseline (n = 5563)	9.9513 (0.625)
Time 1 (n =5479)	10.961 (0.6407)
Time 2 (n = 5556)	12.005 (0.661)
Time 3 (n =5335)	12.919 (0.647)
Time 4 (n =3306)	14.085 (0.688)
Biological Sex at Birth N (%)	
Female	2626 (47.2%)
Male	2938 (52.8%)
Gender Identity N (%)	
Female	2310 (41.5%)
Male	2810 (50.5%)
Another Gender (e.g. non-binary)	214 (3.8%)
Transgender Status N (%)	
Transgender	110 (2.0%)
Racial Identities N (%)	
American Indian/Alaska Native or Native Hawaiian/Pacific Islander	63 (1.1%)
Asian	111 (2.0%)
Black	553 (10.0%)
White	3948 (71.0%)
Multiracial	449 (8.1%)
Other	432 (7.8%)
Ethnic Identities N (%)	
Hispanic or Latino	1021 (18.4%)
Family Income N (%)	
Less than $5,000 through $15,999	311 (5.6%)
$16,000 through $34,999	476 (8.6%)
$35,000 through $49,999	442 (7.9%)
$50,000 through $74,999	758 (13.6%)
$75,000 through $99,999	835 (15.0%)
$100,000 through $199,999	1749 (31.4%)
$200,000 and greater	635 (11.4%)

Aim 1 Results

The 5-group solution was selected because it had the best model fit statistics (see Table A2). The groups were compared based on demographic characteristics and were found to not differ on many demographic characteristics. However, the groups differed in age at Baseline, age at Time 1, age at Time 2, scanner platform, and site ID. See Table A3 for comparison statistics.

Figure 3 shows the person-centered derived groups. Group 1 (n=2,240) was characterized by stable amygdala reactivity, increasing SF reactivity, and decreasing CO-amygdala RSFC. Group 2 (n=562) was characterized by increasing then decreasing amygdala reactivity, increasing then decreasing SF reactivity, and increasing then decreasing RSFC. Group 3 (n=1,492) is characterized by decreasing amygdala reactivity, decreasing then increasing SF reactivity, and decreasing RSFC. Group 4 (n=570) is characterized by increasing then decreasing amygdala reactivity, increasing then decreasing SF reactivity, and decreasing RSFC. Finally, Group 5 (n=699) is characterized by increasing amygdala, decreasing SF reactivity, and decreasing RSFC. Because it is the largest group, Group 1 was selected as the reference group for the following analyses.

Figure 3. Person-Centered Derived Groups for the ABCD Study



Note: CO=cingulo-opercular, RSFC=Resting State Functional Connectivity

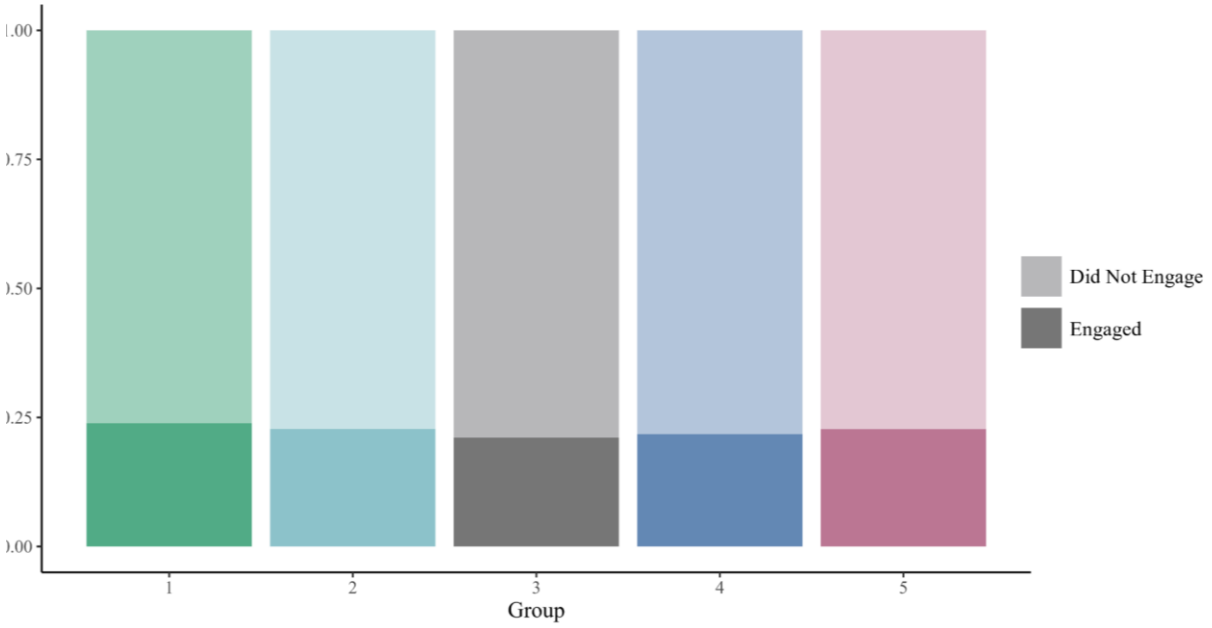
Aim 2 Results

Table 2. History of NSSI Engagement by Group for ABCD Study

	Without CBCL Depression Score	**With CBCL Depression Score**
Coefficient	**OR (CI)**	**OR (CI)**
Intercept	-0.277 (0.219, 0.350)***	0.083 (0.054, 0.128)***
Group 2 Membership	1.389 (0.994, 1.940)	1.295 (0.908, 1.847)
Group 3 Membership	0.862 (0.687, 1.080)	0.851 (0.671, 1.081)
Group 4 Membership	1.227 (0.861, 1.750)	1.135 (0.776, 1.660)
Group 5 Membership	1.040 (0.777, 1.392)	0.927 (0.679, 1.265)
Sex at Birth	1.632 (1.369, 1.944)***	1.672 (1.388, 2.015)***
Baseline Age	0.620 (0.404, 0.951)*	0.588 (0.373, 0.926)*
Age Time 2	1.104 (0.756, 1.613)	1.082 (0.724, 1.618)
Age Time 4	1.521 (1.128, 2.049)**	1.587 (1.154, 2.182)**
Scanner Platform: Phillips	0.591 (0.410, 0.852)**	0.710 (0.483, 1.043)
Scanner Platform: Siemens	0.839 (0.690, 1.020)	0.886 (0.720, 1.091)
Mean CBCL Depression Score		1.450 (1.364, 1.542)***

Note: NSSI=non-suicidal self-injury; Sex at birth coded such that Male=1, Female=2; CBCL=Child Behavior Checklist; OR=Odds Ratio, CI=Confidence Interval; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$.

Figure 4. History of NSSI Engagement by Group for the ABCD Study



Note: NSSI=non-suicidal self-injury

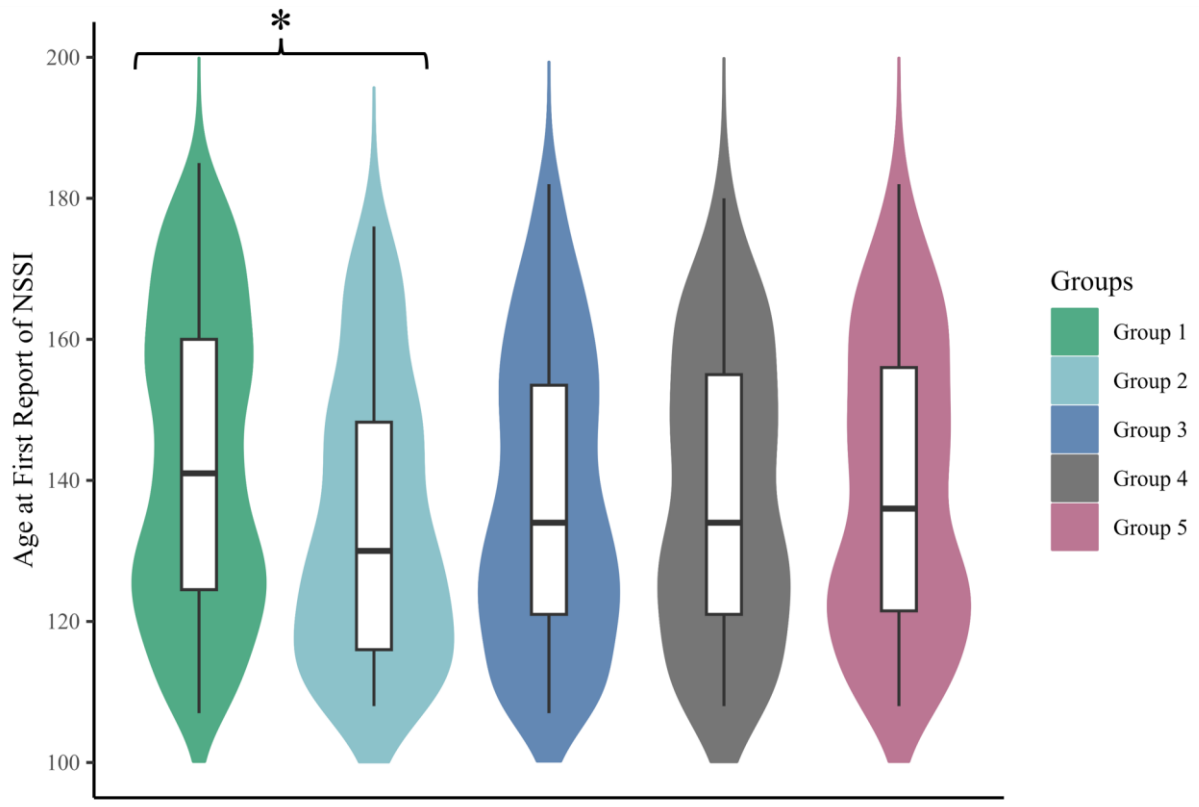
When examining factors related to the history of NSSI engagement, no significant effects of developmental trajectory group membership were found (Table 2). Sex at birth was found to be significantly related to NSSI engagement, with participants AFAB at significantly heightened risk for engagement. Lower Baseline age and higher Time 4 age were associated with a heightened risk of reporting NSSI engagement both with and without the inclusion of CBCL Depression score as a covariate. Heightened CBCL Depression scores were also associated with a greater risk of NSSI engagement. A pairwise comparison of groups yielded no significant differences in NSSI engagement between groups, as shown in Table A4 and Figure 4.

Table 3. Age of First Report of NSSI by Group for the ABCD Study

	Without CBCL Depression Score	**With CBCL Depression Score**
Coefficient	**Beta (SE)**	**Beta (SE)**
Intercept	-30.482 (17.844)	-32.155 (17.776)
Group 2 Membership	-6.860 (2.490)**	-6.474 (2.483)**
Group 3 Membership	-2.239 (1.774)	-2.135 (1.767)
Group 4 Membership	-1.096 (2.632)	-0.759 (2.623)
Group 5 Membership	-0.512 (2.232)	0.192 (2.235)
Sex at Birth	13.487 (1.325)***	13.360 (1.319)***
Baseline Age	0.049 (0.457)	0.059 (0.455)
Age Time 2	0.479 (0.389)	0.447 (0.388)
Age Time 4	0.534 (0.287)	0.574 (0.286)*
Scanner Platform: Phillips	2.042 (2.907)	1.577 (2.899)
Scanner Platform: Siemens	1.759 (1.481)	1.787 (1.474)
Mean CBCL Depression Score		-0.797 (0.278)**

Note: NSSI=non-suicidal self-injury; SE=standard error; Sex at birth coded such that Male=1, Female=2; CBCL=Child Behavior Checklist; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$.

Figure 5. Age at First Report of NSSI by Group for the ABCD Study



Note: NSSI=non-suicidal self-injury; Age in months; * indicates p<0.05, difference significant with and without the inclusion of CBCL Depression score as a covariate.

When examining factors related to the age at which NSSI engagement was first reported, Group 2 membership was found to be significantly associated with younger age at the first report of NSSI engagement, both with and without CBCL Depression score included as a covariate (Table 3, Figure 5). Sex at birth was found to be significantly related to NSSI engagement, with participants AFAB at significantly heightened risk for later age at first report of NSSI engagement. Heightened CBCL Depression score was also associated with younger age at first report of NSSI engagement. The distribution of age at the first report of NSSI by group and the pairwise comparison of groups and age at the first report of NSSI engagement is shown in Table A5. Based on the pairwise test results, there are differences in the age at the first report of NSSI between Groups 1 and 2 and Groups 1 and 3, with Groups 2 and 3 having significantly younger ages at the first report of NSSI than Group 1.

Aim 3 Results

The slope of change in amygdala reactivity, SF reactivity, and CO-amygdala RSFC was 0.000 across all participants, indicating no universal trends in the change of these metrics over the observed time points. The average CBCL Depression score across time points was 1.464, which is indicative of very minimal impairment due to depressive symptoms in the sample as a whole.

The correlation analysis between Baseline values (Table A6) indicates that Baseline SF reactivity is inversely associated with age at the first report of NSSI and positively associated with Baseline amygdala reactivity. Baseline age is positively associated with age at the first report of NSSI and Baseline SF reactivity. As expected, the Baseline CBCL Depression score was positively associated with the history of NSSI engagement and inversely related to age at first report of NSSI.

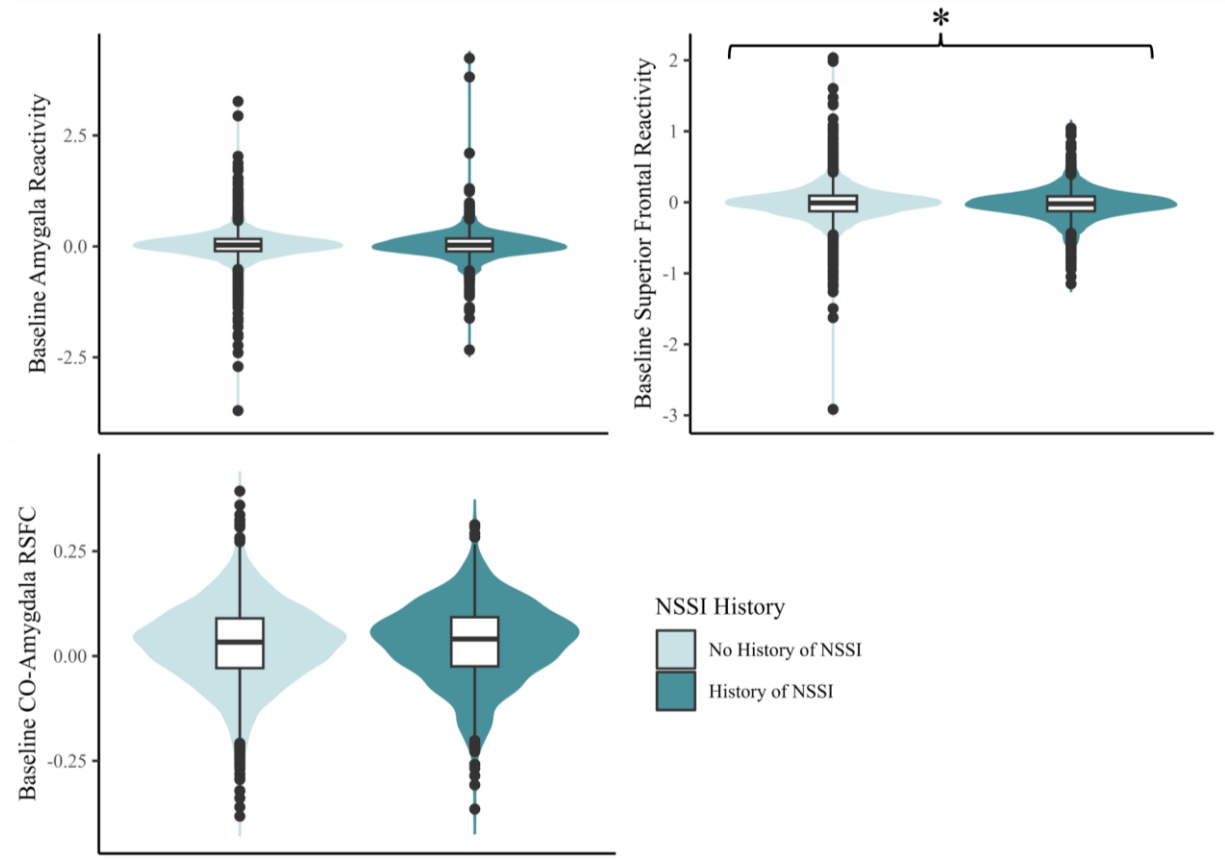
The correlation analysis between slope values (Table A7) indicates that the slope of change in CO-Amygdala RSFC is inversely associated with the history of NSSI engagement. Further, the slope of SF reactivity is positively associated with the slope of change in amygdala reactivity. All age variables were found to be positively associated with age at the first report of NSSI and negatively associated with the slope of change in CO-Amygdala RSFC. Baseline age and age at Time 1 were positively associated with the slope of change in SF reactivity. As expected, a higher CBCL Depression score was associated with a greater risk of a history of NSSI engagement and greater age across all time points. All age variables were found to be associated with the other age variables.

Table 4. History of NSSI Engagement and Baseline Brain Metrics for the ABCD Study

	Without CBCL Depression Score	**With CBCL Depression Score**
Coefficient	**OR (CI)**	**OR (CI)**
Intercept	0.250 (0.201, 0.312)***	0.178 (0.137, 0.230)***
Baseline Amygdala Reactivity	1.203 (0.932, 1.554)	1.255 (0.964, 1.632)
Baseline SF Reactivity	0.669 (0.465, 0.963)*	0.665 (0.458, 0.966)*
Baseline CO-Amygdala RSFC	1.744 (0.763, 3.986)	1.700 (0.729, 3.963)
Sex at Birth	1.466 (1.255, 1.711)***	1.552 (1.322, 1.822)***
Baseline Age	1.042 (0.966, 1.125)	1.033 (0.956, 1.117)
Scanner Platform: Phillips	0.597 (0.430, 0.829)**	0.632 (0.452, 0.883)**
Scanner Platform: Siemens	0.715 (0.597, 0.855)***	0.713 (0.593, 0.857)***
Baseline CBCL Depression Score		1.257 (1.203, 1.314)***

Note: NSSI=non-suicidal self-injury; OR=Odds Ratio; CI=Confidence Interval; SF=superior frontal; CO=cingulo-opercular; RSFC=resting state functional connectivity; Sex at birth coded such that Male=1, Female=2; CBCL=Child Behavior Checklist; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$.

Figure 6. History of NSSI Engagement History and Baseline Brain Metrics for the ABCD Study



Note: NSSI=non-suicidal self-injury; CO=cingulo-opercular; RSFC=resting state functional connectivity; * indicates $p<0.05$, difference significant with and without the inclusion of CBCL Depression score as a covariate.

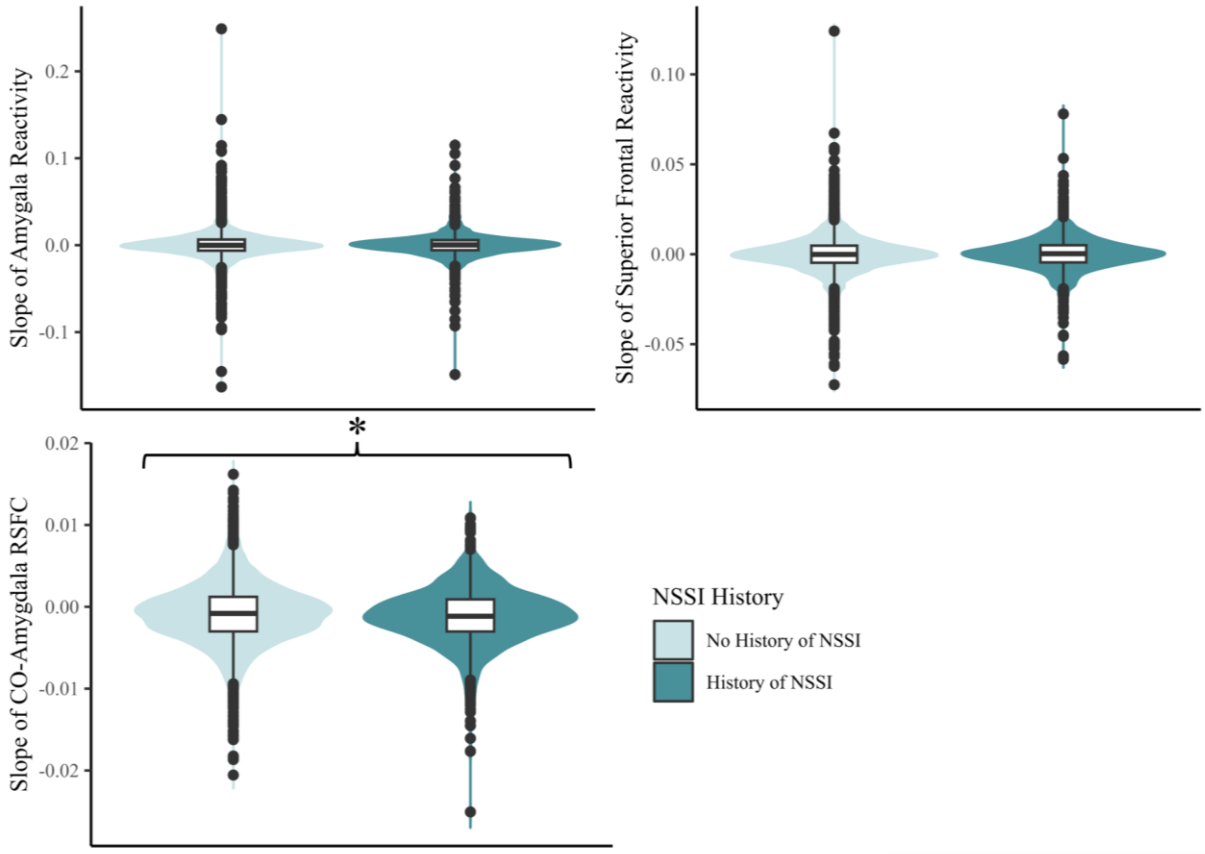
When conducting variable-centered analyses of the relationship between Baseline attributes and the history of NSSI engagement (Table 4), decreased Baseline SF reactivity was found to be significantly related to a higher risk for a history of NSSI engagement, both when CBCL Depression score was included as a covariate and when it was not (Figure 6). Sex at birth was found to be significantly related to the history of NSSI engagement, with participants AFAB at heightened risk for a history of NSSI engagement, with and without CBCL Depression score as a covariate. The scanner platform (Phillips) was also significantly related to the history of NSSI engagement in models with and without CBCL Depression scores as a covariate. Baseline CBCL Depression score was also significantly related to a history of NSSI engagement.

Table 5. History of NSSI Engagement and Slope Brain Metrics for the ABCD Study

	Without CBCL Depression Score	**With CBCL Depression Score**
Coefficient	**OR (CI)**	**OR (CI)**
Intercept	0.279 (0.223, 0.350)***	0.137 (0.101, 0.186)***
Slope of Amygdala Reactivity	0.518 (0.001, 495.485)	0.055 (0.000, 82.645)
Slope of SF Reactivity	17405.440 (0.418, 725149347.701)	46217.817 (0.642, 3329186317.070)
Slope of CO-Amygdala RSFC	0.000 (0.000, 0.014)*	0.000 (0.000, 0.009)*
Sex at Birth	1.623 (1.358, 1.940)***	1.655 (1.368, 2.002)***
Baseline Age	0.618 (0.400, 0.954)*	0.582 (0.366, 0.926)*
Age Time 2	1.096 (0.746, 1.613)	1.069 (0.708, 1.613)
Age Time 4	1.527 (1.125, 2.073)**	1.608 (1.159, 2.232)**
Scanner Platform: Phillips	0.580 (0.396, 0.848)**	0.693 (0.464, 1.036)
Scanner Platform: Siemens	0.833 (0.682, 1.017)	0.887 (0.717, 1.098)
Mean CBCL Depression Score		1.440 (1.354, 1.532)***

Note: NSSI=non-suicidal self-injury; OR=Odds Ratio; CI=Confidence Interval; SF=superior frontal; CO=cingulo-opercular; RSFC=resting state functional connectivity; Sex at birth coded such that Male=1, Female=2; CBCL=Child Behavior Checklist; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

Figure 7. History of NSSI Engagement History and Slope Brain Metrics for the ABCD Study



Note: NSSI=non-suicidal self-injury; CO=cingulo-opercular; RSFC=resting state functional connectivity; * indicates p<0.05, difference significant with and without CBCL Depression score included as a covariate

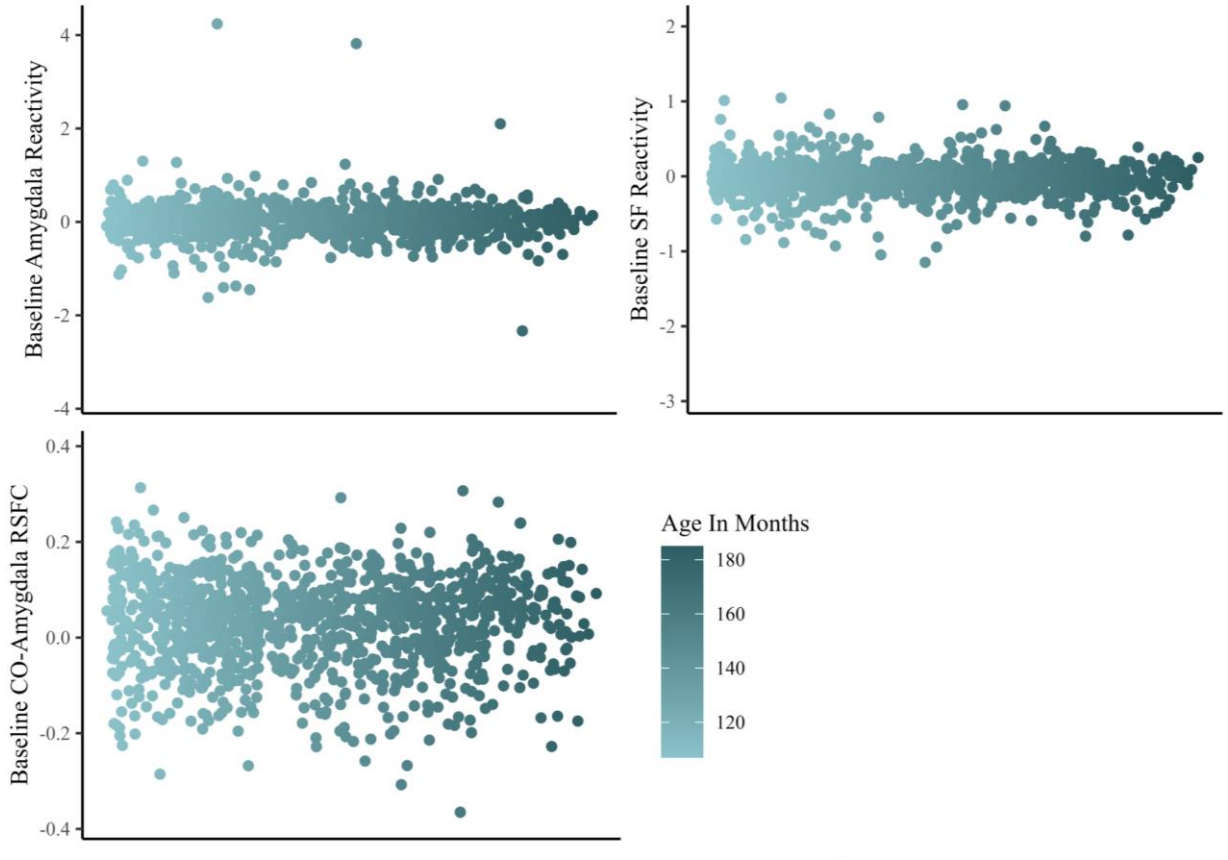
When conducting variable-centered analyses of the relationship between the slope of change of attributes with the history of NSSI engagement (Table 5), a negative slope of change of RSFC was significantly related to heightened risk for a history of NSSI engagement (Figure 7). Demographic factors (sex at birth, Baseline age, age at Time 4) were significantly related to a history of NSSI engagement both when CBCL Depression score was and was not included as a covariate. Female sex at birth, younger age at Baseline, and older age at Time 4 were found to be associated with heightened risk of NSSI. The scanner platform (Phillips) was also significantly related to the history of NSSI engagement when the CBCL Depression score was not included as a covariate. The mean CBCL Depression score was significantly related to the history of NSSI engagement, with higher scores associated with a greater risk of a history of NSSI engagement.

Table 6. Age at First Report of NSSI and Baseline Brain Metrics for the ABCD Study

	Without CBCL Depression Score	**With CBCL Depression Score**
Coefficient	**Beta (SE)**	**Beta (SE)**
Intercept	-9.502 (9.048)	-8.102 (8.931)
Baseline Amygdala Reactivity	0.978 (1.746)	0.711 (1.724)
Baseline SF Reactivity	-1.719 (2.662)	-1.772 (2.626)
Baseline CO-Amygdala RSFC	6.348 (6.038)	6.416 (5.957)
Sex at Birth	11.973 (1.121)***	11.289 (1.113)***
Baseline Age	1.089 (0.074)***	1.104 (0.073)***
Scanner Platform: Phillips	0.47 (2.438)	-0.026 (2.408)
Scanner Platform: Siemens	-0.047 (1.271)	-0.016 (1.254)
Baseline CBCL Depression Score		-1.237 (0.23)***

Note: NSSI=non-suicidal self-injury; SE=standard error; SF=superior frontal; CO=cingulo-opercular; RSFC=resting state functional connectivity; Sex at birth coded such that Male=1, Female=2; CBCL=Child Behavior Checklist; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

Figure 8. Age at First Report of NSSI and Baseline Brain Metrics for the ABCD Study



Note: NSSI=non-suicidal self-injury; SF=superior frontal; CO=cingulo-opercular; RSFC=resting state functional connectivity

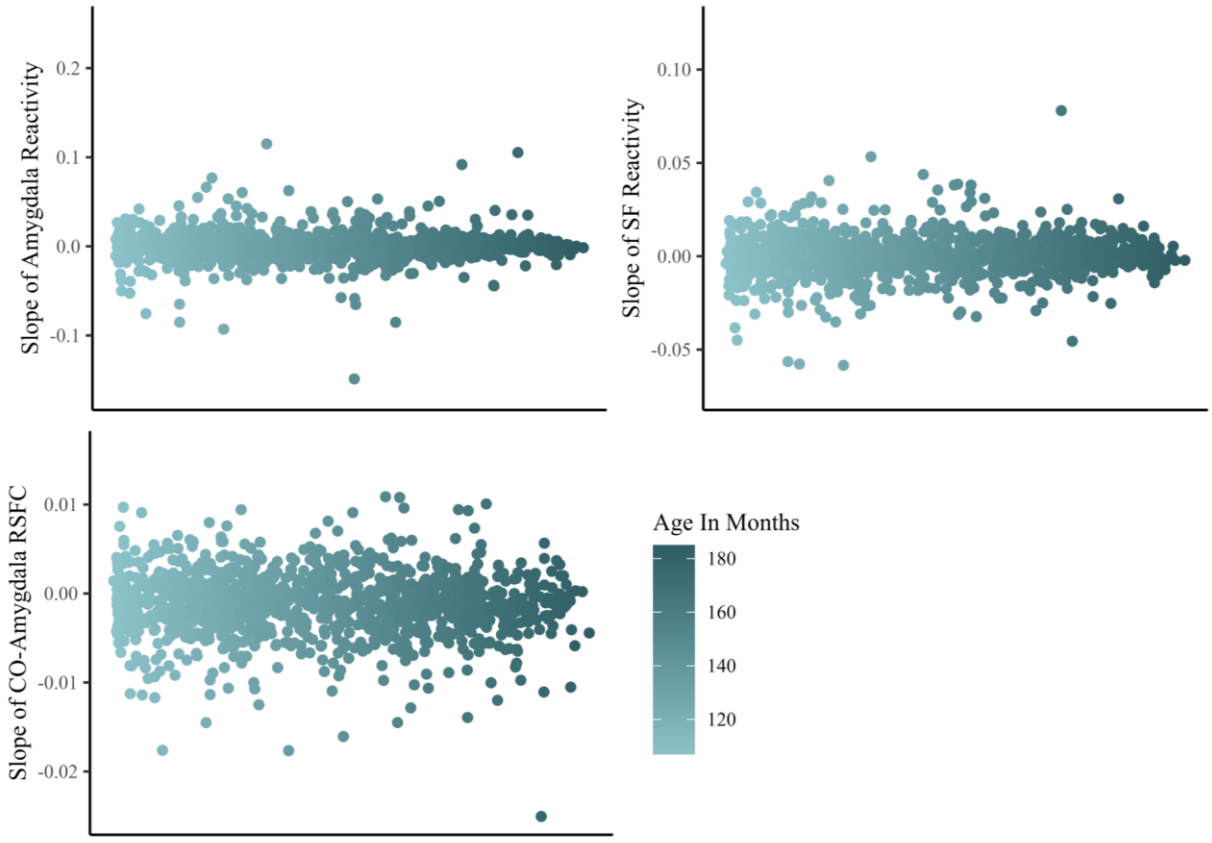
No significant findings emerged when using variable-centered analyses to assess if the Baseline brain metrics are related to the age at which NSSI was first reported (Table 6, Figure 8). Female sex at birth was found to be significantly associated with older age at the first report of NSSI, while CBCL Depression score was and was not included as a covariate. Heightened Baseline CBCL Depression score was associated with younger age at first report of NSSI as well.

Table 7. Age at First Report of NSSI and Slope Brain Metrics for the ABCD Study

	Without CBCL Depression Score	**With CBCL Depression Score**
Coefficient	**Beta (SE)**	**Beta (SE)**
Intercept	-38.615 (18.455)*	-40.146 (18.394)*
Slope of Amygdala Reactivity	35.068 (52.152)	43.544 (52.053)
Slope of SF Reactivity	31.275 (81.387)	17.153 (81.254)
Slope of CO-Amygdala RSFC	-278.989 (209.454)	-269.537 (208.684)
Sex at Birth	13.742 (1.373)***	13.6 (1.369)***
Baseline Age	0.053 (0.467)	0.059 (0.466)
Age Time 2	0.633 (0.401)	0.611 (0.4)
Age Time 4	0.361 (0.297)	0.397 (0.296)
Scanner Platform: Phillips	-0.941 (3.042)	-1.199 (3.032)
Scanner Platform: Siemens	0.865 (1.528)	0.893 (1.522)
Mean CBCL Depression Score		-0.752 (0.286)**

Note: NSSI=non-suicidal self-injury; SE=standard error; SF=superior frontal; CO=cingulo-opercular; RSFC=resting state functional connectivity; Sex at birth coded such that Male=1, Female=2; CBCL=Child Behavior Checklist; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

Figure 9. Age at First Report of NSSI and Slope Brain Metrics for the ABCD Study



Note: NSSI=non-suicidal self-injury; SF=superior frontal; CO=cingulo-opercular; RSFC=resting state functional connectivity

When using variable-centered analyses to assess if the slope of change in brain metrics are related to the age at which NSSI was first reported (Table 7), none of the brain metrics were found to be statistically significantly associated with the age at first report of NSSI(Figure 9). Female sex at birth was found to be significantly associated with older age at first report of NSSI, while CBCL Depression score was and was not included as a covariate. Heightened Baseline CBCL Depression score was associated with younger age at first report of NSSI as well.

Discussion

This study set out to leverage multi-level longitudinal data from a large, epidemiologically informed sample of adolescents to demonstrate the utility of person-centered analyses in tandem with variable-centered analyses to uncover neurodevelopmental patterns associated with the history of NSSI engagement and age at the visit when participants first reported of NSSI engagement. Analyses demonstrated novel findings; distinct patterns of neurodevelopment exist that are associated with the age at which NSSI is first reported, and decreased frontal activation is associated with increased risk of NSSI engagement. In addition, results add to the body of work demonstrating that decreased fronto-limbic RSFC is also associated with increased risk for NSSI engagement. Together, these analyses provide novel insights into the alterations in the development of within-brain interplay associated with the history of NSSI engagement and age at first reporting NSSI, providing critical insights into biological processes that undergird NSSI and consideration of potential points for intervention.

To our knowledge, this is one of the first studies to investigate biological metrics related to engagement in NSSI for adolescents in such a large, longitudinal sample. Our results indicate that as of ages 13-14 years old, there was a documented history of NSSI for 23% of participants, and slightly more than half were AFAB, which is consistent with extant literature (Monto et al., 2018; Wang et al., 2022). Further, when considering the time point at which participants first reported NSSI, participants AMAB were considerably more likely to report at the Baseline assessment (age 9-10 years old), and the rate of participants AMAB reporting NSSI for the first time decreased across subsequent time points. Meanwhile, though participants AFAB reported NSSI at less than ⅔ the rate as participants AMAB at Baseline, their rate of endorsement increased across years such that by the time the sample was 13-14 years old, participants AFAB were reporting new onset of NSSI at more than three times the rate as their assigned male at birth counterparts. This finding is consistent with the limited work available for this age group; Barrocas et al. (2012) showed that in 3rd grade, boys reported NSSI engagement at significantly higher rates than girls, but that by the time they reached 9th grade, girls reported NSSI engagement at higher rates than boys. Prior work in the ABCD sample has examined reports of NSSI engagement at Baseline and found that children who are sexual minorities had significantly higher odds of engaging (Blashill et al., 2021). Another study used epidemiologically informed analyses with ABCD data to derive an estimate of the actual prevalence of NSSI in the US

population for ages 9-10 years old to be 9.1% and also found that risk for NSSI engagement was impacted by increased family conflict and decreased parental monitoring (DeVille et al., 2020). Menken et al. (2022) used Baseline data to demonstrate that children who were bullied were at heightened risk for NSSI. Wen et al. (2023) found that engagement in NSSI was associated with a heightened risk of perpetuating bullying and being a victim of bullying across the first four waves of data collection for the ABCD study. This work provides some important context for the current study, showing that work identifying psychosocial factors relating to NSSI is crucial, as are the existing patterns of NSSI across subgroups (e.g., AFAB). However, the central study goal is to utilize available data in the ABCD sample to understand the neural mechanisms underlying these maladaptive behaviors.

Person-centered analyses identified five groups with distinct neurodevelopmental trajectories. The trajectories of neural indexes varied considerably across the five groups over time. Group 1 resembled the hypothesized Normative Development trajectory and was the largest group. Group 2 may be capturing a group undergoing a great deal of change. Group 3 partially resembles the hypothesized Normative Developmental trajectory, though it was hypothesized that SF reactivity would increase across time points. Group 4 is unlike either hypothesized group and may capture a group undergoing dynamic neurodevelopmental changes. Group 5 generally follows the hypothesized Blunted Frontal Regulatory Control trajectory, though a great deal of dynamic change occurred in the amygdala and SF reactivity. The sporadic pattern of CO-Amygdala RSFC becoming more negative, which appears in the person-centered derived groups but not when examining average slope of the whole sample, may indicate that participants are at disparate points in the process of adolescent neurodevelopment, as only some seem to be undergoing the process of increasing frontal regulatory control of the stress system (increasingly negative RSFC) which occurs in adolescence (Gee, Gabard-Durnam, et al., 2013; Giedd et al., 2002). Further work using later time points in this sample (not yet available) may provide insights into the timing of this neurodevelopmental shift. Further, more work is needed to understand non-linear patterns in regional activation and RSFC across development, as are captured in these person-centered derived groups. Prior work has established non-linear trajectories of development for regional gray and white matter (Giedd et al., 2002) as well as in amygdala reactivity to emotional stimuli and inhibitory control (Ahmed et al., 2015), though further work is needed to identify the specific timing of inflections and the specific conditions

under which these patterns emerge. Additional future work should also assess if multiple longitudinal patterns of neurodevelopment are associated with normative development (i.e., equifinality). Future work should investigate the association between the differential effects of the COVID-19 pandemic and dynamic developmental changes and emotion regulation difficulties, such as NSSI, to provide a greater understanding of the significance of non-linear trajectories in neurodevelopment.

Contrary to predictions, the person-centered derived groups did not differ significantly in the rate of endorsement of the history of NSSI. Figure 4 shows the striking similarities in the reported history of NSSI that are noted across the five groups. Findings do, however, indicate that the timing of the onset of NSSI may be important to consider. When considering the relationship between the age at first report of NSSI and person-centered derived groups, significant differences were found between Group 2 (highly dynamic change; mean age 11.1 years) and Group 1 (similar to the Normative Developmental Trajectory, though SF reactivity decreased; mean age 11.9 years) When conducting a pairwise comparison of age at first report, a difference also emerged between Group 1 and Group 3 as well, with Group 1 having significantly older age at first report compared to Group 3 (mean age 11.4 years). Post-hoc analyses (described in Appendix A, Table A9) indicate that Group 1 had a significantly higher proportion of scans completed prior to the onset of the COVID-19 pandemic, meaning that a greater number of scans for other groups occurred in the context of the early pandemic period. Additionally, Group 2 participants had significantly greater motion in both task and resting state MRI scans, and parent/guardians reported greater externalizing behaviors and more attention difficulties compared to Groups 1 and 3. It may be that the highly dynamic developmental trajectory or increased exposure or susceptibility to environmental stressors (as seen in Group 2) is associated with an earlier onset of impairment in emotion regulation, while participants undergoing more normative development are not at risk of NSSI until later in adolescence. Also, the disruption in linearity seen in groups such as Group 2 could be indexing a disruption in emotion regulatory processes in reaction to the onset of the pandemic at Time 2 and a return to the participants' normative levels by Time 4. No significant differences emerged between groups in relation to pubertal status and sex at birth. However, female sex at birth was consistently found to be associated with a later onset of NSSI (Cheng et al., 2021). Thus far, no significant relationship exists between group membership and engagement across time points (Table A10).

However, future work that includes later time points of this study may provide insights into the risk for persistent engagement across multiple time points. Future work should investigate the association between the differential effects of the COVID-19 pandemic and dynamic developmental changes and emotion regulation difficulties, such as NSSI, to better understand the significance of non-linear trajectories in neurodevelopment. Evidence indicates that stressors in childhood and adolescence are associated with atypical and potentially non-linear neurodevelopment (e.g., Brieant et al., 2021; Gee et al., 2013). Finally, work is needed that can more precisely measure the age at which NSSI onsets (rather than the age when it is first reported).

This study's results align with other work conducted in the ABCD study, which employs person-centered analyses to investigate brain metrics in relation to psychopathology and broader functioning. Huffman and Oshri (2022) used latent transition analyses with the first two time points of data collection to identify patterns in regional brain reactivity in response to emotional stimuli and assess how these patterns relate to working memory performance and psychopathology. This study found distinct patterns in responsivity of the amygdala, ACC, and insula, which were associated with differences in working memory performance but not psychopathology. Lichenstein et al. (2022) used latent profile analysis of Baseline data to identify distinct neurodevelopmental subgroups based on responsivity to neurocognitive tasks. They found seven distinct response patterns associated with inhibition, reward seeking, and emotional responsivity performance metrics. Pollmann et al. (2024) used k-means clustering and latent basic growth models with the first three time points of data to identify groups based on adverse experiences in relation to brain structural connectivity. They found that increased family conflict was associated with increased structural connectivity and that lower socioeconomic status and neighborhood safety were associated with decreasing structural connectivity across study time points.

Variable-centered analyses revealed a pattern relating decreased Baseline SF reactivity and greater risk for a history of NSSI engagement, which is novel in relation to prior work characterizing biological alterations associated with NSSI. This finding could index a blunted frontal response and, thus, less inhibition of the amygdala’s response to stressors, which could result in a failure to inhibit prepotent stress response behaviors, such as NSSI. Decreased Baseline SF reactivity was also associated with a later time point of the first report (Table A11).

The correlation analysis indicates that Baseline SF reactivity is inversely associated with age at the first report of NSSI. Together, these findings may index a dynamic pattern of risk where, as other elements of the brain's stress response system undergo changes across adolescent development, decreased SF reactivity is associated with increasing risk. The other analyses investigating age at the first report of NSSI and engagement in NSSI across time did not yield any significant findings related to SF reactivity. Prior work has linked heightened mPFC and ventrolateral PFC activation to social stressors in adolescents with a history of NSSI (Groschwitz et al., 2016). (Plener et al., 2012) found that participants with a history of NSSI had heightened ACC reactivity to averse pictures compared to participants without a history of NSSI. Considering more dorsal prefrontal structures has yielded some intriguing results. That is, work by Dahlgren et al. (2018) and Zahid et al. (2022) showed that decreased dlPFC reactivity in response to cognitive tasks was seen in participants with a history of NSSI compared to healthy controls. Additionally, work indicates lower within-SF RSFC for adolescents with major depressive disorder and NSSI (Huang et al., 2020). This is the first study to indicate that reactivity in response to fearful or angry faces is related to attributes of NSSI and indicates that this area is ripe for future investigation.

Variable-centered analyses also indicate that increasingly more negative CO-Amygdala RSFC were associated with a greater risk of a history of NSSI engagement and the later time point at the first report of NSSI (Table A12). As RSFC measures the degree to which regions are activating in sync, this finding may index greater discordance between the CO and amygdala, which, in concert with decreased frontal regional activation, may indicate that in the context of stressors, frontal regulatory regions are failing to engage and inhibit limbic activity, producing runaway stress responses that leave the individual at heightened risk for dysfunction. This builds off of prior work, which indicated that more negative fronto-limbic RSFC is associated with NSSI (Başgöze, Mirza, et al., 2021; Santamarina-Perez et al., 2019; Westlund Schreiner et al., 2017). Though it was not hypothesized that CO-Amygdala RSFC would become more negative across time points for typically developing youth (Cunningham et al., 2002; Gee, Gabard-Durnam, et al., 2013; Perlman & Pelphrey, 2011), this finding supports the broader theory that deficits in frontal regulatory control of the limbic system are related to risk for NSSI. The remaining variable-centered analyses examining age at the first report of NSSI and the history of NSSI engagement across time points did not yield any significant results (Tables A13-14). In

sum, lower Baseline SF reactivity and increasingly more negative CO-Amygdala RSFC over time appear to be risk factors for a history of NSSI engagement and older age at first report of NSSI engagement, reinforcing that frontal regulatory control plays an important role in determining risk for NSSI.

Across person-centered and variable-centered analyses, sex at birth and CBCL depression scores were consistently related to NSSI outcomes. Consistent with prior work (Wang et al., 2022), participants AFAB demonstrated heightened risk for NSSI engagement, older age at first report of NSSI, later time point of first report of NSSI, and greater engagement across time points. As expected, CBCL depression scores were highly related to a history of NSSI engagement and engagement across time (Başgöze, Wiglesworth, et al., 2021). In addition, CBCL depression scores were also associated with older age at first report of NSSI and later time point of first report of NSSI. Notably, many of the findings above relating group membership and brain metrics to attributes of NSSI engagement remained significant even when controlling for CBCL depression scores. Further, correlation analyses indicated that CBCL scores are not correlated with the brain metrics explored. Together, these results indicate that although NSSI and depression are frequently comorbid and both share the underlying factor of negative affect, there are diverging precursors, mechanisms, and outcomes; specifically, it seems that NSSI has unique signatures in the brain stress system that result in failures in frontal regulatory control over stress response rather than diffuse difficulties in mitigating negative emotions.

When examined in concert, the person-centered and variable-centered analyses offered insights into neurodevelopmental processes related to NSSI risk. Person-centered analyses identified developmental trajectories with significant differences in the age at the first report of NSSI, and these groups differed significantly in Baseline values of all brain metrics examined as well as the slope of change of amygdala and SF reactivity. However, all demonstrated increasingly more negative CO-Amygdala RSFC. Indeed, Group 2 has significantly decreased SF reactivity compared to Groups 1 and 3, consistent with the variable-centered findings, which showed that lower Baseline SF reactivity is particularly relevant to increased risk for a history of NSSI engagement and later first report of NSSI. Together, these findings may indicate that different patterns of alterations in the brain's stress system are associated with different attributes of NSSI. In this study, person-centered analyses were able to identify meaningful heterogeneity in neurodevelopmental patterns associated with the age at first report of NSSI, among them that

the group with lower SF reactivity, low amygdala reactivity, and more negative CO-Amygdala RSFC at Baseline is at heightened risk for younger age at first report of NSSI. Though the person-centered derived groups all showed more negative CO-Amygdala RSFC, the variable-centered analyses suggest that there are meaningful differences in this slope of change for participants with a history of NSSI and that this slope is also related to the time point of the first report of NSSI. Though no patterns relating amygdala reactivity to NSSI attributes emerged in the variable-centered analyses, person-centered analyses indicate that different trajectories in amygdala reactivity may be meaningfully related to age at the first report of NSSI, with stable reactivity over time associated with older age at the first report of NSSI and dynamic changes associated with an earlier age at the first report of NSSI. The unique strengths and weaknesses of each analytic strategy allowed for different insights; person-centered analyses were able to assess the interplay between stress system components more directly and were able to examine all time points simultaneously but may not have been able to identify strong signals among the noise introduced by variability in the methods of gathering biological metrics. Meanwhile, Variable-centered analyses could identify patterns despite the variability but could not directly assess interplay, within-group heterogeneity, or multiple time points simultaneously. Indeed, the two modes of analysis work in concert to provide greater nuance in the relationship between frontal regulatory control of the amygdala and NSSI attributes than was previously seen.

Limitations

The present study has its limitations. (1) Issues emerged in both person-centered and variable-centered analyses due to missing data due to attrition and partial data availability for the most recent time point. As such, only a subsample of participants with more than half of brain data points were included in this study. Prior work has demonstrated differential attrition from the ABCD sample due to participant race, parental education levels, and study site (Feldstein Ewing et al., 2022). When compared using the methods described in Feldstein Ewing et al. (2022), subsample membership was predicted by age at Baseline, age at Time 2, age at Time 4, scanner platform (potentially due to different MRI scan pre-processing pipelines), and family income. Low family income is a risk factor for NSSI engagement (Liu, 2023), so future work should directly investigate this pattern in the ABCD study. Given these findings, the generalizability of the present findings to the broader ABCD sample and adolescents at large may be restricted. Sex at birth, age at Times 1 and 3, site ID, and race did not impact the

likelihood that a participant was in the subsample. (2) The presently available data only encompasses the early period of adolescent development and cannot give insights into adolescent development as a whole. However, future data releases from ABCD are anticipated to expand the age range represented. (3) Much of the prior literature on NSSI examined specific subregions of the PFC, such as the mPFC, dorsolateral PFC, and ventrolateral PFC. The preprocessed functional activation data did not contain such fine-grained parcellations of the PFC, so the larger SF parcellation was used. This may impair the direct comparison of present findings with prior literature. (4) Much of the prior work on NSSI has examined PFC-amygdala RSFC to index the fronto-limbic RSFC implicated in stress processing. This specific combination of regions is not available in the pre-processed RSFC data. As such, CO-Amygdala RSFC was used as an approximation of fronto-limbic connectivity, as has been done by other work in this sample (Brieant et al., 2021; Thijssen et al., 2022). Ideally, these indexes of connectivity would more closely map onto the regions examined in the context of task activation in order to better compare patterns across modalities. (5) The methods used to capture slope for the variable-centered analyses assume linear change across development. Future work examining normative and psychopathological neurodevelopment patterns in adolescents should be conducted to characterize these processes better. Additionally, similar variable-centered work that can account for non-linear changes over time in relation to NSSI engagement should also be undertaken. (6) The analytic framing of the person-centered and variable-centered analyses differed slightly as person-centered analyses could simultaneously examine all time points of brain data. In contrast, variable-centered analyses could only examine single metrics (i.e., the Baseline and the composite slope metric). Additionally, person-centered analyses are able to interrogate all brain metrics simultaneously to index the interplay between them. In contrast, variable-centered analyses hold them in the same model but do not directly interrogate the relationship between these metrics. This limits the ability to compare findings across analytic strategies directly. (7) Two binary items were used to measure the history of NSSI engagement in the past two weeks and the participant's lifetime. Recent work has identified that this mode of assessing NSSI may not capture all participants who have engaged in NSSI and that participants who do endorse engagement on single items have heightened severity compared to those who would endorse on behavioral checklists (Aspeqvist et al., 2024). This may mean that more adolescents within the ABCD sample have engaged in NSSI but are being missed by current measurement strategies.

Also, the current measurement strategy does not allow for investigation of the severity, frequency, or recency of NSSI engagement. As such, we cannot directly measure the age at which NSSI onset and must use the less precise age at the time point at which NSSI was first reported to approximate onset. (8) The information available about medication use did not provide enough detail to identify which participants were taking medications that could impact the brain metrics of interest. (9) the onset of the COVID-19 pandemic may have significantly impacted the measured brain metrics. However, we cannot assess what facet of this disruption impacted the scan outcomes (i.e., were participants more stressed in general, were scanning procedures different due to safety precautions, etc.).

Future Directions and Clinical Implications

Future work should employ both person-centered in addition to traditional variable-centered approaches to gain previously inaccessible insights into neurodevelopment and NSSI. Future studies should also employ more nuanced measures of NSSI, such as recency, severity, and frequency of engagement. Future work should look at periods later in adolescent development and should consider other brain areas implicated in psychopathology, such as the salience network (Menon, 2011; Uddin, 2015) or the cognitive control network, which has been implicated in NSSI and has been shown to undergo significant shifts across adolescence (Başgöze et al., 2023; Luna, 2009). More work should be done to characterize patterns relating SF reactivity to NSSI risk, as this is a novel finding. Follow-up work investigating the impact of dynamic changes in neural functioning as well as factors known to impact neurodevelopment, such as medication use, puberty, and early life adverse experiences on risk for NSSI, would be of interest.

The current study highlights the potential importance of frontal regulatory control in risk for NSSI and identifies potential patterns of development of these regions that may be important. Understanding these patterns may allow practitioners to provide additional support for emotion regulation skills for children demonstrating highly dynamic change or Blunted Frontal Regulatory Control trajectory. Interventions such as Dialectical Behavior Therapy could reduce behavioral and emotional dysregulation, resulting in a heightened risk of engaging in maladaptive emotion regulation techniques like NSSI (Glenn et al., 2019; Linehan & Kehrer, 1993). Additionally, psychopharmacological interventions such as selective serotonin reuptake inhibitors, atypical antipsychotics, opioid antagonists, and N-acetyl cysteine could disrupt

dysfunctional neural stress processing patterns (Westlund Schreiner et al., 2023). More work is needed to probe the efficacy of reducing NSSI through family-focused interventions that reduce interpersonal dysfunction and CBT by promoting adaptive problem-solving (Westlund Schreiner et al., 2023).

Conclusion

This study investigated neurodevelopmental patterns related to the history of NSSI engagement in a large community sample of adolescents between the ages of 9 and 14. For the first time, the present study used person-centered analysis to identify distinct patterns of development of frontal regulatory control over the amygdala, which is associated with attributes of NSSI. Additionally, it was found for the first time that blunted frontal activation and decreasing fronto-limbic resting state functional connectivity over time are risk factors for NSSI engagement. This work is the first to employ both person-centered and variable-centered analyses to expand and replicate prior work on these phenomena. These findings could inform future interventions for NSSI to avert the harm incurred by the behaviors themselves as well as the risk of future suicidality.

3. Longitudinal Analysis of Stress System Development and Non-Suicidal Self-Injury in a High-Risk Sample

Introduction

Overview

Non-suicidal self-injury (NSSI) is the deliberate harming of oneself without the intention of dying (Plener et al., 2015) and is thought to be used to manage distress (Klonsky, 2007). Prior work points to alterations in the brain and body's threat processing systems being implicated in NSSI (e.g., Başgöze, Mirza, et al., 2021; Brañas et al., 2021; Kaess et al., 2012; Plener et al., 2017). Understanding the biological correlates of this behavior can give insight into the critical points of dysfunction in the stress system, which increases vulnerability to NSSI. A paucity of research considers how these biological processes unfold over time in the context of NSSI. The present study will explore the functioning within and between these systems using person-centered and variable-centered analyses to facilitate the identification of multiple pathways to NSSI. Identifying these relationships may highlight avenues for intervention (Westlund Schreiner et al., 2017).

Non-suicidal self-injury (NSSI) as a maladaptive stress response

NSSI usually onsets between 12 and 14 years old (Cipriano et al., 2017). and is very common in adolescence, with an estimated 17.59% of adolescents (12-18 year-olds) engaging (Monto et al., 2018). Adolescence is a time of dramatic shifts in social, emotional, behavioral, and physical landscapes (Somerville et al., 2010), which may contribute to heightened risk for engagement during this developmental period. NSSI is a transdiagnostic form of psychopathology that frequently co-occurs with depressive symptoms, anxiety symptoms, and suicidal thoughts and behaviors (Başgöze, Wiglesworth, et al., 2021; Klonsky, 2007). In addition to the direct risk of serious injury, NSSI is also associated with a heightened risk for future suicidal thoughts and behaviors (Franklin et al., 2016). Further, those with a history of persistent, repetitive NSSI had higher rates of ongoing self-injury and difficulties in emotion regulation at about two years and ten years later (Daukantaitė et al., 2021; Masi et al., 2023). Additionally, engagement in more dangerous modes of NSSI was associated with greater long-term impairment (Ammerman et al., 2018). Given the significant impact and associated risks of this behavior in adolescents, understanding the developmental and greater biological landscape underpinning NSSI may provide new opportunities for interventions targeting the biological mechanisms instantiating NSSI (Westlund Schreiner et al., 2017).

In the face of stressors, neural and endocrine stress systems work together to interpret the environment and form an appropriate response. These systems are complex and replete with feedback mechanisms that facilitate short- and long-term adaptation to the frequency and severity of stressors (for review: McEwen, 2007). The hypothalamic pituitary adrenal (HPA) axis coordinates the responses of the autonomic nervous and immune systems. A crucial component of this process is the release of glucocorticoids, specifically cortisol, which play an important role in managing how energy is distributed throughout the body (Herman, 2022; Leistner & Menke, 2020). The brain conducts integrative, higher-order analyses of signals from the stressful environment, including multimodal sensory information, which guides physiological and behavioral responses (McEwen, 2007). Adaptive responses to threats require proper coordination within and between each system. Failures in the intra- and inter-system feedback mechanisms can produce inadequate, excessive, or prolonged stress responses, leaving the individual vulnerable to maladaptive responses and psychopathology (Faravelli et al., 2012; van Oort et al., 2017).

The Brain's Stress System and NSSI

Background

The brain interprets external and internal stimuli in an integrative and interactive process involving many disparate brain regions. A crucial structure within networks that subserve these processes is the amygdala, which combines information from sensory, memory, and arousal centers (for review: LeDoux, 2003; Ulrich-Lai & Herman, 2009). This process provides the capacity to identify potentially threatening stimuli and recruit other components of the stress system. Some regions that receive such output include the prefrontal cortex (PFC), locus coeruleus, and hippocampus (Winklewski et al., 2017). In a threatening context, the PFC is thought to exert an inhibitory effect on the amygdala and other components of the stress system to moderate the intensity and length of stress responses (Willner, 2016; Winklewski et al., 2017). Within the PFC, the medial PFC (mPFC) is crucial to integrating information and coordinating outputs from the whole PFC (Gold, 2015). The amygdala also provides input to endocrine systems responsible for managing bodily responses to stressors, including the HPA axis (McEwen, 2007). The relationships between the amygdala, PFC, and HPA axis are particularly relevant to the normative and pathological functioning of the stress systems (Ulrich-Lai & Herman, 2009).

Normative Developmental Changes in the Brain's Stress System

Many neural changes occur as a part of adolescent development, creating conditions that increase the vulnerability of the brain's stress system to dysfunction (Giedd et al., 1999, 2009; Paus et al., 2008). Changes occurring in networks involving the PFC appear particularly relevant to NSSI. During adolescence, there is an increase in structural and functional connectivity between the PFC and amygdala, and, with it, an increase in frontal regulatory control over the brain's stress response (Cunningham et al., 2002; Gee, Gabard-Durnam, et al., 2013; Perlman & Pelphrey, 2011; Silvers et al., 2015; Swartz et al., 2014). At the same time, the PFC and the amygdala have been shown to become more responsive to stressful stimuli (Casey, 2015; Yurgelun-Todd & Killgore, 2006). Together, these changes suggest that the PFC's role as the modulator of the stress response becomes more important in the context of normative adolescent development.

Variable-Centered Findings of Alteration in the Brain's Stress System Associated with NSSI

When examining individuals with a history of engaging in NSSI, alterations in regions in the central stress system have been found. Decreased fronto-limbic resting state functional connectivity (RSFC) has been consistently found in those who engage in NSSI compared to those without a history of NSSI and healthy controls (Başgöze, Mirza, et al., 2021; Santamarina-Perez et al., 2019; Westlund Schreiner et al., 2017). Findings relating to amygdala activation in response to emotionally evocative stimuli have been mixed (for review: Brañas et al., 2021). Compared to those without a history of NSSI, Plener et al. (2012) found heightened amygdala activation in female adolescents, Mayo et al. (2021) and Westlund Schreiner et al., (2017) found no difference in female adolescents, and (Hooley et al., 2020) found heightened activation in female adults with a history of NSSI. Thus far, only a few studies have explored the possibility of within-group heterogeneity in amygdala reactivity. Başgöze, Mirza, et al. (2021) showed that adolescents with moderate NSSI had heightened amygdala activation compared to those with no history of NSSI or a history of mild NSSI. Further, no statistically significant differences were found when comparing the group with severe NSSI to the other groups (Başgöze, Mirza, et al., 2021). Additionally, Carosella, Mirza, et al. (2023) showed that amygdala reactivity was higher in participants who persisted in NSSI after the onset of the COVID-19 pandemic compared to participants with a history of NSSI who did not engage during the pandemic and participants who had no history of NSSI. Together, these results indicate that the amygdala likely plays an

important role in determining risk for NSSI engagement, severity, and persistence. However, more work is needed to understand what that role might be.

The PFC has also been shown to have alterations in functioning in adolescents with a history of engaging in NSSI. In the context of a social evaluative stress task, adolescents who were depressed and had a history of NSSI demonstrated increased activation in medial and ventrolateral PFC compared to adolescents with depression with no history of NSSI and healthy controls (Groschwitz et al., 2016). In a task probing attentional inhibition, women with a history of NSSI demonstrated decreased dlPFC activation compared to healthy controls. Further, decreased dlPFC activation was associated with decreased emotional control and increased impulsivity (Dahlgren et al., 2018). Given that the mPFC is central to the coordination of all other PFC regions and other elements of the stress system, further work is needed that focuses on the mPFC and its role in regulating the degree of the amygdala's response to stress. Thus far, there is a paucity of longitudinal research and investigation of within-group heterogeneity in brain metrics related to NSSI.

The HPA Axis' Stress System

Background

The HPA axis releases cortisol persistently, with levels varying as a function of time of day and environmental and internal conditions (Spencer & Deak, 2017; Stalder & Kirschbaum, 2020). Integral to the proper functioning of this system are many intra-HPA axis feedback mechanisms that work to titrate the amount of cortisol being distributed to the body. When facing a stressor, the production of cortisol increases dramatically, prompting the engagement of negative feedback mechanisms, which eventually cause the cortisol concentration to return to basal levels, usually about 60-90 minutes after stress exposure (Spencer & Deak, 2017; Taborsky et al., 2021). Cortisol levels can be measured in peripheral bodily fluids and tissues such as saliva, blood, and hair (Stalder & Kirschbaum, 2020). Salivary cortisol is frequently used, as it affords temporally specific metrics of HPA axis reactivity without invasive procedures. Measuring cortisol levels in reaction to a stressor offers an index of the health of the HPA axis' stress response (Kaess et al., 2012; Klimes-Dougan et al., 2019; Plener et al., 2017; Spencer & Deak, 2017). Much of the work examining reactive cortisol levels in those with NSSI has employed the Trier Social Stress Test (TSST; Kirschbaum et al., 1993). In this paradigm, participants are asked to prepare and give a speech about themselves to a panel of impassive

judges and then verbally complete a difficult cognitive task with corrective feedback (Kirschbaum et al., 1993).

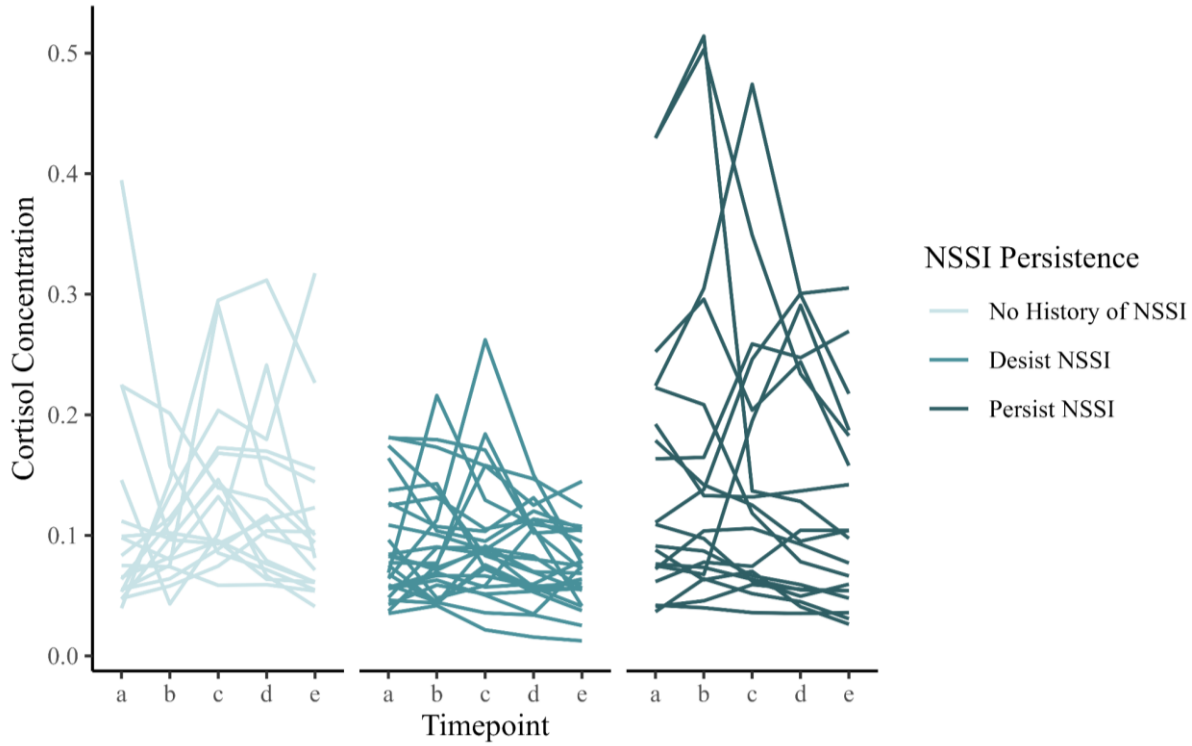
Normative Developmental Changes in the HPA Axis' Stress System

Adolescent development is marked by an increase in the HPA axis's reactivity to stressors (Gunnar et al., 2009; Klimes-Dougan et al., 2001; Stroud et al., 2009). The increase in stress responsivity and cortisol availability can make the HPA axis's feedback mechanisms more open to adulteration, leaving the system unable to maintain optimum levels of stress responses.

Variable-Centered Findings of Alterations in the HPA Axis' Stress System Associated with NSSI

Individuals with a history of NSSI have consistently been shown to display blunted HPA axis reactivity in response to this stressor compared to their peers without a history of NSSI (Kaess et al., 2012; Klimes-Dougan et al., 2019; Plener et al., 2017). Further, work has demonstrated that compared to their peers with major depressive disorder (MDD) but no history of NSSI and healthy controls, those with MDD and NSSI have significantly lower HPA axis responses, pointing to a mechanism that differentiates NSSI from other highly comorbid forms of psychopathology (Klimes-Dougan et al., 2019). Başgöze, Mirza, et al. (2021) found that among the group of adolescents with a history of NSSI, those with a history of severe NSSI showed a significantly lower level of reactive cortisol compared to those with a history of mild NSSI or no history of NSSI. By contrast, while there were subtle differences in the patterns, those with a history of moderate NSSI did not show significant differences compared to those with no history. Another study employing the same sample demonstrated that there may be a bimodal distribution of HPA axis reactivity in adolescents who persisted with NSSI engagement during the COVID-19 pandemic, as is demonstrated in Figure 10. Participants who persisted in NSSI showed significantly higher or lower HPA axis responsivity than those who desisted engagement or had no history of NSSI (Carosella, Mirza, et al., 2023). Together, these studies may indicate that though a pattern of blunted responses to stressors seems reliable in this population as a whole, there is likely meaningful within-group heterogeneity. Further work is needed to explore this within-group heterogeneity and the role of longitudinal changes in the HPA axis in instantiating risk for NSSI.

Figure 10. HPA Axis Reactivity by NSSI Persistence Group from Carosella, Mirza, et al. (2023)



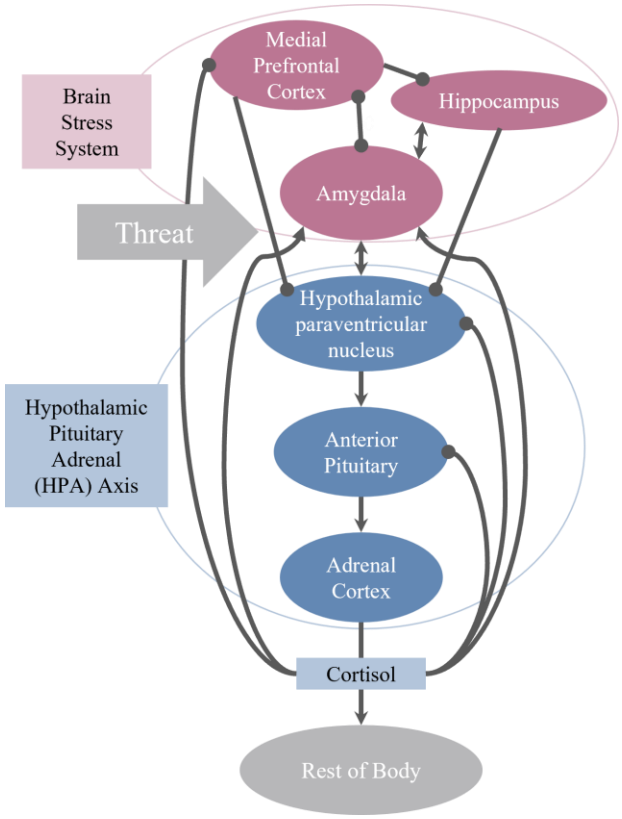
Note: Cortisol Concentration in (µg/dL); Time Point a=Pre-TSST (+0 min); b=Post-TSST (+20 min); c=Post-TSST (+35 min); d=Post-TSST (+50); e=Post-TSST(+65 min).

Interplay Between the Brain and HPA Axis' Stress Systems

Examining the brain and HPA axis' stress processing in isolation from each other has yielded some reproducible patterns of dysfunction that are related to NSSI. However, more work is needed to delineate the biological processes that instantiate this form of maladaptive emotion regulation. The brain and HPA axis are highly integrated (Figure 11); the HPA axis relies on the input from the amygdala to determine the degree of stress response required for the situation, and the brain reacts to changes in cortisol levels (Herman, 2020; Spencer & Deak, 2017; Stalder & Kirschbaum, 2020). Examining these two systems independently does not allow for exploring unique combinations of response patterns and potential compensatory changes that may occur in one system in response to alterations in the other. Analyzing the interplay between these systems is crucial to understanding the dynamics at play in internalizing disorders (Carosella et al., in preparation). Thus far, the limited literature on brain-HPA axis interplay in the context of NSSI indicates that HPA axis reactivity is associated with regional brain volume, functional brain

activation, and connectivity (e.g., Başgöze, Mirza, et al., 2021; Carosella, Mirza, et al., 2023; Thai et al., 2021). In a sample of adolescents assigned female sex at birth (AFAB) oversampled for NSSI, participants with a history of severe NSSI had both more negative amygdala-mPFC RSFC and lower HPA axis reactivity compared to participants with moderate, mild, or no history of NSSI (Başgöze, Mirza, et al., 2021). In participants with a history of depression and NSSI, it was found that higher amygdala-dorsomedial PFC RSFC was associated with decreased HPA axis reactivity compared to participants with depression and no NSSI and healthy controls (Thai et al., 2021). Finally, increased amygdala reactivity to stressors and increased HPA axis reactivity were seen in participants who persisted in NSSI in the context of the COVID-19 pandemic compared to participants who desisted or never engaged (Carosella, Mirza, et al., 2023). These works, alongside studies considering interplay in other populations, are beginning to build the argument that atypical aggregate functioning across the brain and HPA axis ' stress systems may be important in instantiating risk for NSSI rather than dysfunction in the separate systems.

Figure 11. Interplay Between the Brain and HPA Axis' Stress Systems for the BRIDGES Study



Note. Arrows indicate excitatory relationships, while circles indicate inhibitory relationships.

Person-Centered Analyses

Work examining the interplay between the brain and the HPA axis has typically used variable-centered analytic techniques to compare groups of participants (e.g., examining differences between those with and without a history of NSSI engagement). Such analyses are at risk for masking meaningful within-group differences and thus far have yielded only a few consistent findings relating alterations with the brain and HPA axis with NSSI. Recent work has begun to employ person-centered analytic techniques to explore multiple pathways to risk for and resilience from NSSI (Bendezú et al., 2022; Carosella, Wiglesworth, Bendezú, et al., 2023; Wiglesworth et al., 2023). Bendezú and colleagues (2022) employed person-centered analyses to identify groups of self-reported experience of stress, observer-reported expression of stress, and HPA axis reactivity to stress in the context of the TSST in adolescents with and without a major depressive disorder diagnosis. They found that those with discordant responses (high experience, high expression, and low HPA axis reactivity) were more likely to have a lifetime history of NSSI. This study also found relationships between group membership and amygdala-

ventromedial PFC RSFC. Recent work with a sample of adolescent females at heightened risk for maladaptive emotion regulation again examined experience, expression, and HPA axis responsivity in the context of the TSST using the same analytic methods and similarly found that the discordant (high experience, high expression, and low HPA axis responsivity) group was associated with heightened risk of NSSI (Carosella, Wiglesworth, Bendezú, et al., 2023). This study did not, however, identify any differences between groups in relation to the amygdala or mPFC reactivity to stress or amygdala-mPFC RSFC. A follow-up study found that this discordant group demonstrated less resilience over time than the more concordant groups, including a group with similarly low HPA axis reactivity (Wiglesworth et al., 2023). Thus far, this work has shown promise to provide novel views of the psychological and biological patterns that instantiate risk for NSSI. Applying these methods to directly interrogate the interplay between the brain and the HPA axis is needed to test the theory that alterations in intra-stress system functioning play an important role in instantiating NSSI.

Aims

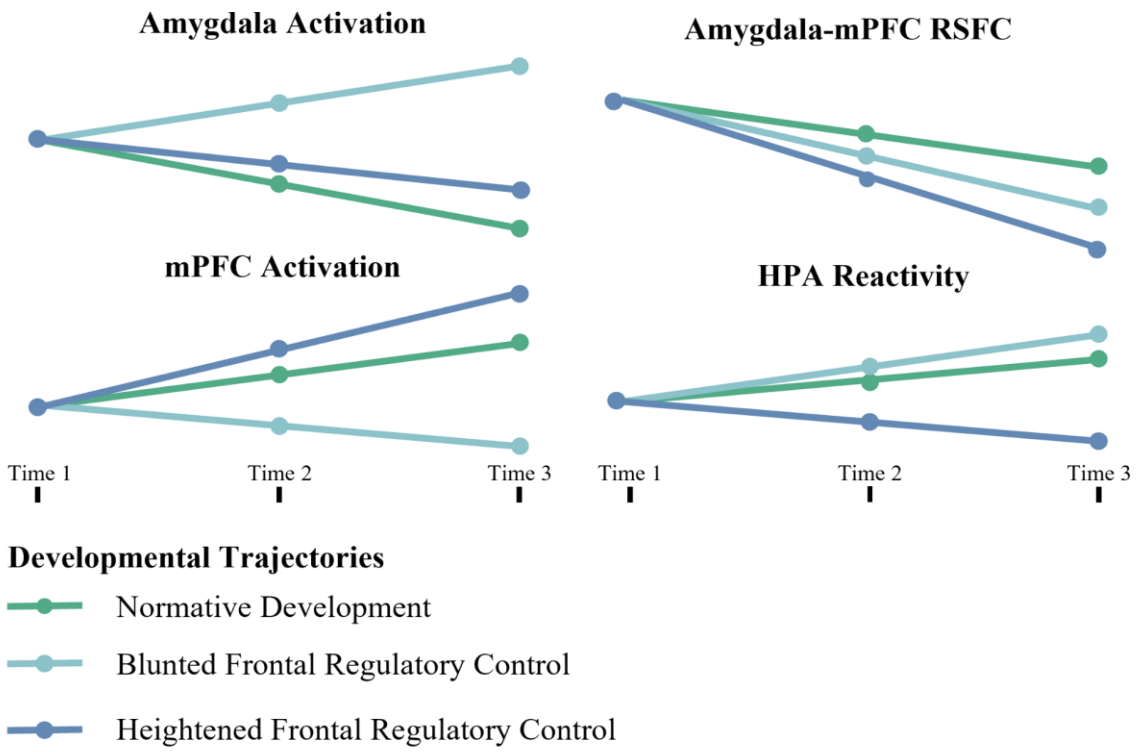
This study will employ a sample of adolescents oversampled for a history of NSSI from the Brain Imaging Development of Girls' Emotion and Self (BRIDGES) Study (see Başgöze, Mirza, et al., 2021; Nair et al., 2023). This study collected neuroimaging, repeated cortisol samples in the context of the TSST, and particularly comprehensive self and parent-reported metrics of NSSI engagement at three time points, each about one year apart. The BRIDGES study recruited a wide range of adolescents (ages 12-17), which will facilitate the investigation of the biological underpinnings of NSSI across the period of adolescent neurodevelopment. The study oversampled for NSSI; about ⅔ of participants had a recent history of engagement at the time of recruitment, while the remaining third did not (though they were not necessarily free from psychopathology). Additionally, this sample was composed solely of participants AFAB, both because NSSI is more common in female adolescents (Wang et al., 2022) and to decrease the amount of sex-related variance in neurodevelopment. Four different indexes were used to capture participant NSSI engagement: (1) the history of NSSI engagement, (2) the severity of NSSI (based on the frequency of NSSI and injury), (3) the estimated total number of lifetime episodes of NSSI and (4) NSSI engagement across time points. The purpose of this study was to characterize the neural and HPA axis developmental patterns across time that relate to

engagement in NSSI using both person-centered and variable-centered analyses. See Table 8 for demographic information.

Aim 1

To use person-centered analytic approaches to identify distinct trajectories of neurodevelopment in the brain's stress system (activation of the amygdala and mPFC in response to evocative stimuli and amygdala-mPFC RSFC) with HPA axis (cortisol levels in response to TSST). Though multiple trajectories will be permitted, it is hypothesized that among them will be the Normative Development group, which is typified by decreased amygdala reactivity, increased mPFC reactivity, increasingly more negative amygdala-mPFC RSFC, and increased HPA axis reactivity. Another hypothesized group is the Blunted Frontal Regulatory Control trajectory, which would be typified by increasing amygdala reactivity, decreasing mPFC reactivity, increasingly more negative amygdala-mPFC RSFC, and increasing HPA axis reactivity. A third hypothesized group is the Heightened Frontal Regulatory Control trajectory, typified by decreased amygdala reactivity, increased mPFC reactivity, slightly more negative amygdala-mPFC RSFC, and decreased HPA axis reactivity. Hypothesized groups are shown in Figure 12.

Figure 12. Diagram of Hypothesized Interplay Developmental Trajectories for the BRIDGES Study



Note: mPFC=medial prefrontal cortex; RSFC=resting state functional connectivity; HPA=Hypothalamic Pituitary Adrenal Axis

Aim 2

To assess whether the neurodevelopmental trajectory groups identified in Aim 1 are related to the four indices of NSSI. It is hypothesized that following the Heightened and Blunted Frontal Regulatory Control trajectories will be at the highest risk for engagement in NSSI and highest severity of NSSI. Analyses centering the number of lifetime episodes of NSSI and NSSI engagement across time points are exploratory as there is limited prior work exploring biological signatures and these metrics. Given the high rate of comorbidity between NSSI and depression, follow-up sensitivity analyses will be conducted using depression symptom severity as a covariate to determine if any observed patterns are uniquely associated with NSSI.

Aim 3

To employ variable-centered analyses to assess if changes in amygdala reactivity, mPFC reactivity, amygdala-mPFC RSFC, and HPA axis reactivity are related to the four indices of

NSSI. Because the person-centered analyses account for both baseline and slope attributes of the biological metrics, both attributes will be explored in the following variable-centered analyses. It is hypothesized that more increasingly negative RSFC and lower HPA axis reactivity will be seen more frequently in those engaging in NSSI than those not engaging in NSSI. Similarly, it is hypothesized that more negative RSFC and lower HPA axis reactivity will be associated with heightened severity of NSSI. Analyses considering the number of lifetime episodes of NSSI and NSSI engagement across time points are exploratory as there is limited to no prior work examining neural signatures and these metrics. While no directional predictions are made because of the mixed/null findings in the literature, we will examine all four indices of NSSI in relation to amygdala activation. Given the high rate of comorbidity between NSSI and depression, follow-up sensitivity analyses will be conducted using depression symptom severity as a covariate to determine if any observed patterns are uniquely associated with NSSI. The analyses investigating Time 1 brain and HPA axis metrics in relation to the history of NSSI engagement, severity of NSSI engagement, and number of lifetime episodes will conceptually replicate work published in (Başgöze, Mirza, et al., 2021), though the present analyses employed imputation, do not examine each hemisphere separately, and combined the severity sub-groups differently. This was aimed to allow for the direct comparison of person-centered and variable-centered analytic findings within the same study.

Significance

The present cross-sequential longitudinal study employs a unique sample of youth at heightened risk for NSSI and includes multilevel data from many points across adolescence, biological measures that are ideal for investigating the interplay between the brain and HPA axis's stress systems, and particularly rich metrics of NSSI engagement. While some work has been conducted to address relevant questions in this data set (e.g., Başgöze et al., 2021, 2023; Carosella et al., 2023; Nair et al., 2023), this study represents the first attempt to use person-centered analyses in addition to variable-centered analyses to investigate the role of interplay in the instantiation of risk for NSSI. In this way, this study could simultaneously provide novel evidence of patterns of the development of interplay across adolescence related to risk for NSSI and afford insights into the robustness of extant variable-centered findings in a longitudinal model. Findings from this study may have important implications for efforts that would help advance understanding of NSSI and contribute to ways to alleviate suffering.

Methods

Sample

Adolescents (ages 12-17) assigned female sex at birth (AFAB) were recruited from around the Minneapolis/St. Paul area to participate in a longitudinal study of NSSI. See Başgöze, Mirza, et al. (2021) and Nair et al. (2023) for a detailed description of study procedures. See Table 8 for demographic information on this sample. Multiple imputation by chained equations (Azur et al., 2011; Buuren & Groothuis-Oudshoorn, 2011) was conducted on all data except NSSI indices to address missingness due to issues including COVID-19 pandemic-related attrition and scanner error. Notably, (Başgöze, Mirza, et al., 2021) did not employ imputation.

Table 8. Demographic Characteristics for the BRIDGES Sample

Mean Age (SD)	
Time 1 (n=164)	14.97 (1.20)
Time 2 (n=127)	16.21 (1.25)
Time 3 (n=97)	17.26 (1.25)
Gender Identity N(%)	
Girl	108 (65.9%)
Boy	3 (1.8%)
Non-Binary/Other	16 (6.1%)
Missing	37 (22.6%)
Racial and Ethnic Identities N(%)	
American Indian/Alaska Native	1 (0.7%)
Asian	1 (0.7%)
Black	5 (3.0%)
White	132 (80.5%)
More than One Race	21 (12.8%)
Other	1 (0.7%)
Ethnic Identities N(%)	
Hispanic or Latino	19 (11.6%)
Family Income N(%)	
Under $5,000-$24,999	9 (5.5%)
$25,000-$59,999	33 (20.1%)
$60,000-$89,999	25 (15.2%)
$90,000-$179,999	62 (37.8%)
Over $180,000	34 (20.7%)
Don’t Know	1 (0.6%)
Clinical Attributes N(%)	
Taking psychotropic medication	77 (47.0%)
History of NSSI Engagement	110 (67.1%)

Measures

Demographic Data

The participant's parent or guardians completed a form to report sociodemographic information, including the participant's date of birth, family income, and race and ethnicity. Time 1 metrics are used throughout this study, except participant age and gender identity. Participants and parents reported on participant gender identity as a part of the diagnostic evaluation (Kiddie-Schedule of Affective Disorders, Computerized Version; Kaufman et al., 2021), and the most recently available participant report was used. Parent-reported gender identity was used when the participant did not provide this information. Early versions of the assessment did not ask about gender identity, so a significant portion of this data is missing.

Functional Activation to Emotionally Evocative Stimuli

Participants completed a task (Hariri et al., 2002) in the context of fMRI scans. The task was implemented using E-prime software (Schneider et al., 2012). Using a mirror, task stimuli were projected onto a screen inside the scanner's bore. For the matching of emotional faces condition, stimuli consisted of black-and-white photographs of human faces depicting anger and fear (Ekman & Friesen, 1976). For the control condition, stimuli consisted of horizontal and vertical ellipses of neutral colors. Participants were instructed to look at the picture in the top row, and, using a response box, they selected one of the two pictures in the bottom row that matched the top row. In the control block, they were asked to match the shapes; in the affective block, they matched the emotions of the faces. The task consisted of 13 counterbalanced blocks, 24 seconds each: five face-matching blocks, five shape-matching blocks, and three blocks where participants viewed a fixation cross. This well-established task has been widely used to probe threat-related amygdala reactivity (Gerin et al., 1992; Swartz et al., 2014) because the facial expressions of negative and high arousal affect (such as the fear and anger faces in the task) prompt robust engagement of the amygdala (Hariri et al., 2002).

FSL FMRI Expert Analysis Tool (Woolrich et al., 2001) was used to conduct a regression analysis measuring neural activation at each parcel of the brain during the emotion-matching task. We included two explanatory variables (emotion face and shape conditions). Our contrast of interest was emotion > shape. The produced emotion > shape z-score statistical maps in matrix form were projected back to CIFTI space for further analyses. Average z-scores for gray ordinates within the left and right amygdala and mPFC for the emotion > shape contrast were

extracted for further analyses. The mPFC (parcellations 10v, 10r, p32, s32, 9m, p32pr, a32pr, d32, 8BM) regions were identified using the Glasser multi-modal parcellation guide (Glasser et al., 2016). Bilateral regions were averaged to produce a singular bilateral value for both the amygdala and mPFC. Notably, (Başgöze, Mirza, et al., 2021) examined each hemisphere separately.

Resting State Functional Connectivity

Participants underwent a 12-minute (912 volume) resting-state scan during which they were instructed to stay awake, keep their eyes open and focused on a fixation cross, and "not think about anything in particular." The CIFTI-space gray-ordinate-wise time series were used to create an average time series for each of the Glasser and Harvard-Oxford parcellations. Then, the average time series from the bilateral amygdala and mPFC were extracted, cross-correlated, and Fisher's z-transformed to yield z-scores representing the connection between the amygdala and mPFC. The mPFC (parcellations 10v, 10r, p32, s32, 9m, p32pr, a32pr, d32, 8BM) regions were identified using the Glasser multi-modal parcellation guide (Glasser et al., 2016). Bilateral regions were averaged to produce a singular bilateral value for amygdala-mPFC RSFC. Notably, (Başgöze, Mirza, et al., 2021) examined each hemisphere separately.

HPA Axis Reactivity

HPA axis reactivity was captured in the context of a modified TSST (adapted from the classic TSST [Kirschbaum et al., 1993]), during which participants were asked to give an introduction speech and perform verbal arithmetic calculations while being observed by two examiners trained to remain neutral and to avoid giving reassurance or feedback based on a validated measure of the procedure used by that reliably elicit a stress response in female youth (Yim et al., 2010, 2015). Participants were scheduled to complete the TSST between 1 and 4 pm and were instructed not to eat, drink, smoke, or brush their teeth within the hour before providing saliva samples.

Five cortisol measurements were collected during the procedure: CORT1 pre-task, CORT2 immediately after the speech and math section (+15 minutes), CORT3 at +30 minutes, CORT4 at +45 minutes, and CORT5 at +60 minutes. For each saliva sample, participants pushed their saliva through a straw and into a 1.5 ml vial (passive drool method). Samples were labeled and stored in a –25 °C freezer until they were shipped to Universitat Trier in Trier, Germany, for analysis. Researchers used assay methods consistent with (Dressendörfer et al., 1992). Cortisol

values at three standard deviations above the mean were winsorized to be within three standard deviations of the mean for all analyses. In addition to the five individual cortisol values (CORT1, CORT2, CORT3, CORT4, CORT5) measured over the course of the TSST, we also computed the area under the curve with respect to increase and used it as the primary summary index for physiological response following prior work (Klimes-Dougan et al., 2019). This index assessed the relative increase in cortisol evoked by the stressor irrespective of the basal level prior to the task (Pruessner et al., 2003) and was assessed as a measure of HPA axis reactivity.

NSSI Engagement

Participant self-reported and parent-reported responses on the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Computerized Version (Barch et al., 2018; Kaufman et al., 1997, 2021) were used to measure NSSI engagement. Participants and their parents were asked, "Sometimes when kids get upset or feel numb, they may do things to hurt themselves, like scratching, cutting, or burning themselves. In the past two weeks, how often [have you/has your child] done any of these things or other things to try to hurt [yourself/themselves]?" to assess for present NSSI engagement and "Was there ever a time in the past when [you/your child] did things to hurt [yourself/themselves] on purpose because [you/they] were upset, like cut, scratch or burn [yourself/themselves]?" to assess past instances of NSSI.

Participants also completed the Self-Injurious Thoughts and Behaviors Interview (SITBI; Nock et al. 2007), a clinician-administered measure of lifetime thoughts of and engagement in self-injurious thoughts and behaviors. Participants were asked to report on the frequency of NSSI in their lifetime, past year, and past month. The SITBI also assesses the severity of each thought or behavior endorsed, on average and at the worst point, as well as whether they received medical treatment due to self-injury.

History of NSSI Engagement. Affirmative response(s) by the parent or the child on the KSADS or the SITBI were coded as "1," while negative responses by both parent and child across all time points were coded as "0".

Severity of NSSI engagement. Three groups were created based on both the number of episodes and the severity of NSSI engagement: No NSSI (no history of NSSI, coded as "0"), Mild/Moderate NSSI (unlimited episodes of NSSI with no tissue damage or four or more past episodes of NSSI, with frequency less than once per month, and with significant tissue damage,

coded as “1”); and Severe NSSI (four or more past episodes of NSSI, with frequency greater than once per month, and with significant tissue damage, coded as “2”). The highest severity of NSSI engagement assigned across all study data points was used for the following analyses. In contrast, (Başgöze, Mirza, et al., 2021) grouped participants with No NSSI and Mild NSSI (fewer than four past episodes involving significant tissue damage or unlimited NSSI episodes with no tissue damage) together while keeping Moderate NSSI and Severe NSSI disaggregated.

Number of Lifetime Episodes of NSSI. Participants were asked to report their estimated lifetime number of episodes of NSSI engagement. The reported number of lifetime episodes at Time 1 was used for this study. A log transformation was performed to address the significant skew in this variable.

NSSI Engagement Across Time Points. A binary metric indicating whether or not NSSI engagement occurred in the past year was captured at each time point.

Depression Symptom Severity

Participants completed the Beck Depression Inventory-II (BDI; Beck et al., 1996) at every time point. This 21-item self-report inventory measures the severity of depression in adolescents and adults. Sum scores, with higher scores indicating greater symptom severity, were used. The scores from the first time point were used for the Aim 3 Time 1 analyses, while the mean score from across all available time points was used for Aim 2 analyses and Aim 3 slope analyses.

Analytic Plan

The same metrics will be used across person-centered and variable-centered analyses, though the different analytic methods frame questions slightly differently. Person-centered analyses (Aims 1 and 2) can simultaneously look at all time points for all metrics, allowing for the direct investigation of interplay across time. Variable-centered analyses (Aim 3) are able to look at the individual metrics separately within the same model and are only able to examine one time point (i.e., Baseline) or a composite measurement formed from data across time points (i.e., slope).

Aim 1

Multi-Trajectory Modeling (Nagin et al., 2018) was conducted using the “gbmt” package (Magrini, 2022) in R (R Core Team, 2023a). Model variables include amygdala activation in the Hariri task, mPFC activation in the Hariri task, and amygdala-mPFC RSFC from Time 1, Time

2, and Time 3. Models were run with and without HPA axis reactivity. The number of derived groups was determined based on model fit statistics (including AIC, BIC, and posterior probability) as well as parsimony as described in (Nagin, 2005). Once the optimum number of groups was identified, the number of polynomial degrees was determined using the same process of iterative model creation and comparison of model fit statistics. The resulting model fit statistics are shown in Table B1. The resulting groups represent neurodevelopmental trajectory groups and are shown in Figure 13. Analyses were repeated without the inclusion of HPA axis reactivity (see Appendix B).

Aim 2

Four models were run to assess if neurodevelopmental trajectory groups were related to NSSI variables. Covariates include age at each time point. Follow-up sensitivity analyses were conducted using the BDI score as a covariate for all four models. All analyses were repeated using the groups created without HPA axis reactivity (see Appendix B).

History of NSSI Engagement. Binomial regressions were conducted using the "lme4" package in R (Bates et al., 2015) to assess whether any neurodevelopmental trajectory groups are associated with a greater number of individuals endorsing a history of NSSI engagement. Follow-up group comparisons were conducted using pairwise t-tests with a Bonferroni correction using the "stats" package in R (R Core Team, 2023b).

Severity of NSSI Engagement. Ordinal Logistic regressions were conducted using the "MASS" package in R (Ripley et al., 2024) to assess whether any neurodevelopmental trajectory groups are associated with greater severity of NSSI engagement. Follow-up group comparisons were conducted using pairwise t-tests with a Bonferroni correction using the "stats" package in R (R Core Team, 2023b).

Number of Lifetime Episodes of NSSI. Linear regressions were conducted using the "stats" package in R (R Core Team, 2023b) to assess if any neurodevelopmental trajectory groups are associated with the number of lifetime episodes of NSSI. Follow-up group comparisons were conducted using pairwise t-tests with a Bonferroni correction using the "stats" package in R (R Core Team, 2023b).

NSSI Engagement Across Time Points. Multilevel binomial logistic regressions were conducted using the "lme4" package in R (Bates et al., 2015) in which past year engagement in NSSI was the dependent variable, group membership and year were the independent variables,

and individual ID number was a random intercept were conducted to assess if any neurodevelopmental trajectory groups were associated with NSSI engagement across time points. Follow-up pairwise Chi-Squared tests were conducted to assess for group differences using the "stats" package in R (R Core Team, 2023b).

Aim 3

History of NSSI Engagement. Binomial regressions were conducted using the "lme4" package in R (Bates et al., 2015) to assess whether any patterns in brain and HPA axis metrics were related to engagement in NSSI.

Severity of NSSI Engagement. Ordinal regressions were conducted using the "MASS" package in R (Ripley et al., 2024) to assess whether any patterns in brain and HPA axis metrics were related to the severity of NSSI engagement.

Number of Lifetime Episodes of NSSI. Linear regressions were conducted using the "stats" package in R (R Core Team, 2023b) to assess if brain and HPA axis metrics are associated with the number of lifetime episodes of NSSI.

NSSI Engagement Across Time Points. Multilevel binomial logistic regressions were conducted using the "lme4" package in R (Bates et al., 2015), in which past year engagement in NSSI was the dependent variable, group membership and year were the independent variables, and individual ID number was a random intercept to assess if any of the brain and HPA axis metrics were related to engagement in NSSI across time points.

Time 1: Time 1 amygdala reactivity, mPFC reactivity, amygdala-mPFC RSFC, and HPA axis reactivity were modeled in relation to NSSI variables. Time 1 age was included as a covariate. Follow-up sensitivity analyses were conducted with the BDI score included as a covariate. All analyses were repeated without HPA axis reactivity included as a covariate (see Appendix B.)

Slope: To compare the change in brain metrics across time points in relation to NSSI variables, the slope of change in each metric was found for each participant by finding the difference between the most recently available data and the Time 1 data and dividing the difference by the change in age (in months). Covariates Time 1 age, Time 2 age, Time 3 age. Follow-up sensitivity analyses were conducted with the BDI score included as a covariate. All analyses were repeated without HPA axis reactivity included as a covariate (see Appendix B.)

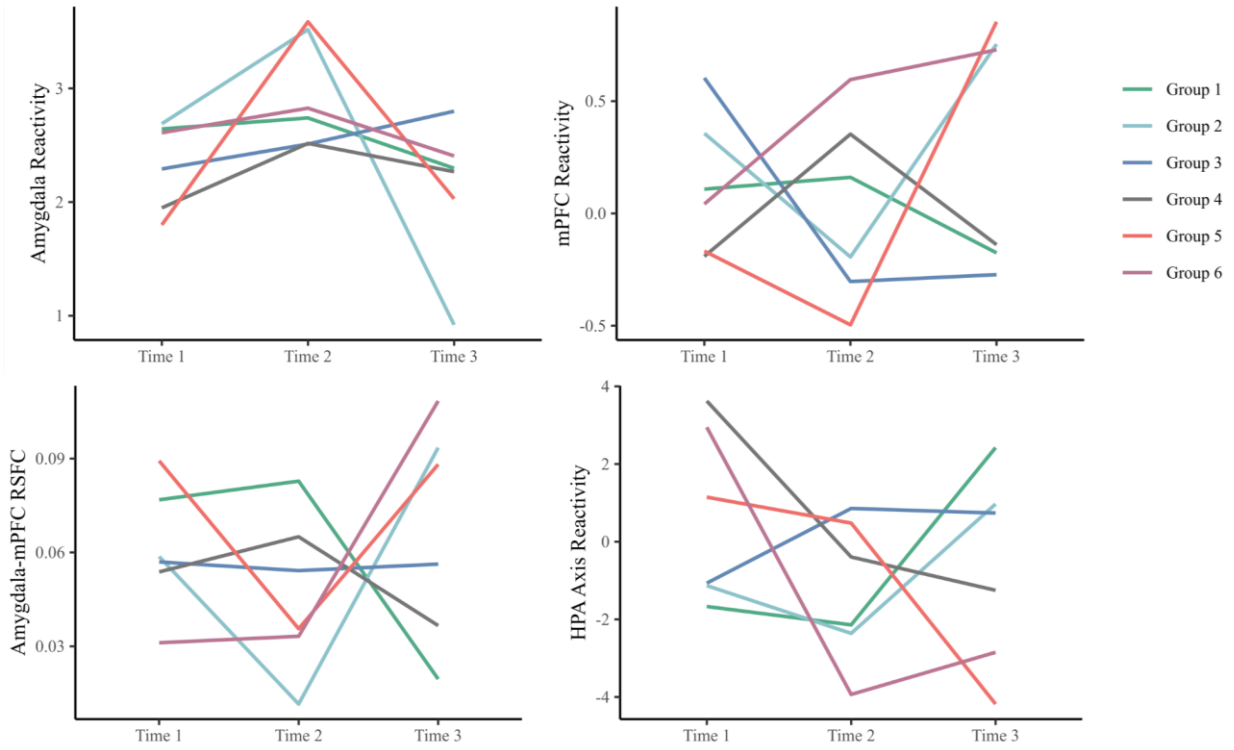
Results

Aim 1 Results

Model fit statistics are shown in Table B1. It was found that two polynomial degrees produced the most ideal model fit statistics. The 6 group solution demonstrated the best fit statistics and is explored below. The model fit statistics, and resulting groups for the solutions without the inclusion of HPA axis reactivity are shown in Table B2 and Figure B1. The overlap between the solutions with and without the inclusion of HPA axis reactivity is shown in Figure B2.

In the six group solution shown in Figure 13, Group 1 (n=29) is characterized by largely stable amygdala reactivity, decreased mPFC reactivity, dramatically decreased amygdala-mPFC RSFC, and dramatically increased HPA axis reactivity. Group 2 (n=20) is characterized by dramatically decreased amygdala reactivity, decreased then increased mPFC reactivity, decreased then increased amygdala-mPFC RSFC, and increased HPA axis reactivity. Group 3 (n=16) is characterized by increased amygdala reactivity, dramatically decreased mPFC reactivity, stable amygdala-mPFC RSFC, and increased HPA axis reactivity. Group 4 (n=30) is characterized by stable amygdala and mPFC reactivity, decreasing amygdala-mPFC RSFC and HPA axis reactivity. Group 5 (n=29) is characterized by stable amygdala reactivity, dramatically increased mPFC reactivity, decreased then stable amygdala-mPFC RSFC, and dramatically decreased HPA axis reactivity. Group 6 (n=40) is characterized by stable amygdala reactivity, increasing mPFC reactivity, dramatically increased amygdala-mPFC RSFC, and dramatically decreased HPA axis reactivity. Groups were examined to determine if differences existed in demographic attributes. No differences were found between groups: race (χ^2=36, p=0.07), ethnicity (χ^2=7, p=0.2), income (χ^2=18, p=0.6), age at Time 1 (F=0.67, p=0.65), age at Time 2 (F=0.95, p=0.45), age at Time 3 (F=1.42, p=0.22), psychotropic medication status (χ^2=7, p=0.2). Group 1 was selected as the reference group because it represents the most median group, with the least number of extreme data points, and is a relatively large group.

Figure 13. Person-Centered Derived Groups with HPA Axis Reactivity for the BRIDGES Study



Note: mPFC=medial prefrontal cortex; RSFC=Resting state functional connectivity; HPA=Hypothalamic Pituitary Adrenal Axis

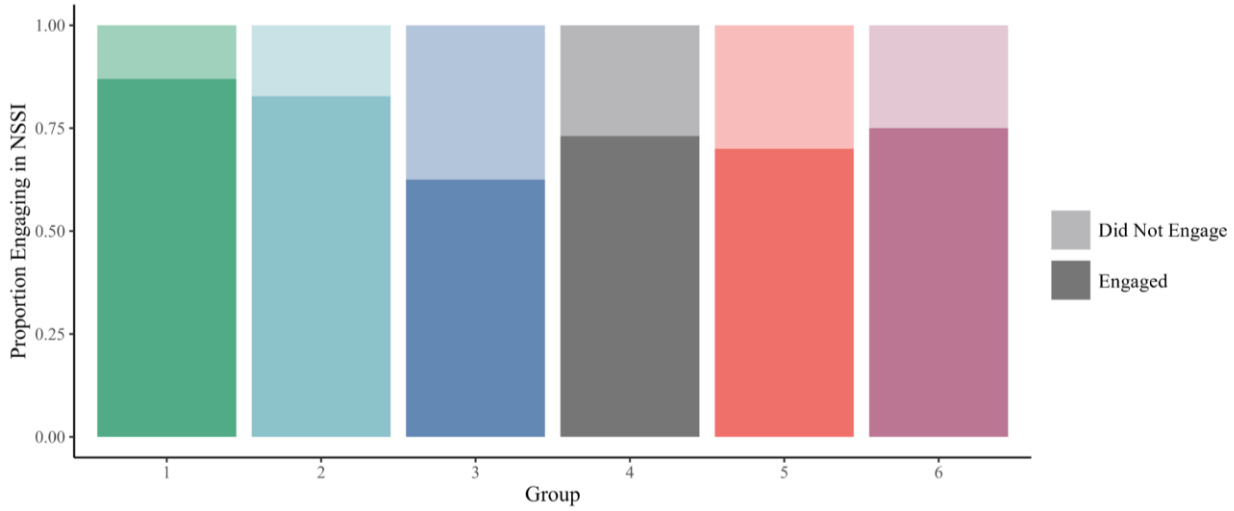
Aim 2 Results

Table 9. History of NSSI Engagement by Group with HPA Axis Reactivity for the BRIDGES Study

	Without BDI Score	**With BDI Score**
Coefficient	**OR (CI)**	**OR (CI)**
Intercept	0.118 (0.001, 19.442)	0.041 (0.000, 20.51)
Group 2 Membership	0.645 (0.118, 3.026)	0.929 (0.132, 5.96)
Group 3 Membership	0.245 (0.049, 0.934)	0.265 (0.041, 1.43)
Group 4 Membership	0.361 (0.068, 1.542)	0.768 (0.119, 4.34)
Group 5 Membership	0.342 (0.067, 1.360)	0.537 (0.086, 2.86)
Group 6 Membership	0.423 (0.078, 1.887)	0.911 (0.137, 5.35)
Time 1 Age	1.164 (0.337, 3.799)	0.599 (0.074, 4.11)
Time 2 Age	1.177 (0.282, 5.078)	2.339 (0.236, 26.97)
Time 3 Age	0.956 (0.458, 2.057)	0.822 (0.318, 2.16)
BDI Score		1.243 (1.156, 1.36)***

Note: OR=Odds Ratio; CI=Confidence Interval; BDI=Beck Depression Inventory

Figure 14. History of NSSI Engagement by Group with HPA Axis Reactivity for the BRIDGES Study



Note: NSSI=non-suicidal self-injury

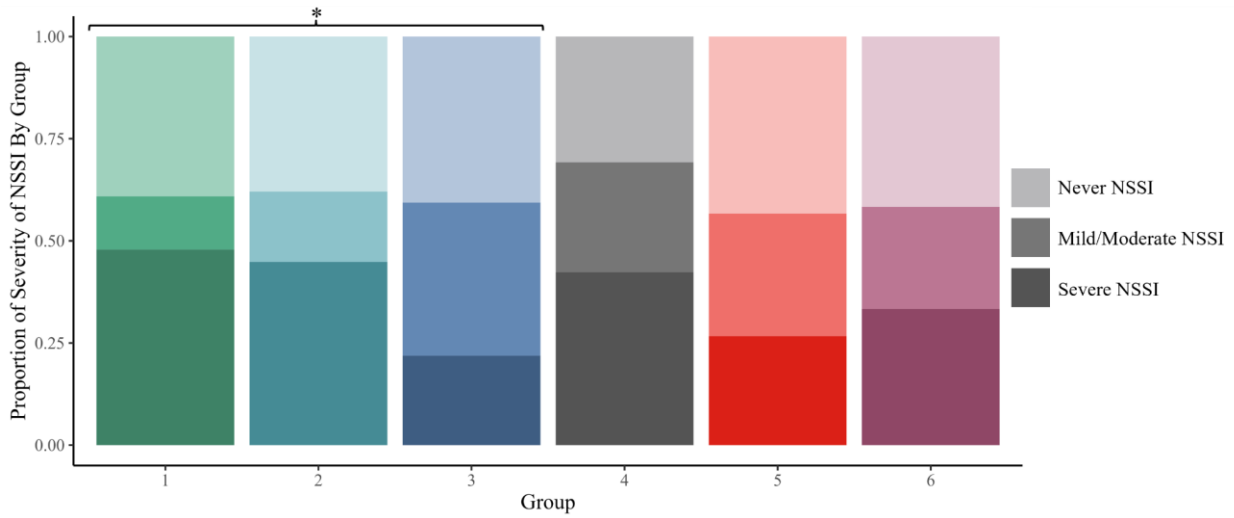
Analyses exploring the relationship between person-centered derived group membership and the history of NSSI engagement (Table 9, Figure 14) were not significant. Additionally, age was not significantly associated with engagement in these analyses. Higher BDI scores were significantly associated with a heightened likelihood of a history of NSSI engagement. The pairwise comparison of the proportion of group members who engage in NSSI is shown in Table B3. Figure 14 indicates some variability despite no significant differences in the regression and pairwise analyses. The analyses conducted without the inclusion of HPA axis reactivity are shown in Table B4-5 and Figure B3.

Table 10. Severity of NSSI Engagement by Group with HPA Axis Reactivity for the BRIDGES Study

	Without BDI Score	**With BDI Score**
Coefficient	**OR (CI)**	**OR (CI)**
Group 2 Membership	0.716 (-1.394, 0.711)	0.587 (-1.654, 0.568)
Group 3 Membership	0.275 (-2.353, -0.264) *	0.256 (-2.480, -0.290)*
Group 4 Membership	0.536 (-1.728, 0.462)	0.814 (-1.358, 0.932)
Group 5 Membership	0.403 (-1.954, 0.113)	0.428 (-1.957, 0.233)
Group 6 Membership	0.556 (-1.692, 0.500)	0.723 (-1.476, 0.816)
Time 1 Age	0.518 (-1.609, 0.267)	0.268 (-2.438, -0.275)*
Time 2 Age	3.386 (0.114, 2.363)*	7.198 (0.740, 3.300)**
Time 3 Age	0.722 (-0.907, 0.252)	0.591 (-1.152, 0.082)
BDI Score		1.092 (0.059, 0.120)***

Note: NSSI=non-suicidal self-injury; BDI=Beck Depression Inventory; SE=standard error; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

Figure 15. Severity of NSSI Engagement by Group with HPA Axis Reactivity for the BRIDGES Study



Note: NSSI=non-suicidal self-injury; * indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001; Group difference is significant with and without BDI score included as a covariate.

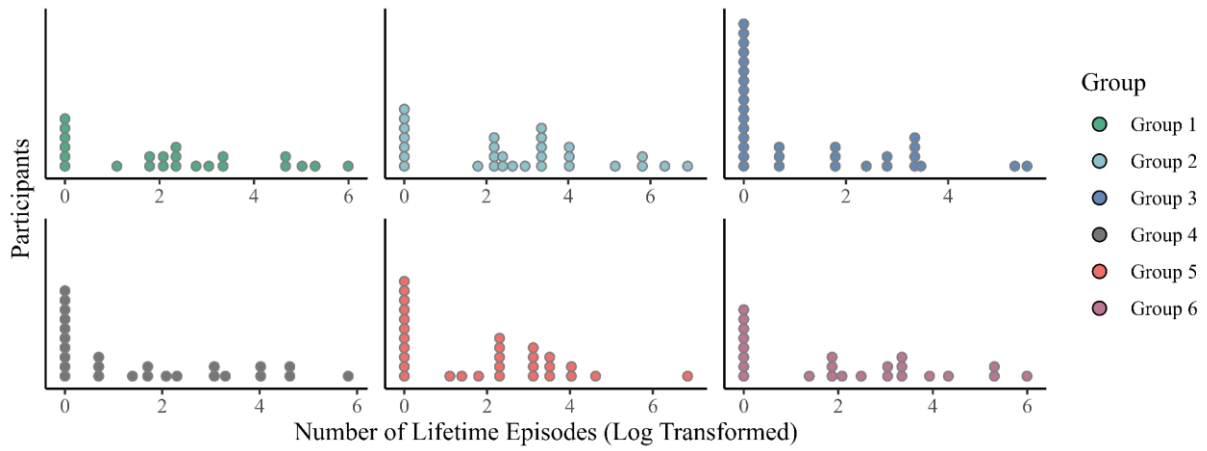
Significant differences were found in the severity of NSSI engagement between person-centered derived groups. In analyses examining the relationship between group membership and severity of NSSI engagement (Table 10, Figure 15), Group 3 was associated with decreased severity NSSI compared to the reference group (Group 1), both in the models with and without BDI score. Higher Time 2 age was also significantly related to greater severity of NSSI engagement in the model with and without the BDI score. Lower Time 1 age was associated with higher severity of NSSI engagement in the model with BDI score included as a covariate. Higher BDI scores were also associated with greater severity of NSSI engagement. Figure 15 demonstrates the distribution of NSSI severity of NSSI engagement across groups. Table B6 shows the distribution of the severity of NSSI engagement across groups and the pairwise comparison of the severity of NSSI engagement between groups. No significant group differences were found in the pairwise comparisons. Analyses conducted without the inclusion of HPA axis reactivity are shown in Tables B7-8 and Figure B4.

Table 11. Number of Lifetime Episodes of NSSI by Group with HPA Axis Reactivity for the BRIDGES Study

	Without BDI Score	**With BDI Score**
Coefficient	**Beta (SE)**	**Beta (SE)**
Intercept	-2.256 (1.191)	-2.214 (1.066) *
Group 2 Membership	0.102 (0.305)	0.084 (0.273)
Group 3 Membership	-0.576 (0.298)	-0.44 (0.267)
Group 4 Membership	-0.515 (0.311)	-0.223 (0.282)
Group 5 Membership	-0.237 (0.3)	-0.095 (0.27)
Group 6 Membership	-0.17 (0.317)	-0.001 (0.285)
Time 1 Age	0.211 (0.276)	0.017 (0.249)
Time 2 Age	0.00 (0.325)	0.184 (0.293)
Time 3 Age	0.077 (0.172)	0.028 (0.154)
BDI Score		0.041 (0.007) ***

Note: NSSI=non-suicidal self-injury; BDI=Beck Depression Inventory; SE=standard error; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

Figure 16. Number of Lifetime Episodes of NSSI by Group with HPA Axis Reactivity for the BRIDGES Study



Note: NSSI=non-suicidal self-injury; * indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001

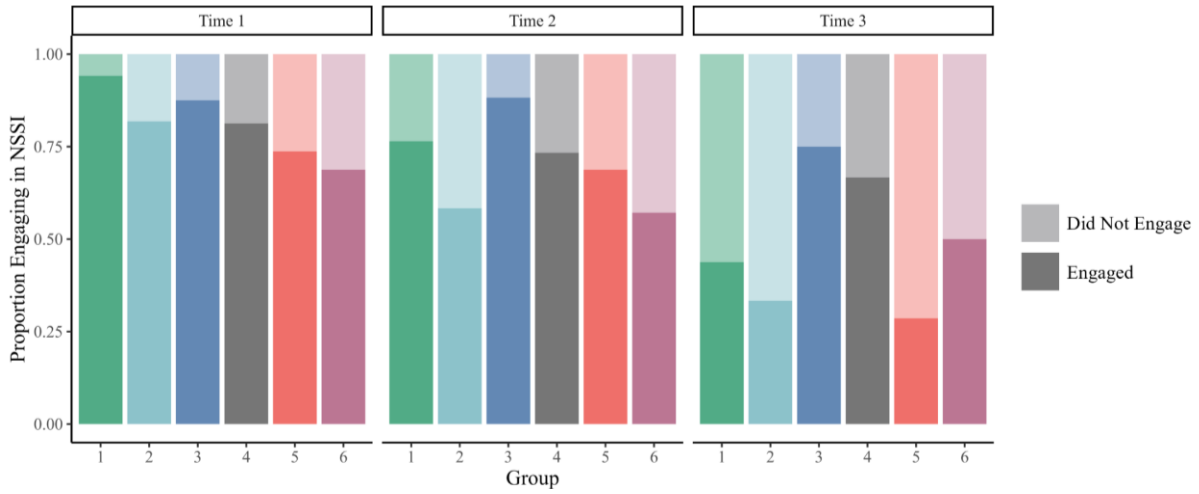
Analyses examining the relationships between the number of lifetime episodes of NSSI and group membership (Table 11, Figure 16) did not indicate any significant relationships. A higher BDI score was also associated with a greater number of lifetime episodes of NSSI. Figure 16 demonstrates the distribution of the number of lifetime episodes of NSSI across groups. None of the pairwise comparisons showed significant differences (Table B9). Analyses conducted without the inclusion of HPA axis reactivity are shown in Tables B10-11 and Figure B5.

Table 12. NSSI Engagement Across Time Points by Group with HPA Axis Reactivity for the BRIDGES Study

	Without BDI Score	**With BDI Score**
Coefficient	**OR (CI)**	**OR (CI)**
Intercept	15771.732 (3.109, 16.223)**	9120.376 (2.709, 15.528)**
Group 2 Membership	0.612 (-2.118, 1.135)	0.599 (-2.131, 1.107)
Group 3 Membership	2.788 (-0.680, 2.730)	2.472 (-0.753, 2.563)
Group 4 Membership	1.417 (-1.229, 1.926)	2.172 (-0.8080, 2.360)
Group 5 Membership	0.440 (-2.390, 0.746)	0.567 (-2.134, 1.001)
Group 6 Membership	0.322 (-2.846, 0.579)	0.364 (-2.713, 0.691)
Time Point	0.525 (-1.325, 0.035)	0.577 (-1.220, 0.121)
Age	0.654 (-0.857, 0.009)	0.614 (-0.921, -0.055)*
BDI Score		1.071 (0.017, 0.119)**

Note: NSSI=non-suicidal self-injury; BDI=Beck Depression Inventory; SE=standard error; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

Figure 17. NSSI Engagement Across Time Points by Group with HPA Axis Reactivity for the BRIDGES Study



Note: NSSI=non-suicidal self-injury; * indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001

Analyses examining the relationship between group membership and engagement in NSSI across study time points (Table 12, Figure 17) indicated no significant group differences. Notably, NSSI engagement decreased in almost every group across time, potentially indexing resilience from NSSI. When the BDI score was included as a covariate, age was inversely associated with NSSI engagement across time. A higher BDI score was also associated with continued NSSI engagement across time. The distribution of engagement in NSSI across time points between groups is shown in Figure 17. Pairwise comparisons revealed non-significant group differences in the distributions of engagement across time (X^2=15, p=0.1). Table B12 shows the proportion of each group engaging across time points. Analyses conducted without HPA axis reactivity are shown in Tables B13-14 and Figure B6.

Aim 3 Results

The average slope of change in amygdala reactivity was 0.280, mPFC reactivity was -0.180, and amygdala-mPFC RSFC was -0.024 across participants. This indicates that, broadly, amygdala reactivity is increasing while mPFC reactivity and amygdala-mPFC RSFC decrease, though these trends are small and indicate a great deal of variability. The average BDI score across time points was 15.301, which indicates moderate depressive symptoms in the sample as a whole (Beck et al., 1996).

The Time 1 correlation table (Table B15) indicates that some brain and HPA axis metrics are related to the history of NSSI engagement. History of NSSI engagement was significantly related to Time 1 amygdala reactivity (positively), Time 1 amygdala-mPFC RSFC (negatively), and Time 1 HPA axis reactivity (negatively). Further, the severity of NSSI engagement and the number of lifetime episodes of NSSI reported at Time 1 were negatively related to Time 1 amygdala-mPFC RSFC and Time 1 HPA axis reactivity. Amygdala-mPFC RSFC was also negatively associated with NSSI engagement at Time 2. Time 1 HPA axis reactivity was also positively associated with Time 1 amygdala and mPFC reactivity. Time 1 age was found to be associated with the severity of NSSI engagement (positively), number of lifetime episodes of NSSI (positively), engagement at Time 1 (negatively), and amygdala-mPFC RSFC (negatively). As expected, Time 1 amygdala reactivity was positively associated with mPFC reactivity. Time 1 BDI scores were positively associated with NSSI history, severity of NSSI engagement, number of lifetime episodes of NSSI, and engagement at Time 1. In addition, it was found that BDI scores were associated with Time 1 amygdala reactivity (positively), Time 1 amygdala-mPFC RSFC (negatively), and Time 1 age (positively). As expected, the severity of NSSI engagement was positively associated with NSSI history and the number of lifetime episodes of NSSI. The number of lifetime episodes of NSSI was also associated with the history of NSSI and engagement at Time 1, engagement at Time 2 was found to be associated with engagement at Time 1 and Time 3.

The correlation between the slope of change variables (Table B16) indicates that the change in mPFC reactivity is positively associated with the slope of change in amygdala reactivity. Additionally, the slope of change in HPA axis reactivity was related to the slope of change in amygdala reactivity (negatively) and amygdala-mPFC RSFC (positively) as well. Time 1 age, Time 2 age, and Time 3 age were all related to the severity of NSSI engagement

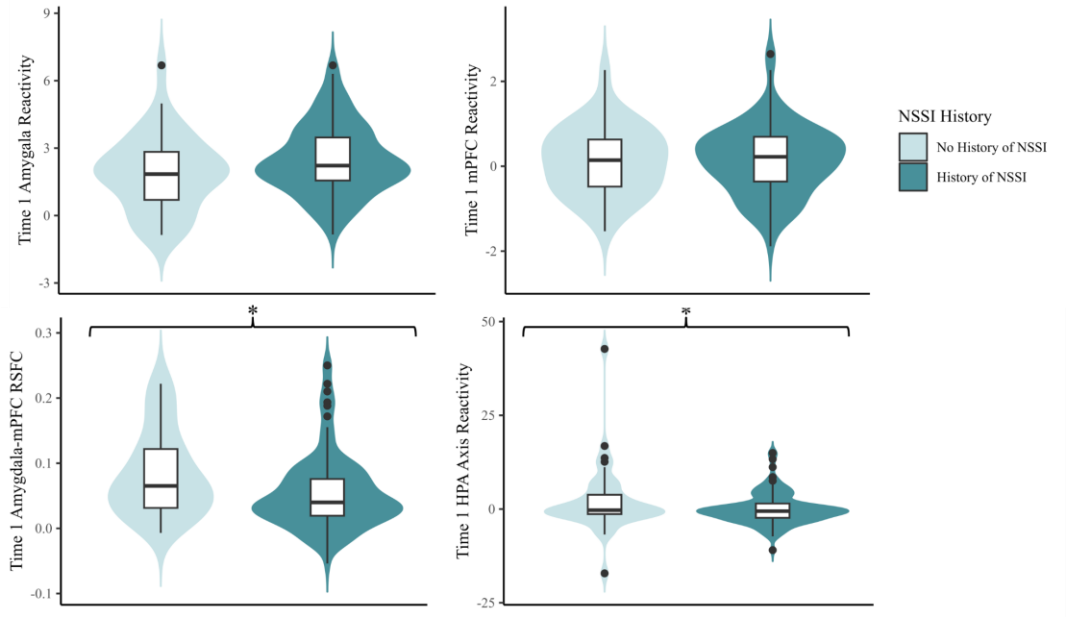
(positively), number of lifetime episodes of NSSI (negatively), and NSSI engagement at Time 1 (negatively). As expected, the BDI score was positively associated with a history of NSSI engagement, severity of NSSI engagement, number of lifetime episodes of NSSI, and engagement at Time 1. Severity of NSSI engagement was also found to be associated with NSSI engagement and the number of lifetime episodes of NSSI. The number of lifetime episodes of NSSI was positively associated with NSSI engagement and engagement at Time 1. NSSI engagement at Time 2 was positively associated with engagement at Time 1 and 3.

Table 13. History of NSSI Engagement and Time 1 Stress System Metrics with HPA Axis Reactivity for the BRIDGES Study

	Without BDI Score	**With BDI Score**
Coefficient	**OR (CI)**	**OR (CI)**
Intercept	0.957 (-4.985, 4.948)	0.548 (-6.328, 5.127)
Time 1 Amygdala Reactivity	1.253 (-0.033, 0.501)	1.068 (-0.240, 0.378)
Time 1 mPFC Reactivity	0.755 (-0.783, 0.212)	0.647 (-1.070, 0.166)
Time 1 Amygdala-mPFC RSFC	0.000 (-14.836, -1.890)*	0.079 (-10.171, 5.116)
Time 1 HPA Axis Reactivity	0.926 (-0.156, -0.008)*	0.995 (-0.383, 0.368)
Time 1 Age	1.090 (-0.237, 0.411)	0.957 (-0.139, 0.034)
Time 1 BDI Score		1.256 (0.141, 0.341)***

Note: NSSI=non-suicidal self-injury; SE=standard error; mPFC=medial pre-frontal cortex; RSFC=resting state functional connectivity; BDI=Beck Depression Inventory; * indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001

Figure 18. History of NSSI Engagement History and Time 1 Stress System Metrics with HPA Axis Reactivity for the BRIDGES Study



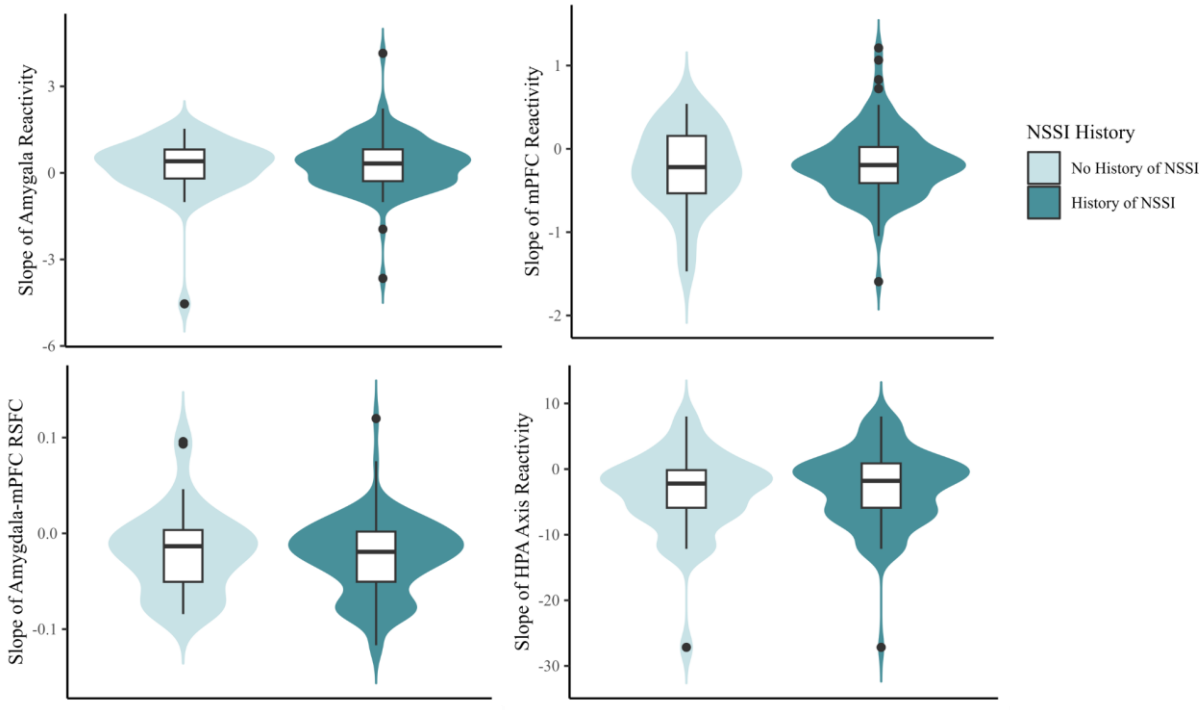
Note: NSSI=non-suicidal self-injury; mPFC=medial pre-frontal cortex; RSFC=resting state functional connectivity; HPA=Hypothalamic Pituitary Adrenal Axis; * indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001; Relationships are significant when BDI score is not included as a covariate.

Table 14. History of NSSI Engagement and Slope Stress System Metrics with HPA Axis Reactivity for the BRIDGES Study

	Without BDI Score	**With BDI Score**
Coefficient	**OR (CI)**	**OR (CI)**
Intercept	0.020 (-8.971, 0.993)	0.007 (-11.131, 0.902)
Slope of Amygdala Reactivity	1.302 (-0.163, 0.696)	1.068 (-0.496, 0.682)
Slope of mPFC Reactivity	1.452 (-0.493, 1.262)	2.058 (-0.366, 1.902)
Slope of Amygdala-mPFC RSFC	0.012 (-14.219, 5.308)	0.216 (-13.310, 10.034)
Slope of HPA Axis Reactivity	1.052 (-0.017, 0.121)	1.029 (-0.050, 0.113)
Time 1 Age	1.287 (-0.961, 1.425)	0.725 (-2.342, 1.497)
Time 2 Age	0.988 (-1.395, 1.416)	1.723 (-1.597, 2.883)
Time 3 Age	1.090 (-0.635, 0.836)	1.011 (-0.919, 0.953)
Mean BDI		1.239 (0.142, 0.304)***

Note: NSSI=non-suicidal self-injury; SE=standard error; mPFC=medial pre-frontal cortex; RSFC=resting state functional connectivity; HPA=Hypothalamic Pituitary Adrenal Axis; BDI=Beck Depression Inventory; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

Figure 19. History of NSSI Engagement History and Slope Stress System Metrics with HPA Axis Reactivity for the BRIDGES Study



Note: NSSI=non-suicidal self-injury; mPFC=medial pre-frontal cortex; RSFC=resting state functional connectivity; HPA=Hypothalamic Pituitary Adrenal Axis; * indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001

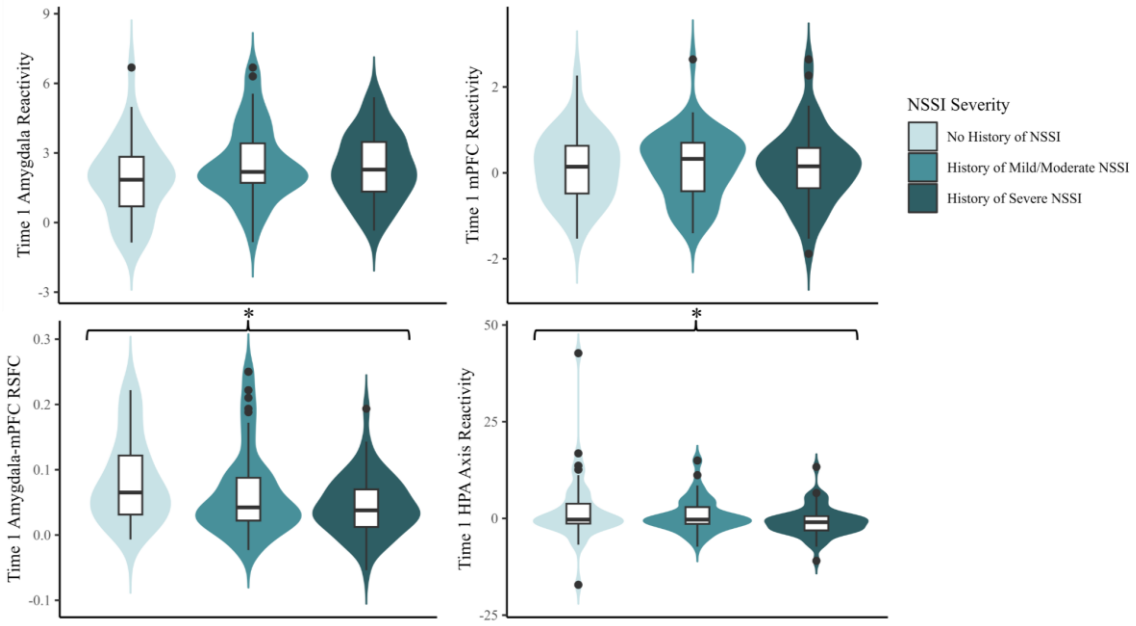
Variable-centered analyses examining the relationships between the Time 1 (Table 13, Figure 18) and slope (Table 14, Figure 19) of brain and HPA axis metrics and the history of NSSI engagement, few significant results were found, though lower Time 1 RSFC and HPA axis reactivity were found to be significantly related to greater likelihood NSSI. These results were no longer significant when the model included the BDI score as a covariate. A higher BDI score was significantly related to the greater likelihood of reporting a history of NSSI engagement in both models. Figures 18 and 19 demonstrate the distribution of brain metrics by history of NSSI engagement. Analyses conducted without HPA axis reactivity are shown in Tables B17-18.

Table 15. Severity of NSSI Engagement and Time 1 Stress System Metrics with HPA Axis Reactivity for the BRIDGES Study

	Without BDI Score	**With BDI Score**
Coefficient	**OR (CI)**	**OR (CI)**
Time 1 Amygdala Reactivity	1.057 (-0.138, 0.253)	0.996 (-0.208, 0.202)
Time 1 mPFC Reactivity	0.811 (-0.598, 0.172)	0.754 (-0.674, 0.105)
Time 1 Amygdala-mPFC RSFC	0.000 (-13.711, -3.015)**	0.005 (-10.901, 0.191)
Time 1 HPA Axis Reactivity	0.911 (-0.159, -0.034)**	0.912 (-0.162, -0.029)**
Time 1 Age	1.097 (-0.162, 0.348)	1.047 (-0.213, 0.307)
Time 1 BDI Score		1.062 (0.036, 0.086)***

Note: NSSI=non-suicidal self-injury; SE=standard error; mPFC=medial pre-frontal cortex; RSFC=resting state functional connectivity; HPA=Hypothalamic Pituitary Adrenal Axis; BDI=Beck Depression Inventory; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

Figure 20. Severity of NSSI Engagement and Time 1 Stress System Metrics with HPA Axis Reactivity for the BRIDGES Study



Note: NSSI=non-suicidal self-injury; mPFC=medial pre-frontal cortex; RSFC=resting state functional connectivity; HPA=Hypothalamic Pituitary Adrenal Axis; * indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001; Relationship with HPA axis reactivity is significant with and without BDI score included as a covariate; Relationship with amygdala-mPFC RSFC is only significant when BDI score is not included as a covariate.

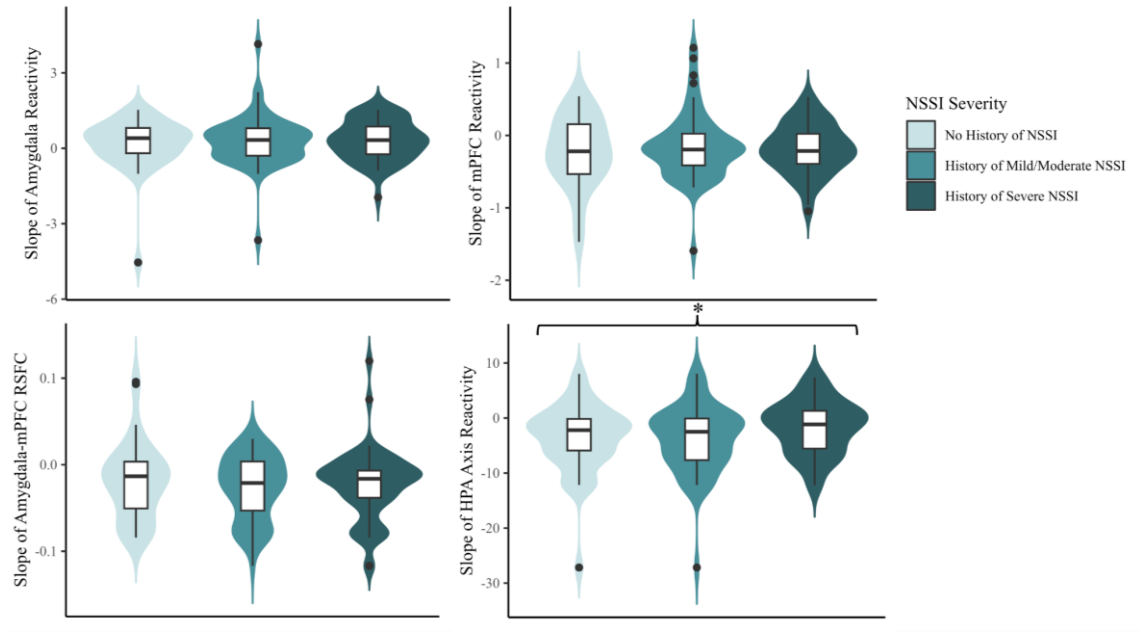
Variable-centered analyses of TIme 1 metrics of brain and HPA axis functioning and severity of NSSI engagement (Table 15, Figure 20) indicate that lower Time 1 amygdala-mPFC RSFC and HPA axis reactivity were significantly related to higher severity of NSSI severity when BDI score was not included as a covariate, but when BDI score was added as a covariate, only HPA axis reactivity related significantly (BDI score also emerged as significant).

Table 16. Severity of NSSI Engagement and Slope Stress System Metrics with HPA Axis Reactivity for the BRIDGES Study

	Without BDI Score	**With BDI Score**
Coefficient	**OR (CI)**	**OR (CI)**
Slope of Amygdala Reactivity	1.306 (-0.069, 0.611)	1.232 (-0.151, 0.578)
Slope of mPFC Reactivity	1.185 (-0.524, 0.868)	1.288 (-0.465, 0.978)
Slope of Amygdala-mPFC RSFC	0.104 (-10.138, 5.569)	0.523 (-8.755, 7.399)
Slope of HPA Axis Reactivity	1.060 (0.003, 0.116)*	1.056 (-0.005, 0.117)
Time 1 Age	0.589 (-1.483, 0.409)	0.334 (-2.197, -0.078) *
Time 2 Age	2.602 (-0.146, 2.087)	4.924 (0.383, 2.895)*
Time 3 Age	0.884 (-0.697, 0.448)	0.752 (-0.900, 0.320)
Mean BDI Score		1.087 (0.055, 0.114)***

Note: NSSI=non-suicidal self-injury; SE=standard error; mPFC=medial pre-frontal cortex; RSFC=resting state functional connectivity; HPA=Hypothalamic Pituitary Adrenal Axis; BDI=Beck Depression Inventory; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

Figure 21. Severity of NSSI Engagement and Slope Stress System Metrics with HPA Axis Reactivity for the BRIDGES Study



Note: NSSI=non-suicidal self-injury; mPFC=medial pre-frontal cortex; RSFC=resting state functional connectivity; HPA=Hypothalamic Pituitary Adrenal Axis; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$; Relationship is only significant when BDI score is not included as a covariate.

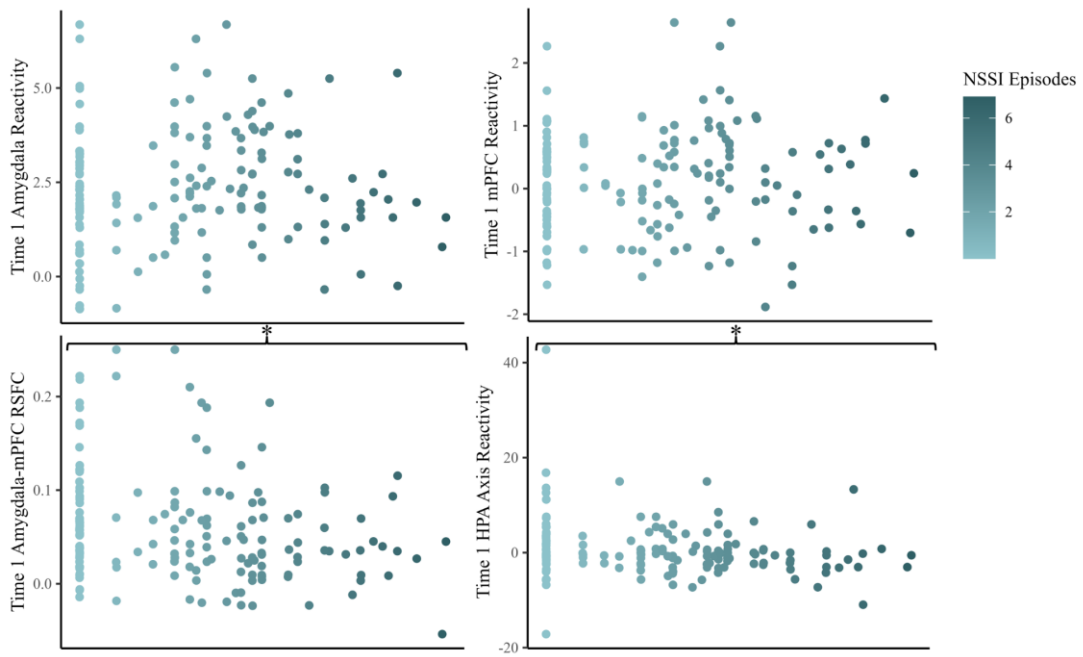
Variable-centered analyses examining the slope of change of brain and HPA axis reactivity in relation to the severity of NSSI engagement (Table 16, Figure 21) without BDI score as a covariate, a more positive slope of change in HPA axis reactivity was significantly related to heightened severity of NSSI engagement. When the BDI score was added as a covariate, Time 1 age and Time 2 age were significant in addition to the BDI score (higher BDI score associated with greater severity of NSSI engagement). Analyses conducted without HPA axis reactivity are shown in Tables B19-20.

Table 17. Number of Lifetime Episodes of NSSI and Time 1 Stress System Metrics with HPA Axis Reactivity for the BRIDGES Study

	Without BDI Score	**With BDI Score**
Coefficient	**Beta (SE)**	**Beta (SE)**
Intercept	-1.062 (1.143)	-1.449 (1.036)
Time 1 Amygdala Reactivity	0.046 (0.056)	0.013 (0.051)
Time 1 mPFC Reactivity	-0.015 (0.109)	-0.043 (0.099)
Time 1 Amygdala-mPFC RSFC	-3.679 (1.486)*	-1.893 (1.377)
Time 1 HPA Axis Reactivity	-0.03 (0.015)*	-0.023 (0.014)
Time 1 Age	0.214 (0.074)**	0.197 (0.067)**
Time 1 BDI Score		0.04 (0.007)***

Note: NSSI=non-suicidal self-injury; SE=standard error; mPFC=medial pre-frontal cortex; RSFC=resting state functional connectivity; HPA=Hypothalamic Pituitary Adrenal Axis; BDI=Beck Depression Inventory; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

Figure 22. Number of Lifetime Episodes of NSSI and Time 1 Stress System Metrics with HPA Axis Reactivity for the BRIDGES Study



Note: Episode data is log transformed; NSSI=non-suicidal self-injury; mPFC=medial pre-frontal cortex; RSFC=resting state functional connectivity; HPA=Hypothalamic Pituitary Adrenal Axis; * indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001; Relationships are only significant when BDI is not included as a covariate.

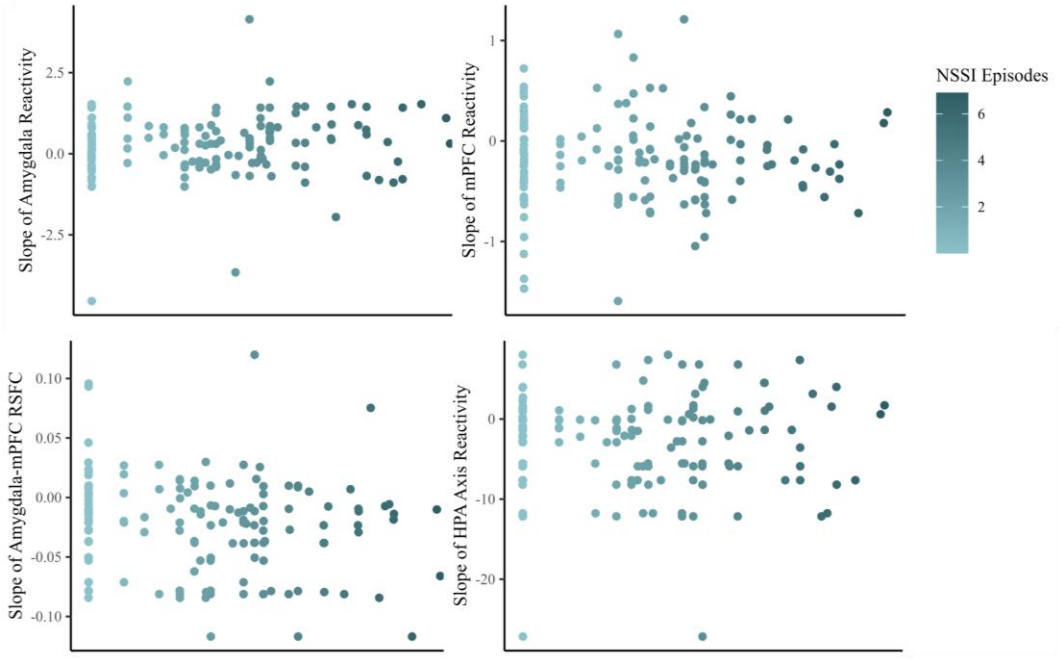
Variable-centered analyses examining the relationship between the number of lifetime episodes of NSSI in relation to Time 1 brain and HPA axis metrics (Table 17, Figure 22) indicate that lower Time 1 RSFC and HPA axis reactivity were related to a higher number of lifetime episodes of NSSI, both when BDI score was and was not included as a covariate. Time 1 age was also associated with a higher number of lifetime episodes of NSSI in the Time 1 model with and without the inclusion of the BDI score. Higher BDI scores were also significantly associated with a greater number of lifetime episodes of NSSI.

Table 18. Number of Lifetime Episodes of NSSI and Slope Stress System Metrics with HPA Axis Reactivity for the BRIDGES Study

	Without BDI Score	**With BDI Score**
Coefficient	**Beta (SE)**	**Beta (SE)**
Intercept	-3.145 (1.178)**	-2.859 (1.055)**
Slope of Amygdala Reactivity	0.177 (0.100)	0.111 (0.09)
Slope of mPFC Reactivity	-0.006 (0.205)	0.009 (0.183)
Slope of Amygdala-mPFC RSFC	-3.252 (2.256)	-1.843 (2.032)
Slope of HPA Axis Reactivity	0.022 (0.016)	0.015 (0.015)
Age Time 1	0.24 (0.278)	0.047 (0.250)
Age Time 2	-0.076 (0.329)	0.102 (0.296)
Age Time 3	0.155 (0.174)	0.105 (0.156)
Mean BDI Score		0.041 (0.006)***

Note: NSSI=non-suicidal self-injury; SE=standard error; mPFC=medial pre-frontal cortex; RSFC=resting state functional connectivity; HPA=Hypothalamic Pituitary Adrenal Axis; BDI=Beck Depression Inventory; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

Figure 23. Number of Lifetime Episodes of NSSI and Slope Stress System Metrics with HPA Axis Reactivity for the BRIDGES Study



Note: Episode data is log transformed; NSSI=non-suicidal self-injury; mPFC=medial pre-frontal cortex; RSFC=resting state functional connectivity; HPA=Hypothalamic Pituitary Adrenal Axis; * indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001

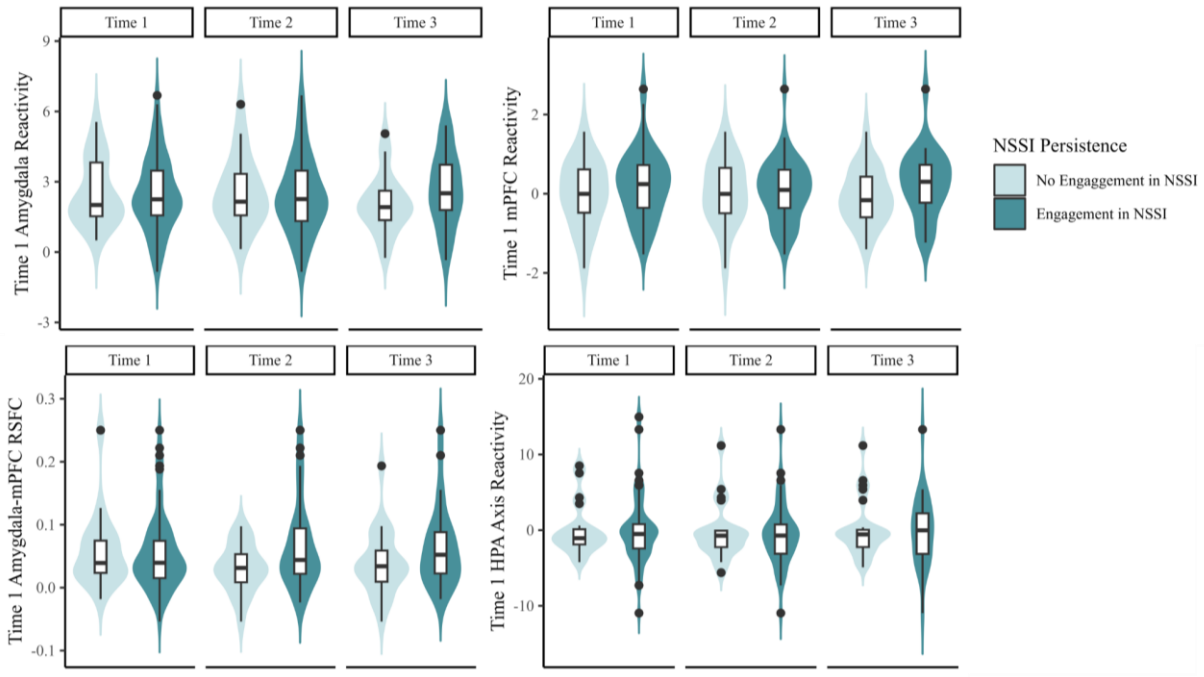
Analyses examining the relationship between the number of lifetime episodes of NSSI and the slope of change of brain and HPA axis metrics (Table 18, Figure 23) did not yield any significant findings, though higher BDI scores were significantly associated with a greater number of lifetime episodes of NSSI. Analyses conducted without HPA axis reactivity are shown in Table B21.

Table 19. NSSI Engagement Across Time Points and Time 1 Stress System Metrics with HPA Axis Reactivity for the BRIDGES Study

	Without BDI Score	**With BDI Score**
Coefficient	**OR (CI)**	**OR (CI)**
Intercept	7.563 (0.244, 3.803)*	2.546 (-0.945, 2.814)
Time Point	0.597 (-1.186, 0.156)	0.629 (-1.133, 0.206)
Time 1 Amygdala Reactivity	1.010 (-0.338, 0.359)	0.991 (-0.363, 0.345)
Time 1 mPFC Reactivity	1.723 (-0.144, 1.231)	1.573 (-0.241, 1.147)
Time 1 Amygdala-mPFC RSFC	366.476 (-3.657, 15.465)	5630.049 (-1.365, 18.637)
Time 1 HPA Axis Reactivity	0.985 (-0.138, 0.107)	0.994 (-0.132, 0.120)
Time 1 Age	0.491 (-1.456, 0.034)	0.463 (-1.520, -0.019)*
Time 1 BDI Score		1.047 (0.005, 0.088)*

Note: NSSI=non-suicidal self-injury; SE=standard error; mPFC=medial pre-frontal cortex; RSFC=resting state functional connectivity; HPA=Hypothalamic Pituitary Adrenal Axis; BDI=Beck Depression Inventory; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

Figure 24. NSSI Engagement Across Time Points and Time 1 Stress System Metrics with HPA Axis Reactivity for the BRIDGES Study



Note: NSSI=non-suicidal self-injury; mPFC=medial pre-frontal cortex; RSFC=resting state functional connectivity; HPA=Hypothalamic Pituitary Adrenal Axis; * indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001

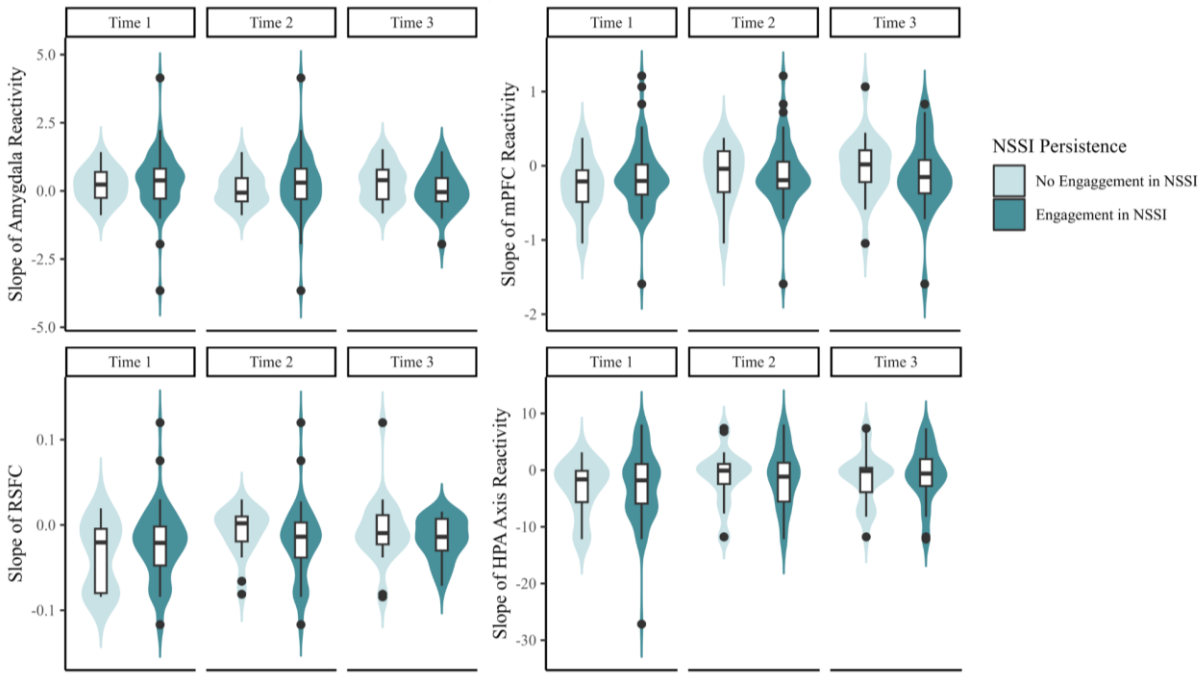
Analyses exploring the relationship between Time 1 metrics of the brain and the HPA axis in relation to engagement in NSSI across time points (Table 19, Figure 24) did not yield any significant findings. Lower Time 1 age was associated with greater NSSI engagement across time points in the Time 1 model, with the BDI score included as a covariate. A greater Time 1 BDI score was also associated with greater engagement in NSSI across time points in the Time 1 model.

Table 20. NSSI Engagement Across Time Points and Slope Stress System Metrics with HPA Axis Reactivity for the BRIDGES Study

	Without BDI Score	**With BDI Score**
Coefficient	**OR (CI)**	**OR (CI)**
Intercept	10.385 (0.703, 3.977)**	2.281 (-0.916, 2.565)
Time Point	0.607 (-1.183, 0.185)	0.675 (-1.058, 0.271)
Slope of Amygdala Reactivity	1.099 (-0.515, 0.703)	0.982 (-0.623, 0.586)
Slope of mPFC Reactivity	0.957 (-1.309, 1.221)	1.067 (-1.171, 1.301)
Slope of Amygdala-mPFC RSFC	0.025 (-17.139, 9.723)	0.010 (-17.605, 8.406)
Slope of HPA Axis Reactivity	1.025 (-0.073, 0.124)	1.017 (-0.078, 0.111)
Age	0.474 (-1.484, -0.009)*	0.433 (-1.563, -0.113)*
Mean BDI Score		1.072 (0.018, 0.121)**

Note: NSSI=non-suicidal self-injury; SE=standard error; mPFC=medial pre-frontal cortex; RSFC=resting state functional connectivity; HPA=Hypothalamic Pituitary Adrenal Axis; BDI=Beck Depression Inventory; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

Figure 25. NSSI Engagement Across Time Points and Slope Stress System Metrics with HPA Axis Reactivity for the BRIDGES Study



Note: NSSI=non-suicidal self-injury; mPFC=medial pre-frontal cortex; RSFC=resting state functional connectivity; HPA=Hypothalamic Pituitary Adrenal Axis; * indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001

Analyses examining the relationship between slope metrics of the brain and HPA axis functioning in relation to engagement in NSSI across time points (Table 20 and Figure 25) did not yield any significant findings. Younger age was associated with greater engagement in NSSI across time points in NSSI both with and without the inclusion of the BDI score as a covariate. A greater mean BDI score was also associated with greater engagement in NSSI across time points. Analyses conducted without HPA axis reactivity are shown in Tables B22-23.

Discussion

This study set out to leverage person-centered analyses, in addition to traditional variable-centered analytic techniques, to explore alterations in the interplay in stress responses between the brain and body. This was done in a longitudinal sample of adolescents, all AFAB, who were overrepresented by those with a history of NSSI. This study collected multi-modal metrics of biological signatures of the functioning of the brain and HPA axis' stress systems, as well as highly detailed reports of the characteristics of NSSI engagement. This allowed for in-depth, nuanced analyses of a variety of NSSI indices, including history of NSSI engagement, severity of NSSI engagement, number of lifetime episodes of NSSI, and engagement in NSSI across study time points. Some of the variable-centered analyses conceptually replicated prior work in this sample. However, no prior studies have simultaneously investigated the longitudinal interplay between the brain and the HPA axis with such extensive measures of NSSI using both person-centered and variable-centered analytic techniques.

Person-centered analyses identified six groups with distinct trajectories of the development of brain-HPA axis interplay. Group 1 partially resembled the hypothesized Blunted Frontal Regulatory Control trajectory, except it was anticipated that amygdala reactivity would decrease. Group 2 almost resembles the pattern of the hypothesized Normative Development group, though it was anticipated that amygdala-mPFC RSFC would become more negative across time points. Group 3 partially resembles the hypothesized Blunted Frontal Regulatory Control trajectory, though it was anticipated that amygdala-mPFC RSFC would become more negative across time points. Groups 4 and 5 differed from all of the hypothesized profiles. Group 6 was the largest group and almost resembles the hypothesized Heightened Frontal Regulatory Control trajectory, though it was anticipated that amygdala-mPFC RSFC would become more negative across time points. Notably, many of the trajectories did not demonstrate linear change over time, as was expected. There is some evidence to suggest that amygdala reactivity to stressful stimuli undergoes non-linear changes across adolescence (Ahmed et al., 2015), however, more work is needed to characterize non-linearity in the development of other brain metrics (mPFC reactivity to stressful stimuli and amygdala-mPFC RSFC) and HPA axis reactivity.

Person-centered derived groups gave some insight into heterogeneity among adolescents with a history of NSSI. These groups did not differ significantly in the rate of endorsement of a

history of NSSI, though they did, however, differ based on the severity of NSSI engagement. Person-centered analyses may not have been able to differentiate participants at heightened risk for NSSI engagement because of the limited variability in the metric as the large majority of the participants in this study had a history of NSSI engagement, however, there was variability in the severity of NSSI engagement. Indeed, Group 3 demonstrated a different distribution of severity of NSSI engagement, while Group 1 included very few members in the "never" category, and the vast majority were split evenly between the "mild/moderate" and "severe" categories, potentially indicating that while this group did not differ significantly from others in rate of reporting NSSI, it may be at heightened risk for more severe NSSI. Group 3 (close to the Blunted Frontal Regulatory Control trajectory) demonstrated almost even distribution across all three severity categories. This seems to indicate that there is meaningful heterogeneity between the two groups resembling the Blunted Frontal Regulatory Control trajectory despite their similar patterns of development. It seems that the central differences between Groups 1 and 3 are in changes in brain metrics across time points; Group 1 demonstrated stable amygdala reactivity, decreasing SF reactivity, and increasingly more negative amygdala-mPFC RSFC as well as significantly heightened risk for severe NSSI compared to Group 3, which showed increasing amygdala reactivity, decreased SF reactivity, and stable amygdala-mPFC RSFC and significantly more mild/moderate NSSI. Indeed, for individuals with decreasing SF reactivity to stressful stimuli, having discordance between frontal and limbic regions, as seen in Group 1, may index runaway stress responses that are not adequately inhibited by frontal regions. In the case of Group 3, the impact of decreased SF reactivity seems to be buffered by the stability of the RSFC between frontal and limbic regions. This indicates that examining amygdala-mPFC RSFC in the context of regional activation could be especially important in understanding the risk of heightened severity of NSSI.

Evidence shows that the relationship between stress system functioning and NSSI may look slightly different if person-centered groups were derived using only brain metrics. Person-centered analyses were repeated without including HPA axis reactivity. The overlap in group membership between the groups that did not include HPA axis reactivity and those that did (Figure B1; Groups are shown in Figure B2) is very limited, except for Group 3. Group 3, made with HPA axis reactivity, contains almost the entirety of the Group 3 made without HPA axis reactivity, with the addition of a few members from Group 1 made without HPA axis reactivity.

Group 3 partially resembles the hypothesized Blunted Frontal Regulatory Control trajectory when made with and without HPA axis reactivity. Multi-trajectory modeling has previously been criticized for the potential of spurious findings (Mésidor et al., 2022), but the finding of near-perfect replication of a group gives greater confidence that these analytic methods are indeed identifying meaningful variance in stress system functioning. Overall, it seems that the addition of HPA axis reactivity significantly affects the patterns identified by person-centered analyses, though it is unclear whether groups of brain-HPA axis interplay provide greater insights into risk for NSSI than are afforded by the groups made by using brain metrics alone.

When comparing results relating metrics of NSSI engagement between person-centered derived groups made with and without HPA reactivity, different insights emerge; the groups made with HPA reactivity showed no significant differences in terms of the lifetime number of episodes of NSSI as well as NSSI engagement across time points, however, there were significant differences found between groups made without HPA axis reactivity (see Tables B10-14 and Figures B5-6). When examining the severity of NSSI engagement, it was found that groups with trajectories resembling the hypothesized Blunted Frontal Regulatory Control trajectory, the Heightened Frontal Regulatory Control trajectory, and an unexpected profile that indexed a breakdown in frontal regulatory control all showed less severe NSSI compared to a group with blunted mPFC reactivity and highly dynamic change in amygdala-mPFC RSFC. Additionally, the group mirroring the Blunted Frontal Regulatory Control trajectory reported fewer lifetime episodes of NSSI compared to the group with blunted mPFC reactivity and dynamic change in amygdala-mPFC RSFC. Finally, it was also found that the group mirroring the Normative Development trajectory showed decreased engagement across time points compared to the group with blunted mPFC reactivity and highly dynamic amygdala-mPFC RSFC. When looking across analyses investigating person-centered derived groups related to all metrics of NSSI engagement, the inclusion of HPA axis reactivity results in fewer significant findings. It may be that the variance introduced by using cross-system measures captured in the context of different stress induction paradigms and frequently on different days is too great to allow for the identification of meaningful patterns of response. Future work that concurrently collects brain and HPA axis reactivity in the context of the same stress induction paradigm may be helpful to assess whether person-centered analyses of brain-HPA axis interplay can provide greater insights into risk for NSSI.

Variable-centered analyses relating Time 1 biological metrics and NSSI engagement found that more negative Time 1 amygdala-mPFC RSFC and lower HPA axis reactivity were both associated with a greater risk of NSSI engagement, though this relationship did not remain significant when controlling for BDI score. These patterns could index discordance between frontal and limbic regions (more negative RSFC) and an inappropriately modest body-wide stress response (HPA axis reactivity). This is congruent with work that established that blunted fronto-limbic RSFC (in this same sample [Başgöze, Mirza, et al., 2021] and other samples [Santamarina-Perez et al., 2019; Westlund Schreiner et al., 2017]) and HPA axis reactivity (Kaess et al., 2012; Klimes-Dougan et al., 2019; Plener et al., 2012) are consistently related to NSSI engagement. Variable-centered analyses of the relationship between Time 1 biological metrics and severity of NSSI found that more negative Time 1 amygdala-mPFC RSFC and HPA axis reactivity both emerged as significantly related to increased severity, though only HPA axis reactivity remained significant when BDI score was added as a covariate. This replicates prior work in the same sample, which demonstrated that more negative RSFC and blunted HPA reactivity were associated with greater severity of NSSI (Başgöze, Mirza, et al., 2021). The loss of significant findings relating amygdala-mPFC RSFC with the severity of NSSI when BDI score was included as a covariate should be considered in the context of prior work by Westlund Schreiner et al., (2017), which showed that in participants with Major Depressive Disorder and NSSI, there was no association ventromedial PFC-amygdala RSFC and HPA axis reactivity and an inverse relationship between dorsomedial PFC-amygdala RSFC and HPA axis reactivity. The difference potentially indicates meaningful subregional differences and/or different biological signatures underlying NSSI in those with Major Depressive Disorder compared to those with NSSI in general. The finding that lower Time 1 HPA axis reactivity was also associated with increased severity builds on prior work, indicating that blunted HPA axis reactivity is associated with heightened risk for NSSI (Başgöze, Mirza, et al., 2021; Kaess et al., 2012; Klimes-Dougan et al., 2019; Plener et al., 2012). The variable-centered analyses investigating Time 1 interplay metrics in relation to the number of NSSI episodes indicated that more negative amygdala-mPFC RSFC and HPA axis reactivity are both associated with a higher number of episodes of NSSI, though this did not remain significant when controlling for the BDI score. This adds texture to prior findings linking amygdala-mPFC RSFC to the severity of NSSI in this sample, as severity metrics take into account the number of episodes of NSSI (Başgöze, Mirza, et al., 2021).

Examining the slope metrics of the brain and HPA axis offers a few novel insights into biological alterations in NSSI. The slopes derived for the variable-centered analyses demonstrated a novel pattern; the slope of change in amygdala reactivity was positively correlated with the slope of change in mPFC reactivity. This is opposite to what would be expected in a normative sample based on prior literature characterizing the increase in frontal reactivity to stressful stimuli (Yurgelun-Todd & Killgore, 2006) and the increasing inhibitory input to the amygdala via frontal regions (Cunningham et al., 2002; Gee, Gabard-Durnam, et al., 2013; Perlman & Pelphrey, 2011; Silvers et al., 2015; Swartz et al., 2014). This unexpected pattern may be indexing this sample's ongoing dysfunctional developmental processes, as ⅔ of participants had a history of NSSI. No significant results emerged when examining the relationship between the slope of change in brain and HPA axis metrics and the history of NSSI engagement. When examining the slope of change of biological metrics in relation to severity of NSSI, increasing HPA axis reactivity was shown to be associated with greater severity of NSSI, though this relationship did not remain significant when BDI score was added as a covariate. This may be indicative that while participants with severe NSSI have lower levels of HPA axis reactivity early in adolescence, HPA axis reactivity may increase to be more similar to their peers as adolescent development progresses, in line with work indicating that recalibration of HPA axis functioning occurs in adolescents exposed to early life stressors (Gunnar et al., 2019; Perry et al., 2022). Variable-centered analyses examining NSSI engagement across time and Time 1 and slope of change of biological metrics yielded no significant findings (including when run without HPA axis reactivity, Tables B22 and B23). It is notable that when examined across time points, the variance of the distribution of HPA axis reactivity increased significantly in the group that reported engaging in NSSI, potentially adding credence to the theory that participants with severe NSSI at Time 1 demonstrate increasing HPA axis reactivity across time points but that the NSSI group as a whole does not, causing the effect to be washed out in these analyses.

Across person-centered and variable-centered analyses, BDI scores were consistently related to NSSI metrics such that higher scores were associated with higher likelihood of engaging in NSSI, higher severity of NSSI, more episodes of NSSI, and more engagement in NSSI across time points. In the person-centered analyses conducted without HPA axis reactivity, the addition of the BDI score as a covariate did not cause any significant findings to disappear, while the addition of BDI scores resulted in more relationships to be significant. This may

indicate that the profiles differ significantly in relation to NSSI metrics but that they have similar levels of depressive symptoms, which obfuscated patterns when the BDI score was not included. The opposite pattern emerged from the variable-centered analyses; many, though not all, of the significant relationships disappeared when the BDI score was added as a covariate. This may indicate that the patterns identified in the variable-centered analysis index general negative affect or emotion dysregulation, less so NSSI specifically. The relationship that remained significant was between decreased HPA axis reactivity and the severity of NSSI engagement, highlighting the importance of this relationship. Together, these patterns may indicate that although NSSI and depression are highly comorbid, there seem to be unique signatures in the brain and body's stress systems that relate to the particular type of difficulty in emotion regulation.

Age was also related to NSSI metrics sporadically across person-centered and variable-centered analyses. Age at Time 1 and 2 was associated with the severity of NSSI in both sets of analyses, with lower age at Time 1 and higher age at Time 2 associated with higher severity of NSSI. Age at Time 1 was also associated with the number of episodes of NSSI in the variable-centered Time 1 analyses, with lower age associated with a higher number of lifetime episodes of NSSI. In both person-centered and variable-centered analyses, lower age was associated with more engagement in NSSI across time. Taken together, it seems that starting the study at a younger age was associated with heightened severity of NSSI, higher number of episodes of NSSI, and increased engagement in NSSI across time. Given that this sample is not representative of the general population of adolescents but instead over-recruited participants based on recent history of NSSI, it is difficult to draw broad inference, but it may be that these findings join with the body of work indicating that engaging in NSSI earlier is associated with more severe and repetitive NSSI (Ammerman et al., 2018). The finding linking higher age at Time 2 with heightened severity may reflect a more prolonged period between the first and second visit due to difficulty scheduling participants with more acute impairments.

When looking across person-centered and variable-centered analyses, more negative amygdala-mPFC RSFC was repeatedly significantly related to risk for NSSI engagement, severity of NSSI, and number of episodes of NSSI. In the context of normative development, there is a shift from positive to negative amygdala-mPFC RSFC, indexing the mPFC taking on an inhibitory role over the amygdala (Gee, Humphreys, et al., 2013). However, more negative amygdala-mPFC has been repeatedly shown to occur in adolescents with a history of NSSI

compared to those without (Başgöze, Mirza, et al., 2021; Santamarina-Perez et al., 2019; Westlund Schreiner et al., 2017), which may index an inappropriately over- or under-active inhibitory activity from the mPFC. In the context of heightened amygdala reactivity, more negative amygdala-mPFC RSFC could index runaway threat signals, resulting in behavior responses out of proportion with the actual threat. In the context of blunted amygdala reactivity, more negative amygdala-mPFC RSFC could index excessive mPFC reactivity and thus exaggerated frontal inhibitory control over threat responses, resulting in a disproportionately low threat response for the stimuli. Indeed, in this study, amygdala reactivity was potentially implicated in the person-centered analyses, while variable-centered analyses also repeatedly implicated HPA axis reactivity in risk for engagement, severity, and number of episodes, though this metric did not seem central in person-centered findings. There were many more significant findings relating person-centered group membership to NSSI metrics when HPA axis reactivity was not included. In this instance, the variable-centered analyses do not seem impacted by the confounds of different systems, stress induction paradigms, and study visit dates as the person-centered analyses appear to be. Person-centered and variable-centered analytic techniques each have their own strengths and weaknesses. Indeed, person-centered analyses allow for a more direct assessment of the interplay between metrics and are able to include all time points in the same model. At the same time, person-centered analyses seemed to have greater difficulty parsing meaningful signals from the noise introduced by measurement-related variability. Variable-centered analyses seemed to be better able to overcome measurement-related variability to identify patterns but were not able to probe the interplay between metrics or hold multiple time points simultaneously. Indeed, these analytic strategies complement each other and underscore the importance of frontal regulatory control in many attributes of NSSI, complementing each other by providing insights not seen in the other.

When comparing findings relating biological metrics with different measures of NSSI, some patterns emerged. It seems that the person-centered derived groups did not distinguish between groups of adolescents who did or did not report a history of NSSI engagement, but they did identify patterns of development that were uniquely related to the severity of NSSI, and when made without HPA axis reactivity, number of episodes of NSSI and engagement across time points as well. This may mean that the groups are more appropriate for predicting the chronicity and the severity of NSSI than the presence or absence of NSSI, though the limited variability in

the history of NSSI engagement in this sample may be obfuscating this pattern. Still, this work is the first to examine nuanced attributes of NSSI using person-centered methods. The variable-centered analyses successfully replicated prior work demonstrating the link between alterations in amygdala-mPFC RSFC and HPA axis reactivity and NSSI engagement history and severity of NSSI. Additionally, this study found for the first time that more positive change in HPA axis reactivity across adolescence is related to NSSI severity. Results relating amygdala-mPFC RSFC and HPA axis reactivity to the number of NSSI episodes are also novel. The examination of more nuanced metrics of NSSI is starting to help disentangle which biological metrics may be related to unique attributes of NSSI. When examined in relation to the interplay between the brain and HPA axis' stress systems, the present results seem to indicate that stable amygdala reactivity in conjunction with increasingly more negative amygdala-mPFC RSFC may correspond with more significant dysfunction than increasing amygdala reactivity with stable amygdala-mPFC RSFC; it may be that the inhibition over the amygdala is more important in determining risk of dysfunction than the actual reactivity of the amygdala itself. Additionally, it was repeatedly found that more negative amygdala-mPFC RSFC, in conjunction with blunted HPA axis reactivity, was associated with heightened NSSI metrics, indicating that in conjunction with lower frontal inhibition over the amygdala, having inappropriately low endocrine responsivity to stress is particularly risky (Thai et al., 2021). It may be that individuals with this profile demonstrate less adaptive stress response behaviors because their bodies are failing to muster the appropriate endocrine response (HPA axis reactivity; Faravelli et al., 2012; Plener et al., 2017) while simultaneously not applying the appropriate "brakes" to the amygdala's stress responses (amygdala-mPFC RSFC; Casey et al., 2011; Perlman & Pelphrey, 2011; van Oort et al., 2017).

Limitations

This study should be interpreted in light of some limitations. (1) There was a great deal of attrition and disruption in data collection due to the COVID-19 pandemic across time points. Additionally, there may have been selective attrition for participants with heightened difficulties in emotion regulation (Nair et al., 2023). The use of multiple imputation and the inclusion of age as a covariate in all analyses was aimed to address this issue. (2) This study did not account for factors such as medication use, experience of adverse events in childhood, genetic predisposition to maladaptive emotion regulation, and the differential effects of the COVID-19 pandemic,

which could impact biological functioning and risk of NSSI. (3) This study relied on participant self-report of NSSI engagement attributes, which could be subject to recall bias and perceived social pressure to appear more or less impaired (Aspeqvist et al., 2024). Additionally, participants frequently struggled to adequately quantify the number of episodes they had engaged in and provided rough estimates. Despite these drawbacks, we believe there is still a great deal of value in examining these data. (4) The present study had a cross-sequential or accelerated longitudinal design such that some participants were recruited at early stages of adolescent development (12 years old) while others were recruited at much later stages (16 years old). Though age was controlled for in all analyses, the observed trajectories could be capturing participants at very different points in adolescent development. (5) The methods used to index the slope of change for the variable-centered analyses assume linear change across development, though emerging work indicates that not all development during this period is linear (Ahmed et al., 2015; Giedd et al., 2002). (6) The analytic framing of the person-centered and variable-centered analyses differed slightly as person-centered analyses were able to simultaneously examine all time points of brain and HPA axis data, while variable-centered analyses were only able to examine single metrics (i.e., Time 1 and the composite slope metric). Additionally, person-centered analyses are able to interrogate all brain and HPA axis metrics simultaneously to index the interplay between them, while variable-centered analyses hold them in the same model but do not directly interrogate the relationship between these metrics. This limits the ability to compare findings across analytic strategies directly. (7) This sample included only individuals AFAB and the majority were non-Hispanic White from an upper Midwestern state. Thus, findings may not generalize to the broader population of adolescents. (8) This study oversampled for a history of NSSI, thus limiting the variability in this metric to allow for the investigation of within-group heterogeneity. This may also limit the ability to detect differences between those with and without a history of NSSI. A larger sample with more variability in the history of NSSI engagement may be more ideal for person-centered analyses aimed to identify patterns related to the risk of having a history of NSSI engagement.

Future Directions and Clinical Implications

Future work should continue exploring within-group heterogeneity by using person-centered analytic methods and traditional variable-centered methods. Also, examining the interplay between the brain and HPA axis' stress systems holds promise in comprehensively

capturing the developmental processes underlying risk for NSSI. Future work that concurrently examines brain regional reactivity in the context of the same stressor as HPA axis stress reactivity could provide clearer insights into the role of intra-brain and inter-system coordination. Future work should also consider the function of NSSI in relation to biological metrics, as it may be that different functions of NSSI (i.e., self-care or communication; Nock et al., 2007b) are associated with different biological alterations. Ideally, these findings should inform treatment studies examining the efficacy of treatment modalities that address multi-system integration and recalibration (ex, Kallianta et al., 2021; for review: Slopen et al., 2014). Notably, Dialectical Behavior Therapy has been shown to alter patterns of functioning in regions implicated in frontal regulatory control in adults with borderline personality disorder (Ruocco et al., 2016). Further, it has been found that adolescents with more negative RSFC between the amygdala and PFC showed the greatest decreases in NSSI following modified DBT (Santamarina-Perez et al., 2019). Pharmacological interventions such as selective serotonin reuptake inhibitors, atypical antipsychotics, opioid antagonists, and N-acetyl cysteine have been shown to decrease engagement in NSSI, however, the precise biological mechanisms for these effects are yet to be characterized (Westlund Schreiner et al., 2023). Further work is needed to identify how novel insights about dysfunctional brain-HPA axis interplay can be leveraged to improve treatment efficacy, as very few options are available to address NSSI (Glenn et al., 2019).

Conclusion

This study investigated developmental patterns in brain-HPA axis interplay across adolescence, which relate to NSSI in a unique, high-risk sample using longitudinal, multi-level metrics. Findings indicate that there are distinct patterns of blunted frontal regulatory control over the stress system which are associated with NSSI severity, which is novel, that more negative amygdala-mPFC RSFC is associated with increased risk of NSSI, increased severity of NSSI, and increased number of episodes of NSSI (a conceptual replication of prior work in this sample), that decreased HPA axis reactivity is associated with increased risk of NSSI and increased severity of NSSI (a conceptual replication of prior work in this sample) and that a greater slope of change in HPA axis reactivity is also associated with increased severity of NSSI as well. This work is the first to employ both person-centered and variable-centered analyses to explore the role of brain-HPA axis interplay to expand upon and replicate prior work. These

findings call for future work centering brain-HPA axis interplay and provide insights into potential points of intervention.

4. General Discussion

The current studies undertook multilevel, longitudinal analyses of the development of the biological stress systems in relation to metrics of NSSI in a community-representative sample of early adolescents and a sample overrepresented for a history of NSSI that spanned the entire adolescent period. In both studies, Aim 1 was to use person-centered analytic techniques to identify distinct patterns of developmental trajectories of the interplay between biological stress system metrics. In the first study, a five group model was selected; in the second study, a six group model was selected. Aim 2 was to test if these person-centered derived profiles were associated with metrics of NSSI. In the first study, significant differences in age at first report were found between a group characterized by highly dynamic developmental change and a group that resembled the hypothesized Normative Development trajectory. Though these groups did not differ significantly in the proportion of participants reporting a history of NSSI, the highly dynamic group was found to have a significantly younger age at first report of NSSI as well as increased externalizing behaviors and attention problem and had more Time 2 visit occurring after the onset of the COVID-19 pandemic compared to the group resembling the Normative Development trajectory. This is the first evidence of neurodevelopmental patterns associated with differences in the age at which NSSI is first reported (though it is notable that we could not directly measure the age of onset of NSSI). In the second study, despite having no significant differences in the proportion of group members reporting a history of NSSI to the hypothesized Blunted Frontal Regulatory Control trajectory, group differences emerged when accounting for severity by classifying participants as none, mild/moderate, and severe NSSI. Person-centered analyses in both studies failed to create groups that differed on the history of NSSI engagement. Some possible explanations are that other metrics of brain and HPA functioning may be better able to distinguish between those with and without a history of NSSI or that there is too much heterogeneity in the biological pathways that leave individuals vulnerable to NSSI engagement to view this construct as a single uniform group. Indeed, the findings relating more nuanced metrics of NSSI (age at first report, severity) with group membership highlight that the person-centered derived groups differ meaningfully, even if not on the binary metric of history of NSSI engagement. Though none of the Aim 2 a priori hypotheses were directly supported, both studies provide evidence of distinct patterns of stress system development associated with meaningful heterogeneity among adolescents reporting NSSI engagement. Additionally, these analyses are

the first to use person-centered methodology to explore the relationship between adolescent biological development and NSSI engagement.

Aim 3 of both studies involved using variable-centered analyses to explore the alterations in the brain and, in the case of the second study, the HPA axis in relation to NSSI. The first study found that decreased frontal reactivity to emotional faces and decreased slope of change of fronto-limbic RSFC were associated with an increased risk of reporting NSSI. The second study found that decreased fronto-limbic RSFC at Time 1 was associated with an increased risk of engaging in NSSI, increased severity of NSSI, and an increased number of episodes of NSSI, that decreased HPA axis reactivity at Time 1 was associated with an increased risk of NSSI and increased severity of NSSI, and that more positive change in HPA axis reactivity across time points was associated with increased severity of NSSI. The consistency of findings relating blunted fronto-limbic RSFC with NSSI engagement across studies adds to the robustness of this pattern seen in other studies (Başgöze, Mirza, et al., 2021; Santamarina-Perez et al., 2019; Westlund Schreiner et al., 2017) and is consistent with hypotheses. The findings relating blunted fronto-limbic RSFC with other metrics of NSSI are novel, consistent with hypotheses, and add to our understanding of the important role that frontal regulatory control plays in determining the severity and repetitiveness of NSSI. Findings relating more positive change in HPA axis reactivity over time with increased severity of NSSI is novel and incongruent with hypotheses but may indicate that the HPA axis reactivity of individuals with severe NSSI undergoes recalibration during adolescence, as has been seen in adolescents who experienced early life stressors (Gunnar et al., 2019; Perry et al., 2022). Finally, the findings relating lower frontal reactivity with increased risk for NSSI are novel but consistent with hypotheses based on the theory that risk for NSSI is, at least in part, rooted in deficits in frontal regulation of limbic regions (Carosella, Wiglesworth, Başgöze, et al., 2023; Casey, 2015).

Across both studies, despite the vastly different samples, some consistent patterns also emerged in covariates. First, depressive symptom severity was consistently related to increased risk for NSSI, more engagement in NSSI across study time points, older age at first report of NSSI in the first study, and increased severity and number of episodes of NSSI in the second study. This is consistent with prior work demonstrating the high rate of comorbidity of depression and NSSI (Başgöze, Wiglesworth, et al., 2021). Age was associated with differential risk across attributes of NSSI. Lower age was associated with a lower risk of reporting NSSI in

the first study, while lower age was associated with higher severity of NSSI, number of episodes of NSSI, and risk of engagement across time points in the second study. The disparity in patterns here is likely due to differential sample and recruitment characteristics; the second study recruited such that ⅔ of participants had a recent history of NSSI engagement at Time 1, and, consistent with prior literature, participants who endorse NSSI at younger ages show increased severity and impairment (Ammerman et al., 2018). Additionally, the second study only included participants AFAB, while the first did not restrict participants based on sex at birth, and prior work has outlined sex-related differences in risk for NSSI and age of onset of NSSI (Barrocas et al., 2012; Wang et al., 2022). In addition, these studies differed in measures used to measure NSSI engagement, the fMRI paradigms used to collect data, the atlases used to parcellate this data, and the demographic distribution of the samples, among other factors. Despite these disparities, the two studies indicated that at later time points, higher age was associated with greater dysfunction (increased risk of NSSI in the first study; increased severity of NSSI in the second study). This may be indexing greater difficulty in scheduling and completing follow-up visits with participants with greater impairment, resulting in a higher age at subsequent time points.

Limitations

These studies should be considered in the context of some limitations. (1) Both studies were impacted by the COVID-19 pandemic and had issues with missing data. The first study used only a subset of the larger sample with more complete data. In the second study, multiple imputation was used to address missingness. (2) Limited untabulated brain data is presently available for the first study, and, as such, brain metrics were restricted to those pre-tabulated. This restricted the ability to select the atlases used to parcellate the data and resulted in the selection of preparcellated regions that did not align with those used in the second study, thus limiting the ability to compare findings across studies directly. (3) Their similar but distinct analytic framing impairs the ability to compare across person-centered and variable-centered approaches. While person-centered analyses could simultaneously examine all time points of brain and HPA axis data, variable-centered analyses could only examine single metrics (i.e., Time 1 or Baseline and the composite slope metric). Further, person-centered analyses can more directly measure the interplay between stress system components by examining all brain and HPA axis metrics simultaneously, however, the present variable-centered analyses are only able

to model them in relation to the same outcome metric and do not measure the interrelatedness of these metrics. (4) Each study has its limitations; ABCD, although large and representative of the US population, did not have in-depth metrics of NSSI or ideal parcellations for available brain data. Meanwhile, BRIDGES had in-depth and ideal metrics of NSSI and both brain and HPA functioning but were small and restricted in demographic and clinical presentation. Conducting these two studies in tandem was intended to provide greater insight than was afforded by each study separately.

Future Directions

Together, these studies identify novel and reinforce previously established patterns of stress system functioning related to attributes of NSSI. They also point to opportunities for future work. (1) The first study was only able to capture early periods of adolescence, and while the cross-sequential longitudinal design of the second study provided some insights into developmental trends in later adolescence, future work should explore similar phenomena using forthcoming data from the ABCD study. (2) Work should be done to explore further the unique pattern of dynamic change in the stress system, which was associated with increased externalizing and attention difficulties as well as younger age at the first report of NSSI in the first study. There may be meaningful heterogeneity among adolescents with NSSI not only in their biological development but also in comorbid psychopathology as well. (3) The impact of the COVID-19 pandemic could not be directly measured in either study, but there were likely differential emotional and practical impacts based on many factors, including family structure, income, medical vulnerability, and geographic region. Future work characterizing the proximal and long-term impact of the pandemic on NSSI engagement should be considered.

Conclusions

Two multilevel, longitudinal studies of adolescent development found novel evidence of distinct profiles of intra-brain and brain-HPA axis interplay, which relate to the age at the first report of NSSI (first study) and severity of NSSI (second study). Additionally, these studies provide novel evidence implicating decreased frontal reactivity and increased change in HPA axis reactivity over adolescence in risk for different attributes of NSSI. Evidence also reinforces previously identified patterns linking decreased fronto-limbic RSFC and HPA axis reactivity with NSSI risk. Together, these studies will, hopefully, inspire future work employing person-centered analyses, the exploration of brain-HPA axis interplay, and the further examination of

the development of frontal regulatory control in relation to psychopathology. Finally, these findings may guide the investigation of interventions that increase frontal regulatory control of the amygdala and HPA axis reactivity to mitigate the risks of NSSI engagement in adolescence.

Bibliography

Achenbach, T. M. (2013). DSM-Oriented Guide for the Achenbach System of Empirically Based Assessment (ASEBA®). *University of Vermont, Research Center for Children, Youth, & Families.*

Achenbach, T. M., & Ruffle, T. M. (2000). The Child Behavior Checklist and Related Forms for Assessing Behavioral/Emotional Problems and Competencies. *Pediatrics In Review*, *21*(8), 265–271. https://doi.org/10.1542/pir.21-8-265

Ahmed, S. P., Bittencourt-Hewitt, A., & Sebastian, C. L. (2015). Neurocognitive bases of emotion regulation development in adolescence. *Developmental Cognitive Neuroscience*, *15*, 11–25. https://doi.org/10.1016/j.dcn.2015.07.006

Ammerman, B. A., Jacobucci, R., Kleiman, E. M., Uyeji, L. L., & McCloskey, M. S. (2018). The Relationship Between Nonsuicidal Self-Injury Age of Onset and Severity of Self-Harm. *Suicide and Life-Threatening Behavior*, *48*(1), 31–37. https://doi.org/10.1111/sltb.12330

Aspeqvist, E., Andersson, H., Korhonen, L., Dahlström, Ö., & Zetterqvist, M. (2024). Measurement and stratification of nonsuicidal self-injury in adolescents. *BMC Psychiatry*, *24*(1), 107. https://doi.org/10.1186/s12888-024-05535-3

Azur, M. J., Stuart, E. A., Frangakis, C., & Leaf, P. J. (2011). Multiple imputation by chained equations: What is it and how does it work? *International Journal of Methods in Psychiatric Research*, *20*(1), 40–49. https://doi.org/10.1002/mpr.329

Barch, D. M., Albaugh, M. D., Avenevoli, S., Chang, L., Clark, D. B., Glantz, M. D., Hudziak, J. J., Jernigan, T. L., Tapert, S. F., Yurgelun-Todd, D., Alia-Klein, N., Potter, A. S., Paulus, M. P., Prouty, D., Zucker, R. A., & Sher, K. J. (2018). Demographic, physical and mental health assessments in the adolescent brain and cognitive development study: Rationale and description. *Developmental Cognitive Neuroscience*, *32*, 55–66. https://doi.org/10.1016/j.dcn.2017.10.010

Barch, D. M., Burgess, G. C., Harms, M. P., Petersen, S. E., Schlaggar, B. L., Corbetta, M., Glasser, M. F., Curtiss, S., Dixit, S., Feldt, C., Nolan, D., Bryant, E., Hartley, T., Footer, O., Bjork, J. M., Poldrack, R., Smith, S., Johansen-Berg, H., Snyder, A. Z., & Van Essen, D. C. (2013). Function in the human connectome: Task-fMRI and individual differences in behavior. *NeuroImage*, *80*, 169–189. https://doi.org/10.1016/j.neuroimage.2013.05.033

Barrocas, A. L., Hankin, B. L., Young, J. F., & Abela, J. R. Z. (2012). Rates of Nonsuicidal Self-Injury in Youth: Age, Sex, and Behavioral Methods in a Community Sample. *Pediatrics*, *130*(1), 39–45. https://doi.org/10.1542/peds.2011-2094

Başgöze, Z., Demers, L., Thai, M., Falke, C. A., Mueller, B. A., Fiecas, M. B., Roediger, D. J., Thomas, K. M., Klimes-Dougan, B., & Cullen, K. R. (2023). A Multi-Level Examination of Cognitive Control in Adolescents with Non-suicidal Self-Injury. *Biological Psychiatry Global Open Science*. https://doi.org/10.1016/j.bpsgos.2023.04.005

Başgöze, Z., Mirza, S. A., Silamongkol, T., Hill, D., Falke, C., Thai, M., Schreiner, M. W., Parenteau, A. M., Roediger, D. J., Hendrickson, T. J., Mueller, B. A., Fiecas, M. B., Klimes-Dougan, B., & Cullen, K. R. (2021). Multimodal assessment of sustained threat in adolescents with nonsuicidal self-injury. *Development and Psychopathology*, *33*(5), 1774–1792. https://doi.org/10.1017/S0954579421000754

Başgöze, Z., Wiglesworth, A., Carosella, K. A., Klimes-Dougan, B., & Cullen, K. R. (2021). Depression, Non-Suicidal Self-Injury, and Suicidality in Adolescents: Common and Distinct Precursors, Correlates, and Outcomes. *Journal of Psychiatry and Brain Science*, *6*(5), e210018. https://doi.org/10.20900/jpbs.20210018

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting Linear Mixed-Effects Models Using lme4. *Journal of Statistical Software*, *67*, 1–48. https://doi.org/10.18637/jss.v067.i01

Beck, A. T., Steer, R. A., & Brown, G. (1996). *Beck Depression Inventory–II*. https://doi.org/10.1037/t00742-000

Bendezú, J. J., Thai, M., Wiglesworth, A., Cullen, K. R., & Klimes-Dougan, B. (2022). Adolescent stress experience–expression–physiology correspondence: Links to depression, self-injurious thoughts and behaviors, and frontolimbic neural circuity. *Journal of Affective Disorders*, *300*, 269–279. https://doi.org/10.1016/j.jad.2021.12.098

Blashill, A. J., Fox, K., Feinstein, B. A., Albright, C. A., & Calzo, J. P. (2021). Nonsuicidal self-injury, suicide ideation, and suicide attempts among sexual minority children. *Journal of Consulting and Clinical Psychology*, *89*(2), 73–80. https://doi.org/10.1037/ccp0000624

Brañas, M. J. A. A., Croci, M. S., Ravagnani Salto, A. B., Doretto, V. F., Martinho, E., Macedo, M., Miguel, E. C., Roever, L., & Pan, P. M. (2021). Neuroimaging Studies of Nonsuicidal Self-Injury in Youth: A Systematic Review. *Life*, *11*(8), 729. https://doi.org/10.3390/life11080729

Brieant, A. E., Sisk, L. M., & Gee, D. G. (2021). Associations among negative life events, changes in cortico-limbic connectivity, and psychopathology in the ABCD Study. *Developmental Cognitive Neuroscience*, *52*, 101022. https://doi.org/10.1016/j.dcn.2021.101022

Brislin, S. J., Martz, M. E., Cope, L. M., Hardee, J. E., Weigard, A., & Heitzeg, M. M. (2021). Heterogeneity Within Youth With Childhood-Onset Conduct Disorder in the ABCD Study. *Frontiers in Psychiatry*, *12*, 701199. https://doi.org/10.3389/fpsyt.2021.701199

Buuren, S. V., & Groothuis-Oudshoorn, K. (2011). **mice**: Multivariate Imputation by Chained Equations in *R*. *Journal of Statistical Software*, *45*(3). https://doi.org/10.18637/jss.v045.i03

Carosella, K. A., Mirza, S., Başgöze, Z., Cullen, K. R., & Klimes-Dougan, B. (2023). Adolescent non-suicidal self-injury during the COVID-19 pandemic: A prospective longitudinal study of biological predictors of maladaptive emotion regulation. *Psychoneuroendocrinology*, *151*, 106056. https://doi.org/10.1016/j.psyneuen.2023.106056

Carosella, K. A., Wiglesworth, A., Başgöze, Z., Cullen, K. R., & Klimes-Dougan, B. (2023). The Brain and Body's Threat-System Functioning in Those With NSSI. In E. E. Lloyd-Richardson, I. Baetens, & J. L. Whitlock (Eds.), *The Oxford Handbook of Nonsuicidal Self-Injury* (p. 0). Oxford University Press. https://doi.org/10.1093/oxfordhb/9780197611272.013.14

Carosella, K. A., Wiglesworth, A., Bendezú, J. J., Brower, R., Mirza, S., Mueller, B. A., Cullen, K. R., & Klimes-Dougan, B. (2023). Patterns of experience, expression, and physiology of stress relate to depressive symptoms and self-injurious thoughts and behaviors in adolescents: A person-centered approach. *Psychological Medicine*, 1–11. https://doi.org/10.1017/S0033291723002003

Casey, B. J. (2015). Beyond Simple Models of Self-Control to Circuit-Based Accounts of Adolescent Behavior. *Annual Review of Psychology*, *66*(1), 295–319. https://doi.org/10.1146/annurev-psych-010814-015156

Casey, B. J., Cannonier, T., Conley, M. I., Cohen, A. O., Barch, D. M., Heitzeg, M. M., Soules, M. E., Teslovich, T., Dellarco, D. V., Garavan, H., Orr, C. A., Wager, T. D., Banich, M.

T., Speer, N. K., Sutherland, M. T., Riedel, M. C., Dick, A. S., Bjork, J. M., Thomas, K. M., … Dale, A. M. (2018). The Adolescent Brain Cognitive Development (ABCD) study: Imaging acquisition across 21 sites. *Developmental Cognitive Neuroscience*, *32*, 43–54. https://doi.org/10.1016/j.dcn.2018.03.001

Casey, B. J., Jones, R. M., & Somerville, L. H. (2011). Braking and Accelerating of the Adolescent Brain. *Journal of Research on Adolescence*, *21*(1), 21–33. https://doi.org/10.1111/j.1532-7795.2010.00712.x

Cheng, T. W., Magis-Weinberg, L., Guazzelli Williamson, V., Ladouceur, C. D., Whittle, S. L., Herting, M. M., Uban, K. A., Byrne, M. L., Barendse, M. E. A., Shirtcliff, E. A., & Pfeifer, J. H. (2021). A Researcher's Guide to the Measurement and Modeling of Puberty in the ABCD Study® at Baseline. *Frontiers in Endocrinology*, *12*, 608575. https://doi.org/10.3389/fendo.2021.608575

Cipriano, A., Cella, S., & Cotrufo, P. (2017). Nonsuicidal Self-injury: A Systematic Review. *Frontiers in Psychology*, *8*. https://www.frontiersin.org/articles/10.3389/fpsyg.2017.01946

Conley, M. I., Dellarco, D. V., Rubien-Thomas, E., Cohen, A. O., Cervera, A., Tottenham, N., & Casey, B. (2018). The Racially Diverse Affective Expression (RADIATE) Face Stimulus Set. *Psychiatry Research*, *270*, 1059–1067. https://doi.org/10.1016/j.psychres.2018.04.066

Conley, M. I., Hernandez, J., Salvati, J. M., Gee, D. G., & Baskin-Sommers, A. (2023). The role of perceived threats on mental health, social, and neurocognitive youth outcomes: A multicontextual, person-centered approach. *Development and Psychopathology*, *35*(2), 689–710. https://doi.org/10.1017/S095457942100184X

Cullen, K. R., Schreiner, M. W., Klimes-Dougan, B., Eberly, L. E., LaRiviere, L. L., Lim, K. O., Camchong, J., & Mueller, B. A. (2020). Neural correlates of clinical improvement in response to N-acetylcysteine in adolescents with non-suicidal self-injury. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *99*, 109778. https://doi.org/10.1016/j.pnpbp.2019.109778

Cunningham, M. G., Bhattacharyya, S., & Benes, F. M. (2002). Amygdalo-cortical sprouting continues into early adulthood: Implications for the development of normal and abnormal function during adolescence. *Journal of Comparative Neurology*, *453*(2), 116–130. https://doi.org/10.1002/cne.10376

Dahlgren, M. K., Hooley, J. M., Best, S. G., Sagar, K. A., Gonenc, A., & Gruber, S. A. (2018). Prefrontal cortex activation during cognitive interference in nonsuicidal self-injury. *Psychiatry Research: Neuroimaging*, *277*, 28–38. https://doi.org/10.1016/j.pscychresns.2018.04.006

Daukantaitė, D., Lundh, L.-G., Wångby-Lundh, M., Claréus, B., Bjärehed, J., Zhou, Y., & Liljedahl, S. I. (2021). What happens to young adults who have engaged in self-injurious behavior as adolescents? A 10-year follow-up. *European Child & Adolescent Psychiatry*, *30*(3), 475–492. https://doi.org/10.1007/s00787-020-01533-4

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, R. L., Dale, A. M., Maguire, R. P., Hyman, B. T., Albert, M. S., & Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, *31*(3), 968–980. https://doi.org/10.1016/j.neuroimage.2006.01.021

DeVille, D. C., Whalen, D., Breslin, F. J., Morris, A. S., Khalsa, S. S., Paulus, M. P., & Barch,

D. M. (2020). Prevalence and Family-Related Factors Associated With Suicidal Ideation, Suicide Attempts, and Self-injury in Children Aged 9 to 10 Years. *JAMA Network Open*, *3*(2), e1920956. https://doi.org/10.1001/jamanetworkopen.2019.20956

Dosenbach, N., Fair, D., Miezin, F., Cohen, A., Wenger, K., Dosenbach, R., Fox, M., Snyder, A., Vincent, J., Raichle, M., Schlaggar, B., & Petersen, S. (2007). Distinct brain networks for adaptive and stable task control in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *104*, 11073–11078. https://doi.org/10.1073/pnas.0704320104

Dressendörfer, R. A., Kirschbaum, C., Rohde, W., Stahl, F., & Strasburger, C. J. (1992). Synthesis of a cortisol-biotin conjugate and evaluation as a tracer in an immunoassay for salivary cortisol measurement. *The Journal of Steroid Biochemistry and Molecular Biology*, *43*(7), 683–692. https://doi.org/10.1016/0960-0760(92)90294-S

Ekman, P., & Friesen, W. V. (1976). Measuring facial movement. *Environmental Psychology & Nonverbal Behavior*, *1*, 56–75. https://doi.org/10.1007/BF01115465

Fair, D. A., Cohen, A. L., Power, J. D., Dosenbach, N. U. F., Church, J. A., Miezin, F. M., Schlaggar, B. L., & Petersen, S. E. (2009). Functional Brain Networks Develop from a "Local to Distributed" Organization. *PLOS Computational Biology*, *5*(5), e1000381. https://doi.org/10.1371/journal.pcbi.1000381

Faravelli, C., Lo Sauro, C., Godini, L., Lelli, L., Benni, L., Pietrini, F., Lazzeretti, L., Talamba, G. A., Fioravanti, G., & Ricca, V. (2012). Childhood stressful events, HPA axis, and anxiety disorders. *World Journal of Psychiatry*, *2*(1), 13–25. https://doi.org/10.5498/wjp.v2.i1.13

Feldstein Ewing, S. W., Dash, G. F., Thompson, W. K., Reuter, C., Diaz, V. G., Anokhin, A., Chang, L., Cottler, L. B., Dowling, G. J., LeBlanc, K., Zucker, R. A., Tapert, S. F., Brown, S. A., & Garavan, H. (2022). Measuring retention within the adolescent brain cognitive development (ABCD)SM study. *Developmental Cognitive Neuroscience*, *54*, 101081. https://doi.org/10.1016/j.dcn.2022.101081

Ferrari, C., Lega, C., Vernice, M., Tamietto, M., Mende-Siedlecki, P., Vecchi, T., Todorov, A., & Cattaneo, Z. (2016). The Dorsomedial Prefrontal Cortex Plays a Causal Role in Integrating Social Impressions from Faces and Verbal Descriptions. *Cerebral Cortex*, *26*(1), 156–165. https://doi.org/10.1093/cercor/bhu186

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., Van Der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., & Dale, A. M. (2002). Whole Brain Segmentation. *Neuron*, *33*(3), 341–355. https://doi.org/10.1016/S0896-6273(02)00569-X

Franklin, J. C., Ribeiro, J. D., Fox, K. R., Bentley, K. H., Kleiman, E. M., Huang, X., Musacchio, K. M., Jaroszewski, A. C., Chang, B. P., & Nock, M. K. (2016). Risk factors for suicidal thoughts and behaviors: A meta-analysis of 50 years of research. *Psychological Bulletin*, *143*(2), 187. https://doi.org/10.1037/bul0000084

Garavan, H., Bartsch, H., Conway, K., Decastro, A., Goldstein, R. Z., Heeringa, S., Jernigan, T., Potter, A., Thompson, W., & Zahs, D. (2018). Recruiting the ABCD sample: Design considerations and procedures. *Developmental Cognitive Neuroscience*, *32*, 16–22. https://doi.org/10.1016/j.dcn.2018.04.004

Garey, L. J. (2006). *Brodmann's Localisation in the Cerebral Cortex By Dr. K. Brodmann*. World Scientific Publishing Co.

Gee, D. G., Gabard-Durnam, L. J., Flannery, J., Goff, B., Humphreys, K. L., Telzer, E. H., Hare,

T. A., Bookheimer, S. Y., & Tottenham, N. (2013). Early developmental emergence of human amygdala–prefrontal connectivity after maternal deprivation. *Proceedings of the National Academy of Sciences, 110*(39), 15638–15643. https://doi.org/10.1073/pnas.1307893110

Gee, D. G., Humphreys, K. L., Flannery, J., Goff, B., Telzer, E. H., Shapiro, M., Hare, T. A., Bookheimer, S. Y., & Tottenham, N. (2013). A Developmental Shift from Positive to Negative Connectivity in Human Amygdala–Prefrontal Circuitry. *Journal of Neuroscience*, *33*(10), 4584–4593. https://doi.org/10.1523/JNEUROSCI.3446-12.2013

Gerin, W., Pieper, C., Levy, R., & Pickering, T. G. (1992). Social support in social interaction: A moderator of cardiovascular reactivity.: *Psychosomatic Medicine*, *54*(3), 324–336. https://doi.org/10.1097/00006842-199205000-00008

Giedd, J. N., Blumenthal, J., Jeffries, N. O., Castellanos, F. X., Liu, H., Zijdenbos, A., Paus, T., Evans, A. C., & Rapoport, J. L. (1999). Brain development during childhood and adolescence: A longitudinal MRI study. *Nature Neuroscience*, *2*(10), Article 10. https://doi.org/10.1038/13158

Giedd, J. N., LALONDE, F. M., CELANO, M. J., WHITE, S. L., WALLACE, G. L., LEE, N. R., & LENROOT, R. K. (2009). Anatomical Brain Magnetic Resonance Imaging of Typically Developing Children and Adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*, *48*(5), 465–470. https://doi.org/10.1097/CHI.0b013e31819f2715

Giedd, J. N., Molloy, E. A., & Blumenthal, J. (2002). Adolescent Brain Maturation. In *Encyclopedia of the Human Brain* (pp. 13–20). Elsevier. https://doi.org/10.1016/B0-12-227210-2/00388-5

Glasser, M. F., Coalson, T. S., Robinson, E. C., Hacker, C. D., Harwell, J., Yacoub, E., Ugurbil, K., Andersson, J., Beckmann, C. F., Jenkinson, M., Smith, S. M., & Van Essen, D. C. (2016). A multi-modal parcellation of human cerebral cortex. *Nature*, *536*(7615), 171–178. https://doi.org/10.1038/nature18933

Glenn, C. R., Esposito, E. C., Porter, A. C., & Robinson, D. J. (2019). Evidence Base Update of Psychosocial Treatments for Self-Injurious Thoughts and Behaviors in Youth. *Journal of Clinical Child & Adolescent Psychology*, *48*(3), 357–392. https://doi.org/10.1080/15374416.2019.1591281

Gold, P. W. (2015). The organization of the stress system and its dysregulation in depressive illness. *Molecular Psychiatry*, *20*(1), 32–47. https://doi.org/10.1038/mp.2014.163

Gordon, E. M., Laumann, T. O., Adeyemo, B., Huckins, J. F., Kelley, W. M., & Petersen, S. E. (2016). Generation and Evaluation of a Cortical Area Parcellation from Resting-State Correlations. *Cerebral Cortex*, *26*(1), 288–303. https://doi.org/10.1093/cercor/bhu239

Groschwitz, R. C., Plener, P. L., Groen, G., Bonenberger, M., & Abler, B. (2016). Differential neural processing of social exclusion in adolescents with non-suicidal self-injury: An fMRI study. *Psychiatry Research: Neuroimaging*, *255*, 43–49. https://doi.org/10.1016/j.pscychresns.2016.08.001

Gunnar, M. R., DePasquale, C. E., Reid, B. M., Donzella, B., & Miller, B. S. (2019). Pubertal stress recalibration reverses the effects of early life stress in postinstitutionalized children. *Proceedings of the National Academy of Sciences*, *116*(48), 23984–23988. https://doi.org/10.1073/pnas.1909699116

Gunnar, M. R., Wewerka, S., Frenn, K., Long, J. D., & Griggs, C. (2009). Developmental changes in hypothalamus–pituitary–adrenal activity over the transition to adolescence:

Normative changes and associations with puberty. *Development and Psychopathology*, *21*(1), 69–85. https://doi.org/10.1017/S0954579409000054

Gusnard, D. A., Akbudak, E., Shulman, G. L., & Raichle, M. E. (2001). Medial prefrontal cortex and self-referential mental activity: Relation to a default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(7), 4259–4264. https://doi.org/10.1073/pnas.071043098

Hagler, D. J., Hatton, SeanN., Cornejo, M. D., Makowski, C., Fair, D. A., Dick, A. S., Sutherland, M. T., Casey, B. J., Barch, D. M., Harms, M. P., Watts, R., Bjork, J. M., Garavan, H. P., Hilmer, L., Pung, C. J., Sicat, C. S., Kuperman, J., Bartsch, H., Xue, F., … Dale, A. M. (2019). Image processing and analysis methods for the Adolescent Brain Cognitive Development Study. *NeuroImage*, *202*, 116091. https://doi.org/10.1016/j.neuroimage.2019.116091

Hare, T. A., Tottenham, N., Galvan, A., Voss, H. U., Glover, G. H., & Casey, B. J. (2008). Biological substrates of emotional reactivity and regulation in adolescence during an emotional go-nogo task. *Biological Psychiatry*, *63*(10), 927–934. https://doi.org/10.1016/j.biopsych.2008.03.015015

Hariri, A. R., Tessitore, A., Mattay, V. S., Fera, F., & Weinberger, D. R. (2002). The amygdala response to emotional stimuli: A comparison of faces and scenes. *NeuroImage*, *17*(1), 317–323. https://doi.org/10.1006/nimg.2002.1179

Harrell, F. E. (2023). *Hmisc: : Harrell Miscellaneous* [Computer software]. https://CRAN.R-project.org/package=Hmisc

Herman, J. P. (2020). Chapter 19—Corticolimbic stress regulatory circuits, hypothalamo–pituitary–adrenocortical adaptation, and resilience. In A. Chen (Ed.), *Stress Resilience* (pp. 291–309). Academic Press. https://doi.org/10.1016/B978-0-12-813983-7.00019-7

Herman, J. P. (2022). The neuroendocrinology of stress: Glucocorticoid signaling mechanisms. *Psychoneuroendocrinology*, *137*, 105641. https://doi.org/10.1016/j.psyneuen.2021.105641

Hooley, J. M., Dahlgren, M. K., Best, S. G., Gonenc, A., & Gruber, S. A. (2020). Decreased Amygdalar Activation to NSSI-Stimuli in People Who Engage in NSSI: A Neuroimaging Pilot Study. *Frontiers in Psychiatry*, *11*. https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00238

Hu, S., Ide, J. S., Zhang, S., & Li, C. R. (2016). The Right Superior Frontal Gyrus and Individual Variation in Proactive Control of Impulsive Response. *Journal of Neuroscience*, *36*(50), 12688–12696. https://doi.org/10.1523/JNEUROSCI.1175-16.2016

Huang, X., Rootes-Murdy, K., Bastidas, D. M., Nee, D. E., & Franklin, J. C. (2020). Brain Differences Associated with Self-Injurious Thoughts and Behaviors: A Meta-Analysis of Neuroimaging Studies. *Scientific Reports*, *10*(1), 2404. https://doi.org/10.1038/s41598-020-59490-6

Huffman, L. G., & Oshri, A. (2022). Continuity versus change in latent profiles of emotion regulation and working memory during adolescence. *Developmental Cognitive Neuroscience*, *58*, 101177. https://doi.org/10.1016/j.dcn.2022.101177

Kaess, M., Hille, M., Parzer, P., Maser-Gluth, C., Resch, F., & Brunner, R. (2012). Alterations in the neuroendocrinological stress response to acute psychosocial stress in adolescents engaging in nonsuicidal self-injury. *Psychoneuroendocrinology*, *37*(1), 157–161. https://doi.org/10.1016/j.psyneuen.2011.05.009

Kallianta, M.-D. K., Katsira, X. E., Tsitsika, A. K., Vlachakis, D., Chrousos, G., Darviri, C., &

Bacopoulou, F. (2021). Stress management intervention to enhance adolescent resilience: A randomized controlled trial. *EMBnet.Journal*, *26*, e967. https://doi.org/10.14806/ej.26.1.967

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., Williamson, D., & Ryan, N. (1997). Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): Initial Reliability and Validity Data. *Journal of the American Academy of Child & Adolescent Psychiatry*, *36*(7), 980–988. https://doi.org/10.1097/00004583-199707000-00021

Kaufman, J., Kobak, K., Birmaher, B., & Lacy, N. de. (2021). KSADS-COMP Perspectives on Child Psychiatric Diagnostic Assessment and Treatment Planning. *Journal of the American Academy of Child & Adolescent Psychiatry*, *60*(5), 540–542. https://doi.org/10.1016/j.jaac.2020.08.470

Kirschbaum, C., Pirke, K.-M., & Hellhammer, D. H. (1993). The 'Trier Social Stress Test' – A Tool for Investigating Psychobiological Stress Responses in a Laboratory Setting. *Neuropsychobiology*, *28*(1–2), 76–81. https://doi.org/10.1159/000119004

Klimes-Dougan, B., Begnel, E., Almy, B., Thai, M., Schreiner, M. W., & Cullen, K. R. (2019). Hypothalamic-pituitary-adrenal axis dysregulation in depressed adolescents with non-suicidal self-injury. *Psychoneuroendocrinology*, *102*, 216–224. https://doi.org/10.1016/j.psyneuen.2018.11.004

Klimes-Dougan, B., Eberly, L. E., Schreiner, M. W., Kurkiewicz, P., Houri, A., Schlesinger, A., Thomas, K. M., Mueller, B. A., Lim, K. O., & Cullen, K. R. (2014). Multilevel assessment of the neurobiological threat system in depressed adolescents: Interplay between the limbic system and hypothalamic–pituitary–adrenal axis. *Development and Psychopathology*, *26*(4pt2), 1321–1335. https://doi.org/10.1017/S0954579414001059

Klimes–Dougan, B., Hastings, P. D., Granger, D. A., Usher, B. A., & Zahn–Waxler, C. (2001). Adrenocortical activity in at-risk and normally developing adolescents: Individual differences in salivary cortisol basal levels, diurnal variation, and responses to social challenges. *Development and Psychopathology*, *13*(3), 695–719. https://doi.org/10.1017/S0954579401003157

Klonsky, E. D. (2007). The functions of deliberate self-injury: A review of the evidence. *Clinical Psychology Review*, *27*(2), 226–239. https://doi.org/10.1016/j.cpr.2006.08.002

Koechlin, E., & Hyafil, A. (2007). Anterior Prefrontal Function and the Limits of Human Decision-Making. *Science*, *318*(5850), 594–598. https://doi.org/10.1126/science.1142995

Krause-Utz, A., Frost, R., Winter, D., & Elzinga, B. M. (2017). Dissociation and Alterations in Brain Function and Structure: Implications for Borderline Personality Disorder. *Current Psychiatry Reports*, *19*(1), 6. https://doi.org/10.1007/s11920-017-0757-y

LeDoux, J. (2003). The emotional brain, fear, and the amygdala. *Cellular and Molecular Neurobiology*, *23*(4–5), 727–738. https://doi.org/10.1023/a:1025048802629

Leistner, C., & Menke, A. (2020). Chapter 4—Hypothalamic–pituitary–adrenal axis and stress. In R. Lanzenberger, G. S. Kranz, & I. Savic (Eds.), *Handbook of Clinical Neurology* (Vol. 175, pp. 55–64). Elsevier. https://doi.org/10.1016/B978-0-444-64123-6.00004-7

Li, W., Qin, W., Liu, H., Fan, L., Wang, J., Jiang, T., & Yu, C. (2013). Subregions of the human superior frontal gyrus and their connections. *NeuroImage*, *78*, 46–58. https://doi.org/10.1016/j.neuroimage.2013.04.011

Lichenstein, S. D., Roos, C., Kohler, R., Kiluk, B., Carroll, K. M., Worhunsky, P. D., Witkiewitz, K., & Yip, S. W. (2022). Identification and Validation of Distinct Latent

Neurodevelopmental Profiles in the Adolescent Brain and Cognitive Development Study. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *7*(4), 352–361. https://doi.org/10.1016/j.bpsc.2021.02.013

Linehan, M. M., & Kehrer, C. A. (1993). Borderline personality disorder. In *Clinical handbook of psychological disorders: A step-by-step treatment manual, 2nd ed* (pp. 396–441). The Guilford Press.

Liu, R. T. (2023). The epidemiology of non-suicidal self-injury: Lifetime prevalence, sociodemographic and clinical correlates, and treatment use in a nationally representative sample of adults in England. *Psychological Medicine*, *53*(1), 274–282. https://doi.org/10.1017/S003329172100146X

Luna, B. (2009). Developmental Changes in Cognitive Control through Adolescence. In P. Bauer (Ed.), *Advances in Child Development and Behavior* (Vol. 37, pp. 233–278). JAI. https://doi.org/10.1016/S0065-2407(09)03706-9

Magrini, A. (2022). Assessment of agricultural sustainability in European Union countries: A group-based multivariate trajectory approach. *AStA Advances in Statistical Analysis*, *106*(4), 673–703. https://doi.org/10.1007/s10182-022-00437-9

Masi, G., Pisano, S., Sesso, G., Mazzullo, C., Berloffa, S., Fantozzi, P., Narzisi, A., Placini, F., Valente, E., Viglione, V., & Milone, A. (2023). Persistent Non-Suicidal Self-Injury and Suicidality in Referred Adolescents: A Longitudinal Study Exploring the Role of Cyclothymic Temperament. *Brain Sciences*, *13*(5), Article 5. https://doi.org/10.3390/brainsci13050755

Mayo, L. M., Perini, I., Gustafsson, P. A., Hamilton, J. P., Kämpe, R., Heilig, M., & Zetterqvist, M. (2021). Psychophysiological and Neural Support for Enhanced Emotional Reactivity in Female Adolescents With Nonsuicidal Self-injury. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *6*(7), 682–691. https://doi.org/10.1016/j.bpsc.2020.11.004

McEwen, B. S. (2007). Physiology and neurobiology of stress and adaptation: Central role of the brain. *Physiological Reviews*, *87*(3), 873–904. https://doi.org/10.1152/physrev.00041.2006

Menken, M. S., Isaiah, A., Liang, H., Rivera, P. R., Cloak, C. C., Reeves, G., & Chang, L. (2022). Peer victimization (bullying) on mental health, behavioral problems, cognition, and academic performance in preadolescent children in the ABCD Study. *Frontiers in Psychology*, *13*. https://doi.org/10.3389/fpsyg.2022.925727

Menon, V. (2011). Large-scale brain networks and psychopathology: A unifying triple network model. *Trends in Cognitive Sciences*, *15*(10), 483–506. https://doi.org/10.1016/j.tics.2011.08.003

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: A network model of insula function. *Brain Structure and Function*, *214*(5), 655–667. https://doi.org/10.1007/s00429-010-0262-0

Mésidor, M., Rousseau, M.-C., O'Loughlin, J., & Sylvestre, M.-P. (2022). Does group-based trajectory modeling estimate spurious trajectories? *BMC Medical Research Methodology*, *22*(1), 194. https://doi.org/10.1186/s12874-022-01622-9

Mihailoff, G. A., & Haines, D. E. (2018). Chapter 25 - Motor System II: Corticofugal Systems and the Control of Movement. In D. E. Haines & G. A. Mihailoff (Eds.), *Fundamental Neuroscience for Basic and Clinical Applications (Fifth Edition)* (pp. 360-376.e1). Elsevier. https://doi.org/10.1016/B978-0-323-39632-5.00025-6

Monto, M. A., McRee, N., & Deryck, F. S. (2018). Nonsuicidal Self-Injury Among a Representative Sample of US Adolescents, 2015. *American Journal of Public Health*, *108*(8), 1042–1048. https://doi.org/10.2105/AJPH.2018.304470

Muehlenkamp, J. J., Xhunga, N., & Brausch, A. M. (2019). Self-injury Age of Onset: A Risk Factor for NSSI Severity and Suicidal Behavior. *Archives of Suicide Research*, *23*(4), 551–563. https://doi.org/10.1080/13811118.2018.1486252

Nagin, D. S. (2005). *Group-Based Modeling of Development:* Harvard University Press.

Nagin, D. S., Jones, B. L., Passos, V. L., & Tremblay, R. E. (2018). Group-based multi-trajectory modeling. *Statistical Methods in Medical Research*, *27*(7), 2015–2023. https://doi.org/10.1177/0962280216673085

Nair, A. U., Brekke-Riedl, J. A., DiMaggio-Potter, M. E., Carosella, K. A., Lasch, C., Brower, R., Papke, V., Reigstad, K., Klimes-Dougan, B., & Cullen, K. R. (2023). Clinical Trajectories in Adolescents with and without a History of Non-Suicidal Self-Injury: The BRIDGES Longitudinal Study. *Journal of Psychiatry and Brain Science*, *8*, e230007. https://doi.org/10.20900/jpbs.20230007

Narayanan, N. S., & Laubach, M. (2006). TOP-DOWN CONTROL OF MOTOR CORTEX ENSEMBLES BY DORSOMEDIAL PREFRONTAL CORTEX. *Neuron*, *52*(5), 921–931. https://doi.org/10.1016/j.neuron.2006.10.021

Nock, M. K., Holmberg, E. B., Photos, V. I., & Michel, B. D. (2007a). Self-Injurious Thoughts and Behaviors Interview: Development, reliability, and validity in an adolescent sample. *Psychological Assessment*, *19*(3), 309. https://doi.org/10.1037/1040-3590.19.3.309

Nock, M. K., Holmberg, E. B., Photos, V. I., & Michel, B. D. (2007b). Self-Injurious Thoughts and Behaviors Interview: Development, reliability, and validity in an adolescent sample. *Psychological Assessment*, *19*(3), 309. https://doi.org/10.1037/1040-3590.19.3.309

Paus, T., Keshavan, M., & Giedd, J. N. (2008). Why do many psychiatric disorders emerge during adolescence? *Nature Reviews Neuroscience*, *9*(12), 947–957. https://doi.org/10.1038/nrn2513

Perini, I., Gustafsson, P. A., Hamilton, J. P., Kämpe, R., Mayo, L. M., Heilig, M., & Zetterqvist, M. (2019). Brain-based Classification of Negative Social Bias in Adolescents With Nonsuicidal Self-injury: Findings From Simulated Online Social Interaction. *EClinicalMedicine*, *13*, 81–90. https://doi.org/10.1016/j.eclinm.2019.06.016

Perlman, S. B., & Pelphrey, K. A. (2011). Developing connections for affective regulation: Age-related changes in emotional brain connectivity. *Journal of Experimental Child Psychology*, *108*(3), 607–620. https://doi.org/10.1016/j.jecp.2010.08.006

Perry, N. B., Donzella, B., & Gunnar, M. R. (2022). Pubertal stress recalibration and later social and emotional adjustment among adolescents: The role of early life stress. *Psychoneuroendocrinology*, *135*, 105578. https://doi.org/10.1016/j.psyneuen.2021.105578

Petersen, A. C., Crockett, L., Richards, M., & Boxer, A. (1988). A self-report measure of pubertal status: Reliability, validity, and initial norms. *Journal of Youth and Adolescence*, *17*(2), 117–133. https://doi.org/10.1007/BF01537962

Plener, P. L., Bubalo, N., Fladung, A. K., Ludolph, A. G., & Lulé, D. (2012). Prone to excitement: Adolescent females with non-suicidal self-injury (NSSI) show altered cortical pattern to emotional and NSS-related material. *Psychiatry Research: Neuroimaging*, *203*(2), 146–152. https://doi.org/10.1016/j.pscychresns.2011.12.012

Plener, P. L., Schumacher, T. S., Munz, L. M., & Groschwitz, R. C. (2015). The longitudinal

course of non-suicidal self-injury and deliberate self-harm: A systematic review of the literature. *Borderline Personality Disorder and Emotion Dysregulation*, *2*(1), 2. https://doi.org/10.1186/s40479-014-0024-3

Plener, P. L., Zohsel, K., Hohm, E., Buchmann, A. F., Banaschewski, T., Zimmermann, U. S., & Laucht, M. (2017). Lower cortisol level in response to a psychosocial stressor in young females with self-harm. *Psychoneuroendocrinology*, *76*, 84–87. https://doi.org/10.1016/j.psyneuen.2016.11.009

Pollmann, A., Bates, K., & Fuhrmann, D. (2024). Making Connections: Neurodevelopmental Changes in Brain Connectivity After Adverse Experiences in Early Adolescence. *J Neurosci.*, *21*(44(8)). https://doi.org/10.1523/JNEUROSCI.0991-23.2023

Pruessner, J. C., Kirschbaum, C., Meinlschmid, G., & Hellhammer, D. H. (2003). Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology*, *28*(7), 916–931. https://doi.org/10.1016/S0306-4530(02)00108-7

R Core Team. (2023a). *R: A language and environment for statistical computing*. [Computer software]. R Foundation for Statistical Computing. https://www.R-project.org/

R Core Team. (2023b). *R: The R Stats Package*. https://stat.ethz.ch/R-manual/R-devel/library/stats/html/stats-package.html

Ripley, B., Venables, B., Hornik, K., Gebhardt, A., & Firth, D. (2024). *Package 'MASS'* [Computer software]. http://www.stats.ox.ac.uk/pub/MASS4/

Rosenberg, M. D., Martinez, S. A., Rapuano, K. M., Conley, M. I., Cohen, A. O., Cornejo, M. D., Hagler, D. J., Meredith, W. J., Anderson, K. M., Wager, T. D., Feczko, E., Earl, E., Fair, D. A., Barch, D. M., Watts, R., & Casey, B. J. (2020). Behavioral and Neural Signatures of Working Memory in Childhood. *The Journal of Neuroscience*, *40*(26), 5090–5104. https://doi.org/10.1523/JNEUROSCI.2841-19.2020

Ruocco, A. C., Rodrigo, A. H., McMain, S. F., Page-Gould, E., Ayaz, H., & Links, P. S. (2016). Predicting Treatment Outcomes from Prefrontal Cortex Activation for Self-Harming Patients with Borderline Personality Disorder: A Preliminary Study. *Frontiers in Human Neuroscience*, *10*. https://www.frontiersin.org/articles/10.3389/fnhum.2016.00220

Santamarina-Perez, P., Romero, S., Mendez, I., Leslie, S. M., Packer, M. M., Sugranyes, G., Picado, M., Font, E., Moreno, E., Martinez, E., Morer, A., Romero, M., & Singh, M. K. (2019). Fronto-Limbic Connectivity as a Predictor of Improvement in Nonsuicidal Self-Injury in Adolescents Following Psychotherapy. *Journal of Child and Adolescent Psychopharmacology*, *29*(6), 456–465. https://doi.org/10.1089/cap.2018.0152

Schneider, W., Eschman, A., & Zuccolotto, A. (2012). E-Prime User's Guide. *Pittsburgh: Psychology Software Tools, Inc.*

Silvers, J. A., Shu, J., Hubbard, A. D., Weber, J., & Ochsner, K. N. (2015). Concurrent and lasting effects of emotion regulation on amygdala response in adolescence and young adulthood. *Developmental Science*, *18*(5), 771–784. https://doi.org/10.1111/desc.12260

Slopen, N., McLaughlin, K. A., & Shonkoff, J. P. (2014). Interventions to Improve Cortisol Regulation in Children: A Systematic Review. *Pediatrics*, *133*(2), 312–326. https://doi.org/10.1542/peds.2013-1632

Somerville, L. H., Jones, R. M., & Casey, B. J. (2010). A time of change: Behavioral and neural correlates of adolescent sensitivity to appetitive and aversive environmental cues. *Brain and Cognition*, *72*(1), 124–133. https://doi.org/10.1016/j.bandc.2009.07.003

Spencer, R. L., & Deak, T. (2017). A users guide to HPA axis research. *Physiology & Behavior*,

178, 43–65. https://doi.org/10.1016/j.physbeh.2016.11.014
Stalder, T., & Kirschbaum, C. (2020). Cortisol. In M. D. Gellman (Ed.), *Encyclopedia of Behavioral Medicine* (pp. 561–567). Springer International Publishing. https://doi.org/10.1007/978-3-030-39903-0_171
Stevens, F. L., Hurley, R. A., Taber, K. H., Hurley, R. A., Hayman, L. A., & Taber, K. H. (2011). Anterior Cingulate Cortex: Unique Role in Cognition and Emotion. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *23*(2), 121–125. https://doi.org/10.1176/jnp.23.2.jnp121
Stroud, L. R., Foster, E., Papandonatos, G. D., Handwerger, K., Granger, D. A., Kivlighan, K. T., & Niaura, R. (2009). Stress response and the adolescent transition: Performance versus peer rejection stressors. *Development and Psychopathology*, *21*(1), 47–68. https://doi.org/10.1017/S0954579409000042
Swartz, J. R., Carrasco, M., Wiggins, J. L., Thomason, M. E., & Monk, C. S. (2014). Age-related changes in the structure and function of prefrontal cortex–amygdala circuitry in children and adolescents: A multi-modal imaging approach. *NeuroImage*, *86*, 212–220. https://doi.org/10.1016/j.neuroimage.2013.08.018
Sylvester, C. M., Yu, Q., Srivastava, A. B., Marek, S., Zheng, A., Alexopoulos, D., Smyser, C. D., Shimony, J. S., Ortega, M., Dierker, D. L., Patel, G. H., Nelson, S. M., Gilmore, A. W., McDermott, K. B., Berg, J. J., Drysdale, A. T., Perino, M. T., Snyder, A. Z., Raut, R. V., … Dosenbach, N. U. F. (2020). Individual-specific functional connectivity of the amygdala: A substrate for precision psychiatry. *Proceedings of the National Academy of Sciences*, *117*(7), 3808–3818. https://doi.org/10.1073/pnas.1910842117
Taborsky, B., English, S., Fawcett, T. W., Kuijper, B., Leimar, O., McNamara, J. M., Ruuskanen, S., & Sandi, C. (2021). Towards an Evolutionary Theory of Stress Responses. *Trends in Ecology & Evolution*, *36*(1), 39–48. https://doi.org/10.1016/j.tree.2020.09.003
Tang, W.-C., Lin, M.-P., You, J., Wu, J. Y.-W., & Chen, K.-C. (2021). Prevalence and psychosocial risk factors of nonsuicidal self-injury among adolescents during the COVID-19 outbreak. *Current Psychology (New Brunswick, N.J.)*, 1–10. https://doi.org/10.1007/s12144-021-01931-0
Thai, M., Schreiner, M. W., Mueller, B. A., Cullen, K. R., & Klimes-Dougan, B. (2021). Coordination between frontolimbic resting state connectivity and hypothalamic–pituitary–adrenal axis functioning in adolescents with and without depression. *Psychoneuroendocrinology*, *125*, 105123. https://doi.org/10.1016/j.psyneuen.2020.105123
Thijssen, S., Collins, P. F., & Luciana, M. (2022). Does pubertal stage mediate the association between family environment and structure and function of the amygdala-mPFC circuit? A replication study of the longitudinal ABCD cohort. *Developmental Cognitive Neuroscience*, *56*, 101120. https://doi.org/10.1016/j.dcn.2022.101120
Tottenham, N., Tanaka, J. W., Leon, A. C., McCarry, T., Nurse, M., Hare, T. A., Marcus, D. J., Westerlund, A., Casey, B., & Nelson, C. (2009). The NimStim set of facial expressions: Judgments from untrained research participants. *Psychiatry Research*, *168*(3), 242–249. https://doi.org/10.1016/j.psychres.2008.05.006
Uddin, L. Q. (2015). Salience processing and insular cortical function and dysfunction. *Nature Reviews Neuroscience*, *16*(1), Article 1. https://doi.org/10.1038/nrn3857
Ulrich-Lai, Y. M., & Herman, J. P. (2009). Neural regulation of endocrine and autonomic stress

responses. *Nature Reviews Neuroscience*, *10*(6), Article 6. https://doi.org/10.1038/nrn2647

van Oort, J., Tendolkar, I., Hermans, E. J., Mulders, P. C., Beckmann, C. F., Schene, A. H., Fernández, G., & van Eijndhoven, P. F. (2017). How the brain connects in response to acute stress: A review at the human brain systems level. *Neuroscience & Biobehavioral Reviews*, *83*, 281–297. https://doi.org/10.1016/j.neubiorev.2017.10.015

Volz, K. G., Schubotz, R. I., & Cramon, D. Y. von. (2005). Variants of uncertainty in decision-making and their neural correlates. *Brain Research Bulletin*, *67*(5), 403–412. https://doi.org/10.1016/j.brainresbull.2005.06.011

Wang, Y.-J., Li, X., Ng, C. H., Xu, D.-W., Hu, S., & Yuan, T.-F. (2022). Risk factors for non-suicidal self-injury (NSSI) in adolescents: A meta-analysis. *eClinicalMedicine*, *46*. https://doi.org/10.1016/j.eclinm.2022.101350

Wen, X., Shu, Y., Qu, D., Wang, Y., Cui, Z., Zhang, X., & Chen, R. (2023). Associations of bullying perpetration and peer victimization subtypes with preadolescent's suicidality, non-suicidal self-injury, neurocognition, and brain development. *BMC Medicine*, *21*(1), 141. https://doi.org/10.1186/s12916-023-02808-8

Westlund Schreiner, M., Frandsen, S. B., Molina, N. C., & Dillahunt, A. K. (2023). Bridging Brain and Behavior: Using Biology to Inform NSSI Interventions. In E. Lloyd-Richardson, I. Baetens, & J. Whitlock (Eds.), *The Oxford Handbook of Nonsuicidal Self-Injury* (p. 0). Oxford University Press. https://doi.org/10.1093/oxfordhb/9780197611272.013.19

Westlund Schreiner, M., Klimes-Dougan, B., Mueller, B. A., Eberly, L. E., Reigstad, K. M., Carstedt, P. A., Thomas, K. M., Hunt, R. H., Lim, K. O., & Cullen, K. R. (2017). Multi-modal neuroimaging of adolescents with non-suicidal self-injury: Amygdala functional connectivity. *Journal of Affective Disorders*, *221*, 47–55. https://doi.org/10.1016/j.jad.2017.06.004

Wiglesworth, A., Butts, J., Carosella, K. A., Mirza, S., Papke, V., Bendezú, J. J., Klimes-Dougan, B., & Cullen, K. R. (2023). Stress system concordance as a predictor of longitudinal patterns of resilience in adolescence. *Development and Psychopathology*, 1–18. https://doi.org/10.1017/S0954579423000731

Willner, P. (2016). The chronic mild stress (CMS) model of depression: History, evaluation and usage. *Neurobiology of Stress*, *6*, 78–93. https://doi.org/10.1016/j.ynstr.2016.08.002

Winklewski, P. J., Radkowski, M., Wszedybyl-Winklewska, M., & Demkow, U. (2017). Stress Response, Brain Noradrenergic System and Cognition. *Advances in Experimental Medicine and Biology*, *980*, 67–74. https://doi.org/10.1007/5584_2016_204

Wood, J. N., & Grafman, J. (2003). Human prefrontal cortex: Processing and representational perspectives. *Nature Reviews. Neuroscience*, *4*(2), 139–147. https://doi.org/10.1038/nrn1033

Woolrich, M. W., Ripley, B. D., Brady, M., & Smith, S. M. (2001). Temporal autocorrelation in univariate linear modeling of FMRI data. *NeuroImage*, *14*(6), 1370–1386. https://doi.org/10.1006/nimg.2001.0931

Yim, I. S., Granger, D. A., & Quas, J. A. (2010). Children's and adults' salivary alpha-amylase responses to a laboratory stressor and to verbal recall of the stressor. *Developmental Psychobiology*, *52*(6), 598–602. https://doi.org/10.1002/dev.20453

Yim, I. S., Quas, J. A., Rush, E. B., Granger, D. A., & Skoluda, N. (2015). Experimental manipulation of the Trier Social Stress Test-Modified (TSST-M) to vary arousal across

development. *Psychoneuroendocrinology*, *57*, 61–71. https://doi.org/10.1016/j.psyneuen.2015.03.021

Yurgelun-Todd, D. A., & Killgore, W. D. S. (2006). Fear-related activity in the prefrontal cortex increases with age during adolescence: A preliminary fMRI study. *Neuroscience Letters*, *406*(3), 194–199. https://doi.org/10.1016/j.neulet.2006.07.046

Zahid, Z., McMahon, L., & Lynch, M. (2022). Neural Activity Across the Dorsolateral Prefrontal Cortex and Risk for Suicidal Ideation and Self-Injury. *Archives of Suicide Research*, *26*(1), 187–207. https://doi.org/10.1080/13811118.2020.1779154

Zetterqvist, M., Jonsson, L. S., Landberg, Å., & Svedin, C. G. (2021). A potential increase in adolescent nonsuicidal self-injury during covid-19: A comparison of data from three different time points during 2011 – 2021. *Psychiatry Research*, *305*, 114208. https://doi.org/10.1016/j.psychres.2021.114208

Zhuo, H., Xiao, J., Tseng, W.-L., & Liew, Z. (2022). Developmental Milestones of Infancy and Associations with Later Childhood Neurodevelopmental Outcomes in the Adolescent Brain Cognitive Development (ABCD) Study. *Children*, *9*(10), Article 10. https://doi.org/10.3390/children9101424

Appendix A: Study 1 Supplement

Table A1. NSSI Reports by Time Point and Sex at Birth for the ABCD Study

Time Point	**NSSI Reported^ N(%)**	**First Report of NSSI by Sex at Birth**	
		Male	Female
Baseline^	485 (8.7%)	303	182
Time 1	256 (4.7%)	89	71
Time 2	390 (7.0%)	80	116
Time 3	392 (7.3%)	57	154
Time 4	434 (13.1%)	48	161

Note: NSSI=non-suicidal self-injury; ^Baseline NSSI represents lifetime engagement rather than past year

Table A2. Model Fit Statistics for Person-Centered Analyses for the ABCD Study

	Number of Groups				
Parameter	2	3	4	5	6
AIC	139235.6	199560.3	115330.9	126311.9	214857.3
BIC	139451.8	199915.5	115647.6	126922	215575.5
Posterior Probability	1, 0.9999949	0.9765862, 1, 0.9567834	.9999844, .9904772, .9998913	.9998776, 1, .9966239, .9999060, .9999961	.9987206, .9995686, .9999983, .9999875, .9991158, .9997990

Table A3. Comparison of Demographic Attributes by Group for the ABCD Study

Variable	**Test Statistic, p**
Race	$\chi 2=29$, p=0.4
Ethnicity	$\chi 2=1$, p=0.9
Family Income	$\chi 2=15$, p=0.9
Sex at Birth	$\chi 2=2$, p=0.7
Gender Identity	$\chi 2=7$, p=0.5
Transgender Identity	$\chi 2=9$, p=0.07
Baseline Age	F=3.59, p=0.01*
Age at Time 1	F=3.29, p=0.01*
Age at Time 2	F=2.51, p=0.04*
Age at Time 3	F=1.97, p=0.96
Age at Time 4	F=0.86, p=0.49
Scanner Platform	$\chi 2=26$, p=0.00***
Site ID	$\chi 2=191$, p=0.00***

Note: * indicates p<0.05, ** indicates p<0.01, *** indicates

Table A4. Pairwise Comparison of NSSI Engagement by Group for the ABCD Study

Group	**NSSI History N(%)**	**Pairwise Comparison With Group (p)**			
		1	2	3	4
1	535 (23.9%)	n/a			
2	128 (22.8%)	1.0	n/a		
3	315 (21.1%)	.5	1.0	n/a	
4	124 (21.8%)	1.0	1.0	1.0	n/a
5	159 (22.7%)	1.0	1.0	1.0	1.0

Note: NSSI=non-suicidal self-injury;* indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001

Table A5. Pairwise Comparison of Age at First Report of NSSI by Group for the ABCD Study

Group	**Age in Months Mean (SD)**	**Pairwise Comparison With Group (p)**			
		1	2	3	4
1	142.476 (21.328)	n/a			
2	133.500 (19.239)	0.048*	n/a		
3	136.908 (20.265)	0.003**	1.000	n/a	
4	137.718 (19.902)	0.174	1.000	1.000	n/a
5	138.522 (20.296)	0.667	1.000	1.000	1.000

Note: NSSI=non-suicidal self-injury; SD=standard deviation; * indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001

Table A6. Correlation Table of Variables in Baseline Analyses for the ABCD Group

	1	2	3	4	5	6
1. NSSI History	1.000					
2. Age at First Report of NSSI	NA	1.000				
3. Baseline Amygdala Reactivity	0.000	-0.016	1.000			
4. Baseline SF Reactivity	-0.027	-0.059*	0.389***	1.000		
5. Baseline CO-Amygdala RSFC	0.011	0.005	0.007	0.015	1.000	
6. Baseline Age	0.003	0.410***	-0.021	-0.029*	-0.026	1.000
7. Baseline CBCL Depression Score	0.190***	-0.148***	-0.018	-0.019	0.003	0.013

Note: NSSI=non-suicidal self-injury; NSSI History is coded such that Yes =1, No=0; SF=superior frontal; CO=cingulo-opercular; RSFC=resting state functional connectivity; CBCL=Child Behavior Checklist; * indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001

Table A7. Correlation Table of Variables in Slope Analyses for the ABCD Sample

	1	2	3	4	5	6	7	8	9	10
1. NSSI History	1.000									
2. Age at First Report of NSSI	NA	1.000								
3. Slope Amygdala Reactivity	0.001	0.026	1.000							
4. Slope SF Reactivity	0.008	0.055	0.383 ***	1.000						
5. Slope CO-Amygdala RSFC	-0.030 *	-0.026	-0.020	-0.014	1.000					
6. Baseline Age	0.003	0.410 ***	0.019	0.028 *	-0.064 ***	1.000				
7. Age at Time 1	0.007	0.414 ***	0.021	0.030 *	-0.061 ***	0.985 ***	1.000			
8. Age at Time 2	-0.005	0.390 ***	0.015	0.021	-0.060 ***	0.945 ***	0.937 ***	1.000		
9. Age at Time 3	0.004	0.403 ***	0.015	0.026	-0.061 ***	0.960 ***	0.953 ***	0.946 ***	1.000	
10. Age at Time 4	0.014	0.386 ***	0.024	0.028	-0.051 **	0.954 ***	0.950 ***	0.942 ***	0.943 ***	1.000
11. CBCL Depression Score Mean	0.273 ***	-0.041	0.024	0.017	-0.005	0.036 **	0.036 **	0.030 *	0.044 **	0.028

Note: NSSI=non-suicidal self-injury; NSSI History is coded such that Yes =1, No=0; SF=superior frontal; CO=cingulo-opercular; RSFC=resting state functional connectivity; CBCL=Child Behavior Checklist; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

Time Point of First Report

Methods

Analyses mirroring those investigating age at the time of the first report of NSSI were conducted using the time point of that report. The results of these analyses are below.

Results

Table A8. Time Point of First Report of NSSI Engagement by Group for the ABCD Study

	Without CBCL Depression Score	**With CBCL Depression Score**
Coefficient	**Beta (SE)**	**Beta (SE)**
Intercept	-1.428 (0.662)*	-1.457 (0.647)*
Group 2 Membership	0.016 (0.103)	-0.025 (0.101)
Group 3 Membership	-0.1 (0.065)	-0.096 (0.064)
Group 4 Membership	0.068 (0.109)	0.036 (0.107)
Group 5 Membership	-0.012 (0.087)	-0.057 (0.085)
Sex at Birth	0.515 (0.051)***	0.506 (0.05)***
Baseline Age	-0.037 (0.017)*	-0.036 (0.017)*
Age Time 2	0.008 (0.014)	0.006 (0.014)
Age Time 4	0.031 (0.011)**	0.031 (0.011)**
Scanner Platform: Phillips	-0.224 (0.104)*	-0.139 (0.102)
Scanner Platform: Siemens	-0.051 (0.059)	-0.024 (0.058)
CBCL Depression Score		0.163 (0.014)***

Note: NSSI=non-suicidal self-injury; SE=standard error; CBCL=Child Behavior Checklist; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

These results indicate no significant relationship between group membership and the time point at which NSSI was first reported. Female sex at birth was associated with reporting engagement at later time points. Younger age at Baseline and older age at Time 4 were associated with reporting engagement at later time points. A higher CBCL Depression score was associated with later reporting of NSSI engagement.

Post-Hoc Group Comparisons

Methods

Post-hoc analyses were conducted to understand the differences between groups on various metrics.

Measures

Participant Pubertal Stage: Parent/guardian report of their child's pubertal stage at Time 2 was found using the sum score for their assigned sex at birth on the Pubertal Development Scale (Cheng et al., 2021; Petersen et al., 1988).

Sex at Birth: Parents/guardians reported on the participant's sex at birth in demographic surveys.

Depression, Externalizing Issues, Attention Difficulties: Parents/guardians of participants completed the Child Behavior Checklist (CBCL; Achenbach & Ruffle, 2000) at each time point. The CBCL assesses for various externalizing and internalizing problems in children and adolescents. The pre-calculated Depression DSM-5 Scale t-score (Achenbach, 2013) at Time 2 was used to index the severity of depressive symptoms, with higher scores indicating heightened depressive symptom severity. The pre-calculated Externalizing Syndromes Scale was used to capture the degree of externalizing issues, with higher scores indicating heightened difficulties (Achenbach, 2013). The pre-calculated Attention Syndromes Scale was used to capture the degree of attention difficulties, with higher scores indicating heightened difficulties (Achenbach, 2013).

Number of Traumas: Parent-reported responses on the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children-Computerized Version (Barch et al., 2018; Kaufman et al., 1997, 2021) was used to measure the number of experiences in which the participant experienced or was faced with threatened harm to themselves or others. Each type of trauma endorsed was coded as "1" if endorsed and "0" if not endorsed. The sum of the number of types of traumas experienced was found.

Scan Date Relative to the Onset of the COVID-19 Pandemic: The date of the MRI scan was categorized as either "before" or "after" the onset of the COVID-19 pandemic (here operationalized as 3/1/2020).

Motion: The pre-tabulated average framewise displacement for each scan type (task fMRI and RSFC) was used to measure the level of motion during MRI segments for Time 2 (Hagler et al., 2019).

Quality Control Inclusion Score: The binary recommendation for inclusion for each scan type was used to index the quality of the participant's MRI scans, with "0" indicating a recommendation to exclude and "1" indicating a recommendation to include (Hagler et al., 2019). The sum of the number of scans indicated for inclusion was found for each participant to index the overall quality of the participant's MRI scans across time points.

Site Switching: A binary variable was created to indicate whether participants were scanned at different sites across the three imaging time points such that "0" indicated that all site IDs were the same and "1" indicated that at least one site differed from the others.

Analytic Plan

Pairwise comparisons assessed whether the groups differed on the aforementioned metrics. T-tests with a Bonferroni correction were conducted for dimensional metrics (pubertal status, CBCL Depression score, CBCL Externalizing Syndrome Score, CBCL Attention Syndrome Score, number of traumas, and movement). Chi-Square tests were conducted for binary metrics (sex at birth, scan date relative to the onset of the COVID-19 pandemic, and site switching). Results are shown in Table B9.

Results

Table A9. Post-Hoc Group Comparisons for the ABCD Study

Measure	**Outcome**
Demographic	
Pubertal Status	No significant differences between groups
Sex at Birth	No significant differences between groups
Psychopathology	
Depression	No significant differences between groups
Externalizing Difficulties	Group 2 significantly higher than Group 1 (p=0.007) Group 2 significantly higher than Group 1 (p=0.006)
Attention Issues	Group 2 significantly higher than Group 1 (p=0.004) Group 2 significantly higher than Group 1 (p=0.016)
Number of Traumas	No significant differences between groups
Scan Attributes	
Scan Date Relative to the Onset of the COVID-19 Pandemic	Group 1 had a significantly higher proportion collected prior to the onset of the COVID-19 pandemic compared to Group 2 (p=0.000), Group 3 (p=0.000), Group 4 (p=0.000), and Group 5 (p=0.000).
Motion, Task fMRI	Group 2 had significantly higher motion compared to Group 1 (p=0.000), Group 3 (p=0.010), and Group 4 (p=0.000). Group 5 had significantly higher motion than Group 1 (p=0.020) and Group 4 (0.030).
Motion, RSFC	Group 2 had significantly higher motion compared to Group 1 (p=0.000), Group 3 (p=0.001), Group 4 (p=0.000), and Group 5 (p=0.018). Group 3 has significantly higher motion compared to group 4 (p=0.023) Group 5 had significantly higher motion compared to Group 4 (0.028).
Quality Control	No significant differences between groups
Site Switching	No significant differences between groups

Note: fMRI=functional magnetic resonance imaging, RSFC=Resting state functional connectivity

NSSI Engagement Across Time Points

Methods

Aim 2: Multilevel binomial logistic regressions were conducted using the "lme4" package in R (Bates et al., 2015) in which past year engagement in NSSI was the dependent variable, group membership and year were the independent variable, and individual ID number was a random intercept were conducted to assess if any neurodevelopmental trajectory groups were associated with NSSI engagement across time points. Group 1 served as the reference group for these analyses.

Aim 3: Multilevel binomial logistic regressions were conducted using the "lme4" package in R (Bates et al., 2015), in which past-year engagement in NSSI was the dependent variable, group membership and year were the independent variables, and individual ID number was a random intercept to assess whether any of the Baseline brain and HPA axis metrics were related to engagement in NSSI across time points.

Results

Table A10. NSSI Engagement Across Time Points by Group for the ABCD Study

	Without CBCL Depression Score	**With CBCL Depression Score**
Coefficient	**OR (CI)**	**OR (CI)**
Intercept	0.018 (0.012, 0.026)***	0.011 (0.008, 0.016)***
Group 2 Membership	1.118 (0.817, 1.529)	1.003 (0.880, 1.144)
Group 3 Membership	0.972 (0.778, 1.215)	1.002 (0.751, 1.338)
Group 4 Membership	1.011 (0.739, 1.382)	0.977 (0.796, 1.199)
Group 5 Membership	1.013 (0.760, 1.351)	0.961 (0.719, 1.283)
Sex at Birth	1.637 (1.369, 1.957)***	0.944 (0.724, 1.230)***
Time Point	0.935 (0.813, 1.076)	1.591 (1.349, 1.875)
Age	1.391 (1.139, 1.698)**	1.246 (1.035, 1.499)*
Scanner Platform: Phillips	0.581 (0.402, 0.839)**	0.696 (0.494, 0.980)*
Scanner Platform: Siemens	0.743 (0.604, 0.914)**	0.821 (0.679, 0.993)*
Mean CBCL Depression Score		1.479 (1.420, 1.541)***

Note: NSSI=non-suicidal self-injury; OR=Odds Ratio; CI=Confidence Interval; CBCL=Child Behavior Checklist; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

These results indicate no significant relationship between group membership and NSSI engagement across time points. Female sex at birth was associated with reporting greater engagement across time points. Older age was also associated with greater engagement across time points. A higher CBCL Depression score was also associated with greater engagement across time.

Table A11. Time point of First Report of NSSI Engagement and Baseline of Brain Metrics for the ABCD Study

	Without CBCL Depression Score	**With CBCL Depression Score**
Coefficient	**Beta (SE)**	**Beta (SE)**
Intercept	-0.47 (0.306)	-0.523 (0.305)
Baseline Amygdala Reactivity	0.096 (0.063)	0.104 (0.063)
Baseline SF Reactivity	-0.227 (0.09)*	-0.224 (0.089)*
Baseline CO-Amygdala RSFC	0.333 (0.202)	0.321 (0.201)
Sex at Birth	0.372 (0.038)***	0.381 (0.037)***
Baseline Age	0.005 (0.002)*	0.005 (0.002)
Scanner Platform: Phillips	-0.218 (0.078)**	-0.2 (0.077)*
Scanner Platform: Siemens	-0.151 (0.045)**	-0.147 (0.045)**
Baseline CBCL Depression Score		0.062 (0.01)***

Note: NSSI=non-suicidal self-injury; SE=standard error; SF=superior frontal; CO=cingulo-opercular; RSFC=resting state functional connectivity; CBCL=Child Behavior Checklist; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

Analyses investigating the time point at which NSSI was first reported in relation to Baseline brain metrics indicate that lower Baseline SF reactivity is related to later time points at which NSSI is first reported. Female sex at birth was associated with later time points of first engagement in NSSI, and higher Baseline age was also associated with later time points at which NSSI was first endorsed. A higher Baseline CBCL Depression score was associated with a later time point at which NSSI engagement was first reported.

Table A12. Time Point of First Report of NSSI Engagement and Slope of Brain Metrics for the ABCD Study

	Without CBCL Depression Score	**With CBCL Depression Score**
Coefficient	**Beta (SE)**	**Beta (SE)**
Intercept	-1.79 (0.689)**	-1.801 (0.673)**
Slope of Amygdala Reactivity	0.093 (2.053)	-0.655 (2.011)
Slope of SF Reactivity	5.882 (3.153)	5.806 (3.088)
Slope of CO-Amygdala RSFC	-16.524 (8.091)*	-16.075 (7.921)*
Sex at Birth	0.52 (0.053)***	0.508 (0.052)***
Baseline Age	-0.037 (0.018)*	-0.036 (0.017)*
Age Time 2	0.009 (0.015)	0.007 (0.015)
Age Time 4	0.029 (0.011)*	0.029 (0.011)**
Scanner Platform: Phillips	-0.279 (0.109)*	-0.193 (0.107)
Scanner Platform: Siemens	-0.069 (0.061)	-0.039 (0.06)
Mean CBCL Depression Score		0.161 (0.014)***

Note: NSSI=non-suicidal self-injury; SE=standard error; SF=superior frontal; CO=cingulo-opercular; RSFC=resting state functional connectivity; CBCL=Child Behavior Checklist; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

Analyses investigating the time point at which NSSI was first reported in relation to the slope of change in brain metrics indicate that a more significant increase in CO-Amygdala RSFC was associated with earlier age at the first report of NSSI. Female sex at birth was associated with the first report of NSSI occurring at later time points. Lower Baseline age and higher Time 4 age were associated with younger age at the first report of NSSI in this analysis. Finally, higher CBCL Depression scores were associated with older age at the first report of NSSI.

Table A13. NSSI Engagement Across Time Points and Baseline Brain Metrics for the ABCD Study

	Without CBCL Depression Score	**With CBCL Depression Score**
Coefficient	**OR (CI)**	**OR (CI)**
Intercept	0.010 (0.006, 0.017)***	0.008 (0.005, 0.013)***
time point	0.900 (0.767, 1.055)	0.928 (0.797, 1.080)
Baseline Amygdala Reactivity	1.235 (0.881, 1.731)	1.283 (0.934, 1.763)
Baseline SF Reactivity	0.698 (0.430, 1.134)	0.717 (0.455, 1.132)
Baseline CO-Amygdala RSFC	1.918 (0.643, 5.717)	1.815 (0.647, 5.095)
Sex at Birth	1.620 (1.323, 1.984)***	1.714 (1.415, 2.077)***
Baseline Age	1.513 (1.207, 1.898)***	1.440 (1.162, 1.785)**
Scanner Platform: Phillips	0.537 (0.350, 0.826)**	0.600 (0.399, 0.901)*
Scanner Platform: Siemens	0.695 (0.547, 0.882)**	0.714 (0.570, 0.895)**
Baseline CBCL Depression Score		1.330 (1.270, 1.394)***

Note: NSSI=non-suicidal self-injury; OR=Odds Ratio, CI=Confidence Interval; SF=superior frontal; CO=cingulo-opercular; RSFC=resting state functional connectivity; CBCL=Child Behavior Checklist; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

Table A14. NSSI Engagement Across Time Points and Slope Brain Metrics for the ABCD Study

	Without CBCL Depression Score	**With CBCL Depression Score**
Coefficient	**OR (CI)**	**OR (CI)**
Intercept	0.010 (0.006, 0.017)***	0.007 (0.004, 0.010)***
time point	0.913 (0.783, 1.065)	0.983 (0.852, 1.133)
Slope of Amygdala Reactivity	0.039 (0.000, 38.782)	0.004 (0.000, 1.946)
Slope of SF Reactivity	7.546 (0.000, 219641.306)	4.476 (0.000, 45619.486)
Slope of CO-Amygdala RSFC	2.007 (0.704, 5.725)	1.626 (0.625, 4.232)
Sex at Birth	1.583 (1.302, 1.925)***	1.537 (1.286, 1.838)***
Age	1.469 (1.181, 1.828)**	1.310 (1.071, 1.602)**
Scanner Platform: Phillips	0.546 (0.359, 0.831)**	0.665 (0.451, 0.978)*
Scanner Platform: Siemens	0.748 (0.594, 0.943)*	0.827 (0.670, 1.020)
Mean CBCL Depression Score		1.484 (1.419, 1.552)***

Note: NSSI=non-suicidal self-injury; OR=Odds Ratio, CI=Confidence Interval; SF=superior frontal; CO=cingulo-opercular; RSFC=resting state functional connectivity; CBCL=Child Behavior Checklist; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

Analyses investigating NSSI engagement across time points in relation to Baseline brain metrics indicate no significant relationships. Female sex at birth, older age at Baseline, and higher CBCL Depression score were associated with greater engagement across time. Similarly, analyses investigating NSSI engagement across time points in relation to slope brain metrics indicate no significant relationships. Again, female sex at birth, older age at Baseline, and higher CBCL Depression score were associated with greater engagement across time.

Data Source Acknowledgement

Data used in the preparation of this project were obtained from the Adolescent Brain Cognitive Development (ABCD) Study (https://abcdstudy.org), held in the NIMH Data Archive (NDA). This is a multisite, longitudinal study designed to recruit more than 10,000 children ages 9-10 and follow them over 10 years into early adulthood. The ABCD Study® is supported by the National Institutes of Health and additional federal partners under award numbers U01DA041048, U01DA050989, U01DA051016, U01DA041022, U01DA051018, U01DA051037, U01DA050987, U01DA041174, U01DA041106, U01DA041117, U01DA041028, U01DA041134, U01DA050988, U01DA051039, U01DA041156, U01DA041025, U01DA041120, U01DA051038, U01DA041148, U01DA041093, U01DA041089, U24DA041123, U24DA041147. A full list of supporters is available at https://abcdstudy.org/federal-partners.html. A listing of participating sites and a complete listing of the study investigators can be found at https://abcdstudy.org/consortium_members/. ABCD consortium investigators designed and implemented the study and/or provided data but did not necessarily participate in the analysis or writing of this report. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or ABCD consortium investigators. The ABCD data used in this report came from release 5.1 (DOI: 10.15154/z563-zd24). DOIs can be found at https://dx.doi.org/10.15154/z563-zd24.

Appendix B: Study 2 Supplement

Table B1. Multi-Trajectory Model Fit Statistics with HPA Axis Reactivity for the BRIDGES Study

	Number of Groups				
Parameter	2	3	4	5	6
AIC	3341.179	3241.442	3128.799	3102.765	3006.396
BIC	3458.737	3413.58	3384.907	3426.048	3396.854
Posterior Probability	0.9809371, 0.9513227	0.9755385, 0.9412246, 0.9590261	0.9862859, 0.9680394, 0.9677618, 0.9606515	0.9838462, 0.9841918, 0.9391923, 0.9824671, 0.9690147	0.9658071, 0.9711420, 0.9793286, 0.9582167, 0.9772542, 0.9931604

Table B2. Multi-Trajectory Model Fit Statistics without HPA Axis Reactivity for the BRIDGES Study

	Number of Groups				
Parameter	2	3	4	5	6
AIC	4518.306	4471.867	4352.167	4278.404	4220.912
BIC	4694.642	4748.967	4730.03	4748.634	4783.508
Posterior Probability	0.9956995, 0.9532082	0.9551059, 0.9570357, 0.9870198	0.9870257, 0.9706624, 0.9475382, 0.9924259	0.9798101, 0.9851448, 0.9840318, 0.9801988, 0.9923870	0.9516468, 0.9880006, 0.9842573, 0.9789493, 0.9774500, 0.9835027

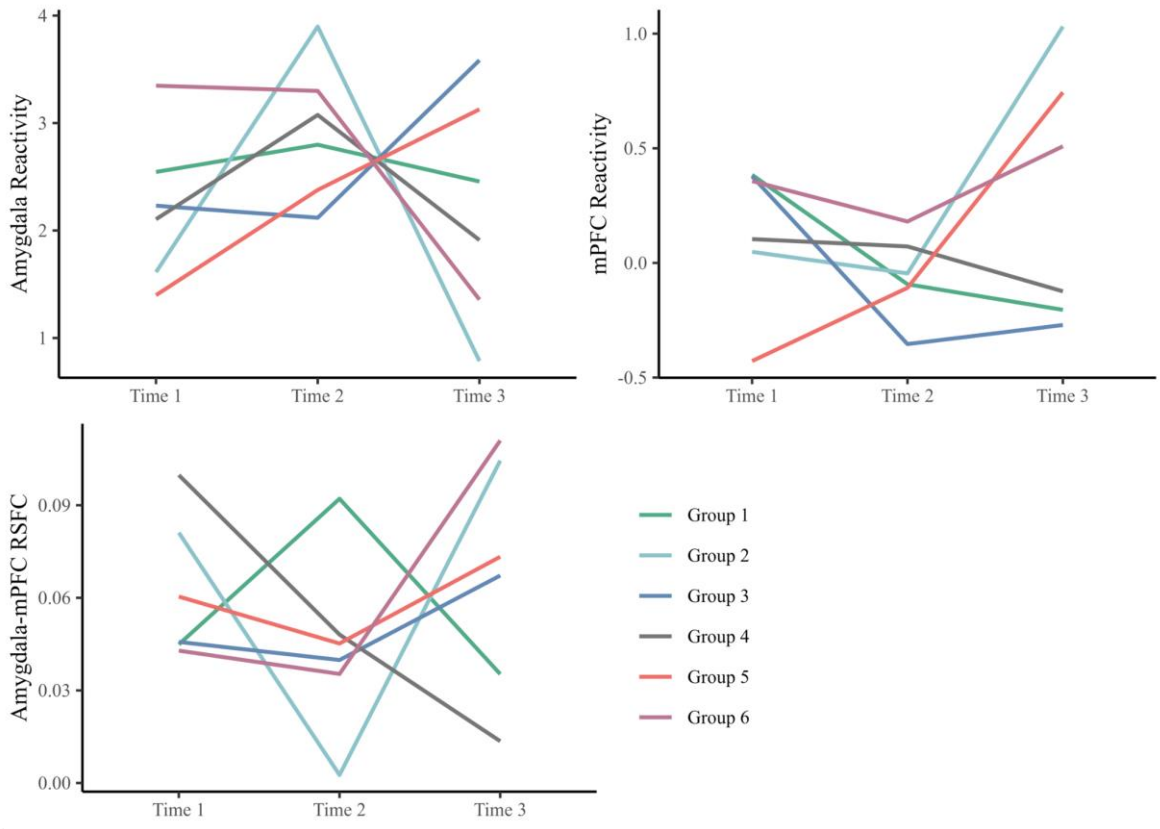
Table B3. Pairwise Comparison of NSSI Engagement History by Group with HPA Axis Reactivity for the BRIDGES Study

		Pairwise Comparison With Group (p)				
Group	**NSSI History N (%)**	1	2	3	4	5
1	20 (87.0%)	n/a				
2	24 (82.8%)	1.0	n/a			
3	20 (62.5%)	0.6	1.0	n/a		
4	19 (73.1%)	1.0	1.0	1.0	n/a	
5	21 (70.0%)	1.0	1.0	1.0	1.0	n/a
6	18 (75.0%)	1.0	1.0	1.0	1.0	1.0

Note: NSSI=non-suicidal self-injury; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

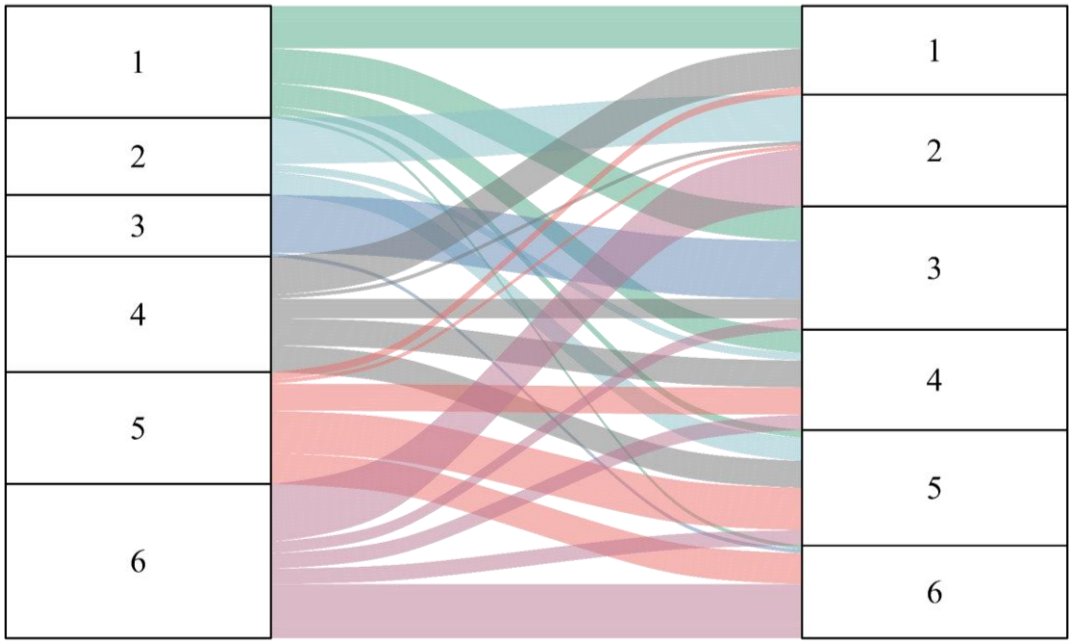
In the 6 group solution without HPA axis reactivity, as shown in Figure B1, Group 1 (n=29) is characterized by stable amygdala reactivity, slightly decreased mPFC reactivity, and increased then decreased amygdala-mPFC RSFC demonstrated unexpected changes across time. Group 2 (n=20) is characterized by increased then decreased amygdala reactivity, dramatically increased mPFC reactivity, and decreased then increased amygdala-mPFC RSFC, resembling the hypothesized Heightened Frontal Regulatory Control trajectory. Group 3 (n=16) is characterized by increased amygdala reactivity, decreased mPFC reactivity, and increased amygdala-mPFC RSFC, in part resembled the hypothesized Blunted Frontal Regulatory Control trajectory, though it was expected that amygdala-mPFC RSFC would decrease. Group 4 (n=30) was characterized by increased then decreased amygdala reactivity, stable mPFC reactivity, and dramatically decreased amygdala-mPFC RSFC, demonstrating unexpected changes across time. Group 5 (n=29) is characterized by increased amygdala reactivity, dramatically increased mPFC reactivity, and slightly increased amygdala-mPFC RSFC, which was also unexpected but may represent a breakdown in frontal regulatory control where the increase in mPFC and amygdala-mPFC RSFC is not properly dampening amygdala reactivity. Group 6 (n=40) is characterized by dramatically decreased amygdala reactivity, slightly increased mPFC reactivity, and dramatically increased amygdala-mPFC RSFC. It was the largest group and nearly resembles the hypothesized pattern of the Normative Development group, though it was hypothesized that amygdala-mPFC RSFC would decrease over time. Groups were examined to determine if differences existed in demographic attributes. Groups did not differ significantly on race (χ^2=29, p=0.3), ethnicity (χ^2=4, p=0.5), family income (χ^2=21, p=0.4), age at Time 1 (F=1.59, p=0.17), age at Time 2 (F=1.3, p=0.27), age at Time 3 (F=2.19, p=0.06), or psychotropic medication status (χ^2=5, p=0.4).

Figure B1. Person-Centered Derived Groups without HPA Axis Reactivity for the BRIDGES Study



Note: mPFC=medial prefrontal cortex; RSFC=Resting State Functional Connectivity

Figure B2. Membership Overlap Between Person-Centered Derived Groups with and without HPA Axis Reactivity for the BRIDGES Study



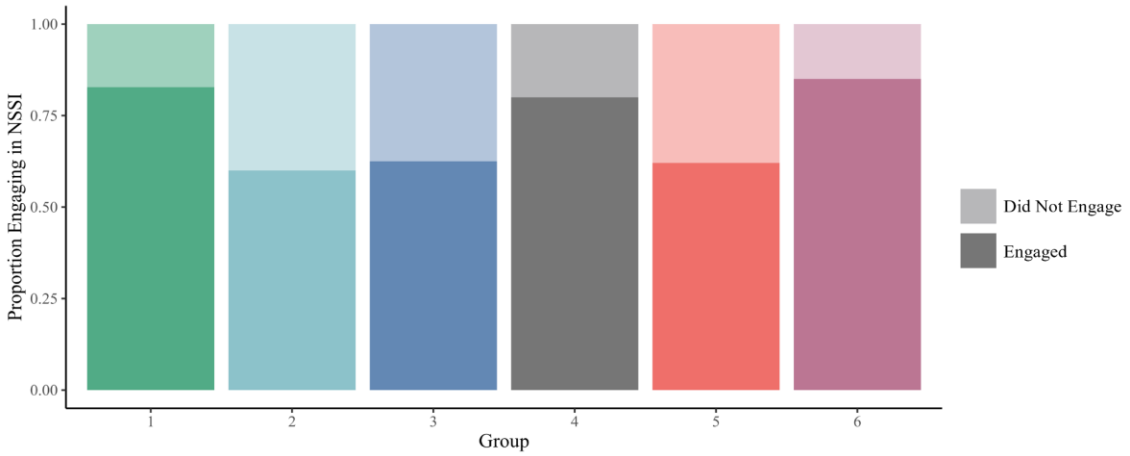
Note: The left column represents the groups without HPA axis reactivity; the right column represents the groups with HPA axis reactivity.

Table B4. History of NSSI Engagement by Group without HPA Axis Reactivity for the BRIDGES Study

	Without BDI Score	**With BDI Score**
Coefficient	**OR (CI)**	**OR (CI)**
Intercept	0.050 (0.000, 8.282)	0.020 (0.000, 10.305)
Group 2 Membership	0.256 (0.060, 0.996)	0.168 (0.027, 0.926)
Group 3 Membership	0.340 (0.079, 1.392)	0.090 (0.011, 0.604)
Group 4 Membership	0.785 (0.198, 2.985)	0.519 (0.103, 2.461)
Group 5 Membership	0.310 (0.082, 1.045)	0.205 (0.039, 0.942)
Group 6 Membership	0.976 (0.244, 3.756)	0.627 (0.124, 3.023)
Time 1 Age	0.829 (0.232, 2.778)	0.457 (0.049, 3.404)
Time 2 Age	1.429 (0.345, 6.239)	2.370 (0.238, 28.861)
Time 3 Age	1.103 (0.531, 2.379)	1.095 (0.418, 2.954)
BDI Score		1.249 (1.159, 1.374)***

Note: OR=Odds Ratio; CI=Confidence Interval; BDI=Beck Depression Inventory

Figure B3. History of NSSI Engagement Group without HPA Axis Reactivity for the BRIDGES Study



Note: NSSI=non-suicidal self-injury

Table B5. Pairwise Comparison of History of NSSI Engagement without HPA Axis Reactivity for the BRIDGES Study

		Pairwise Comparison With Group (p)				
Group	**NSSI History N (%)**	1	2	3	4	5
1	24 (82.8%)	n/a				
2	12 (60.0%)	1.0	n/a			
3	10 (62.5%)	1.0	1.0	n/a		
4	24 (80.0%)	1.0	1.0	1.0	n/a	
5	18 (62.1%)	1.0	1.0	1.0	1.0	n/a
6	34 (85.0%)	1.0	0.5	1.0	1.0	0.5

Note: NSSI=non-suicidal self-injury; * indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001

Table B6. Pairwise Comparison of Severity of NSSI Engagement with HPA Axis Reactivity for the BRIDGES Study

Group	**No NSSI N(%)**	**Mild/Moderate NSSI N(%)**	**Severe NSSI N(%)**	**Pairwise Comparison With Group (p)**				
				1	2	3	4	5
1	3 (13.0%)	9 (39.1%)	11 (47.8%)	n/a				
2	5 (17.2%)	11 (37.9%)	13 (44.8%)	1.0	n/a			
3	12 (37.5%)	13 (40.6%)	7 (21.9%)	0.3	0.4	n/a		
4	7 (26.9%)	8 (30.8%)	11 (42.3%)	1.0	1.0	1.0	n/a	
5	9 (30.0%)	13 (43.3%)	8 (26.7%)	1.0	1.0	1.0	1.0	n/a
6	6 (25.0%)	10 (41.7%)	8 (33.3%)	1.0	1.0	1.0	1.0	1.0

Note: NSSI=non-suicidal self-injury; * indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001

Table B7. Severity of NSSI Engagement by Group without HPA Axis Reactivity for the BRIDGES Study

	Without BDI Score	**With BDI Score**
Coefficient	**OR (CI)**	**OR (CI)**
Group 2 Membership	0.317 (-2.331, 0.00907)	0.256 (-2.609, -0.149)*
Group 3 Membership	0.299 (-2.402, -0.04167)*	0.162 (-3.136, -0.564)**
Group 4 Membership	0.419 (-1.847, 0.08391)	0.401 (-1.948, 0.095)
Group 5 Membership	0.433 (-1.883, 0.19075)	0.322 (-2.248, -0.046)*
Group 6 Membership	0.584 (-1.490. 0.39393)	0.430 (-1.870, 0.151)
Time 1 Age	0.441 (-1.801, 0.14403)	0.254 (-2.504, -0.315)*
Time 2 Age	3.695 (0.184, 2.46335)	7.217 (0.734, 3.306)**
Time 3 Age	0.793 (-0.795, 0.32514)	0.647 (-1.047, 0.161)
BDI Score		1.094 (0.061, 0.121)***

Note: NSSI=non-suicidal self-injury; BDI=Beck Depression Inventory; SE=standard error; * indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001

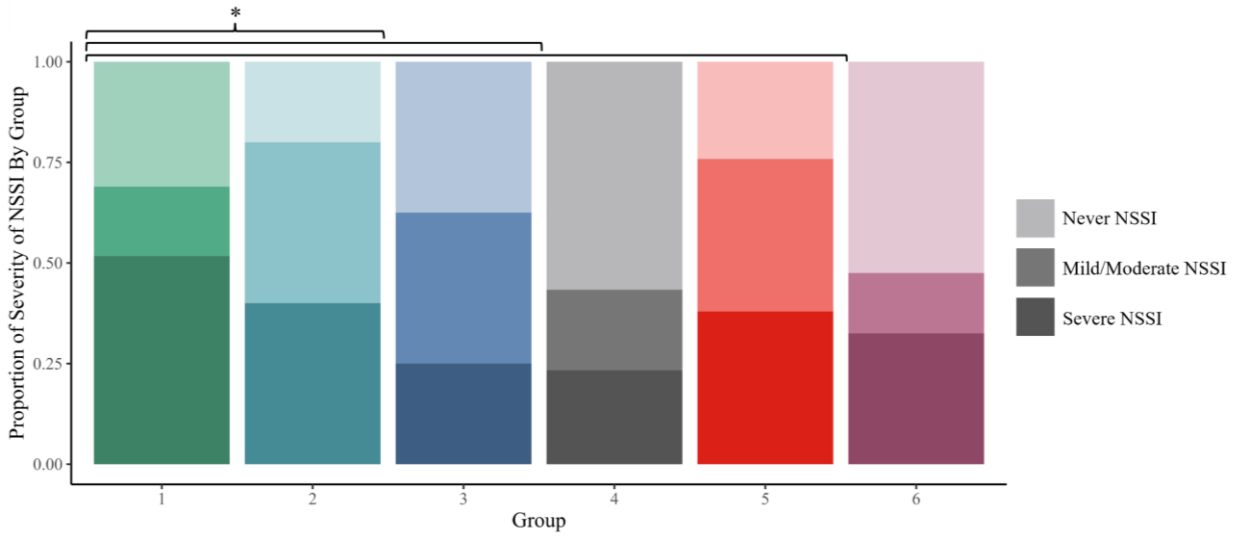
Table B8. Pairwise Comparison of Severity of NSSI Engagement by Group without HPA Axis Reactivity for the BRIDGES Study

Group	**No NSSI N(%)**	**Mild/Moderate NSSI N (%)**	**Severe NSSI N(%)**	**Pairwise Comparison With Group (p)**				
				1	2	3	4	5
1	5 (17.2%)	9 (31.0%)	15 (51.7%)	n/a				
2	8 (40.0%)	4 (20.0%)	8 (40.0%)	1.0	n/a			
3	6 (37.5%)	6 (37.5%)	4 (25.0%)	0.8	1.0	n/a		
4	6 (20.0%)	17 (56.7%)	7 (23.3%)	1.0	1.0	1.0	n/a	
5	11 (37.9%)	7 (24.1%)	11 (37.9%)	1.0	1.0	1.0	1.0	n/a
6	6 (15.0%)	21 (52.5%)	13 (32.5%)	1.0	1.0	1.0	1.0	1.0

Note: NSSI=non-suicidal self-injury; * indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001

Analyses examining the relationship between group membership without HPA axis reactivity and the severity of NSSI engagement demonstrated significant differences between groups. Group 3 was associated with decreased severity compared to Group 1 in the model with and without BDI score as a covariate. Groups 2 and 5 were also associated with decreased severity compared to Group 1, but only when the BDI score was included as a covariate. A higher Time 2 age was significantly related to heightened severity in the model both with and without a BDI score as a covariate, while a lower Time 1 age was associated with greater severity in the model with a BDI score included as a covariate. Higher BDI scores were also found to be associated with greater NSSI severity.

Figure B4. Severity of NSSI Engagement by Group without HPA Axis Reactivity for the BRIDGES Study



Note: NSSI=non-suicidal self-injury; * indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001; Noted differences are significant when BDI score is included as a covariate; the only difference between Groups 1 and 3 are significant without BDI score as a covariate

Table B9. Pairwise Comparison of Number of Lifetime Episodes of NSSI with HPA Axis Reactivity for the BRIDGES Study

Group	**Mean (SD)**	**Pairwise Comparison (p)**				
		1	**2**	**3**	**4**	**5**
1	13.353 (24.308)	n/a				
2	22.500 (48.084)	1.0	n/a			
3	9.688 (12.919)	1.0	1.0	n/a		
4	34.875 (84.817)	1.0	1.0	1.0	n/a	
5	10.632 (14.732)	1.0	1.0	1.0	1.0	n/a
6	35.938 (66.814)	1.0	1.0	1.0	1.0	1.0

Note: NSSI=non-suicidal self-injury; SD=standard deviation; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

Table B10. Number of Lifetime Episodes of NSSI by Group without HPA Axis Reactivity for the BRIDGES Study

	Without BDI Score	**With BDI Score**
Coefficient	**Beta (SE)**	**Beta (SE)**
Intercept	-2.453 (1.198) *	-2.247 (1.053) *
Group 2 Membership	-0.007 (0.327)	-0.023 (0.287)
Group 3 Membership	-0.493 (0.339)	-0.641 (0.299) *
Group 4 Membership	-0.066 (0.284)	-0.045 (0.249)
Group 5 Membership	-0.305 (0.289)	-0.37 (0.254)
Group 6 Membership	0.133 (0.273)	0.029 (0.24)
Time 1 Age	0.172 (0.288)	0.022 (0.254)
Time 2 Age	-0.033 (0.334)	0.121 (0.294)
Time 3 Age	0.143 (0.17)	0.081 (0.149)
BDI Score		0.044 (0.006) ***

Note: NSSI=non-suicidal self-injury; BDI=Beck Depression Inventory; SE=standard error; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

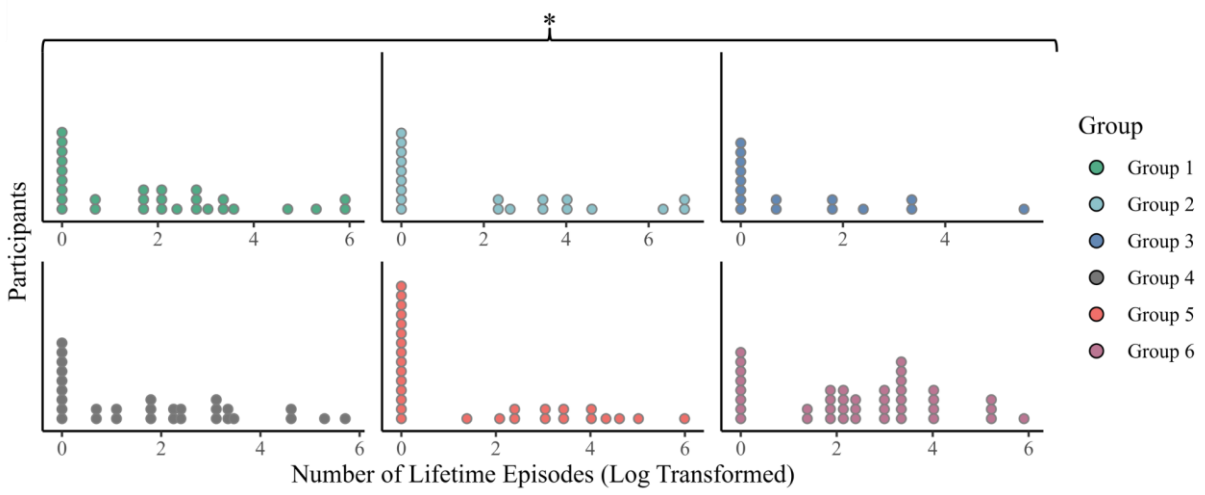
Analyses assessing the relationships between the number of lifetime episodes of NSSI and group membership without HPA axis reactivity indicate a significant relationship between these constructs. Indeed, Group 3 was associated with fewer lifetime number of episodes compared to Group 1 when the BDI score was included as a covariate. A higher BDI score was also associated with a greater number of episodes in models with and without HPA axis reactivity. Figure B5 demonstrates the distribution of the number of episodes across groups. None of the pairwise comparisons had significant results.

Table B11. Pairwise Comparison of Number of Lifetime Episodes of NSSI with HPA Axis Reactivity for the BRIDGES Study

Group	Mean (SD)	Pairwise Comparison With Group (p)				
		1	2	3	4	5
1	26.450 (73.842)	n/a				
2	48.636 (65.990)	1.0	n/a			
3	5.875 (7.736)	1.0	0.9	n/a		
4	9.762 (23.065)	1.0	0.5	1.0	n/a	
5	31.571 (53.327)	1.0	1.0	1.0	1.0	n/a
6	14.188 (35.637)	1.0	0.7	1.0	1.0	1.0

Note: NSSI=non-suicidal self-injury; SD=standard deviation; * indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001

Figure B5. Number of Lifetime Episodes of NSSI by Group without HPA Axis Reactivity for the BRIDGES Study



Note: NSSI=non-suicidal self-injury; * indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001; Group difference is only significant when BDI score is included as a covariate.

Table B12. Pairwise Comparison of NSSI Engagement Across Time Points with HPA Axis Reactivity for the BRIDGES Study

Group	**Engagement at Time 1 N (%)**	**Engagement at Time 2 N (%)**	**Engagement at Time 3 N (%)**
1	16 (32.0%)	13 (26.0%)	7 (14.0%)
2	18 (48.7%)	7 (18.9%)	1 (2.7%)
3	14 (31.1%)	15 (33.3%)	9 (20.0%)
4	13 (28.3%)	11 (23.9%)	10 (21.7%)
5	14 (33.3%)	11 (26.2%)	2 (4.8%)
6	11 (37.9%)	4 (13.8%)	3 (10.3%)

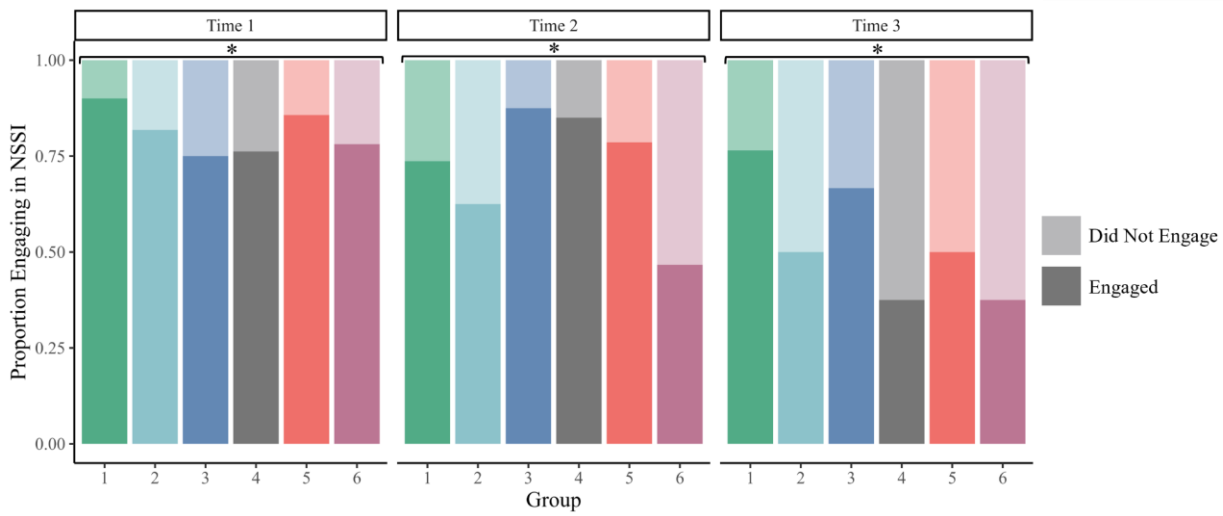
Note: NSSI=non-suicidal self-injury

Table B13. NSSI Engagement Across Time Points by Group without HPA Axis Reactivity for the BRIDGES Study

	Without BDI Score	**With BDI Score**
Coefficient	**OR (CI)**	**OR (CI)**
Intercept	31165.793 (3.445, 17.249)**	16688.344 (3.052, 16.393)**
Group 2 Membership	0.293 (-3.265, 0.807)	0.224 (-3.505, 0.514)
Group 3 Membership	0.751 (-2.392, 1.819)	0.383 (-3.056, 1.134)
Group 4 Membership	0.300 (-2.774, 0.3667)	0.327 (-2.640, 0.403)
Group 5 Membership	0.588 (-2.227, 1.166)	0.428 (-2.556, 0.858)
Group 6 Membership	0.187 (-3.268, -0.090)*	0.177 (-3.321, -0.145)*
Time Point	0.518 (-1.353, 0.039)	0.566 (-1.257, 0.118)
Age	0.660 (-0.863, 0.031)	0.630 (-0.904, -0.020)*
BDI Score		1.073 (0.017, 0.123)**

Note: NSSI=non-suicidal self-injury; BDI=Beck Depression Inventory; SE=standard error; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

Figure B6. NSSI Engagement Across Time Points by Group without HPA Axis Reactivity for the BRIDGES Study



Note: NSSI=non-suicidal self-injury; * indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001; Group difference is significant with and without BDI score included as a covariate.

Analyses examining the relationship between group membership without HPA axis reactivity and engagement in NSSI across study time points indicated that group membership is significantly related to continued engagement in NSSI. Group 6 was associated with decreased engagement in NSSI across time points compared to Group 1 both with and without BDI score included as a covariate. When the BDI score was included as a covariate, age was inversely associated with NSSI engagement across time. A higher BDI score was also associated with continued NSSI engagement across time. The distribution of engagement in NSSI across time points between groups is shown in Figure B6. Chi-squared analyses revealed nonsignificant group differences in the distributions of engagement in NSSI across time ($\chi 2=15$, $p=0.1$)

Table B14. Pairwise Comparison of NSSI Engagement Across Time Points without HPA Axis Reactivity for the BRIDGES Study

Group	**Engagement at Time 1 N (%)**	**Engagement at Time 2 N (%)**	**Engagement at Time 3 N (%)**
1	18 (32.1%)	14 (25.0%)	13 (23.2%)
2	9 (42.9%)	5 (23.8%)	1 (4.8%)
3	6 (27.3%)	7 (31.8%)	4 (18.2%)
4	16 (28.1%)	17 (29.8%)	6 (10.5%)
5	12 (31.6%)	11 (29.0%)	5 (13.2%)
6	25 (45.5%)	7 (12.7%)	3 (5.5%)

Note: NSSI=non-suicidal self-injury

Table B15. Correlation Table of Variables in Time 1 Analyses for the BRIDGES Study

	1	2	3	4	5	6	7	8	9	10	11
1. NSSI History	1.00										
2. NSSI Severity	0.83***	1.00									
3. NSSI Episodes	0.63***	0.72***	1.00								
4. NSSI Time 1	NA	0.17	0.27**	1.00							
5. NSSI Time 2	NA	-0.07	0.00	0.51***	1.00						
6. NSSI Time 3	NA	0.15	-0.15	0.08	0.33*	1.00					
7. Time 1 Amygdala Reactivity	0.17*	0.11	0.09	-0.02	-0.04	0.22	1.00				
8. Time 1 mPFC Reactivity	0.01	0.00	0.05	0.10	0.01	0.22	0.27***	1.00			
9. Time 1 Amygdala-mPFC RSFC	-0.21**	-0.25**	-0.25**	-0.02	0.24*	0.21	-0.10	-0.07	1.00		
10. Time 1 HPA Axis Reactivity	-0.16*	-0.20**	-0.17*	-0.01	-0.03	-0.02	-0.18*	-0.21**	-0.13	1.00	
11. Time 1 Age	0.14	0.16*	0.30***	-0.21*	-0.15	-0.14	0.14	0.10	-0.29***	-0.12	
12. Time 1 BDI Score	0.51***	0.46***	0.47***	0.28**	0.07	-0.06	0.22**	0.13	-0.30***	-0.12	0.19*

Note: NSSI=non-suicidal self-injury; NSSI History and engagement at each time point are coded such that Yes =1, No=0; NSSI severity is coded such that Never=0, Mild/Moderate=1, Severe=2; mPFC=medial pre-frontal cortex; RSFC=resting state functional connectivity; BDI=Beck Depression Inventory; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

Table B16. Correlation Table of Variables in Slope Analyses for the BRIDGES Study

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. NSSI History (Y = 1, N = 0)	1.00												
2. NSSI Severity	0.83 ***	1.00											
3. NSSI Episodes	0.63 ***	0.72 ***	1.00										
4. NSSI Time 1 (Y = 1, N = 0)	NA	0.17	0.27 **	1.00									
5. NSSI Time 2 (Y = 1, N = 0)	NA	-0.07	0.00	0.51 ***	1.00								
6. NSSI Time 3 (Y = 1, N = 0)	NA	0.15	-0.15	0.08	0.33 *	1.00							
7. Slope of Amygdala Reactivity	0.05	0.05	0.08	0.06	0.08	-0.19	1.00						
8. Slope of mPFC Reactivity	0.06	0.03	-0.01	0.11	0.02	-0.12	0.16 *	1.00					
9. Slope of Amygdala-mPFC RSFC	-0.05	-0.03	-0.11	0.11	-0.17	-0.15	-0.05	0.06	1.00				
10. Slope of HPA Axis Reactivity	0.07	0.15	0.03	0.03	0.00	0.09	-0.31 ***	-0.04	0.20 *	1.00			
11. Time 1 Age	0.14	0.16 *	0.30 ***	-0.21 *	-0.15	-0.14	-0.11	-0.09	0.02	-0.01	1.00		
12. Time 2 Age	0.14	0.19 *	0.31 ***	-0.22 *	-0.14	-0.08	-0.13	-0.10	-0.01	0.02	0.97 ***	1.00	
13. Time 3 Age	0.14	0.16 *	0.31 ***	-0.26 **	-0.13	-0.11	-0.09	-0.09	-0.10	-0.07	0.88 ***	0.92 ***	1.00
14. Mean BDI Score	0.52 ***	0.46 ***	0.44 ***	0.26 **	0.20	0.06	0.09	-0.01	-0.10	-0.01	0.14	0.12	0.13

Note: NSSI=non-suicidal self-injury; NSSI History and engagement at each time point are coded such that Yes =1, No=0; NSSI severity is coded such that Never=0, Mild/Moderate=1, Severe=2; mPFC=medial pre-frontal cortex; RSFC=resting state functional connectivity; BDI=Beck Depression Inventory; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

Aim 3 Results Without HPA Reactivity

All Aim 3 analyses were repeated without HPA axis reactivity. The results are below.

Table B17. History of NSSI Engagement and Time 1 Brain Metrics without HPA Axis Reactivity for the BRIDGES Study

	Without BDI Score	**With BDI Score**
Coefficient	**Beta (SE)**	**Beta (SE)**
Intercept	0.339 (-5.943, 3.802)	0.275 (-6.879, 4.262)
Time 1 Amygdala Reactivity	1.277 (-0.005, 0.513)	1.071 (-0.234, 0.377)
Time 1 mPFC Reactivity	0.845 (-0.649, 0.310)	0.693 (-0.981, 0.221)
Time 1 Amygdala-mPFC RSFC	0.002 (-12.649, 0.433)*	0.285 (-8.515, 6.070)
Time 1 Age	1.150 (-0.180, 0.461)	1.028 (-0.342, 0.395)
Time 1 BDI Score		1.264 (0.147, 0.347)***

Note: NSSI=non-suicidal self-injury; SE=standard error; mPFC=medial pre-frontal cortex; RSFC=resting state functional connectivity; BDI=Beck Depression Inventory; * indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001

Table B18. History of NSSI Engagement and Slope Brain Metrics without HPA Axis Reactivity for the BRIDGES Study

	Without BDI Score	**With BDI Score**
Coefficient	**Beta (SE)**	**Beta (SE)**
Intercept	0.024 (-8.746. 1.140)	0.007 (-11.065, 0.990)
Slope of Amygdala Reactivity	1.179 (-0.238, 0.568)	1.007 (-0.530, 0.584)
Slope of mPFC Reactivity	1.424 (-0.503, 1.234)	2.037 (-0.378, 1.893)
Slope of Amygdala-mPFC RSFC	0.036 (-12.956, 6.261)	0.254 (-13.052, 10.152)
Time 1 Age	1.108 (-1.106, 1.254)	0.665 (-2.425, 1.418)
Time 2 Age	1.249 (-1.142, 1.636)	1.976 (-1.468, 3.007)
Time 3 Age	0.981 (-0.728, 0.717)	0.950 (-0.968, 0.886)
Mean BDI Score		1.240 (0.144, 0.305)***

Note: NSSI=non-suicidal self-injury; SE=standard error; mPFC=medial pre-frontal cortex; RSFC=resting state functional connectivity; BDI=Beck Depression Inventory; * indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001

As was seen in the models that included HPA axis reactivity, decreased Time 1 amygdala-mPFC RSFC was significantly related to a history of NSSI engagement, but again, this effect did not remain significant when the BDI score was included as a covariate. None of the brain stress system metrics were significantly related to NSSI engagement in the slope model. Once again, BDI scores were significantly related to NSSI engagement in both the Time 1 (Table B17) and slope (Table B18) models.

Table B19. Severity of NSSI Engagement and Time 1 Brain Metrics without HPA Axis Reactivity for the BRIDGES Study

	Without BDI Score	**With BDI Score**
Coefficient	**OR (CI)**	**OR (CI)**
Time 1 Amygdala Reactivity	1.092 (-0.101, 0.280)	1.016 (-0.183, 0.217)
Time 1 mPFC Reactivity	0.898 (-0.482, 0.264)	0.823 (-0.581, 0.188)
Time 1 Amygdala-mPFC RSFC	0.002 (-11.486, -1.324)*	0.037 (-8.626, 1.938)
Time 1 Age	1.160 (-0.103, 0.403)	1.108 (-0.153, 0.361)
Time 1 BDI Score		1.063 (0.037, 0.088)***

Note: NSSI=non-suicidal self-injury; SE=standard error; mPFC=medial pre-frontal cortex; RSFC=resting state functional connectivity; BDI=Beck Depression Inventory; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

Table B20. Severity of NSSI Engagement and Slope Brain Metrics without HPA Axis Reactivity for the BRIDGES Study

	Without BDI Score	**With BDI Score**
Coefficient	**OR (CI)**	**OR (CI)**
Slope of Amygdala Reactivity	1.171 (-0.160, 0.479)	1.106 (-0.235, 0.439)
Slope of mPFC Reactivity	1.204 (-0.500, 0.877)	1.290 (-0.459, 0.977)
Slope of Amygdala-mPFC RSFC	0.385 (-8.712, 6.770)	1.518 (-7.621, 8.359)
Time 1 Age	0.491 (-1.650, 0.200)	0.282 (-2.363, -0.250)*
Time 2 Age	3.443 (0.167, 2.344)*	6.460 (0.672, 3.150)**
Time 3 Age	0.780 (-0.811, 0.310)	0.660 (-1.017, 0.175)
Mean BDI Score		1.088 (0.056, 0.115)***

Note: NSSI=non-suicidal self-injury; SE=standard error; mPFC=medial pre-frontal cortex; RSFC=resting state functional connectivity; BDI=Beck Depression Inventory; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

As was seen in the models that included HPA axis reactivity, decreased Time 1 Amygdala-mPFC RSFC was significantly related to higher severity of NSSI, but again, this effect did not remain significant when the BDI score was included as a covariate. None of the brain stress system metrics were significantly related to NSSI engagement in the slope model. Once again, Time 1 and Time 2 age were associated with NSSI severity in the slope model. Additionally, BDI scores were significantly related to the severity of NSSI engagement in both the Time 1 (Table B19) and slope (Table B20) models.

Table B21. Number of Episodes of NSSI Engagement and Time 1 Brain Metrics without HPA Axis Reactivity for the BRIDGES Study

	No BDI	**With BDI**
Coefficient	**Beta (SE)**	**Beta (SE)**
Intercept	-1.462 (1.135)	-1.757 (1.024)
Time 1 Amygdala Reactivity	0.06 (0.056)	0.022 (0.051)
Time 1 mPFC Reactivity	0.022 (0.109)	-0.015 (0.098)
Time 1 Amygdala-mPFC RSFC	-3.114 (1.472)*	-1.427 (1.354)
Time 1 Age	0.235 (0.074)**	0.212 (0.067)**
Time 1 BDI		0.041 (0.007)***

Note: NSSI=non-suicidal self-injury; SE=standard error; mPFC=medial pre-frontal cortex; RSFC=resting state functional connectivity; BDI=Beck Depression Inventory; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

Table B22. Number of Episodes of NSSI Engagement and Slope Brain Metrics without HPA Axis Reactivity for the BRIDGES Study

Slope Model		
	No BDI	**With BDI**
Coefficient	**Beta (SE)**	**Beta (SE)**
Intercept	-3.097 (1.18)*	-2.822 (1.055)**
Slope of Amygdala Reactivity	0.138 (0.096)	0.083 (0.086)
Slope of mPFC Reactivity	-0.005 (0.205)	0.01 (0.183)
Slope of Amygdala-mPFC RSFC	-2.741 (2.23)	-1.471 (2.001)
Age Time 1	0.176 (0.274)	0 (0.246)
Age Time 2	0.028 (0.321)	0.177 (0.287)
Age Time 3	0.108 (0.171)	0.072 (0.152)
Mean BDI		0.041 (0.006)***

Note: NSSI=non-suicidal self-injury; SE=standard error; mPFC=medial pre-frontal cortex; RSFC=resting state functional connectivity; BDI=Beck Depression Inventory; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

As was seen in the models that included HPA axis reactivity, Time 1 Amygdala-mPFC RSFC was significantly related to the number of episodes of NSSI engagement, but again, this effect did not remain significant when the BDI score was included as a covariate. None of the brain stress system metrics were significantly related to NSSI engagement in the slope model. As in the model with HPA axis reactivity, Time 1 age was related to the number of episodes of NSSI in the Time 1 model. Once again, BDI scores were significantly related to the number of episodes of NSSI engagement in both the Time 1 (Table B21) and slope (Table B22) model.

Table B23. NSSI Engagement Across Time Points and Time 1 Brain Metrics without HPA Axis Reactivity for the BRIDGES Study

	No BDI	**With BDI**
Coefficient	**OR (CI)**	**OR (CI)**
Intercept	7.544 (0.242, 3.800)*	2.538 (-0.946, 2.808)
Time Point	0.593 (-1.191, 0.147)	0.627 (-1.134, 0.201)
Time 1 Amygdala Reactivity	1.012 (-0.335, 0.359)	0.991 (-0.363, 0.344)
Time 1 mPFC Reactivity	1.736 (-0.134, 1.238)	1.576 (-0.237, 1.147)
Time 1 Amygdala-mPFC RSFC	453.404 (-3.310, 15.544)	6145.097 (-1.111, 18.558)
Time 1 Age	0.498 (-1.433, 0.039)	0.466 (-1.505, -0.023)*
Time 1 BDI		1.047 (0.005, 0.088)*

Note: NSSI=non-suicidal self-injury; SE=standard error; mPFC=medial pre-frontal cortex; RSFC=resting state functional connectivity; BDI=Beck Depression Inventory; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

Table B24. NSSI Engagement Across Time Points and Slope Brain Metrics without HPA Axis Reactivity for the BRIDGES Study

	No BDI	**With BDI**
Coefficient	**OR (CI)**	**OR (CI)**
Intercept	9.699 (0.665, 3.879)**	2.144 (-0.938, 2.463)
Time Point	0.620 (-1.156, 0.201)	0.685 (-1.036, 0.280)
Slope of Amygdala Reactivity	1.060 (-0.534, 0.649)	0.958 (-0.629, 0.542)
Slope of mPFC Reactivity	0.960 (-1.310, 1.229)	1.072 (-1.165, 1.303)
Slope of Amygdala-mPFC RSFC	0.043 (-16.448, 10.134)	0.013 (-17.194, 8.582)
Age	0.466 (-1.502, -0.024)*	0.428 (-1.572, -0.125)*
Mean BDI		1.073 (0.019, 0.121)**

Note: NSSI=non-suicidal self-injury; SE=standard error; mPFC=medial pre-frontal cortex; RSFC=resting state functional connectivity; BDI=Beck Depression Inventory; * indicates $p<0.05$, ** indicates $p<0.01$, *** indicates $p<0.001$

As was seen in the models that included HPA axis reactivity, none of the brain metrics were significantly related to NSSI engagement across time points. None of the brain stress system metrics were significantly related to NSSI engagement across time points in the slope model. Once again, Time 1 age was related to NSSI engagement across time points in the Time 1 model, Age was related to NSSI engagement across time points in the slope model, and BDI scores were significantly related to NSSI engagement across time points in both the Time 1 (Table B23) and slope (Table B24) model.

Data Funding Acknowledgement

The National Institute of Mental Health (R01MH107394-01, PI: Cullen) supported the Brain Imaging Development of Girl's Emotion and Self (BRIDGES) study and provided funds for the larger, longitudinal grant.