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Research Protocol:

A Longitudinal Study Examining Three RDoC Constructs in Adolescents with Non-Suicidal Self-Injury

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Funding Sponsor: National Institute of Mental Health

Protocol Number: IRB #1605M88102

Version: Version 34 – April 26, 2022

CONFIDENTIAL

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2. Report of prior investigations

2.1. Non-Suicidal Self-Injury (NSSI) in adolescents is a serious clinical problem. NSSI is common in adolescents (prevalence rates range from 13- 23%[2]) and is associated with impaired functioning, high rates of psychiatric hospitalizations, and future suicide attempts.[3-6] Treatments for NSSI are very limited.[7-9] Although

the origins of NSSI likely stem from a combination of biological, psychological and social roots, most research to date has focused on clinical features measured by self-report. In particular, there has been a major gap in neuroscience research to understand the neurobiological underpinnings of NSSI, which has hindered the advancement of new, biologically-targeted interventions.

2.2. Applying an RDoC Approach to Advancing Knowledge about NSSI. NSSI is a behavior that cuts across psychiatric diagnoses, and the underlying circuitry/physiology/cognitive processes are also trans-diagnostic. Therefore the RDoC approach is ideally suited for trying to understand the biological roots of NSSI.[10]

The RDoC initiative was developed to address the problem that psychiatry research using traditionally-defined psychiatric disorder classification has failed to reveal any clinically useful biomarkers. RDoC promotes research that examines brain-behavior relationships in basic dimensions of functioning that occur across disorders, rather than focusing on patients within diagnostic categories, using multiple units of analysis.[11,12] Since individuals with NSSI primarily use NSSI to regulate negative affect[13] and are characterized by interpersonal disturbances and negative self-conceptions,[14-20] and impulsivity,[21] candidate RDoC domains for further study include Negative Valence, Social Processes and Cognitive Systems. While a range of constructs are likely relevant to NSSI, as described below, our pilot data in adolescents with NSSI pointed to Sustained Threat, Self-Knowledge and Cognitive Control as the most relevant constructs for further examination.

2.3. Importance of Examining the Dynamic Interaction of Neural Systems Across Development. Longitudinal studies of at-risk children have demonstrated developmental cascades for psychopathology,[22] where problems in one system emerge as a result of cumulative effects in another system.[23-25] RDoC leaders have recently articulated: a "neurodevelopmental concept that may enrich RDoC investigations is the dynamic interactions of systems across development . Early in development, brain circuits across different regions interact dynamically. The cumulative consequences of these interactions among developing systems alter the course of development. Thus, a deficit occurring early in development can give rise to a cascade of more complex deficits as different brain regions mature and interact over time. The interaction of differentially maturing brain systems with developmental time raises challenges and opportunities for extending basic RDoC principles. In particular, it highlights the need to simultaneously examine associations among multiple domains of function, brain systems, and/or developmental periods, including how these interact with environmental events and other contextual factors."[1] To address this, in concert with the multi-modal examination of RDoC constructs, it will be critically important to examine the dynamic interaction between these constructs across development.

2.4. Sustained Threat: Relevance to NSSI. Since most individuals with NSSI use the behavior to regulate negative affect,[13] research in Negative Valence domain is a natural first step toward understanding the neurobiology of NSSI. In particular, the threat system is implicated because of the association between NSSI and negative adverse experiences such as child abuse[26] and bullying.[27,28] NSSI is typically chronic (e.g. current NSSI predicts future NSSI),[3,29,30] suggesting that Sustained Threat (an aversive emotional state caused by prolonged exposure to danger cues) may be more relevant than Acute Threat. Sustained Threat may be particularly implicated in those with more severe/chronic NSSI; animal models of NSSI have shown that prolonged exposure to social defeat leads to increased NSSI severity.[31] The detection and response to threat stimuli comprises a complex brain/body system. Initially, threat triggers a response in the amygdala, which is linked with the anterior cingulate cortex (ACC) and prefrontal cortex, regions that monitor conflict, interpret, regulate emotional reactivity, and direct behavioral responses.[32,33] Prior research studies in adults[34] and adolescents[35] with NSSI using fMRI and threat stimuli (e.g. negative pictures, fear or angry faces) have shown exaggerated amygdala responses. Amygdala-frontal connectivity may be impaired in humans and primates with anxiety and exaggerated responses to threat.[36] This circuit is tightly connected to the neuroendocrine arm of threat response. However, two studies that examined hypothalamic-pituitary-adrenal (HPA) functioning showed attenuated responses (despite elevated subjective emotional experiences) in adolescents[37] and young adults with NSSI.[38] Hypo-responsive HPA functioning may suggest an allostatic shift in the threat system to accommodate chronic stress. Together these findings suggest significant abnormalities in threat response in adolescents with NSSI, but provide an example of how multiple units of analysis of a construct may in some cases diverge, highlighting the complexity of the system and the need for a multi-modal approach.

2.5. Sustained Threat: Developmental Changes. Prior work has demonstrated developmental changes in Sustained Threat indices during adolescence. In animals, fibers projecting from amygdala to prefrontal cortex continue to mature through adolescence and into adulthood.[39] Cross-sectional studies comparing adolescents to adults have shown that adolescents engage prefrontal regions to a lesser degree than adults when faced with threat imagery (fear faces)[40] and that the ratio of prefrontal/amygdala fear response increases across adolescence.[41] Research examining physiological indices of the threat system have found that both cortisol and sympathetic nervous system responses to threat challenges are greatest in mid- adolescence as opposed to late childhood / early adolescence, and that these indices are correlated with fearful temperament, anxiety and depression symptoms in adolescents.[42,43] It is possible that adolescents with NSSI

may exhibit aberrant developmental trajectories of these systems, underpinning their vulnerability to develop and maintain NSSI.

2.6. Relevance of Self-Knowledge in NSSI. Youth who engage in NSSI commonly suffer from poor self-esteem [14-20,44] and difficulties identifying their feelings.[45,46] Self-criticism has been shown to negatively influence the course of NSSI.[47,48] Therefore, Self-Knowledge (the ability to judge one's current cognitive or emotional internal states, traits, and/or abilities) is a promising candidate construct to study in this population. We propose that the tendency of individuals with NSSI to show negative self-evaluations, and to struggle with handling challenges to the self could be associated with disrupted self-referential processing. Self-related processes are mediated by the medial cortical network (MCN) involving the rostral anterior cingulate, posterior cingulate and precuneus.[49,50] This network has not yet been directly examined in NSSI research.

2.7. Self-Knowledge: Developmental Changes. Prior work documenting developmental changes in brain and behavior indices relevant to Self- Knowledge provides the backdrop for understanding aberrant trajectories in adolescent NSSI. Adolescents commonly struggle with a sense of identity.[51] Adolescence is a period of significant development in Self-Knowledge including a growing sense of uniqueness and connection with others.[52] Comparisons of children/early adolescents to adults suggest that, in response to tasks designed to assess self-evaluation (making judgments about oneself), young people engage MCN to a greater extent than adults.[53,54] Recently, Pfeifer and colleagues[55] showed that self-evaluations engaged MCN in children and adolescents, and within this network, rostral ACC activation during self evaluations increased from age 10 to 13.[55] Additionally, studies using resting-state fMRI have found that functional connectivity within a related/overlapping network (referred to as "default mode") increases through adolescence.[56] Vulnerability for and maintenance of NSSI in adolescence could involve abnormal development of the MCN.

2.8. Cognitive Control in NSSI. Individuals with NSSI may have increased impulsivity. In the RDoC matrix, impulsivity falls under the Cognitive Control construct and in particular, the sub-construct Response Inhibition. Research paradigms examining Response Inhibition have utilized tasks that require inhibiting a prepotent response, such as the Go/No-go or the stop-signal task. Research to date investigating Response Inhibition in NSSI has been somewhat mixed. Some [57-59] but not all[60] studies have suggested that self- reported impulsivity is elevated in patients with NSSI. One study found that youth with low-severity NSSI demonstrated poor performance on the stop signal task compared to youth with high-severity NSSI and healthy controls.[61] Another study showed that adolescents with NSSI have elevated levels of self-reported impulsivity but no group differences with behavioral measures of cognitive control.[57] Discrepancies in the literature could stem from the possibility that

impulsivity in this population primarily occurs within the context of negative affect.[62] One study found no stop signal task group differences, but did find that patients with NSSI differed from controls with respect to Negative Urgency (committing rash decisions when faced with negative emotions).[63] Negative Urgency has been associated with severity of NSSI [64,65] and has predicted both new onset and NSSI maintenance in young adults.[66] Further investigation of Response Inhibition in NSSI may benefit from its measurement in the context of negative emotion, which could be most relevant to NSSI pathology.

2.9. Cognitive Control Systems: Developmental Changes. Developmental research to date using tasks such as the Go/Nogo and the stop-signal task have shown that performance improves linearly with age from childhood to adulthood.[67] However, the fMRI studies of inhibition have shown mixed findings, with some studies showing increased recruitment of frontal areas with age during these tasks ("frontalization")[68,69] and other studies showing a pattern of moving from diffuse to focal cortical recruitment during such tasks.[70] The discrepancies in the literature could stem from the need to better tease apart motivational influences upon cognitive control systems.[1] For example, our co-investigator Dr. Thomas has shown that negative emotional contexts disrupt inhibitory control to a greater degree in early adolescence than childhood or later adolescence/adulthood.[71] The onset and maintenance of NSSI in adolescents could involve deficits in the development of cognitive control systems, particularly in the context of negative emotion.

2.10. Promise of longitudinal studies for charting clinical course of NSSI. Research to date has made considerable strides in characterizing the clinical phenomena of NSSI such as underlying motivations and psychological predispositions. More recently, longitudinal work has even begun to chart clinical trajectories. For example, depression symptoms in mid-adolescence predict NSSI chronicity during late adolescence, and negative attributional style distinguishes high versus low severity NSSI.[72] Other work has suggested that self-criticism and self-reported impulsive behaviors moderate the course of NSSI.[48] However, longitudinal NSSI research to date has not incorporated multiple units of analysis including neurobiological measurement.

2.11. Summary. NSSI is a highly prevalent, maladaptive behavior that occurs across diagnoses and is associated with significant negative outcomes including chronicity and risk for suicide. Development of new treatment strategies is limited by the currently poor understanding of the neurobiology of NSSI in adolescents. An RDoC approach is suitable for investigating the development of abnormal brain-behavior relationships relevant to NSSI. Sustained Threat, Self-Knowledge and Cognitive Control represent promising candidate constructs for further study in adolescents with NSSI. Measurements within these putative neural systems are known to undergo developmental change during adolescence. The status of

current knowledge, in combination with the pilot data from our group described below on adolescents with NSSI, provides the backdrop for the current proposal that will use multiple units of analysis and a longitudinal approach to examine the development and dynamic interaction of these systems across adolescent development.

3. Investigational plan

3.1 Objectives of the clinical investigation:

3.1.1 Primary objective.

To test how different units of analysis (circuits, physiology, behavior, self-report) of Sustained Threat, Self-Knowledge and Cognitive Control relate to NSSI severity in post-menarchal adolescent girls aged 12-16 years who exhibit a continuum of NSSI severity

3.1.2 Secondary objective(s).

a. To test whether the baseline measures of RDoC constructs listed in Aim 1 predict future (after 1 and 2 years) NSSI severity levels.

b. To delineate changes over time in the RDoC measures of Aim 1 across adolescence

3.2 Title of clinical protocol:

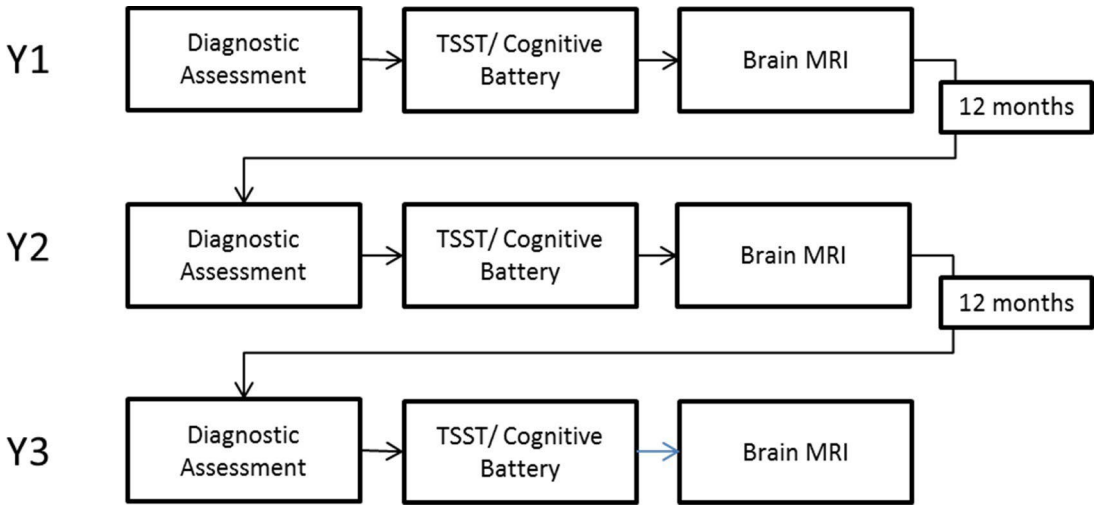
Development of Sustained Threat, Self-Knowledge, and Cognitive Control in Adolescents with Non-Suicidal Self-Injury

3.3 Study design:

3.3.1 General study design.

This study is a longitudinal study that consists of three separate in-person appointments conducted once a year for a period of 3 years including a clinical assessment (interview and questionnaires), the Trier Social Stress Test (TSST) and cognitive battery, and a brain MRI. An additional "online appointment" will also be completed once a year, where participants answer online questionnaires to reduce time spent at other 3 appointments.

3.3.2 Study design schematic.



3.4 Subject selection:

3.4.1 General characteristics of the proposed subject population(s).

Female adolescents aged 12-16 years old who are post-menarche with varying severity of Non-Suicidal Self-Injury (NSSI)

3.4.2 Anticipated number of research subjects.

The goal is to have baseline data on 152 participants – 38 with no history of self-harm, 38 with mild NSSI, 38 with moderate NSSI, and 38 with severe NSSI. In order to get this amount of data, we estimate that up to 200 participants will need to be enrolled into the study (anticipating that some participants will not meet inclusion criteria after the diagnostic interview, and some will not have usable baseline MRI scans). We anticipate that with drop-out, we will have at least 30 participants per group by the last follow-up visit.

3.4.3 Inclusion/Exclusion criteria.

		Inclusion Criteria	Exclusion Criteria
All Participants		12-16 years old Female Post-menarche Willingness to have deidentified data shared with RDoCdb	Male Pregnancy MRI Incompatibility Intellectual Disability Major Medical Illness Primary Psychotic Disorder Bipolar Spectrum Disorder Autism Spectrum Disorder Current Substance Use Disorder[1, 2] Inability to Pass UCSB Brief Assessment of Capacity to Consent (UBACC) Non-English Speaker
		Inclusion Criteria	**Exclusion Criteria**
NSSI Groups	Severe NSSI	≥ 4 past episodes of NSSI with significant tissue damage ≥ 1/month frequency	
	Moderate NSSI	≥ 4 past episodes of NSSI with significant tissue damage < 1/month frequency	
	Mild NSSI	< 4 NSSI episodes with significant tissue damage OR an unlimited number of episodes with mild or no tissue damage	
	No NSSI		Any history of NSSI

[1]In the case of a history of substance use, if criteria are met for a substance use disorder, it must be in early or sustained remission as defined by the DSM-5.

[2]The study will still include individuals meeting criteria for nicotine substance use disorder.

3.5 Study procedures:

3.5.1 Recruitment.

1. We will send letters and study brochures to local clinicians who treat adolescent mood disorders.

2. We will post flyers and other advertisements through social media (Facebook, Pandora, Tumblr, etc.) and community outlets about our study.

3. We will be using the services of BUMP Digital Marketing to advertise online with Google Ad Words. Upon clicking the link in the advertisement, users will be brought to a landing page which describes the study and has a link to a REDCap survey. The REDCap survey asks for contact information, birth date of the potential participant, and also if they have ever self-injured. The REDCap survey and responses are to be maintained by the study team, so BUMP does not have any access to PHI. We are trying to target our NSSI group with these advertisements. After 3 months of Google Ad Words, the company has agreed to launch Facebook advertisements as a contingency if Google does not perform well.

4. We will screen electronic medical records of adolescents with a history of self-injurious behavior treated in the clinics and hospital services of the University of Minnesota, Medical Center and Masonic Children's Hospital. We will only look at the records of those patients who have not opted-out of having their medical records used for research on the Consent for Services form they complete at intake. When potential cases are identified, we will contact the treating physician to discuss the patient and whether they might be suitable for consideration for the study. If yes, we will ask the physician (or they physician may choose to delegate this to another member of the treatment team) to approach the parent or guardian about the study. The physician (or delegated treatment team member) will let parents know that their daughter may be eligible to participate in a research study being conducted at the University of Minnesota, and will ask the parent or guardian whether they would like to be contacted by the research team to learn more about the study. The physician (or delegated treatment team member) will explain that participation is completely voluntary and in no way related to the treatment for their daughter. Information about study opportunities will also be provided for potential participants on a research board on the unit. The board will

(a) post information about the study, (b) provide small cards with study information that parents can take home, and (c) provide permission to contact forms which families may complete if they would like the study team to contact them. Families are instructed to turn permission to contact forms into the front desk of the unit who then deliver the forms to the study team in a secure fashion.

5. We will recruit participants from the Riverside Behavioral Health Outpatient Clinic and M Health Fairview Adolescent Day Treatment Program using multiple strategies. First, patients in this clinic are invited to participate in a research recruitment registry. Patients in the Day Treatment Program will be offered a blank version of form for their records. Our research staff will use the research registry to contact potential participants who have indicated they are interested in research using the contact information provided in the registry. Secondly, we will use a direct, in-person recruitment approach. Research staff will connect with providers in the clinic to discuss patients who could be potential participants. For specific patients we will ask the provider to give an IRB-approved study brochure to the patient, along with a general introduction about the study. The research staff will be available to meet with the patient and their parent in the clinic to provide further information about the study; interested families will have the option to meet briefly with a researcher in person to allow face-to-face discussion, or to have the researcher follow up with them by phone. The Behavioral Health Research Recruitment Committee and Fairview have approved this process.

   We will post information about the study and business cards with our contact information on them on the recruitment boards outside of the psychiatry clinic and inpatient units.

6. We will recruit for the study at the Minnesota State Fair in the Driven to Discover Research Facility (D2D). We will be sharing the booth assigned to the D2D: Games for Brains study. Signs for the booth will indicate both studies to attract interested and eligible State Fair visitors to our booth. We will have flyers and brochures about the study at the booth. For parents or guardians who tell us they have a daughter in our study age range (12 to 16) we will encourage them to complete a permission to contact form to indicate their interest in being contacted about the study and gather their contact information. To encourage participation, each eligible family that completes a contact form will receive (a) a small item (a pencil or item of equal/similar value), and (b) an entry into a drawing for a larger item

($25 target gift card) which will be determined at the end of each shift at the fair (5 shifts total).
6a. We will be recruiting for the study at the Minnesota State Fair Driven to Discover Research Facility (D2D) at a recruitment booth for our lab again in 2019. We will have flyers and brochures about the study at the booth. For parents or guardians who tell us they have a daughter in our study age range (12 to 16) we will encourage them to complete a permission to contact form to indicate their interest in being contacted about the study and gather their contact information. We will be giving away small prizes for those who sign their daughter up to be contacted.

7. We will be recruiting from PrairieCare. We will share the inclusion and exclusion criteria for our study, and PrairieCare will send letters to a set of patients that they have determined to be potentially eligible based on our criteria and their review of their electronic medical record system. In the letters, participants are provided with information about the study and contact information about the study.

8. We will use the Fairview research recruitment mailing process. Fairview has approved a research letter to be sent to parents of female inpatients aged 12-15 who had been admitted to a behavioral health unit (6A, 7A, 7ITC, 3C) for any diagnosis. Sixteen year olds will not receive letters due to HIPAA and independent clinical/medical care laws applying to services independently acquired by adolescents.](Fairview policy "Confidentiality Considerations for Minors") to parents of patients ages 12-15, because a manual review of consents would be required for 16 year old patients.

9. We will send out letters and/or emails describing the study to professional, trained school counselors, psychologists, social workers, and/or guidance counselors. We will also attach a flyer of the study to the communication requesting they share information, as appropriate, with parents, adolescents, and other school professionals.

10. We will make presentations about self-harm, self-injury, and research findings to middle and high school classrooms, as well as community organizations including in-person and online neighborhood groups, parent groups, and spiritual groups. Potential participants will not be identified by research staff. Potential participants-- or parents of potential participants-- will have the opportunity to self-identify and request more information about research participation. Flyers and business cards, and the Psychiatry Research Registry, will be available for interested participants to pass on to their parent/guardians.

11. We will post this study on the Psychiatry Research Opportunities website. It will include inclusion/exclusion criteria, the reason for the study (what we hope to learn), and contact information for the study.

3.5.2 Screening, consent, clinical assessment and diagnostic procedures.

(a) The parent/guardian of each potential participant will first complete an initial, brief telephone interview with a research team member. The study will be briefly explained by the team member to the parent/guardian (possibly also to the potential participant), and we will ask a set of questions about the child's medical history. This will serve to select children likely to meet inclusionary criteria and to screen out children who meet exclusionary criteria. Families that are interested in pursuing the study and who pass this screen will be scheduled for a diagnostic interview. The diagnostic interview, including the consent process will take place via Zoom, a HIPAA-compliant communication platforms approved for use at the University of Minnesota. One of the members of the research staff will review the study procedures, risks and benefits as described in the consent form with the parent/guardian and in the assent form with the adolescent. The families will be given time to read the materials and ask any questions they have about the study. The research staff member will pose a set of questions to the parent/guardian and the adolescent to ensure that they fully understand the procedures, risks, and voluntary nature of the study. This takes the form of the UCSB Brief Assessment of Capacity to Consent (UBACC), which consists of questions tailored to this particular study. We will also offer participants the opportunity to indicate on their HIPAA form if they would like to allow the research team to access to specific portions of their medical records. Prior to the appointment, research staff will send copies of the consent form and HIPAA Authorization, as available, via email. Participants will be able to opt into receiving unencrypted email communication and SMS message communication from study staff for reminders about appointments or instructions. The participant will not be required to communicate via email or SMS messaging, and they may change their mind about email or SMS communication at any point during the study by informing the study team of their decision.

(b) Due to the longitudinal 3-year nature of the study, participants who are 15 or 16 when they enter the study may turn 18 over the course of the study. We plan to re-consent these participants as adults, using an adult consent form, after they turn 18 and before continuing

participation in the study. The 18 and older participant will be able to opt into receiving unencrypted email communication from study staff for reminders about appointments or instructions. The participant will not be required to communicate via email, and they may change their mind about email communication at any point during the study by informing the study team of their decision.

(c) To describe our sample and to determine criteria for ineligibility, we will screen for the presence of DSM-5 psychiatric diagnoses. We will conduct separate clinical interviews with parent and adolescent using the The Computerized Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS-COMP), a semi-structured clinical interview, administered by a clinician using a laptop or tablet that generates current and lifetime diagnoses and elicits ages of onset and offset. Clinicians will also administer the Children's Depression Rating Scale-Revised (CDRS-R) to both subject and parent to gauge severity of depression symptoms.

To reduce participants' fatigue, the clinical interviews will be limited to three hours. Participants who would like to come back and complete the interview will be compensated extra for each hour that their interview continues for.

Clinicians will also complete the following measures with adolescents only:

The Self-Injurious Thoughts and Behaviors Interview (SITBI) to assess self-harm. The SITBI measures NSSI frequency in the past month, past year, and lifetime; average age of onset; severity of injuries (number of injuries per episode, severity of tissue damage -- worst point and average), function (automatic versus social, negative versus positive) and other information. The participant's SITBI will be used to determine in which of the four NSSI groups they belong. If not complete at the first appointment due to time limitations or other factors, the study coordinator can administer the assessment to the participant at other visits (i.e., TSST, MRI). The clinician will complete this through REDCap.

The Beck Scale for Suicidal Ideation (BSSI), a 19-item interview, assesses current suicidal ideation, with ratings for active suicidal desire, specific suicide plans, and passive suicidal desire. If not complete at the first appointment due to time limitations or other factors, the study coordinator can administer the assessment to the

participant at other visits (i.e., TSST, MRI). The participant will complete this via a REDCap survey.

The Timeline Followback Method TLFB for NSSI, a calendar format measure to retrospectively collect behavioral data that was adapted from an instrument for alcohol use, will be used to measure NSSI episodes that had occurred in the year between visits. The TLFB demonstrates good reliability and validity when used over a 1-year period. If not complete at the first appointment due to time limitations or other factors, the study coordinator can administer the assessment to the participant at other visits (i.e., TSST, MRI). The participant will complete this via a REDCap survey.

The Generalized Anxiety 7-Item (GAD-7) scale is a self-report instrument covering 7 items, to rate the presence and severity of generalized anxiety symptoms. A second portion of the questionnaire asks participants to rate the severity of the collective problems they have endorsed, from "not difficult at all" to "extremely difficult." If not complete at the first appointment due to time limitations or other factors, the study coordinator can administer the assessment to the participant at other visits (i.e., TSST, MRI). The participant will complete this via a REDCap survey.

The Childhood Trauma Questionnaire (CTQ) is a self-report instrument covering 28 items, to rate the presence and severity of emotional abuse and neglect, physical abuse and neglect and sexual abuse. If not complete at the first appointment due to time limitations or other factors, the study coordinator can administer the assessment to the participant at other visits (i.e., TSST, MRI). The participant will complete this via a REDCap survey.

The Wechsler Abbreviated Scale for Intelligence-II (IQ) will be used to estimate intellectual functioning. This measure can be administered at any visit, but if IQ is determined as below 80 we will have to exclude the participant and their data from the rest of the study. The Edinburgh Handedness Inventory will be used to determine handedness, which will be incorporated into the analysis. This measure can also be administered at any visit as will only be used for data analysis.

Tanner Staging will be obtained via a self-report questionnaire with outline drawings of the pubertal stages. We will include Tanner

stage as covariates in the analyses. As noted by Casey et al.,1 it will be critical to understand the learning histories in the environment that shape the development of neural systems. The participant will complete this via a REDCap survey.

Participants will also complete the Beck Depression Inventory (BDI-2) and a modified Everyday Discrimination Scale (EDS) via REDCap survey. We will also gather information on urges to self- injure during the past week using the Self Injury Assessment Scale (SIAS). The administration of these questionnaires (BDI, SIAS) is to be flexible, and if the first appointment is becoming too long, can be done at the MRI or Trier appointment. These will also be completed via REDCap surveys.

In addition, participants will complete the COVID-19 Health Changes questionnaire which will be administered to them via RedCap survey.

The participant's primary parent/guardian will complete the Child Behavior Checklist (CBCL), Emotion Socialization and Demographics forms. All of these will be completed via REDCap surveys.

For participants who have turned 18, we will continue to ask the parent or guardian to complete the same measures as they had been doing earlier in the study. In the case of participants who have turned 18 and who no longer wish to have their parent or guardian involved in the study with them, we will have the participant complete the demographics form on their own behalf; we will not collect the CBCL or the ES measure in those cases, and the KSADS and the CDRS will be completed with the participant alone.

(e) After the diagnostic assessment is complete, a consensus meeting takes place among the research team to integrate the combined information from parent/guardian and adolescent KSADS interviews, rating scales and medical records (if available), to confirm the DSM-5 psychiatric diagnoses. If participants meet the above inclusion criteria and do not have any of the exclusion criteria, they will be invited to participate in the remaining portions of the study.

(e.a) "If at the consensus meeting the research team is unable to determine final diagnosis, due to discrepant reports from the parent and child, or the presence of other confounding factors in the assessment, the research team may take one or more of the following steps:

1) Request permission to review medical records from prior medical or psychiatric evaluations;

2) Request permission to reach out to the adolescent's current or past providers to seek their input on the diagnosis; and/or

3) Invite the adolescent and their parent/guardian to participate in a follow-up clinical interview (either in person at the ARC or by phone) with one of the faculty clinical investigators on the study (Dr. Cullen, Dr. Klimes-Dougan, or Dr. Reigstad) to further evaluate the potential diagnoses in question with a focus on resolving the conflicting information.

Following these steps, the clinical evaluation team will confirm the diagnosis and finalize the inclusion/exclusion determination."

(f) At each of the second and third assessments (12 and 24 months, respectively, after the initial assessment), the scales described in (c-d) will be collected again.

(g) Participants will be asked to complete a number of additional questionnaires (described below) that will be accessible online. All questionnaires will be completed at home at the participant's own pace. In total, these online assessments will take participants approximately 1 hour and 45 minutes to complete all of the questionnaires. Participants will be compensated if they complete the questionnaires.

The questionnaires to be completed at home are: Rejection Sensitivity Questionnaire – Adolescent Version (RSQ-A), Symptoms Checklist 90 (SCL-90), Toronto Alexithymia Scale (TAS-20), Satisfaction with Life Scale, The UPPS Impulsive Behavior Scale (UPPS-P), and the Positive and Negative Affect Schedule (PANAS-X), the Eating Disorder Examination Questionnaire (EDEQ), and the Personality Assessment Inventory for Adolescents (PAI-A), the Pittsburgh Sleep Quality Index (PSQI), and the Cash Choice Task.

3.5.3 Stress Biology Procedures

At a separate visit (for each of the three assessments, 12 months apart), we will use a procedure that is a version of the Trier Social Stress Test (TSST) to elicit a mild stress response. It consists of a 5-minute preparation period, 5-minute speech period, and a 5- minute mental arithmetic task in front of an audience. In the speech part, children are asked to describe themselves in front of an audience of 2 adults. Five

samples of salivary cortisol will be collected according to the following schedule: prior to and immediately following the TSST, as well as 15, 30 and 45 minutes following the TSST. Due to the nature of this visit, as we are collecting behavioral data that cannot be interrupted while collecting saliva samples, there is a possibility that saliva samples may be +/- approximately 5 minutes from the intended sample time.

While we are collecting the saliva samples after the completion of the TSST, we will have the participant complete a number of cognitive batteries including the ANT Task, Attention Bias Task which utilizes an eye-tracker, and the Iowa Gambling Task (IGT). In the event that the Attention Bias Task is not functional, the Dot- Probe task will instead be used as a measure of attention.

Participants will be given contact information of the study PIs and coordinators and instructed to call if the TSST triggers any emotional difficulties or if they have any questions.

We will also be asking participants to provide home saliva samples, taken on a day that is separate from the day of the TSST. We will ask participants to complete five saliva samples at home, over the course of one day. The five samples should be collected following this schedule: right when waking up, 15 minutes after waking up, and 30 minutes after. The fourth sample will be collected in the afternoon, to serve as comparison to the start time of the TSST (between 1:00PM and 4:00PM), and the fifth sample is to be taken at bedtime (approximately 10:00PM). As the participants are completing these samples at home and at their own discretion, there is a possibility that they will not directly follow the sample collection times. The study team provides a letter explaining the times that samples should be collected, but does not have control over when the adolescent completes there samples.
We will have participants document the times that they collected their at home saliva samples, as well as any medications, caffeine, or events that occurred during the day that could affect their saliva samples via a "Daily Diary"- a type of self-report form for the day. We will compensate participants for their time spent collecting and documenting the saliva samples.

Remote Conduct of Study Procedures
In the interest of disease containment and prevention during COVID-19, study staff will use HIPAA-compliant communication platforms approved for use at the University of Minnesota (e.g., Zoom) and adjust this visit as follows:

(a) Participants will be mailed a saliva collection kit prior to the scheduled appointment. To ensure data adequacy, participants will also receive a set of standardized instructions for collecting saliva samples. Participants will complete the attached survey measure in the online REDCap platform.

Researchers will meet with participant via Zoom, and ensure that the participant still has a private location to complete the study. Saliva collection procedures will be reviewed again. After the initial acclimation period, the participant will be introduced to two judges that will also be on screen. Participants will receive instructions for preparing their speech, will provide the 5-minute speech, and will then perform verbal arithmetic for the next 5 minutes as in the in-person visits. Participants will be aware that the entire session will be recorded for behavioral coding and to ensure proper saliva collection. Judges will be trained research assistants who have participated in multiple TSST administrations. Judges will not provide positive or negative feedback at any point during the study and will only display neutral expressions. They will then complete the usual surveys via REDCap.

The TSST over Zoom will be recorded and the recording saved on a local HST supported computer. The file will then be uploaded to Box and the local copy will be deleted.

Participants will be asked to store the samples in their refrigerator until that can return the samples by mail via a pre-addressed and postage-paid envelope provided by the researchers.

For participants who complete the TSST on zoom, the ANT and IGT will be done at the MRI visit.

For participants who prefer to complete visits in person, we will conduct the TSST visit at the Masonic Institute for the Developing Brain (MIDB).

3.5.4 MRI Procedures

At a separate visit (for each of the three assessments, 12 months apart), we will conduct a brain scanning session at the University of Minnesota Center for Magnetic Resonance Research (CMRR) using a Siemens 3 Tesla Prisma scanner (Erlangen, Germany) and a 32- channel coil radio-frequency (RF) head coil. Prior to the scan, subjects will provide

a urine sample for drug screening and fill out an MRI safety questionnaire. If the drug screening is positive, we will complete the MRI scan but will use the information in our analysis. We will also gather information on urges to self-injure during the past week using the Self Injury Assessment Scale (SIAS). Following the scan, participants will complete a Resting State Post Scan Questionnaire (RSPSQ), which collects data on their experience during the resting state fMRI as well as menstrual status. Participants will also provide information about their experiences with the fMRI tasks through an Emotion Go No Go Questionnaire and a Hariri Post-Scan Questionnaire. Participants will also complete the Self-Perception Profile for Adolescents (SPPA) questionnaire after the scan. These surveys will be conducted via REDCap.

The research team will utilize the CMRR Center's screening tools and adhere to the screening SOP during enrollment of all research participants in this protocol. The CMRR Center's screening tools and SOP are IRB approved under the CMRR Center Grant (HSC# 1406M51205) and information regarding screening procedures is publically available on the CMRR website (CMRR Policies / Procedures).
Individuals will complete a screening questionnaire for contraindications of MRI scanning. Any affirmative responses on the questionnaire will result in an interview regarding the possible contraindication. An attempt will be made to secure any records to better understand the nature of the possible contraindication and this information will be reviewed by the PI, MRI Co-Investigator, and CMRR staff at the University of Minnesota. If staff suspects metal in a participant's body, the participant will have the option to undergo a low dose, whole body Computed Tomography (CT) scan prior to the MRI in order to ensure their safety and eligibility. The CT scan will take place at the CMRR at the University of Minnesota. The CT scan results will be reviewed by a CMRR radiologist. Based on the results, a determination will be made regarding the level of risk to the subject and whether they are approved for scanning. If the participant has certain problematic iron or steel implants in their body that cannot be removed, the subject may not have the scan and will be excluded from that part of the study. If the CT scan does not show evidence of problematic metal in the body, and the participant is approved for scanning by professionals, the results of the CT scan, all risks to the participant, including any concerns from the PI, CMRR staff and/or MRI co-investigator, will be conveyed to the participant (and if the participant is under 18, the parent/guardian) so they can decide whether or not they want to complete the MRI procedure. If a participant chooses to undergo a CT scan and are subsequently found to be ineligible for the MRI scan, or if they decide not to proceed with the MRI scan, they will be compensated on a pro-rated hourly basis of $20 per hour.

During the COVID-19 pandemic, scans will be conducted in accordance to the CMRR policy. Participants will be asked safety screening questions ahead of the scan, and will also be given an information sheet issued by the CMRR regarding COVID-19 safety.

Moreover, since many of these scans will be conducted months after the participants' latest clinical interview, participants whose interviews would have taken place three months prior to the scheduled scan time will be asked to complete the BDI-II and SITBI over Zoom again. Lifetime questions on the SITBI will be omitted.

The WASI, ANT, and IGT, will also be conducted at the MRI visit due to the in-person nature of these tasks/assessments, and the switch to remote study procedures for the Intake and Trier.

Anatomical Data. A high-resolution T1 (7 minutes) and T2 (6 minutes) weighted images will be collected with 0.8mm isotropic voxel resolution. Field Map. Two HCP spin echo EPI field map scans (AP and PA phase encode, 1 minute total) will be acquired with voxel parameters matching those of the fMRI task acquisition 2mm isotropic voxel resolution and will be used to correct the fMRI data for the geometric distortion caused by magnetic field inhomogeneity.

Functional Data. All functional data will be acquired using the HCP multiband echo planar imaging sequence. Whole brain T2*- weighted functional volumes with 2mm isotropic voxel resolution will be obtained during rest and in conjunction with the tasks listed below. Resting-state fMRI data will be collected for twelve minutes with eyes open while viewing a fixation cross. The duration of 12 minutes and the choice of fixation cross as the resting condition are selected to optimize reliability.120,121 The subject will then complete three tasks –Threat (emotion matching task, 1 run @ 7 minutes), Self-Evaluation (or Self vs. Change, 2 runs @ 5 minutes each) and the Emotional Go-NoGo (2 runs @ 5 minutes each) in the scanner.

Diffusion Weighted Imaging. Two whole brain diffusion weighted scans (AP and PA phase encode) will be acquired using the CMRR multi-band diffusion weighted sequence. These scans have a 1.5mm isotropic voxel resolution, include 159 volumes, and last 8 minutes per scan.

3.5.5 Data Sharing with RDoCdb

Every 6 months, data from this study will be submitted to the Research Domain Criteria Database (RdoCdb). RdoCdb is a data repository run by the National Institute of Mental Health (NIMH) that allows researchers studying mental illness to collect and share deidentified information with each other. Other researchers nationwide can then file an application with the NIMH to obtain access to deidentified study data for research purposes. Study information will be de-identified using NIMH's Global Unique Identifier system (GUID) allowing for subjects to be identified across research labs without having any personally identifiable information being transmitted or shared.

3.5.6 Schedule of activities (Study Table).

Activities	Clinician or Administered (CA) Selfreport (SR)	Child (C) or Parent/ Guardian (PG)	Assessment			TSST			MRI			Online
			Y1	Y2	Y3	Y1	Y2	Y3	Y1	Y2	Y3	
Consent/ HIPAA	CA	PG	X									
Assent	CA	C	X									
UBACC	CA	PG/C	X									
KSADS	CA	PG/C	X	X	X							
WASI-II	CA	C	X									
Edinburgh	CA	C	X									
Demographics Form	SR	PG	X	X	X							
TLFB for NSSI	CA	C	X	X	X							
CDRS-R	CA	PG/C	X	X	X							
GAD-7	SR	C	X	X	X							
Tanner Staging	SR	C	X	X	X							
EDS	SR	C		X	X							
CTQ	SR	C	X	X	X							
SITBI	CA	C	X	X	X							
BSSI	SR	C	X	X	X							
RSQ-A	SR	C										X

SCL-90	SR	C										X
PAI-A	SR	C	X	X	X							
SPPA	SR	C							X	X	X	
TAS-20	SR	C										X
UPPS-P	SR	C										X
BDI-II	SR	C	X	X	X							
EDE-Q	SR	C										X
Satisfaction with Life	SR	C										X
PANAS-X	SR	C										X
PSQI	SR	C										X
Cash Choice	SR	C										X
EAC	SR	PG	X	X	X							
CBCL	SR	PG	X	X	X							
SIAS	SR	C	X	X	X				X	X	X	
COVID-19 Health Changes	SR	C		X	X							
Attention Bias Task	CA	C				X	X	X				
IGT	CA	C				X	X	X				
ANT	CA	C				X	X	X				
TSST	CA	C				X	X	X				
Basal Saliva	SR	C				X	X	X				
Structural MRI	CA	C							X	X	X	
Diffusion Tensor	CA	C							X	X	X	

Imaging (DTI)												
Resting State fMRI	CA	C							X	X	X	
RSPSQ	SR	C							X	X	X	
Hariri Task	CA	C							X	X	X	
HPSQ	SR	C							X	X	X	
Self-Knowledge Task	CA	C							X	X	X	
Emotional Go-No-Go Task	CA	C							X	X	X	
EGNGQ	SR	C							X	X	X	

3.5.7 Compensation

Payment Method: Participants will be given a pre-paid debit card called Greenphire ClinCard. After each completed visit for the study, money will be added to the card. The debit card system is administered by an outside company. The company, Greenphire, will be given the name of each participant. They will use this information only as part of the payment system. The information will not be used for any other purposes and will not be given or sold to any other company. Greenphire will not receive any information about health status or the study.

Payment received as compensation for participation in research is considered taxable income. If payment to an individual exceeds $600 in any one calendar year, the University of Minnesota is required to report this information to the Internal Revenue Service (IRS). Research payments to study participants exceeding $600.00 during any calendar year will result in a FORM 1099 (Miscellaneous Income) being issued to the participant and a copy sent to the IRS.

Compensation per Visit (adjusted for the pandemic):

- Clinical assessment visit. For each of the clinical assessment visits, adolescents receive $40. As noted above, the clinical interviews are limited to 3 hours to limit participant fatigue. If the interviews are not complete in that time frame, participants are invited to complete them in an additional session on a different day. In that case, they receive $20 per each additional hour for completing the interview.

- Speech task and cortisol samples. For each of the speech task appointments, which take place in person or online, adolescents receive $20. For each time they complete the home saliva samples and diary, they will receive $10.
- MRI + cognitive task visits. For each of these in-person visits, which now include MRI and cognitive assessments, the adolescents receive $60. If the adolescent needs to return to the CMRR to repeat any procedures, such as if technical errors occurred during data collection, they will be compensated of $20 per each additional hour of time at the CMRR. In the IGT task, the participants are told that they will be able to keep any winnings (anything above the starting amount of $5.00) but that they will not have to pay if they lose money in the game (i.e., if they have less than $5.00 at the end). Any winnings (maximum = $5.00) will be added to the usual compensation for that visit ($60).
- On-line assessments. Each time they complete the online battery of assessments, adolescents will receive $20. If participants prefer to complete these in-person, we will arrange a visit at MIDB.
- Lodging may be provided for participants residing out of the state, and participants in need of transportation assistance will be compensated for transportation.
- Participants will be reimbursed for parking costs related to each visit.
- Compensation is pro-rated according to each completed visit.

3.6 Study outcome evaluations:

3.6.1 Study endpoints.

All participants will be asked to complete the clinical assessments, Trier Social Stress Test (TSST), online questionnaires, and MRI 3 times, once every 12 months.

3.6.2 Sample size determination.

By recruiting 152 participants, we expect a final sample size of 30 participants in each of the 4 groups with usable data at the third (last) study time point. The study is powered to achieve Specific Aims 1 and 3 based on our cross-sectional pilot data. Type I error is 5% except where otherwise specified.

Specific Aim 1. H1A, H1B: With N=152, we will have 85% power to detect correlations as small as 0.25 of NSSI severity with RDoC measures. If considering NSSI severity on a continuous scale is unreasonable, we have 85% power to detect group differences in RDoC measures as shown in Table 6, using Bonferroni correction of type I error for 6 pairwise comparisons among the 4 groups. Larger differences than those listed were found in our pilot data; for these outcomes this large of a sample

size is not needed, but the larger sample size will allow testing for significant differences in other RDoC indices that showed trends in pilot data. H1C: With N=38 per NSSI group with complete data at visit 1, we will have 85% power to detect correlations within NSSI group as small as 0.50 among imaging and clinical measures, or as small as 0.25 if NSSI groups can be pooled.

Specific Aim 3 (longitudinal trajectories). With N=30 expected at last follow-up per group, we have 85% power to detect group differences in changes in circuits as shown in Table 7, using Bonferroni correction of type I error for 6 pairwise comparisons among the 4 groups. The minimum differences listed are smaller than those observed in our pilot exploration of the interaction between age group and NSSI vs. HC group. With N=152 recruited, we will have 85% power to detect correlations as small as 0.25 of changes in circuits self-reports or physiology with NSSI severity.

Table 6. Minimum detectable differences among NSSI severity groups at baseline and over time

Sustained Threat	Minimum group difference at baseline	Self-Knowledge	Minimum group difference at baseline
Rejection Sensitivity	19.2	Alexithymia (TAS)	7.6
Amygdala-Frontal RSFC	0.723	Rostral-Posterior Cingulate RSFC	.231

Table 7. Minimum detectable differences among NSSI severity groups over time

Sustained Threat	Minimum group difference in changes	Self Knowledge	Minimum group difference in changes
Amygdala activation to threat	0.87	Rostral ACC- Post. cingulate RSFC	.181
Frontal activation to threat	1.23	Precuneus activation to threat	.72

3.6.3 Outcome data and data analysis.

Aim 1: Self-report, physiology, behavior and circuit measures will be summarized, by group and overall, graphically and using summary statistics to examine and compare their distributions (e.g., mean shifts, variability, skewness). In relating NSSI severity to multi-modal assessments of Sustained Threat, Self Knowledge and Cognitive Control, we will consider continuous scales (based on number of lifetime episodes

and frequency) if NSSI severity varies smoothly, and if not we will consider the categorical NSSI groups.

Hypothesis 1A and 1B. We will utilize a supervised learning approach for classification (specifically, Distance Weighted Discrimination) to identify which individual (1A) and combinations of (1B) characteristics (all levels included: neural, clinical, self-report) most strongly distinguish the NSSI severity groups from each other. Models will adjust for age, IQ, SES, and other covariates (e.g. depressive symptoms, family history, adverse experiences) identified as potential confounders. Classification accuracy will be quantified using 10-fold cross- validation.

Hypothesis 1C. Simple graphical displays of data and their correlations across units of analysis will be done, with color- coding by NSSI group and construct. We will then use confirmatory factor analysis (CFA) to test the hypothesis that all units of analysis (circuits, physiology, behavior, self-report) cohere within the proposed RDoC constructs. We expect that some of these measures will not converge within constructs, in which case exploratory factor analysis (EFA) will be the next step to elucidate the latent constructs to which these measures do adhere.
Data reduction: If the factor analysis developed for Hypothesis 1.C. strongly identifies underlying latent constructs based on the combination of circuits, physiology, behavior, and selfreport, we will use the factor loadings as the predictors of NSSI severity rather than the separate levels of measurement. The factor analysis can be repeated using each visit's data so that time- updated factor loadings can be used in modeling for Aim 3.

For all analyses, model appropriateness will be assessed using diagnostics, and transformations, covariate functional forms, and models will be altered if needed.

Aim 1 Expected Outcomes: This approach, using all levels of data together at baseline, will allow inference of which adolescent characteristics best differentiate the NSSI severity groups, separately for each pair of groups (e.g., the characteristics distinguishing moderate from mild NSSI groups may not be the same as the characteristics that distinguishing mild from no NSSI). We expect that within-construct and across-construct indices will incrementally predict NSSI severity (H1A and H1B), supporting the proposed relevance of these constructs to NSSI. If indices from some units predict NSSI severity to a greater extent than others, this would guide future researchers in selecting the measures

most predictive of NSSI severity. We expect that within constructs, across-unit measures will show some evidence of convergence (H.1.C), supporting the proposed conceptualization of the neurobehavioral dimensions. If we find evidence of divergence, this could guide future research on these constructs (i.e., selection of measures that might have stronger inter-relationships, and fine- tune current conceptualization of the construct.)

Aim 2. We will use multi-state modeling to examine how baseline measures of the 3 study constructs predict NSSI severity at follow- up. In this approach, the response is group membership, and we model the transition from any group to the other at any time point. Multi-state models provide estimates of the transition intensities (reflecting the 'risk' of transitioning from each state to each other state) as a function of patient characteristics, including potential confounders as discussed in Aim 1.

Aim 2 Expected Outcomes: We will identify which individual and combination of characteristics predict transitions, including which specific transitions and the direction of association (e.g., protective vs. risk factor).

Aim 3.
Longitudinal trajectories in RDoC constructs: We will conduct a series of repeated measures ANOVAs using linear mixed models, with each RDoC index listed above as the outcome and NSSI severity group as the between-subject variable, adjusting for covariates such as SES, IQ, psychopathology, and treatments received in the intervening periods. In these models, we will use age-at-visit rather than date-of-visit as the time axis; this will accommodate the inevitable irregularity in actual visit dates targeted to occur every 12 months and will align the data across participants in time more closely with developmental stages. Because of concerns that psychopathology will differ substantially across groups, as an alternative to the proposed covariate adjustment, we will consider Inverse Probability Weighting (IPW; see e.g. Lunceford and Davidian, Stat Med 2004; 23:2937). IPW first predicts the probability of NSSI group membership based on, for example, the psychopathology features as well as other relevant measures such as family history of these conditions. Then the linear mixed models for estimating construct developmental trajectories over time are reweighted using the inverse of these estimated probabilities, which imposes a covariate balance on the sample. Estimated differences in developmental trajectories between NSSI severities are then interpreted as differences due to NSSI that we would see if the psychopathology and family history were balanced across the

severity groups. We will estimate the weights using random forests (see e.g. Hastie et al., Elements of Statistical Learning, Springer) for a multinomial outcome (NSSI severity groups); the random forest approach is a more robust way to estimate group probabilities (than e.g. a simple multinomial model) and will guard against overfitting.

Missing data considerations: We will compare (within group and between groups) the clinical and imaging characteristics of any dropouts to those who did not drop out, and use this to inform the interpretation of the magnitude and direction of NSSI group differences in longitudinal trajectories.

Between-construct dynamic interactions: Through comprehensive measurement of the three proposed systems over time, we aim to examine dynamic interaction between the systems. For example, we anticipate that abnormalities within the sustained threat domain in early adolescence could lead to abnormalities in the self- knowledge system at a later stage, because of the impact of sustained stress responses on the developmental processes of self- perception during adolescence. We would predict that this interaction would be associated with a worsening or persistent NSSI course. Another possible dynamic interaction could be that baseline abnormalities in cognitive control could, over time, exacerbate abnormalities in the sustained threat system (because of the impact of sustained impairments in self-regulation generally).
These hypotheses can be tested using cascade analyses (see e.g. Klimes-Dougan et al. Devel Psychopath 2010; 22:849). To implement such an approach, we will postulate specific ways in which the systems might plausibly interact and impact NSSI severity; our postulations will be based on psychopathology theory and our clinical experience with NSSI. Interaction models will then be built and estimated (one based on each postulation) and then compared to each other to identify the model with the best fit for predicting NSSI severity.

Aim 3 Expected Outcomes: Adolescents with no NSSI at baseline or the follow-ups will demonstrate developmental trajectories similar to that in published literature (if any) for healthy adolescents in this age group and will be considered as the normative trajectory. Trajectories in adolescents with NSSI will deviate from the norm, in a pattern where the adolescents with the most severe NSSI will show the most abnormal trajectories. Among adolescents whose baseline group assignment is transient NSSI, those who ultimately transition to higher-severity NSSI will show more abnormal trajectories, whereas those who ultimately remit will show more normal trajectories.

4. Risk analysis

4.1 Anticipated risks:

4.1.1 Screening Visit

Our clinical assessment of all adolescents and parents of children enrolled in the study involves asking questions about feelings, past experiences, and family history. Some of these topics may cause the subjects and/or their parents discomfort or distress. Participants are encouraged to share only what they feel comfortable with and will not be induced to discuss anything that makes them too uncomfortable.

4.1.2 Trier Social Stress Test

This procedure is designed to elicit a mild stress response. Some participants may become distressed by this procedure. The research team members who have been trained to administer the TSST are also trained to recognize signs of distress. If at any point the participant becomes too stressed, the research staff will stop the procedure. Additionally, if the participant wishes to discontinue the procedure, they may do so.

4.1.3. MRI and CT Scanning

The device to be used in the study is a 3 Tesla Siemens Prisma MRI machine.

The magnet in the scanner may cause electronic devices like watches to malfunction, and some metal objects can be pulled into the scanner. Participants will be screened prior to the scan to make sure they have nothing in their body that could be magnetic or affected by the magnetic field of the scanner. Participants will be asked to change into scrubs to ensure they have no metal on their person.

It may be uncomfortable lying still in the scanner for the amount of time required. The participant may experience some stiffness and soreness in the muscles from being still. To make participants as comfortable as possible, we will provide soft pads to help support the next, back, and legs.

The scanner itself makes a lot of noise while it is running. This can be uncomfortable and may affect the participant's hearing. Participants will be asked to wear ear plugs which will significantly reduce the amount of noise. Participants will also be wearing headphones in addition to the earplugs to allow them to hear the investigators and listen to music.

Some people may become uncomfortable in the scanner because they are not comfortable being in enclosed spaces. We will screen for claustrophobia before we bring the participant to the scan center. They will have the option of using a mock scanner prior to going into the scanner to assess their level of comfort. They will not be required to participate in the scan or continue the scan if they are uncomfortable.

There is a chance we might find something abnormal when we look at the images of the participant's brain. If a member of the research team notices something unusual in the MRI results, they will send it to a trained radiologist after the scan so they can be assessed for abnormalities. These images will not have any identifying information about the patient. If the radiologist recommendation is to further investigate the unusual results of the pictures, the investigator will contact the participant.

Part of the MRI scan is designed to induce different kinds of feelings, both negative and positive. Because of this, it is possible that the participant may become sad or distressed by the negative pictures. We will encourage the participant to let us know if they are feeling upset, and we will plan to discontinue the procedure whenever they wish to stop. The participant will be shown examples of the images in the scan before going into the scanner. If the participant decides that the images would be too much for them to tolerate, the scan will be skipped in its entirety.

CT Scan: If the study team suspects that the participant may have metal in their body, they will be given the option of having a CT scan. The CT scan involves exposure to ionizing radiation in the form of x-rays. Everyone receives a small amount of unavoidable radiation each year from space and from naturally occurring radioactive materials in the environment. The amount of radiation exposure received from a CT scan varies according to the size of the patient and the portion of the body that is scanned. The low dose CT scan performed for this study gives the body the equivalent of about 1 year or less of natural background radiation. At such low radiation exposures scientists disagree about the amount of risk,

and there may be no extra risk at all. The radiation discussed here does not include any exposure a subject might receive from his/her regular medical care. The radiation, and procedures used in this study and any other studies may involve risks to an infant, embryo, fetus or nursing infant, which are not known at this time. Therefore, if a subject is pregnant, planning to become pregnant, or nursing, they will be told they cannot participate in the CT scan and therefore also not the MRI portion of this study.

4.1.4. Loss of Confidentiality

As with all research, there is a chance participants may suffer a loss of confidentiality. We will do everything in our power to limit the chances of this occurring. Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

4.1.5 Email Risks

Participants will be able to opt in to communicating with study staff via unencrypted email to arrange their appointments and receive study instructions. There are risks associated with email communication, and these risks increase when the emails are sent without an encryption service. Risks of sending or receiving emails without encryption include, but are not limited to:

- Others can intercept messages
- If messages are sent or received on an employer-owned device, the employer may have the right to save and read the messages. The

internet or cell-phone provider may also have the right to save and read email messages.

- A copy of the message may be saved on a device or computer system, even if it is deleted.
- If an email address is not typed correctly, it can be sent to the wrong person
- Emails can spread computer viruses.
- Others may be able to access messages on devices that were lost, stolen, or thrown away.
- If a user changes emails without notifying study staff, they may miss communications.

4.1.6 Text Message Risks

Participants will be able to opt in to communicating with study staff via text message to arrange their appointments and receive study instructions. There are risks associated with communication via text message. Risks of sending or receiving text messages include, but are not limited to:

- Others can intercept messages
- Text messages may be viewed by University of Minnesota staff depending on the nature and timing of said messages, and may be monitored by the University to ensure appropriate use.

If messages are sent or received on an employer-owned device, the employer may have the right to save and read the messages. The cell-phone provider may also have the right to save and read text messages.

4.2 Adverse event recording/reporting

4.2.1 Adverse event definitions.

Adverse effect. Any untoward medical occurrence in a clinical study of an investigational device; regardless of the causal relationship of the problem with the device or, if applicable, other study treatment or diagnostic product(s).

Associated with the investigational device or, if applicable, other study treatment or diagnostic product(s). There is a reasonable possibility that the adverse effect may have been caused by the investigational device or, if applicable, the other study treatment or diagnostic product(s).

Disability. A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse effect. Any adverse effect that places the subject, in the view of the investigator-sponsor, at immediate risk of death from the effect as it occurred (i.e., does not include an adverse effect that, had it actually occurred in a more severe form, might have caused death).

Serious adverse effect. Any adverse effect that results in any of the following outcomes: death, a life-threatening adverse effect, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

- *Hospitalization* shall include any initial admission (even if less than 24 hours) to a healthcare facility as a result of a precipitating clinical adverse effect; to include transfer within the hospital to an intensive care unit. Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse effect (e.g., for a preexisting condition not associated with a new adverse effect or with a worsening of the preexisting condition; admission for a protocol-specified procedure) is not, in itself, a serious adverse effect.

Unexpected adverse effect. Any adverse effect, the frequency, specificity or severity of which is not consistent with the risk information described in the clinical study protocol(s) or elsewhere in the current IDE application, as amended.

Unanticipated adverse device effect. Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

4.2.2 Eliciting adverse effect information.

Clinical study subjects will be routinely questioned about adverse effects at study visits.

4.2.3 Recording and assessment of adverse effects.

All observed or volunteered adverse effects (serious or non-serious) and abnormal test findings, will be recorded in the subjects' case histories. For all adverse effects, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the effect (i.e., whether the effect should be classified as a *serious adverse effect*) and; 2) an assessment of the casual relationship between the adverse effect and the study activities.

Adverse effects or abnormal test findings felt to be associated with the studywill be followed until the effect (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator-sponsor.

4.2.3.1 *Abnormal test findings*:

An abnormal test finding will be classified as an *adverse effect* if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms.
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug or other therapy. (Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse effect.)

- The test finding leads to a change in study dosing or exposure or discontinuation of subject participation in the clinical study.

- The test finding is considered an adverse effect by the investigatorsponsor.

4.2.3.2 *Causality and severity assessment*:

The investigator-sponsor will promptly review documented adverse effects and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse effect; 2) if there is a reasonable possibility that the adverse effect was caused by the investigational device or, if applicable, other study treatment or diagnostic product(s); and 3) if the adverse effect meets the criteria for a *serious adverse effect*.

If the investigator-sponsor's final determination of causality is "unknown and of questionable relationship to the investigational device or, if applicable, other study treatment or diagnostic product(s)", the adverse effect will be classified as *associated with the use of the investigational device or study treatment or diagnostic drug product(s)* for reporting purposes. If the investigator-sponsor's final determination of causality is "unknown but not related to the investigational device or, if applicable, other study treatment or diagnostic product(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

4.2.4 Reporting of adverse effects to the responsible IRB.

In accordance with applicable policies of the University of Minnesota Institutional Review Board (IRB), the investigator-sponsor will report, to the IRB, any observed or volunteered adverse effect that is determined to meet all of the following criteria: 1) *associated with the investigational device or, if applicable, other study treatment or diagnostic product(s)*; 2) *a serious adverse effect*; and 3) an *unexpected adverse effect*. Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures. Applicable adverse effects will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the investigator-sponsor's receipt of the respective information. Adverse effects which are 1) *associated with the investigational drug or, if applicable, other study treatment or diagnostic product(s)*; 2) *fatal or life-threatening*; and 3) *unexpected* will be reported to the IRB within 24 hours of the investigator-sponsor's receipt of the respective information.

Follow-up information to reported adverse effects will be submitted to the IRB as soon as the relevant information is available. If the results of the sponsor-investigator's follow-up investigation show that an adverse effect that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting; the investigator-sponsor will report the adverse effect to the IRB as soon as possible, but in no event later than 10 calendar days, after the determination was made.

4.3 Withdrawal of subjects due to adverse effects:

Subjects who experience severe adverse events will be immediately withdrawn from the study. Subjects who experience mild to moderate adverse events will be allowed to discontinue if they would like to.

Subjects withdrawn from study participation due to an adverse effect will not be replaced as we have included more people than necessary in our original sample size for situations such as subject withdrawal or bad MRI data.

4.4 Population-specific Considerations

The population being researched in this study has a higher risk for suicidal ideation, suicide attempts, and serious injury due to self-harm. The research team will monitor depression, suicidal ideation, and self-harm behaviors at each assessment. Participants who indicate suicidal ideation or significantly increased self-harm behaviors will be asked to meet with one of the investigators of the study to assess risk.

Participants with suicidal ideation with no plan or intent who agree to a safety plan (either developed with the investigator or a pre-existing safety plan) will be allowed to continue in the study. The investigator will inform parents of the discussion and safety plan (if applicable).

Participants with severe self-harm (requiring stitches or hospitalization), suicidal ideation with intent, or those who cannot or will not agree to a safety plan will be referred to the Emergency Room. The study team will assist with determining the need to call emergency services (e.g. 911, county crisis teams) versus recommending that parents transport the adolescent to the emergency room on their own.

5. References

1. Casey BJ, Oliveri ME, Insel T. A neurodevelopmental perspective on the research domain criteria (RDoC) framework. Biological psychiatry. Sep 1 2014;76(5):350-353.

2. Jacobson CM, Gould M. The epidemiology and phenomenology of non-suicidal self-injurious behavior among adolescents: a critical review of the literature. Archives of suicide research : official journal of the International Academy for Suicide Research. 2007;11(2):129-147.

3. Asarnow JR, Porta G, Spirito A, et al. Suicide attempts and nonsuicidal self-injury in the treatment of resistant depression in adolescents: findings from the TORDIA study. Journal of the American Academy of Child and Adolescent Psychiatry. Aug 2011;50(8):772-781.

4. Hall DJ, O'Brien F, Stark C, et al. Thirteen-year follow-up of deliberate self-harm, using linked data. The British journal of psychiatry : the journal of mental science. Mar 1998;172:239-242.

5. Kuehl S, Nelson K, Collings S. Back so soon: rapid re-presentations to the emergency department following intentional self-harm. The New Zealand medical journal. Dec 14 2012;125(1367):70-79.

6. Tang J, Yu Y, Wu Y, et al. Association between non-suicidal self-injuries and suicide attempts in Chinese adolescents and college students: a cross-section study. PloS one. 2011;6(4):e17977.

7. Brent DA, McMakin DL, Kennard BD, et al. Protecting adolescents from self-harm: a critical review of intervention studies. Journal of the American Academy of Child and Adolescent Psychiatry. Dec 2013;52(12):1260-1271.

8. De Silva S, Parker A, Purcell R, et al. Mapping the evidence of prevention and intervention studies for suicidal and self-harming behaviors in young people. Crisis. Jan 1 2013;34(4):223-232.

9. Taylor TL, Hawton K, Fortune S, et al. Attitudes towards clinical services among people who self-harm: systematic review. The British journal of psychiatry : the journal of mental science. Feb 2009;194(2):104-110.

10. Westlund Schreiner M, Klimes-Dougan B, Begnela EG, et al. Conceptualizing the neurobiology of non-suicidal self-injury from the perspective of the research domain criteria project (available online 28 September 2015). Neuroscience & Biobehavioral Reviews. in press.

11. Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. The American journal of psychiatry. Jul 2010;167(7):748-751.

12. Insel TR. The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry. The American journal of psychiatry. Apr 2014;171(4):395-397.

13. Klonsky ED. The functions of deliberate self-injury: a review of the evidence. Clinical psychology review. Mar 2007;27(2):226-239.

14. Andrews T, Martin G, Hasking P, et al. Predictors of onset for non-suicidal self- injury within a school-based sample of adolescents. Prevention science : the official journal of the Society for Prevention Research. Dec 2014;15(6):850-859.

15. Cawood CD, Huprich SK. Late adolescent nonsuicidal self-injury: the roles of coping style, self-esteem, and personality pathology. Journal of personality disorders. Dec 2011;25(6):765-781.

16. Hawton K, Kingsbury S, Steinhardt K, et al. Repetition of deliberate self-harm by adolescents: the role of psychological factors. Journal of adolescence. Jun 1999;22(3):369-378.

17. Iannaccone M, Cella S, Manzi SA, et al. My body and me: self-injurious behaviors and body modifications in eating disorders--preliminary results. Eating disorders. 2013;21(2):130-139.

18. Leong CH, Wu AM, Poon MM. Measurement of perceived functions of non-suicidal self-injury for Chinese adolescents. Archives of suicide research : official journal of the International Academy for Suicide Research. 2014;18(2):193-212.

19. Nelson A, Muehlenkamp JJ. Body attitudes and objectification in non-suicidal self-injury: comparing males and females. Archives of suicide research : official journal of the International Academy for Suicide Research. 2012;16(1):1-12.
20. Tatnell R, Kelada L, Hasking P, et al. Longitudinal analysis of adolescent NSSI:
the role of intrapersonal and interpersonal factors. Journal of abnormal child psychology. Aug 2014;42(6):885-896.
21. Hamza CA, Willoughby T, Heffer T. Impulsivity and nonsuicidal self-injury: A review and meta-analysis. Clinical psychology review. Jun 2015;38:13-24.
22. Klimes-Dougan B, Long JD, Lee CY, et al. Continuity and cascade in offspring of bipolar parents: a longitudinal study of externalizing, internalizing, and thought problems. Development and psychopathology. Nov 2010;22(4):849-866.
23. Alon U. An introduction to systems biology: Design principles of biological circuits (chapter 6). New York: Chapman & Hall/CRC; 2007.
24. Cole DA, Maxwell SE. Testing mediational models with longitudinal data: questions and tips in the use of structural equation modeling. Journal of abnormal psychology. Nov 2003;112(4):558-577.
25. Masten AS, Curtis WJ. Integrating competence and psychopathology: pathways toward a comprehensive science of adaptation in development. Development and psychopathology. Summer 2000;12(3):529-550.
26. van der Kolk BA, Perry JC, Herman JL. Childhood origins of self-destructive behavior. The American journal of psychiatry. Dec 1991;148(12):1665-1671.
27. Fisher HL, Moffitt TE, Houts RM, et al. Bullying victimisation and risk of self harm in early adolescence: longitudinal cohort study. Bmj. 2012;344:e2683.
28. McMahon EM, Reulbach U, Keeley H, et al. Bullying victimisation, self harm and associated factors in Irish adolescent boys. Social science & medicine. Oct 2010;71(7):1300-1307.
29. Cox LJ, Stanley BH, Melhem NM, et al. A longitudinal study of nonsuicidal self- injury in offspring at high risk for mood disorder. The Journal of clinical psychiatry. Jun 2012;73(6):821-828.
30. Tuisku V, Kiviruusu O, Pelkonen M, et al. Depressed adolescents as young adults - predictors of suicide attempt and non-suicidal self-injury during an 8-year follow-up. Journal of affective disorders. Jan 2014;152-154:313-319.
31. Muehlmann AM, Kies SD, Turner CA, et al. Self-injurious behaviour: limbic dysregulation and stress effects in an animal model. Journal of intellectual disability research : JIDR. May 2012;56(5):490-500.
32. Allman JM, Hakeem A, Erwin JM, et al. The anterior cingulate cortex. The evolution of an interface between emotion and cognition. Annals of the New York Academy of Sciences. May 2001;935:107-117.
33. Phillips ML, Drevets WC, Rauch SL, et al. Neurobiology of emotion perception I: The neural basis of normal emotion perception. Biological psychiatry. Sep 1 2003;54(5):504-514.
34. Niedtfeld I, Schulze L, Kirsch P, et al. Affect regulation and pain in borderline personality disorder: a possible link to the understanding of self-injury. Biological psychiatry. Aug 15 2010;68(4):383-391.

35. Plener PL, Bubalo N, Fladung AK, et al. Prone to excitement: adolescent females with Non-suicidal self-injury (NSSI) show altered cortical pattern to emotional and NSS-related material. Psychiatry research. Aug-Sep 2012;203(2-3):146-152.

36. Birn RM, Shackman AJ, Oler JA, et al. Evolutionarily conserved prefrontal-amygdalar dysfunction in early-life anxiety. Molecular psychiatry. Aug 2014;19(8):915-922.

37. Kaess M, Hille M, Parzer P, et al. Alterations in the neuroendocrinological stress response to acute psychosocial stress in adolescents engaging in nonsuicidal self-injury. Psychoneuroendocrinology. Jan 2012;37(1):157-161.

38. Powers SI, McArdle ET. Coping strategies moderate the relation of hypothalamus-pituitary-adrenal axis reactivity to self-injurious behavior. Annals of the New York Academy of Sciences. Dec 2003;1008:285-288.

39. Cunningham MG, Bhattacharyya S, Benes FM. Amygdalo-cortical sprouting continues into early adulthood: implications for the development of normal and abnormal function during adolescence. The Journal of comparative neurology. Nov 11 2002;453(2):116-130.

40. Monk CS, McClure EB, Nelson EE, et al. Adolescent immaturity in attention-related brain engagement to emotional facial expressions. NeuroImage. Sep 2003;20(1):420-428.

41. Yurgelun-Todd DA, Killgore WD. Fear-related activity in the prefrontal cortex increases with age during adolescence: a preliminary fMRI study. Neuroscience letters. Oct 9 2006;406(3):194-199.

42. Stroud LR, Foster E, Papandonatos GD, et al. Stress response and the adolescent transition: performance versus peer rejection stressors. Development and psychopathology. Winter 2009;21(1):47-68.

43. Gunnar MR, Wewerka S, Frenn K, et al. Developmental changes in hypothalamus-pituitary-adrenal activity over the transition to adolescence: normative changes and associations with puberty. Development and psychopathology. Winter 2009;21(1):69-85.

44. Claes L, Houben A, Vandereycken W, et al. Brief report: the association between non-suicidal self-injury, self-concept and acquaintance with self-injurious peers in a sample of adolescents. Journal of adolescence. Oct 2010;33(5):775-778.

45. Howe-Martin LS, Murrell AR, Guarnaccia CA. Repetitive nonsuicidal self-injury as experiential avoidance among a community sample of adolescents. Journal of clinical psychology. Jul 2012;68(7):809-829.

46. Swannell S, Martin G, Page A, et al. Child maltreatment, subsequent non-suicidal self-injury and the mediating roles of dissociation, alexithymia and self-blame. Child abuse & neglect. Jul-Aug 2012;36(7-8):572-584.

47. Cohen JN, Stange JP, Hamilton JL, et al. The interaction of affective states and cognitive vulnerabilities in the prediction of non-suicidal self-injury. Cognition & emotion. 2015;29(3):539-547.

48. You J, Lin MP, Leung F. A longitudinal moderated mediation model of nonsuicidal self-injury among adolescents. Journal of abnormal child psychology. Feb 2015;43(2):381-390.

49. Gusnard DA, Akbudak E, Shulman GL, et al. 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. Mar 27 2001;98(7):4259-4264.

50. Northoff G, Qin P, Feinberg TE. Brain imaging of the self--conceptual, anatomical and methodological issues. Consciousness and cognition. Mar 2011;20(1):52-63.

51. Wiley RE, Berman SL. Adolescent identity development and distress in a clinical sample. Journal of clinical psychology. Dec 2013;69(12):1299-1304.

52. Harter S. The construction of the self: A developmental perspective. Guilford; 1999.

53. Pfeifer JH, Lieberman MD, Dapretto M. "I know you are but what am I?!": neural bases of self- and social knowledge retrieval in children and adults. Journal of cognitive neuroscience. Aug 2007;19(8):1323-1337.

54. Pfeifer JH, Masten CL, Borofsky LA, et al. Neural correlates of direct and reflected self-appraisals in adolescents and adults: when social perspective-taking informs self-perception. Child development. Jul-Aug 2009;80(4):1016-1038.

55. Pfeifer JH, Kahn LE, Merchant JS, et al. Longitudinal change in the neural bases of adolescent social self-evaluations: effects of age and pubertal development.
The Journal of neuroscience : the official journal of the Society for Neuroscience. Apr 24 2013;33(17):7415-7419.

56. Fair DA, Cohen AL, Dosenbach NU, et al. The maturing architecture of the brain's default network. Proceedings of the National Academy of Sciences of the United States of America. Mar 11 2008;105(10):4028-4032.

57. Janis IB, Nock MK. Are self-injurers impulsive?: Results from two behavioral laboratory studies. Psychiatry research. Oct 30 2009;169(3):261-267.

58. Claes L, Vandereycken W, Vertommen H. Self-injurious behaviors in eating-disordered patients. Eating behaviors. Autumn 2001;2(3):263-272.

59. Herpertz S, Sass H, Favazza A. Impulsivity in self-mutilative behavior: psychometric and biological findings. Journal of psychiatric research. Jul-Aug 1997;31(4):451-465.

60. Claes L, Fagundo AB, Jimenez-Murcia S, et al. Is non-suicidal self-injury related to impulsivity in anorexia nervosa? Results from self-report and performance- based tasks. European eating disorders review : the journal of the Eating Disorders Association. Jan 2015;23(1):28-33.

61. Fikke LT, Melinder A, Landro NI. Executive functions are impaired in adolescents engaging in non-suicidal self-injury. Psychological medicine. Mar 2011;41(3):601- 610.

62. Bresin K, Carter DL, Gordon KH. The relationship between trait impulsivity, negative affective states, and urge for nonsuicidal self-injury: a daily diary study. Psychiatry research. Feb 28 2013;205(3):227-231.

63. Glenn CR, Klonsky ED. A multimethod analysis of impulsivity in nonsuicidal self- injury. Personality disorders. Jan 2010;1(1):67-75.

64. Peterson CM, Fischer S. A prospective study of the influence of the UPPS model of impulsivity on the co-occurrence of bulimic symptoms and non-suicidal self- injury. Eating behaviors. Dec 2012;13(4):335-341.

65. Claes L, Muehlenkamp J. The Relationship between the UPPS-P Impulsivity

Dimensions and Nonsuicidal Self-Injury Characteristics in Male and Female HighSchool Students. Psychiatry journal. 2013;2013:654847.

66. Riley EN, Combs JL, Jordan CE, et al. Negative Urgency and Lack of Perseverance: Identification of Differential Pathways of Onset and Maintenance Risk in the Longitudinal Prediction of Nonsuicidal Self-Injury. Behavior therapy. Jul 2015;46(4):439-448.

67. Luna B, Garver KE, Urban TA, et al. Maturation of cognitive processes from late childhood to adulthood. Child development. Sep-Oct 2004;75(5):1357-1372.

68. Rubia K, Overmeyer S, Taylor E, et al. Functional frontalisation with age: mapping neurodevelopmental trajectories with fMRI. Neuroscience and biobehavioral reviews. Jan 2000;24(1):13-19.

69. Rubia K, Smith AB, Woolley J, et al. Progressive increase of frontostriatal brain activation from childhood to adulthood during event-related tasks of cognitive control. Human brain mapping. Dec 2006;27(12):973-993.

70. Durston S, Davidson MC, Tottenham N, et al. A shift from diffuse to focal cortical activity with development. Developmental science. Jan 2006;9(1):1-8.

71. Cohen-Gilbert JE, Thomas KM. Inhibitory control during emotional distraction across adolescence and early adulthood. Child development. Nov-Dec 2013;84(6):1954-1966.

72. Barrocas AL, Giletta M, Hankin BL, et al. Nonsuicidal self-injury in adolescence:
longitudinal course, trajectories, and intrapersonal predictors. Journal of abnormal child psychology. Feb 2015;43(2):369-380.

73. Gratz KL. Measurement of deliberate self-harm: preliminary data on the Deliberate Self-Harm Inventory. J Psychopathol Beh Assess. 2001;23:253-263.

74. Klonsky ED, Glenn CR. Assessing the functions of non-suicidal self-injury: Psychometric propoerties of the Inventory of Statements About Self-injury (ISAS). J Psychopathol Behav Assess. 2009;31:215-219.

75. Morey LC. Personality Assessment Inventory Professional Manual, second edition. Odessa, FL: Psychological Assessment Resources; 2007.

76. Downey G, Feldman SI. Implications of rejection sensitivity for intimate relationships. Journal of personality and social psychology. Jun 1996;70(6):1327- 1343.

77. Derogatis LR. Symptom Checklist-90-R: Adminmistration, Scoring, and Procedures Manual (3rd ed.). Minneapolis, MN: National Computer Systems; 1994.

78. Power JD, Barnes KA, Snyder AZ, et al. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage. Feb 1 2012;59(3):2142-2154.

79. Hariri AR, Tessitore A, Mattay VS, et al. The amygdala response to emotional stimuli: a comparison of faces and scenes. NeuroImage. Sep 2002;17(1):317-323.

80. Raichle ME, MacLeod AM, Snyder AZ, et al. A default mode of brain function. Proceedings of the National Academy of Sciences of the United States of America. Jan 16 2001;98(2):676-682.

81. Kirschbaum C, Pirke KM, Hellhammer DH. The 'Trier Social Stress Test'--a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology. 1993;28(1-2):76-81.

82. Somerfeldt S, Cullen KR, Han G, et al. Executive attention impairment in adolescents with major depressive disorder. Journal of Clinical Child and Adolescent Psychology. in press.

83. Han G, Klimes-Dougan B, Jepsen S, et al. Selective neurocognitive impairments in adolescents with major depressive disorder. Journal of adolescence. Feb 2012;35(1):11-20.

84. Hare TA, Tottenham N, Galvan A, et al. Biological substrates of emotional reactivity and regulation in adolescence during an emotional go-nogo task. Biological psychiatry. May 15 2008;63(10):927-934.

85. Glenn CR, Klonsky ED. Prospective prediction of nonsuicidal self-injury: a 1-year longitudinal study in young adults. Behavior therapy. Dec 2011;42(4):751-762.

86. Skegg K. Self-harm. Lancet. Oct 22-28 2005;366(9495):1471-1483.

87. Whitlock J, Muehlenkamp J, Eckenrode J. Variation in nonsuicidal self-injury: identification and features of latent classes in a college population of emerging adults. Journal of clinical child and adolescent psychology : the official journal for the Society of Clinical Child and Adolescent Psychology, American Psychological Association, Division 53. Oct 2008;37(4):725-735.

88. Lenroot RK, Giedd JN. Sex differences in the adolescent brain. Brain and cognition. Feb 2010;72(1):46-55.

89. Zetterqvist M, Lundh LG, Dahlstrom O, et al. Prevalence and function of non-suicidal self-injury (NSSI) in a community sample of adolescents, using suggested DSM-5 criteria for a potential NSSI disorder. Journal of abnormal child psychology. Jul 2013;41(5):759-773.

90. Andover MS. Non-suicidal self-injury disorder in a community sample of adults. Psychiatry research. Oct 30 2014;219(2):305-310.

91. Giedd JN, Castellanos FX, Rajapakse JC, et al. Sexual dimorphism of the developing human brain. Progress in neuro-psychopharmacology & biological psychiatry. Nov 1997;21(8):1185-1201.

92. Giedd JN, Clasen LS, Lenroot R, et al. Puberty-related influences on brain development. Molecular and cellular endocrinology. Jul 25 2006;254-255:154-162.

93. Goddings AL, Mills KL, Clasen LS, et al. The influence of puberty on subcortical brain development. NeuroImage. Mar 2014;88:242-251.

94. DSM-5. Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) at <http://www.dsm5.org/Pages/Default.aspx>. 2013.

95. Kaufman J, Birmaher B, Brent D, et al. 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 and Adolescent Psychiatry. Jul 1997;36(7):980-988.

96. Wechsler D. Wechsler Abbreviated Scale of Intelligence -- Second Edition (WASI-II). San Antonio, TX: NCS Pearson; 2011.

97. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia. Mar 1971;9(1):97-113.

98. Hollingshead AB. Hollingshead Four Factor Scale. New Haven, CT: Yale University Department of Sociology; 1975.
99. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Archives of disease in childhood. Jun 1969;44(235):291-303.
100. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys.
Archives of disease in childhood. Feb 1970;45(239):13-23.
101. Bernstein DP, Fink L. Childhood Trauma Questionnaire: A retrospective self-report manual. San Antonio, TX: The Psychological Corporation; 1998.
102. Nock MK, Holmberg EB, Photos VI, et al. Self-Injurious Thoughts and Behaviors Interview: development, reliability, and validity in an adolescent sample.
Psychological assessment. Sep 2007;19(3):309-317.
103. Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: the Scale for Suicide Ideation. Journal of consulting and clinical psychology. Apr 1979;47(2):343-352.
104. Sobell LC, Sobell MB. Timeline followback: A technique for assessing self-reported alcohol consumption. In: Litten RZ, Allen J, eds. Measuring alcohol consumption: Psychosocial and biological methods. Totowa, NJ: Humana Press; 1992:41-72.
105. Sobell LC, Sobell MB. Alcohol consumption measures. In: Allen JP, Wilson V, eds. Assessing alcohol problems. 2nd ed. Rockville, MN: National Institute on Alcohol Abuse and Alcoholism; 2003:75-99.
106. Watson D, O'Hara MW, Chmielewski M, et al. Further validation of the IDAS: evidence of convergent, discriminant, criterion, and incremental validity.
Psychological assessment. Sep 2008;20(3):248-259.
107. Watson D, O'Hara MW, Naragon-Gainey K, et al. Development and validation of new anxiety and bipolar symptom scales for an expanded version of the IDAS (the IDAS-II). Assessment. Dec 2012;19(4):399-420.
108. Watson D, O'Hara MW, Simms LJ, et al. Development and validation of the Inventory of Depression and Anxiety Symptoms (IDAS). Psychological assessment. Sep 2007;19(3):253-268.
109. Lindstrom KM, Guyer AE, Mogg K, et al. Normative data on development of neural and behavioral mechanisms underlying attention orienting toward social- emotional stimuli: an exploratory study. Brain research. Oct 6 2009;1292:61-70.
110. Britton JC, Bar-Haim Y, Clementi MA, et al. Training-associated changes and stability of attention bias in youth: Implications for Attention Bias Modification Treatment for pediatric anxiety. Developmental cognitive neuroscience. Apr 2013;4:52-64.
111. Carlson JM, Reinke KS, Habib R. A left amygdala mediated network for rapid orienting to masked fearful faces. Neuropsychologia. Apr 2009;47(5):1386-1389.
112. McCrory EJ, De Brito SA, Kelly PA, et al. Amygdala activation in maltreated children during pre-attentive emotional processing. The British journal of psychiatry : the journal of mental science. Apr 2013;202(4):269-276.

113. DeRose LM, Klimes-Dougan B, Shircliff EA, et al. Stress reactivity and regulation across the adolescent transition. Philadelphia, PA: Society for Adolescent Research; 2010 March.
114. Klimes-Dougan B, Eberly LE, Westlund Schreiner M, et al. Multilevel assessment of the neurobiological threat system in depressed adolescents: interplay between the limbic system and hypothalamic-pituitary-adrenal axis. Development and psychopathology. Nov 2014;26(4 Pt 2):1321-1335.
115. Musgrove D, Eberly L, Klimes-Dougan B, et al. Impaired Bottom-Up Effective Connectivity Between Amygdala and Subgenual Anterior Cingulate Cortex in Unmedicated Adolescents with Major Depression: Results from a Dynamic Causal Modeling Analysis. Brain connectivity. Jun 7 2015.
116. Harter S. Manual for the self-perception profile for children. Denver, CO: University of Denver; 1985.
117. Harter S. The Self Perception Profile for Adolescents. Denver, CO: University of Denver; 2012.
118. Taylor GJ, Ryan D, Bagby RM. Toward the development of a new self-report alexithymia scale. Psychotherapy and psychosomatics. 1985;44(4):191-199.
119. Jankowski KF, Moore WE, Merchant JS, et al. But do you think I'm cool? Developmental differences in striatal recruitment during direct and reflected social self-evaluations. Developmental cognitive neuroscience. Apr 2014;8:40- 54.
120. Birn RM, Molloy EK, Patriat R, et al. The effect of scan length on the reliability of
resting-state fMRI connectivity estimates. NeuroImage. Dec 2013;83:550-558.
121. Patriat R, Molloy EK, Meier TB, et al. The effect of resting condition on resting- state fMRI reliability and consistency: a comparison between resting with eyes open, closed, and fixated. NeuroImage. Sep 2013;78:463-473.
122. Anand A, Li Y, Wang Y, et al. Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study. Biological psychiatry. May 15 2005;57(10):1079-1088